Ramb'S 2021
Journal Citation
Reports-Impact Factor:
1,712

ISSN 0104-4230
ISSN 1806-9282 (On-line)

RAMB

Journal of The Brazilian Medical Association

Volume 68, Number 9
September, 2022

AMB
Associação Médica Brasileira

WMA

RAMB

Journal of The Brazilian Medical Association

Ramb'S 2021 Journal Citation Reports-Impact Factor: 1,712

AMB Associação Médica Brasileira

WMA

Volume 68, Number 9, September, 2022

ISSN 0104-4230
ISSN 1806-9282 (On-line)

SECTIONS

ARTICLES

RAMB
Journal of The Brazilian Medical Association

AMB
Associação Médica Brasileira

MASTOLOGY
Gil Facina

MEDICAL GENETICS
Ida Vanessa D. Schwartz

NEUROSURGERY
Manoel Jacobsen Teixeira

NEPHROLOGY
Andrea Pio de Abreu

NEUROLOGY
Marcondes Cavalcante França Jr.

NUCLEAR MEDICINE
Diego Pianta

NUTROLOGY
Aline Zanetta

OCCUPATIONAL MEDICINE
Andrea Franco Amoras Magalhães

OPHTHALMOLOGY
Eduardo Melani Rocha

ORTHOPAEDICS AND TRAUMATOLOGY
Sergio Luiz Checchia

OTOLARYNGOLOGY
Thiago Freire Pinto Bezerra

PAEDIATRIC
Lilian dos Santos Rodrigues Sadeck

PAEDIATRIC SURGERY
Lisieux Eyer Jesus

PATHOLOGY
Monique Freire Santana

PHYSICAL MEDICINE AND REHABILITATION
Eduardo de Melo Carvalho Rocha

PLASTIC SURGERY
Daniela Francescato Veiga

PREVENTIVE MEDICINE AND HEALTH ADMINISTRATION
Antônio Eduardo Fernandes D´Aguiar

PSYCHIATRY
Leonardo Rodrigo Baldaçara

PULMONOLOGY / PHTHISIOLOGY
Suzana Erico Tanni Minamoto

RADIOTHERAPY
Wilson José Almeida Jr.

RADIOLOGY
Alexandre Bezerra

RHEUMATOLOGY
Ricardo Machado Xavier

SPORTS MEDICINE
Neuza Mitsuanga

SURGICAL ONCOLOGY
Héber Salvador de Castro Ribeiro

TRAFFIC MEDICINE
José Heverardo da Costa Montal

THORACIC SURGERY
Juliana Dias Nascimento Ferreira

UROLOGY
Roni de Carvalho Fernandes

RAMB - REVISTA DA ASSOCIAÇÃO MÉDICA BRASILEIRA
(JOURNAL OF THE BRAZILIAN MEDICAL ASSOCIATION)

Editors-in-Chief: Renato Deláscio Lopes, José Maria Soares Jr and Roseli Nomura.
Managing Editor: Cesar Teixeira
E-mail: ramb@amb.org.br
Website: www.ramb.org.br

ADDRESS: Rua São Carlos do Pinhal, 324
Bela Vista – São Paulo
Postal Code: 01333-903
Phone no.: (+55 11) 3178-6800 Ext. 177
The RAMB, Journal of The Brazilian Medical Association, is an official publication of the Associacao Medica Brasileira (AMB – Brazilian Medical Association), indexed in Medline, Science Citation Index Expanded, Journal Citation Reports, Index Copernicus, Lilacs, and Qualis B1 Capes databases, and licensed by Creative CommonsR.
Registered in the 1st Office of Registration of Deeds and Documents of Sao Paulo under n. 1.083, Book B, n. 2.

Publication norms are available on the website www.ramb.org.br

THE RAMB IS INDEXED IN SCIELO - SCIENTIFIC ELECTRONIC LIBRARY ONLINE.

Editorial Production

ZEPPELINI PUBLISHERS

EDITORIAL

https://doi.org/10.1590/1806-9282.20220768

Management of the infectious diseases during palliative care

Mehmet Göl[1*], Yusuf Hoşoğlu[2], İbrahim Halil Türkbeyler[3]

According to the World Health Organization, palliative care is an ameliorative perspective which begins from the very beginning such as preventive measurements and proceeds through the alleviation of signs and symptoms regarding all physical, psychosocial, and spiritual aspects by means of early diagnosis followed by a flawless assessment and therapy and consequently aims at enhancing the quality of life of patients and their families confronting with the problems as a consequence of a life-threatening illnesses. As this is the case worldwide, the percentage of the elderly population is increasing in Turkey. The percentage of the elderly is estimated to reach up to 10.2% by the year 2023 in this country. This increase also concomitantly results in an increment of cases of illnesses and comorbidities in the elderly population. The incidence of the infectious disease and resultant mortality has likewise been increasing among the elderly. It is considered that one-third of all deaths among the elderly are due to infectious diseases[1,2].

Infectious diseases are ordinarily seen in the elderly who need palliative care and are considered to be one of the most important causes of mortality. Whether to apply treatment or not for an elderly patient with an infectious disease has to be clarified in the light of predetermined palliative care objectives. The main establishment should be the prevention of the infectious disease and the protection of the patients from the foregone conclusions[3] (Table 1).

In elderly patients, particularly those receiving palliative care, the course of infectious diseases displays atypical symptoms. Around 48% of the patients with a bacterial infection do not exhibit fever initially and even white blood cell count does not increase in 44% of them. Patients might present symptoms related to the infectious disease, such as loss of appetite, fatigue, and functional restriction. Sudden confusional state, worsening of the symptoms of dementia, experiencing incontinence, and painful urination might be indicative of a type of infectious disease in the elderly[4,5]. As numerous patients have been dying under the antibiotherapy treatment, the following questions need to be answered: whether antibiotherapy is strictly necessary, if needed when to apply, and its schedule

Table 1. Precautions considered to prevent infectious diseases.

Keep away from getting in touch with individual possibly having a pathogen or ambience which was possibly contaminated
Taking the advantage of aseptic techniques in skin or wound care
Maximizing the patient's physical functions
Regular and proper catheter care
Taking care of teeth and mouth
Regular examination of oral mucosa
Monitoring and regulation of patient nutrition
Assessment of patient's weight regularly
Hand hygiene
Drinking tepid water
Ensuring good hydration
Taking the advantage of air humidifiers

[1]Gaziantep Islam Science and Technology University, Faculty of Medicine, Department of Physiology – Gaziantep, Turkey.
[2]Ersin Arslan Education and Research Hospital, Department of Cardiology – Gaziantep, Turkey.
[3]Gaziantep Islam Science and Technology University, Faculty of Medicine, Ersin Arslan Education and Research Hospital, Department of Internal Medicine, Division of Geriatric Medicine – Gaziantep, Turkey.
*Corresponding author: fatih172@gmail.com, mehmet.gol@gibtu.edu.tr
Conflicts of interest: the authors declare there is no conflicts of interest. Funding: none.
Received on May 29, 2022. Accepted on July 06, 2022.

Table 2. Minimum criteria for initiating antibiotic treatment in elderly who are in advanced stage of dementia, living in a nursing home, and with a suspect of an infectious disease.

Suspect of having an urinary tract infection	Suspect of having an lower respiratory tract infection	Suspect of a skin infection	Existence of fever
a. No indwelling foley catheter Acute dysuria alone **OR** Temperature >37.9°C AND ≥1 of following: 1 – New or worse frequency 2 – Urgency 3 – Costovertebral tenderness 4 – Gross hematuria 5 – Suprapubic pain 6 – Mental status change 7 – Rigors	a. Temperature ≥38.9°C ≥1 of following: 1 – Respiratory rate <25 breaths per minute 2 – New productive cough b. Temperature ≤38.9°C New productive cough **AND** ≥1 of the following: 1 – Pulse >100 beats per minute 2 – Respiratory rate >25 breaths per minute 3 – Rigors 4 – Change in mental status c. A febrile with COPD New/increased cough with purulent sputum	New or increased purulent drainage **OR** ≥1 of following: 1 – Temperature >37.9°C 2 – Redness 3 – New or increased swelling 4 – Warmth 5 – Tenderness	Temperature ≥37.9°C **AND** ≥1 of following: 1 – Change in mental status 2 – Rigors 3 – Unstable vital signs
b. Indwelling foley catheter ≥1 of following: 1 –Temperature >37.9°C 2 – Rigors 3 – Change in mental status			

to achieve the best benefit. The reverse of the medal may even result in the supererogatory perpetuation of suffering of the patient. The clinician must have enough accusative evidence in favor of infectious disease in order to start antibiotic treatment in an elderly patient. For this reason, antibiotic stewardship, a phrase recently introduced in the medical field[6], points out a medical tenet that brings into focus the aim of optimizing antibiotherapy.

It seems that most clinicians are deciphering an infectious situation as one of the curable acute complications of the underlying disease. It was observed that urinary tract infection (UTI) and respiratory tract infection (RTI) were the most encountered infections in palliative care unit[7,8]. Although findings support the effectiveness of antibiotherapy in patients with UTIs, amelioration of signs and symptoms following antibiotherapy has been verified as a deduction of mostly subjective observations based upon individual professional experiences of clinicians[9]. In one of those studies, 79% of cancer patients with UTI who were subjected to hospice care for considerable symptomatic alleviation have been studied[10].

In addition, oral, intramuscular, or intravenous administration of the antibiotic has been shown to make no difference in terms of survival. As for the antibiotherapy for patients with UTIs in hospice, it is regarded to have no effect on survival despite providing a symptomatic relief[11]. These data indicate that it is possible to keep away from hospitalization and aggressive parenteral antibiotherapies and to maintain oral treatment, even in elderly patients in whom the main medical purpose is to improve survival[12,13].

The Society for Healthcare Epidemiology of America documented a guideline that depicts an algorithm defining the required criteria that allow clinicians to start an antibiotic treatment in the elderly with a type of infectious disease who are living in a nursing home. Afterward, that guideline was adjusted for the evaluation of advanced-stage dementia patients having an infectious disease[14,15] (Table 2).

AUTHORS' CONTRIBUTIONS

MG: Data curation, Formal Analysis, Investigation, Writing – original draft. **YH:** Writing – review & editing. **İHT:** Conceptualization, Visualization.

REFERENCES

1. Türkiye İstatistik Kurumu. Data portal for statistics. 2017 [cited on May 20, 2022]. Available from: https://data.tuik.gov.tr/Bulten/Index?p=Istatistiklerle-Yaslilar-2016-24644.
2. Mouton CP, Bazaldua OV, Pierce B, Espino DV. Common infections in older adults. Am Fam Physician. 2001;63(2):257-68. PMID: 11201692
3. Centers for Disease Control and Prevention. Prevention guide to infection prevention for outpatients setting: minimum expectations for safe care. 2016; [cited on May 13, 2022]. Available from: https://www.cdc.gov/hai/settings/outpatient/outpatient-care-guidelines.html
4. Meyer KC. Lung infections and aging. Ageing Res Rev. 2004;3(1):55-67. https://doi.org/10.1016/j.arr.2003.07.002

5. Castle SC, Norman DC, Yeh M, Miller D, Yoshikawa TT. Fever response in elderly nursing home residents: are the older truly colder? J Am Geriatr Soc. 1991;39(9):853-7. https://doi.org/10.1111/j.1532-5415.1991.tb04450.x
6. Charani E, Cooke J, Holmes A. Antibiotic stewardship programmes--what's missing? J Antimicrob Chemother. 2010;65(11):2275-7. https://doi.org/10.1093/jac/dkq357
7. Vitetta L, Kenner D, Sali A. Bacterial infections in terminally ill hospice patients. J Pain Symptom Manage. 2000;20(5):326-34. https://doi.org/10.1016/s0885-3924(00)00189-5
8. Dagli O, Tasdemir E, Ulutasdemir N. Palliative care infections and antibiotic cost: a vicious circle. Aging Male. 2020;23(2):98-105. https://doi.org/10.1080/13685538.2019.1575353
9. Furuno JP, Noble BN, Fromme EK. Should we refrain from antibiotic use in hospice patients? Expert Rev Anti Infect Ther. 2016;14(3):277-80. https://doi.org/10.1586/14787210.2016.1128823
10. Reinbolt RE, Shenk AM, White PH, Navari RM. Symptomatic treatment of infections in patients with advanced cancer receiving hospice care. J Pain Symptom Manage. 2005;30(2):175-82. https://doi.org/10.1016/j.jpainsymman.2005.03.006
11. White PH, Kuhlenschmidt HL, Vancura BG, Navari RM. Antimicrobial use in patients with advanced cancer receiving hospice care. J Pain Symptom Manage. 2003;25(5):438-43. https://doi.org/10.1016/s0885-3924(03)00040-x
12. Givens JL, Jones RN, Shaffer ML, Kiely DK, Mitchell SL. Survival and comfort after treatment of pneumonia in advanced dementia. Arch Intern Med. 2010;170(13):1102-7. https://doi.org/10.1001/archinternmed.2010.181
13. Goronzy JJ, Fulbright JW, Crowson CS, Poland GA, O'Fallon WM, Weyand CM. Value of immunological markers in predicting responsiveness to influenza vaccination in elderly individuals. J Virol. 2001;75(24):12182-7. https://doi.org/10.1128/JVI.75.24.12182-12187.2001
14. Loeb M, Bentley DW, Bradley S, Crossley K, Garibaldi R, Gantz N, et al. Development of minimum criteria for the initiation of antibiotics in residents of long-term-care facilities: results of a consensus conference. Infect Control Hosp Epidemiol. 2001;22(2):120-4. https://doi.org/10.1086/501875
15. Mitchell SL, Shaffer ML, Kiely DK, Givens JL, D'Agata E. The study of pathogen resistance and antimicrobial use in dementia: study design and methodology. Arch Gerontol Geriatr. 2013;56(1):16-22. https://doi.org/10.1016/j.archger.2012.08.001

https://doi.org/10.1590/1806-9282.2022D687

Sugammadex in awakening from general anesthesia: systematic review and meta-analysis

Adriano Anzai[1], Armelin Utino[1], Giuliano Tosello[1], Haroldo Katayama[1], Ighor Alexander Zamuner Spir[1], Luca Schiliró Tristão[1], Mary Martins Nery[1], Mauricio Anhesini[1], Osvaldo Silvestrini Tiezzi[1], Patricia Rodrigues Naufal Spir[1], Pericles Otani[1], Wanderley Marques Bernado[1]*

INTRODUCTION

General anesthesia (GA) is used in surgical procedures, and it consists of the induced, reversible, and controlled loss of consciousness, which maintains the patient in a state of sedation, analgesia, amnesia, and muscle paralysis induced by neuromuscular blockers (NMBs). Although the mechanism of action of GA is not entirely clear, it is known that signals along the nerves responsible for passing stimuli are interrupted and not processed by the central nervous system after anesthetic administration. The entire anesthetic process requires protection of the airways and/or mechanical ventilation, because by causing muscle paralysis, the agents cause the inhibition of spontaneous breathing, together with uncontrolled hemodynamic processes. Some of the neuroblockers (NBs) available for use in GA are as follows:

1) *Rocuronium* – Androstanol non-depolarizing neuromuscular blocking agent (NMBA), with a mono-quaternary structure, being a weaker nicotinic antagonist than pancuronium (pancuronium bromide is a non-depolarizing long-acting neuromuscular blocking amino ester).
2) *Vecuronium bromide* – Mono-quaternary homolog of pancuronium and a non-depolarizing NMBA, with a shorter action than pancuronium, which may provide an advantage or be used as an alternative, as it does not have significant cardiovascular effects, does not depend on good renal function, and has a short duration of action and easy reversibility compared to other NB agents.
3) *Succinylcholine* – Quaternary skeletal muscle relaxant usually used in the form of bromide, chloride, or iodide. It is a depolarizing relaxant, with action in approximately 30 s and an average duration of 3–5 min, used in medical procedures when a brief period of muscle relaxation is required.
4) *Cisatracurium* – NMB, indicated as an adjunct to GA to facilitate tracheal intubation and skeletal muscle relaxation during surgical procedures or mechanical ventilation in intensive care unit (ICU) environments.

NMB should be monitored through quantitative (accelerometry, electromyography, cinematography) or qualitative measurements. The latter is performed using a peripheral nerve stimulator that determines the depth of block (TOF) considering the TOF measurement >0.9 as an indicative parameter for extubation[1] (Appendix IV).

At the end of the anesthetic process, NMB reversers are used in order to shorten the muscle activity recovery time. The drugs most frequently used for this purpose are as follows:

1) Sugammadex – A selective antagonist of steroidal NMBA (e.g., rocuronium, vecuronium, and pancuronium). It is a water-soluble substance that, by displacing the NMBA from the neuromuscular junction receptors, forms a stable compound with it, producing cessation of the NMB action in anesthesia.
2) Neostigmine – Cholinesterase inhibitor used in the treatment of myasthenia gravis and to reverse the myorelaxant effects of muscle blockers.

[1]Unimed, Center for Evidence-Based Medicine – Presidente Prudente (SP), Brazil.
*Corresponding author: wbernardo@usp.br
Conflicts of interest: the authors declare there is no conflicts of interest. Funding: none.
Received on April 20, 2022. Accepted on April 20, 2022.

3) Pyridostigmine bromide— Cholinesterase inhibitor with a slightly longer duration of action than neostigmine.
4) Edrophonium – A rapid-onset, short-acting cholinesterase inhibitor used in cardiac arrhythmias and in the diagnosis of myasthenia gravis. It has also been used as an antidote to curare poisons and as a muscarinic antagonist.
5) Atropine sulfate is indicated for the temporary blocking of serious or potentially lethal muscarinic effects, for example, as an antisialogogue, an anti-vagal agent, an antidote for organophosphorus, carbamate, or muscarinic mushroom poisoning, and to treat symptomatic bradycardia.
6) Glycopyrrolate – A muscarinic antagonist used as an antispasmodic in some disorders of the gastrointestinal tract and to reduce salivation.

This study aimed to compare the efficacy and safety of *sugammadex* with other substances commonly used in the reversal of NMB in GA, such as *neostigmine* and *pyridostigmine* associated with atropine sulfate or glycopyrrolate.

METHODS

In this section, the clinical question, the structured question (PICO), eligibility criteria of the studies, sources of information consulted, search strategies used, critical evaluation method (risk of bias), quality of evidence, data extracted, measures used to express the results, and method of analysis are discussed.

Clinical question

Is there evidence of efficacy and safety in the use of sugammadex compared to neostigmine or prostigmine in reversing NMB in inhaled general anesthesia (IGA)?

Structured question

P (population): Patients undergoing GA using NMBs.
I (intervention): Reversal of the blockade using sugammadex.
C (comparison): Reversal of conventional block with neostigmine or neostigmine+atropine.
O (outcome)[1]: Time to extubation, recovery time to reach TOF 90% (0.9), nausea, vomiting, hypoxemia, hypotension, bradycardia, hypertension.

Eligibility criteria

- Components of PICO;
- Randomized clinical trials (RCTs);
- No date restriction;
- Languages: English, Spanish, and Portuguese;
- Full text or abstract with necessary data;
- Outcomes expressed in absolute number of events or mean/median with variation.

Exclusion criteria

- Observational and non-comparative studies;
- In vitro and/or animal studies;
- Case series or case reports;
- Narrative or systematic reviews.

Sources of information consulted and search strategies

Medline via PubMed, EMBASE

Search strategy: Sugammadex AND Random*

Risk of bias and quality of evidence

For the RCTs, the following risks of bias were evaluated: focal question, randomization, blindfolded allocation, double blinding, evaluator blinding, losses, analysis by intention to treat (ITT), definition of outcomes, and sample size calculation.

Data extracted

Author, year of publication, study design, characteristics and number of patients, intervention, comparison, outcomes: time to extubation, recovery time to reach TOF 90% (0.9)[1], nausea, vomiting, hypoxemia, hypotension, bradycardia, hypertension.

Outcome measures

For categorical variables, we used absolute numbers, percentage, absolute risk, risk reduction or increase, number needed to treat (NNT) or number needed to harm (NNH), and 95% confidence interval (95%CI). For continuous variables, means or difference in means (MD) with standard deviation.

Expression of the results

When there was the possibility of aggregating the results of the included studies with respect to one or more common outcomes, a meta-analysis was performed using the RevMan version 5.3 software (Cochrane)[2].

To calculate the mean and standard deviation, when not presented in the study, the software VassarStats: Website for Statistical Computation was used[3].

Analysis of the quality of evidence

The quality of the evidence was assessed using GRADEpro software[4].

RESULTS

The results are presented using flowchart (Figure 1) of study selection, summaries of RCTs (Appendix 1), risk of bias (Appendix 2), results by outcome, quality of GRADE evidence (Appendix 3), and summary of the evidence.

In total, 265 studies were retrieved (Medline via PubMed), as well as 65 from the EMBASE database. After applying the eligibility criteria and evaluating titles and abstracts, 55 studies were selected, of which 36 were included[5-40] for evaluation of the full text and inclusion in the meta-analysis, with 19 studies excluded[41-59] (Figure 1). Three studies retrieved from EMBASE (Quang[5], Lemmens[6] and Woo[7]) were also found in the Medline search via PubMed. The studies by Pişkin[8] and Yağan[9] were included only once because they were cited twice with different PMIDs.

Characteristics of the included studies

The included studies met the eligibility criteria, being all RCTs, including pediatric and adult patients, with different doses of intervention (sugammadex), compared with neostigmine with or without association, during small, medium, and large surgeries. The summary of the characteristics of the included studies can be found in Appendix 1.

Risk of bias and quality of evidence

Regarding biases, randomization was adequate in most studies; considering the blinded allocation of distribution, there was a small preponderance of studies that performed blinded allocation in relation to those that did not; double blinding and evaluator blinding either did not occur or was not informed in most studies; the losses in most studies were not significant; the prognostic features in almost all studies were reported and adequate; the outcomes, with the exception of one study, were adequate; most studies did not analyze ITT; in most studies, the sample calculation was performed; and in only two studies, there was an early interruption.

The risk of bias and the quality of evidence can be found in Appendix 2.

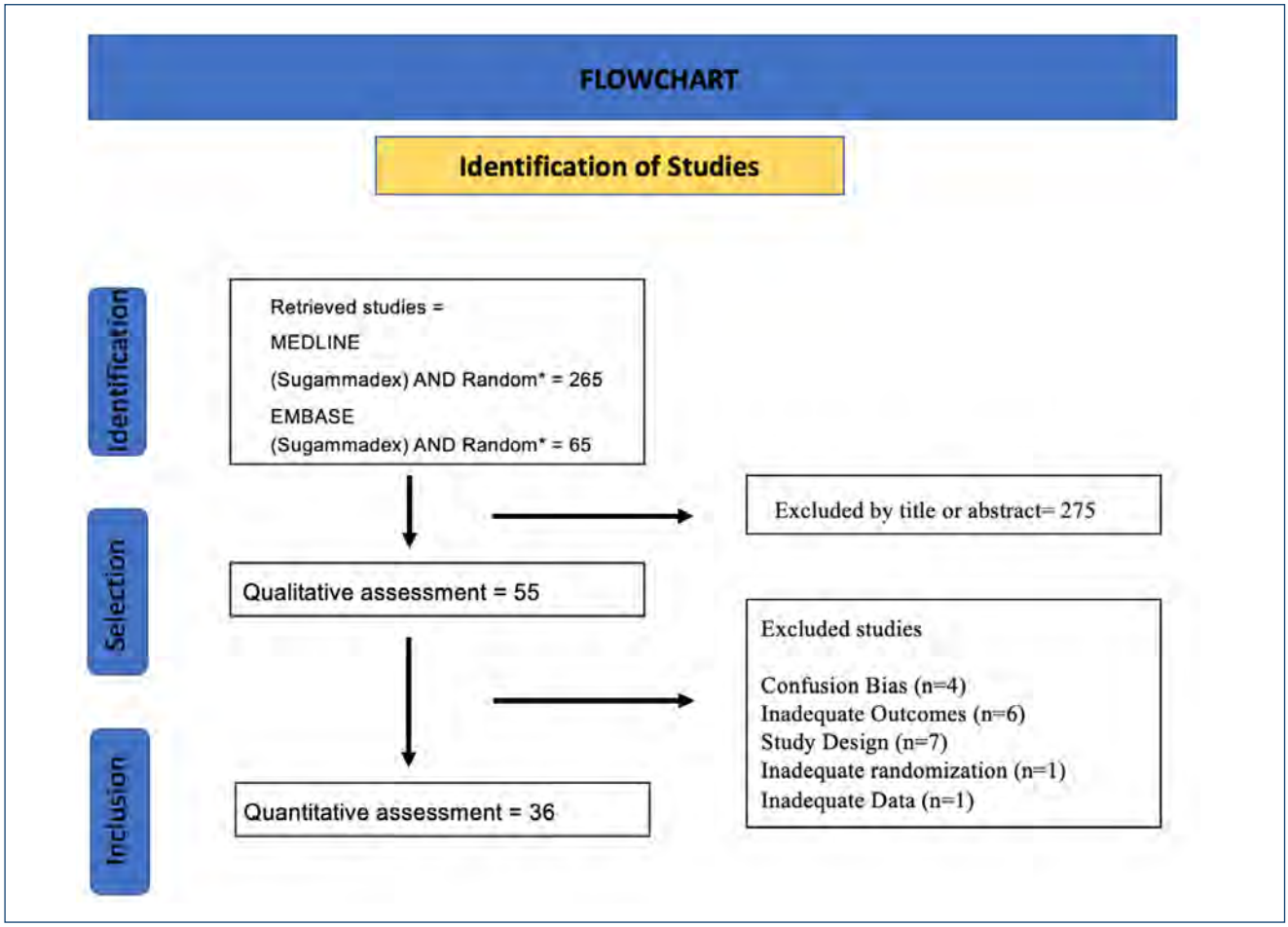


Figure 1. Flowchart of selected studies.

Analysis of results by outcome

1) Extubation time

In the evaluation of time to extubation (min), 12 studies were included, with 699 patients in the SUGAMMADEX group and 708 in the NEOSTIGMINE group.

With the drug SUGAMMADEX, extubation time was shorter compared to NEOSTIGMINE, with a significant reduction, MD= -3.67 (95%CI 5.24 – 2.11) (Figure 2). The quality of available evidence is VERY LOW.

2) time to recover TOF>0.9

In the evaluation of the recovery time (min) to reach a TOF ratio >0.9, 20 studies were included, with 855 patients in the SUGAMMADEX group and 812 in the NEOSTIGMINE group.

SUGAMMADEX significantly reduced recovery time from NMB compared to NEOSTIGMINE. A mean risk difference (RD) was found of -12.57 (95%CI 15.12– -10.03) (Figure 3). The quality of available evidence is VERY LOW.

3) Time of permanence in recovery room

In assessing the length of stay in the post-anesthesia care unit (PACU, in min), 6 studies were included, with 364 patients in the SUGAMMADEX group and 370 in the NEOSTIGMINE group.

With SUGAMMADEX, the time spent in the PACU was shorter compared to NEOSTIGMINE. The time reduction was significant, with a mean RD of -9.91 (95%CI -15.66– -4.16) (Figure 4). The quality of available evidence is VERY LOW.

4) Bradycardia

In the evaluation of bradycardia with the use of block-reversing medication, 9 studies were included, with 621 patients in the SUGAMMADEX group and 563 in the NEOSTIGMINE group.

With SUGAMMADEX, bradycardia occurred less frequently when compared with NEOSTIGMINE, with an absolute reduction in the RD of -0.09 (95%CI -0.14– -0.04) (Figure 5). The quality of available evidence is LOW.

5) Hypertension

In the evaluation of arterial hypertension with the use of block-reversing medication, 3 studies were included, with 174 patients in the SUGAMMADEX group and 174 in the NEOSTIGMINE group.

With SUGAMMADEX, hypertension was more frequent when compared with NEOSTIGMINE, with a significant RD of 0.06 (95%CI 0.02–0.11) (Figure 6). The quality of available evidence is VERY LOW.

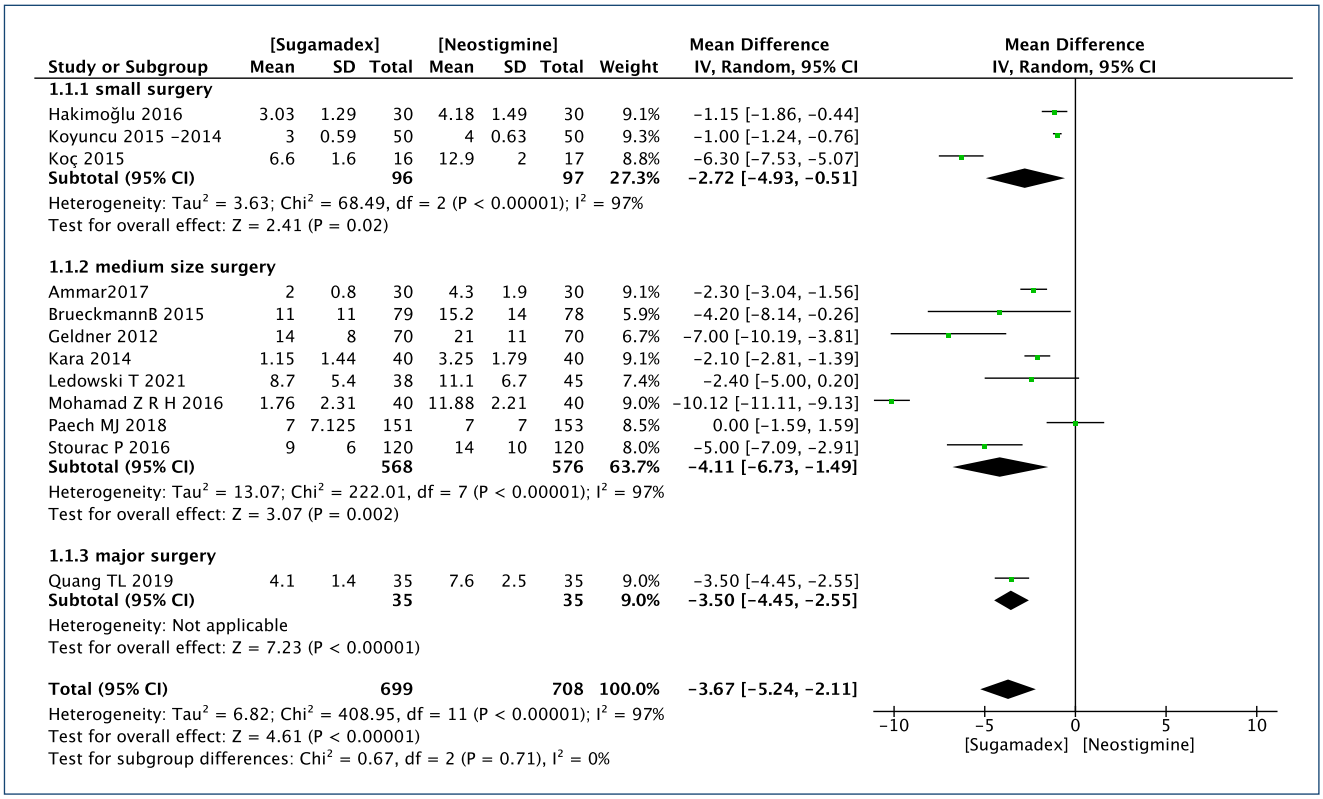


Figure 2. Forest plot comparing sugammadex versus neostigmine in extubation time.

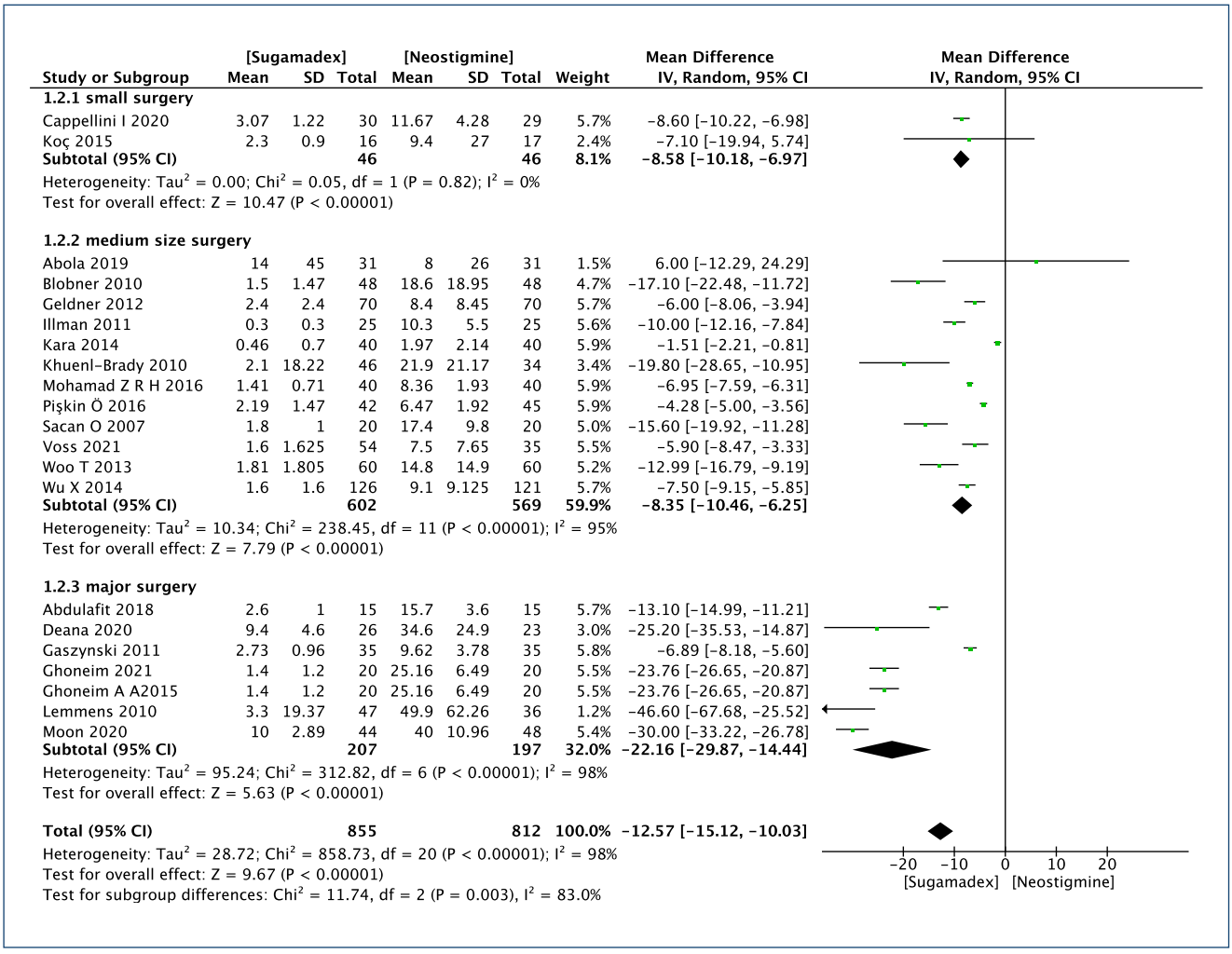


Figure 3. Forest plot comparing sugammadex versus neostigmine in neuromuscular block recovery time.

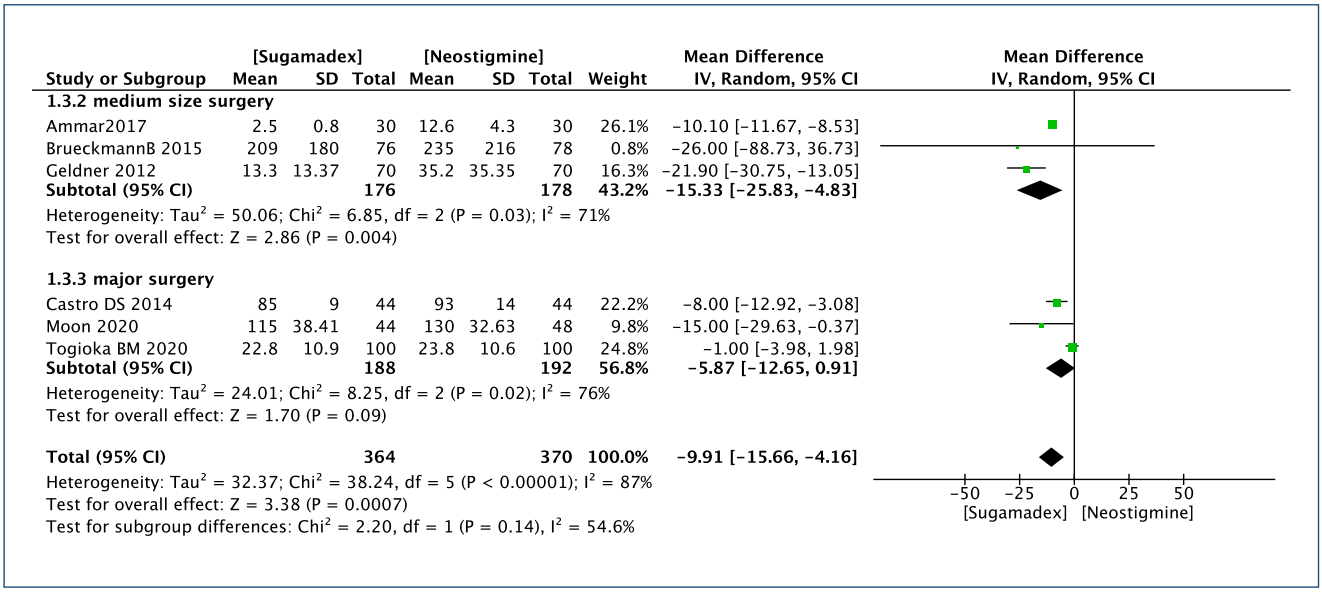


Figure 4. Forest plot comparing sugammadex versus neostigmine in time in the post-anesthesia care unit.

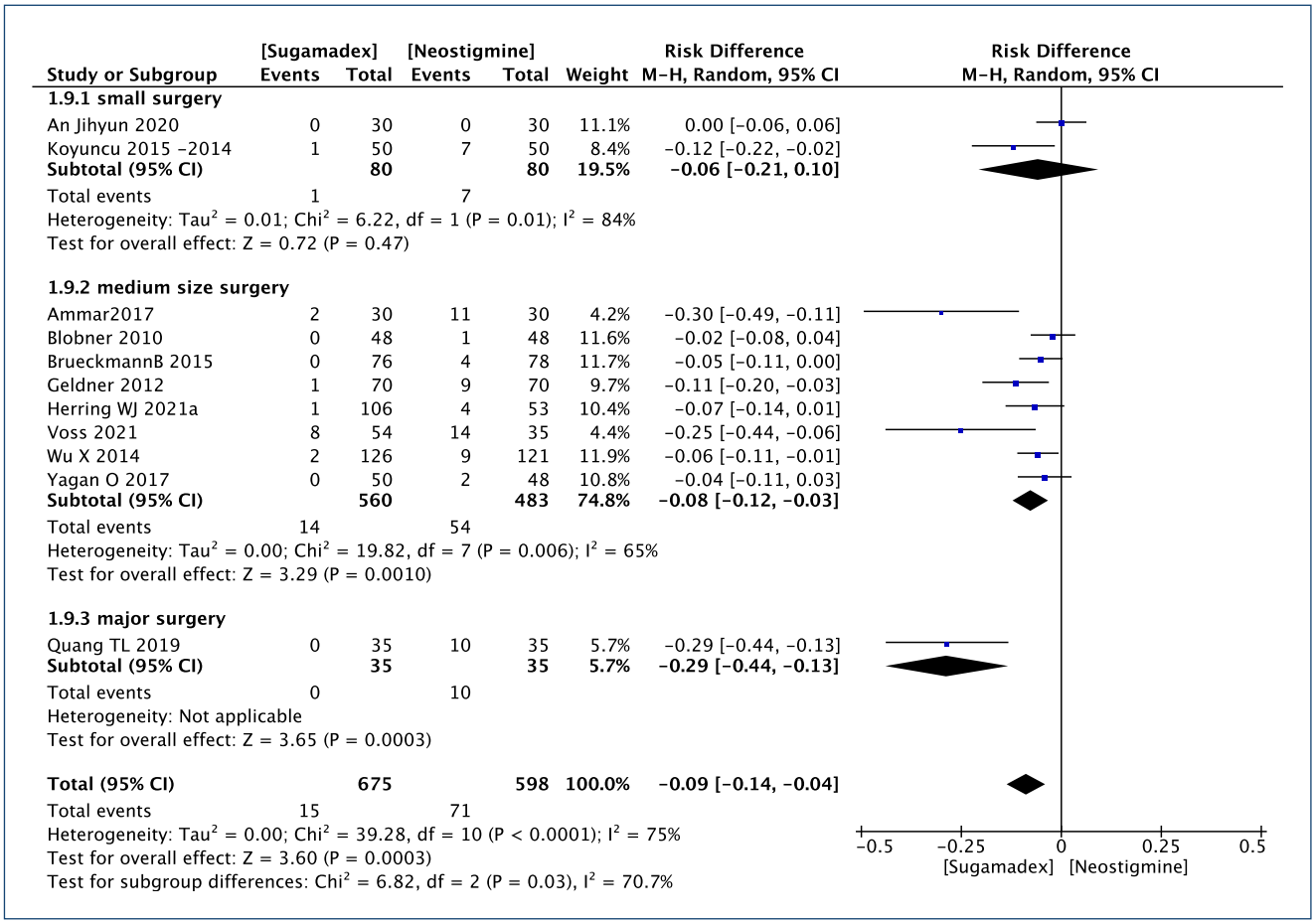


Figure 5. Forest plot comparing sugammadex versus neostigmine in evidence of bradycardia.

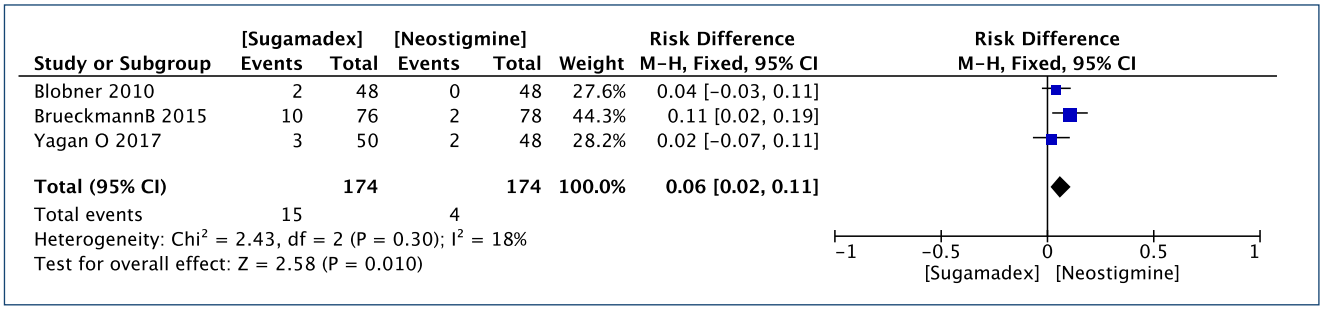


Figure 6. Forest plot comparing sugammadex versus neostigmine in evidence of hypertension.

6) Hypotension

In the evaluation of arterial hypotension with the use of block-reversing medication, 2 studies were included, with 126 patients in the SUGAMMADEX group and 128 in the NEOSTIGMINE group.

For the hypotension outcome, SUGAMMADEX showed no difference compared to NEOSTIGMINE, with an RD of −0.00 (95%CI -0.04–0.03) (Figure 7). The quality of available evidence is MODERATE.

7) Hypoxemia

In the evaluation of hypoxemia with the use of block-reversing medication, 5 studies were included, with 388 patients in the SUGAMMADEX group and 395 in the NEOSTIGMINE group.

For the hypoxemia outcome, there was no statistically significant difference between SUGAMMADEX and NEOSTIGMINE (RD=0.04; 95%CI -0.03–0.12) (Figure 8). The quality of available evidence is VERY LOW.

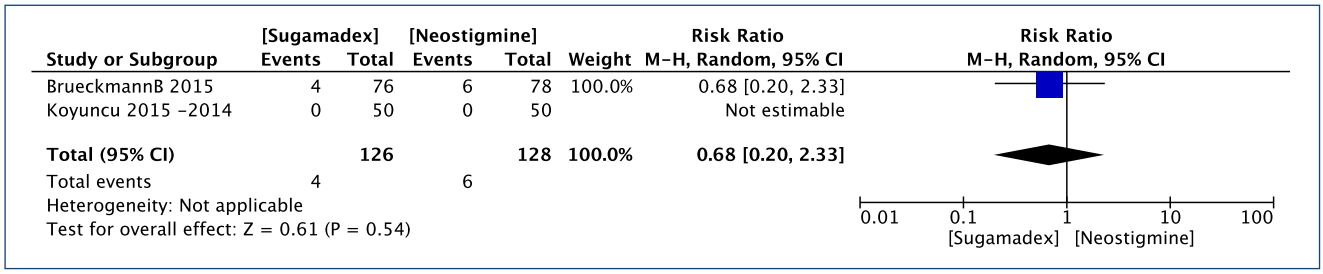


Figure 7. Forest plot comparing sugammadex versus neostigmine in evidence of hypotension.

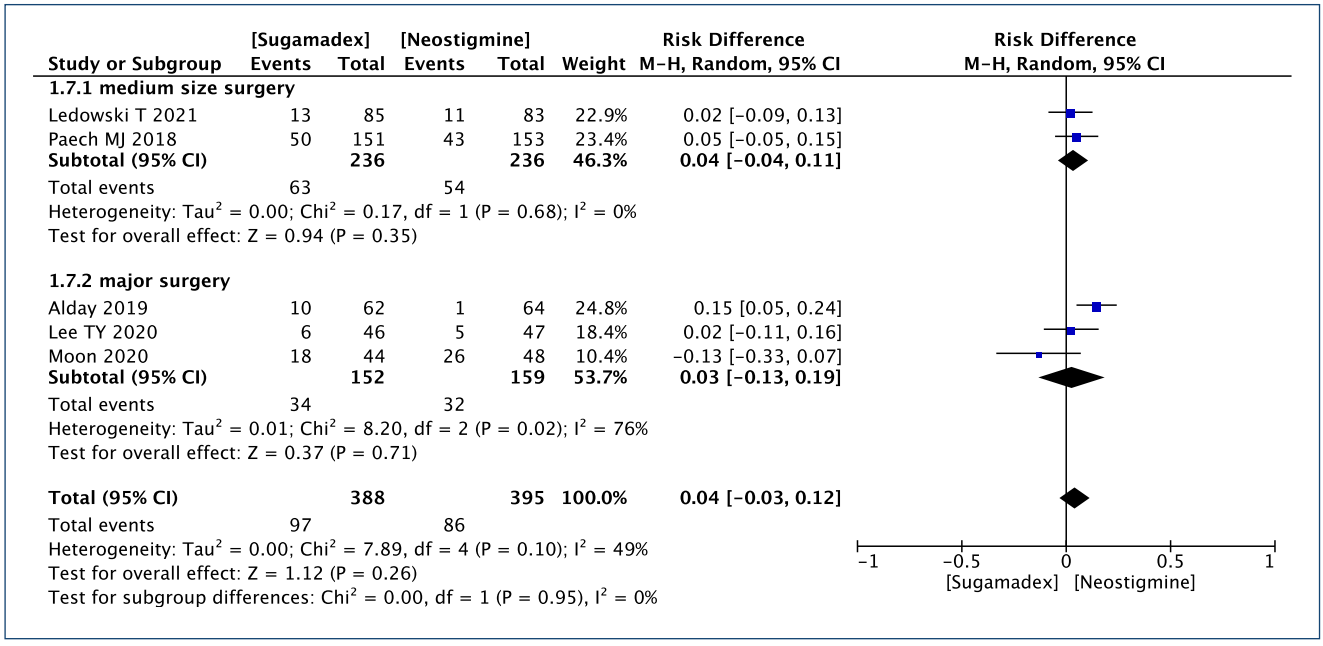


Figure 8. Forest plot comparing sugammadex versus neostigmine in evidence of hypoxemia.

8) Nausea

In the assessment of nausea with the use of block-reversing medication, 14 studies were included, with 819 patients in the SUGAMMADEX group and 800 in the NEOSTIGMINE group.

> No difference was found between the groups that used SUGAMMADEX and NEOSTIGMINE in the incidence of nausea (RD= -0.02; 95%CI -0.05–0.01) (Figure 9). The quality of available evidence is VERY LOW.

9) Vomiting

In the evaluation of vomiting with the use of block-reversing medication, 12 studies were included, with 720 patients in the SUGAMMADEX group and 620 in the NEOSTIGMINE group.

> For postoperative vomiting, there was no statistically significant difference between the SUGAMMADEX and NEOSTIGMINE groups (RD= -0.01; 95%CI -0.05–0.03) (Figure 10). The quality of available evidence is VERY LOW.

Quality of evidence (Appendix 3)

We used the principles of the GRADE approach to prepare an overall assessment of the quality of evidence. For hypotension and bradycardia outcomes, the quality of evidence was moderate. In the outcomes such as time to extubation, recovery time for TOF>0.9, time of permanence in the recovery room, nausea, vomiting, and hypoxemia, the quality of evidence was very low, regardless of the size of surgery or disease severity.

The complete GRADE assessment is available in Appendix 3.

Summary of the evidence

In the evaluation of extubation time in surgeries with NMB, sugammadex was shown to be superior, with a small difference in the analysis of the size of the surgery. The quality of available evidence is very low.

In reversing the block to TOF>0.9, there is benefit from the use of sugammadex, with the best evidence for medium

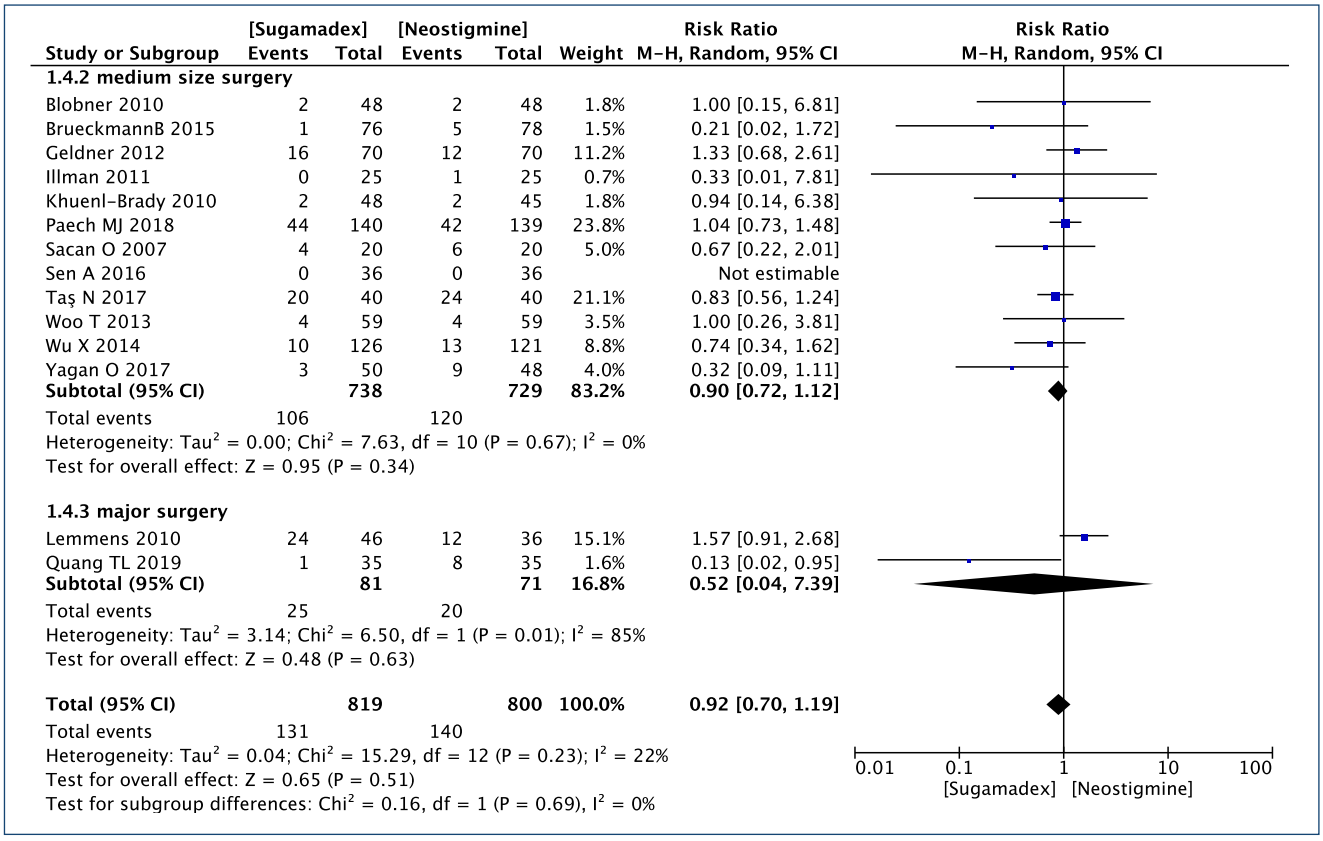


Figure 9. Forest plot comparing sugammadex versus neostigmine in evidence of nausea.

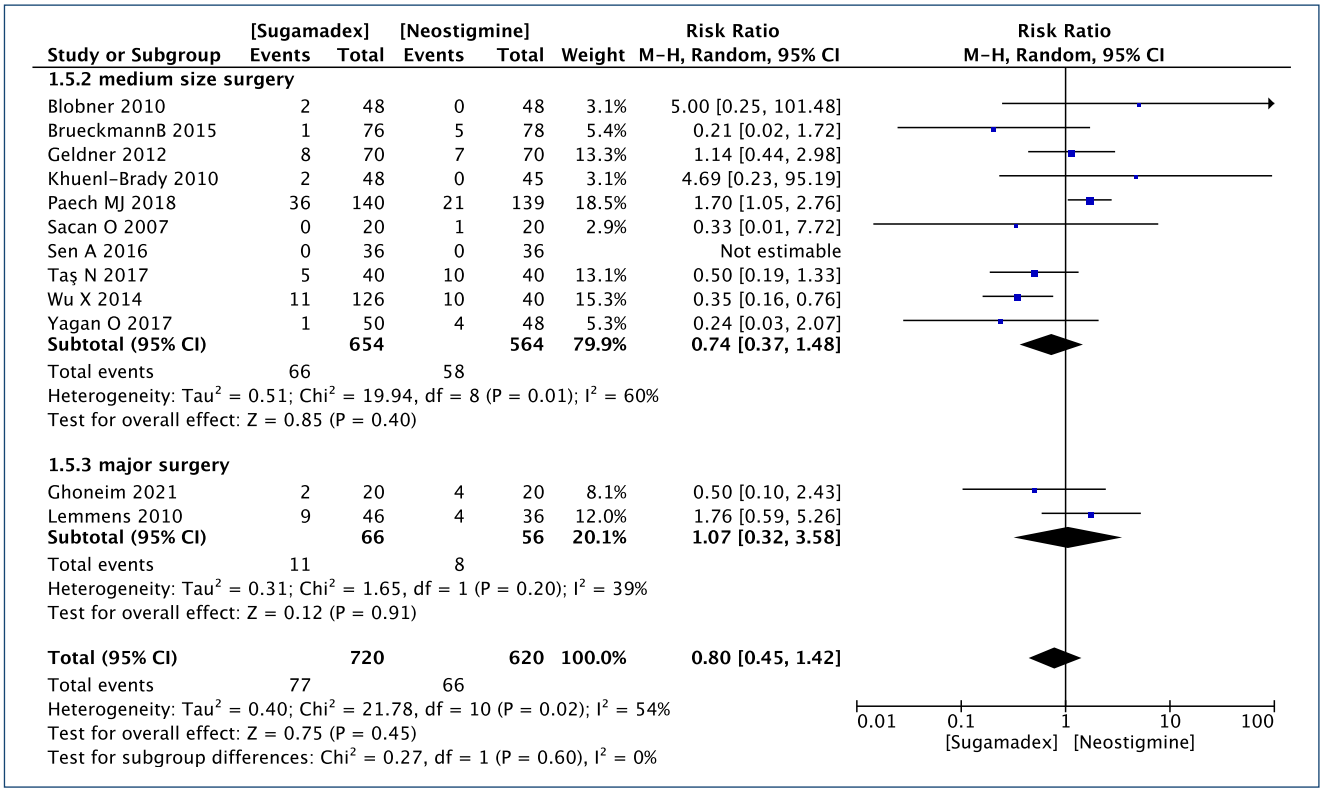


Figure 10. Forest plot comparing sugammadex versus neostigmine in the outcome vomiting.

and large anesthetic surgeries in relation to small surgeries. The quality of available evidence is very low.

For blood pressure indices, the incidence of hypertension was more frequent and significant in the use of sugammadex when compared with neostigmine. The quality of available evidence is very low.

The incidence of hypotension was without significance. The quality of available evidence is moderate.

The incidence of bradycardia was less frequent using sugammadex, with a significant reduction; the RD is -29% in major surgeries and quality of evidence is very low, -6% in medium-sized surgeries, and no difference in small-sized surgeries. The quality of available evidence is low.

For other evaluated events such as nausea, vomiting, and hypoxemia, there is no evidence of an RD in the comparative use of the drugs. The quality of available evidence is very low.

With the exception of the hypertension and hypotension outcomes, in the other evaluations, we showed high heterogeneity, so care should be taken in the interpretation of the results obtained.

DISCUSSION

Numerous studies have compared sugammadex versus neostigmine in the reversal of rocuronium-induced NMB. In the observational cohort study by Kheterpal[60], 45,712 patients were included for this purpose. The outcomes evaluated were pulmonary complications (primary composite outcome), pneumonia, and respiratory failure. The reported results were as follows: for pulmonary complications (primary composite outcome), 1.3% RD reduction (3.5 sugammadex vs. 4.8% neostigmine), with an NNT=77; for pneumonia, there was RD reduction of 0.9% (1.3 vs. 2.2%), with NNT=111; and for respiratory failure, 0.9% RD reduction (0.8 vs. 1.7%), with an NNT=111.

In this systematic review and meta-analysis of 36 RCTs, comparing the efficacy and safety of sugammadex and neostigmine, it was found that sugammadex led to shorter extubation time, shorter recovery time to reach TOF>0.9, and fewer cases of bradycardia. On the other hand, more cases of hypertension were reported in patients in the sugammadex group.

The extubation time outcome with sugammadex was significantly shorter compared to neostigmine, although this difference is only a few minutes (3.67 min, 95%CI -5.24– -2.11). In another meta-analysis, Carron et al.[61] also found a shorter extubation time in the sugammadex group (RD=0.18, 95%CI 0.14–0.22).

When the outcome recovery time to reach TOF>0.9 was evaluated, the meta-analysis composed of 20 studies showed a large and significant difference in NMB reversal time, favoring sugammadex over neostigmine 0.05 mg/kg (-12.57, 95%CI -15.12– -10.03). In the review by Hristovska et al.[62], this time interval was approximately 6.6 times shorter with sugammadex (MD -10.22, 95%CI -11.96– -8.48). Carron et al.[61] evaluating vecuronium-induced NMB reversal confirmed that sugammadex is faster than neostigmine in reversing rocuronium-induced blockade (MD -1.82; 95%CI -2.18– -1.46). In the evaluation of subgroups of these 20 RCTs according to the size of the surgeries, the major surgeries (e.g., cardiac surgery, transplantation, and bariatric surgery) presented a significant and favorable reduction with sugammadex, at the same dosages mentioned above. In medium-sized surgeries, the variation was also significant in favor of the sugammadex group.

Considering the adverse events evaluated, the differences were small. With the use of sugammadex, there was a lower incidence of bradycardia (8%, NNT=12) and a higher incidence of hypertension (6%, NNT=17). Hristovska et al.[62] showed no differences in their review.

For hypotension, nausea, and vomiting outcomes, there is no evidence of differences.

Regarding the high heterogeneity observed in the meta-analysis, we evaluated that although the inclusion criteria were well established and met, the disparities between the selected studies are evident, which may partly explain the high heterogeneity observed in the result. In addition, we cite the difficulty regarding the clinical selection of patients with very different pathologies and wide variation in disease severity. Comparing our meta-analysis with that performed by Cochrane[62], our numbers differ because those authors assessed relative risk and we used RD and MD.

CONCLUSION

The results suggest that sugammadex is as effective in reversing vecuronium or pancuronium-induced NMB as neostigmine, although the time difference in minutes to extubation is very small and the certainty of evidence analyzed using GRADE is low.

In the analysis of time to extubation, time to recover TOF>0.9, and bradycardia, there was statistical significance in favor of sugammadex. The hypertension outcome was unfavorable to sugammadex. However, high heterogeneity was found in the majority of outcomes.

Sugammadex, due to its faster reversal and similar adverse events, appears to have a more favorable safety profile, although the cost is much higher.

We understand that future studies are needed with larger samples and a low risk of bias to confirm the findings reported above.

AUTHORS' CONTRIBUTIONS

AA: Conceptualization, Data curation, Formal Analysis, Writing – original draft, Writing – review & editing. **AU:** Conceptualization, Data curation, Formal Analysis, Writing – original draft, Writing – review & editing. **GT:** Conceptualization, Writing – review & editing. **HK:** Conceptualization, Writing – original draft, Writing – review & editing. **IAZS:** Conceptualization, Data curation, Formal Analysis, Writing – original draft, Writing – review & editing. **LST:** Conceptualization. **MMN:** Conceptualization, Data curation, Formal Analysis, Writing – original draft, Writing – review & editing. **MA:** Conceptualization, Data curation, Formal Analysis, Writing – original draft, Writing – review & editing. **OST:** Conceptualization, Data curation, Formal Analysis, Writing – original draft, Writing – review & editing. **PRNS:** Conceptualization, Data curation, Formal Analysis, Writing – original draft, Writing – review & editing. **PO:** Conceptualization, Data curation, Formal Analysis, Writing – original draft, Writing – review & editing. **WMB:** Conceptualization, Data curation, Formal Analysis, Writing – original draft.

REFERENCES

1. Tardelli MA. Monitorização do Bloqueio Neuromuscular. In: Sociedade Brasileira de Anestesiologia. Curso de Educação à Distância em Anestesiologia. São Paulo: Office; 2002. p.177-90.
2. Review Manager (RevMan) [Computer program]. Version 5.3. Copenhagen: The Nordic Cochrane Centre, The Cochrane Collaboration; 2014.
3. Hozo SP, Djulbegovic B, Hozo I. Estimating the mean and variance from the median, range, and the size of a sample. BMC Med Res Methodol. 2005;5:13. https://doi.org/10.1186/1471-2288-5-13
4. GRADEpro GDT: GRADEpro Guideline Development Tool [Software]. Ontario: McMaster University, 2015.
5. Quang TL, Thu HNT, Quoc KN, Thu HN, Van DP, Tien NLB, et al. Neuromuscular blockade agents reversal with sugammadex compared to neostigmine in the living kidney donors. Open Access Maced J Med Sci. 2019;7(24):4420-5. https://doi.org/10.3889/oamjms.2019.874
6. Lemmens HJ, El-Orbany MI, Berry J, Morte JB Jr, Martin G. Reversal of profound vecuronium-induced neuromuscular block under sevoflurane anesthesia: Sugammadex versus neostigmine. BMC Anesthesiol. 2010;10:15. https://doi.org/10.1186/1471-2253-10-15
7. Woo T, Kim KS, Shim YH, Kim MK, Yoon SM, Lim YJ, et al. Sugammadex versus neostigmine reversal of moderate rocuronium-induced neuromuscular blockade in Korean patients. Korean J Anesthesiol. 2013;65(6):501-7. https://doi.org/10.4097/kjae.2013.65.6.501
8. Pişkin Ö, Küçükosman G, Altun DU, Çimencan M, Özen B, Aydın BG, et al. O efeito de sugamadex sobre a função cognitiva e recuperação no pós-operatório [The effect of Sugammadex on postoperative cognitive function and recovery]. Rev Bras Anestesiol. 2016;66(4):376-82. https://doi.org/10.1016/j.bjan.2016.04.003
9. Yağan Ö, Taş N, Mutlu T, Hancı V. Comparison of the effects of Sugammadex and neostigmine on postoperative nausea and vomiting. Braz J Anesthesiol. 2017;67(2):147-52. https://doi.org/10.1016/j.bjane.2015.08.003
10. Abdulatif M, Lotfy M, Mousa M, Afifi MH, Yassen K. Sugammadex antagonism of rocuronium-induced neuromuscular blockade in patients with liver cirrhosis undergoing liver resection: a randomized controlled study. Minerva Anestesiol. 2018;84(8):929-37. https://doi.org/10.23736/S0375-9393.18.12217-6
11. Abola RE, Romeiser J, Rizwan S, Lung B, Gupta R, Bennett-Guerrero E. A randomized-controlled trial of Sugammadex versus neostigmine: impact on early postoperative strength. Can J Anaesth. 2020;67(8):959-69. https://doi.org/10.1007/s12630-020-01695-4
12. Alday E, Muñoz M, Planas A, Mata E, Alvarez C. Effects of neuromuscular block reversal with Sugammadex versus neostigmine on postoperative respiratory outcomes after major abdominal surgery: a randomized-controlled trial. Can J Anaesth. 2019;66(11):1328-37. https://doi.org/10.1007/s12630-019-01419-3
13. Ammar AS, Mahmoud KM, Kasemy ZA. A comparison of Sugammadex and neostigmine for reversal of rocuronium-induced neuromuscular blockade in children. Acta Anaesthesiol Scand. 2017;61(4):374-80. https://doi.org/10.1111/aas.12868
14. An J, Lee JH, Kim E, Woo K, Kim H, Lee D. Comparison of Sugammadex and pyridostigmine bromide for reversal of rocuronium-induced neuromuscular blockade in short-term pediatric surgery: A prospective randomized study. Medicine (Baltimore). 2020;99(7):e19130. https://doi.org/10.1097/MD.0000000000019130
15. Blobner M, Eriksson LI, Scholz J, Motsch J, Della Rocca G, Prins ME. Reversal of rocuronium-induced neuromuscular blockade with Sugammadex compared with neostigmine during sevoflurane anaesthesia: results of a randomised, controlled trial. Eur J Anaesthesiol. 2010;27(10):874-81. https://doi.org/10.1097/EJA.0b013e32833d56b7
16. Brueckmann B, Sasaki N, Grobara P, Li MK, Woo T, de Bie J, et al. Effects of Sugammadex on incidence of postoperative residual neuromuscular blockade: a randomized, controlled study. Br J Anaesth. 2015;115(5):743-51. https://doi.org/10.1093/bja/aev104
17. Cappellini I, Ostento D, Loriga B, Tofani L, De Gaudio AR, Adembri C. Comparison of neostigmine vs. Sugammadex for recovery of muscle function after neuromuscular block by means of diaphragm ultrasonography in microlaryngeal surgery: a randomised controlled trial. Eur J Anaesthesiol. 2020;37(1):44-51. https://doi.org/10.1097/EJA.0000000000001055
18. Castro Júnior DS, Leão P, Borges S, Gomes L, Pacheco M, Figueiredo P. Sugammadex reduces postoperative pain after laparoscopic bariatric surgery: a randomized trial. Surg Laparosc Endosc Percutan Tech. 2014;24(5):420-3. https://doi.org/10.1097/SLE.0000000000000049
19. Deana C, Barbariol F, D'Incà S, Pompei L, Rocca GD. SUGAMMADEX versus neostigmine after ROCURONIUM continuous infusion in patients undergoing liver transplantation. BMC Anesthesiol. 2020;20(1):70. https://doi.org/10.1186/s12871-020-00986-z
20. Gaszynski T, Szewczyk T, Gaszynski W. Randomized comparison of Sugammadex and neostigmine for reversal of rocuronium-induced muscle relaxation in morbidly obese undergoing general anaesthesia. Br J Anaesth. 2012;108(2):236-9. https://doi.org/10.1093/bja/aer330

21. Geldner G, Niskanen M, Laurila P, Mizikov V, Hübler M, Beck G,et al. A randomised controlled trial comparing Sugammadex and neostigmine at different depths of neuromuscular blockade in patients undergoing laparoscopic surgery. Anaesthesia. 2012;67(9):991-8. https://doi.org/10.1111/j.1365-2044.2012.07197.x
22. Ghoneim AA, El Beltagy MA. Comparative study between Sugammadex and neostigmine in neurosurgical anesthesia in pediatric patients. Saudi J Anaesth. 2015;9(3):247-52. https://doi.org/10.4103/1658-354X.154696
23. Hakimoğlu S, Tuzcu K, Davarcı I, Karcıoğlu M, Ayhan Tuzcu E, Hancı V, et al. Comparison of Sugammadex and neostigmine-atropine on intraocular pressure and postoperative effects. Kaohsiung J Med Sci. 2016;32(2):80-5. https://doi.org/10.1016/j.kjms.2016.01.009
24. Illman HL, Laurila P, Antila H, Meretoja OA, Alahuhta S, Olkkola KT. The duration of residual neuromuscular block after administration of neostigmine or Sugammadex at two visible twitches during train-of-four monitoring. Anesth Analg. 2011;112(1):63-8. https://doi.org/10.1213/ANE.0b013e3181fdf889
25. Kara T, Ozbagriacik O, Turk HS, Isil CT, Gokuc O, Unsal O, et al. Sugammadex versus neostigmina em pacientes pediátricos: estudo prospectivo e randomizado [Sugammadex versus neostigmine in pediatric patients: a prospective randomized study]. Rev Bras Anestesiol. 2014;64(6):400-5. https://doi.org/10.1016/j.bjan.2014.03.001
26. Khuenl-Brady KS, Wattwil M, Vanacker BF, Lora-Tamayo JI, Rietbergen H,Alvarez-Gómez JA. Sugammadex provides faster reversal of vecuronium-induced neuromuscular blockade compared with neostigmine: a multicenter, randomized, controlled trial. Anesth Analg. 2010;110(1):64-73. https://doi.org/10.1213/ane.0b013e3181ac53c3
27. Koyuncu O, Turhanoglu S, Ozbakis Akkurt C, Karcıoglu M, Ozkan M, Ozer C, et al. Comparison of Sugammadex and conventional reversal on postoperative nausea and vomiting: a randomized, blinded trial. J Clin Anesth. 2015;27(1):51-6. https://doi.org/10.1016/j.jclinane.2014.08.010
28. Ledowski T, Szabó-Maák Z, Loh PS, Turlach BA, Yang HS, Boer HD, et al. Reversal of residual neuromuscular block with neostigmine or Sugammadex and postoperative pulmonary complications: a prospective, randomised, double blind trial in high-risk older patients. Br J Anaesth. 2021;127(2):316-23. https://doi.org/10.1016/j.bja.2021.04.026
29. Lee TY, Jeong SY, Jeong JH, Kim JH, Choi SR. Comparison of postoperative pulmonary complications between Sugammadex and neostigmine in lung cancer patients undergoing video-assisted thoracoscopic lobectomy: a prospective double-blinded randomized trial. Anesth Pain Med (Seoul). 2021;16(1):60-7. https://doi.org/10.17085/apm.20056
30. Moon TS, Reznik S, Pak T, Jan K, Pruszynski J, Kim A, et al. Sugammadex versus neostigmine for reversal of rocuronium-induced neuromuscular blockade: a randomized, double-blinded study of thoracic surgical patients evaluating hypoxic episodes in the early postoperative period. J Clin Anesth. 2020;64:109804. https://doi.org/10.1016/j.jclinane.2020.109804
31. Paech MJ, Kaye R, Baber C, Nathan EA. Recovery characteristics of patients receiving either Sugammadex or neostigmine and glycopyrrolate for reversal of neuromuscular block: a randomised controlled trial. Anaesthesia. 2018;73(3):340-7. https://doi.org/10.1111/anae.14174
32. Sacan O, White PF, Tufanogullari B, Klein K. Sugammadex reversal of rocuronium-induced neuromuscular blockade: a comparison with neostigmine-glycopyrrolate and edrophonium-atropine. Anesth Analg. 2007;104(3):569-74. https://doi.org/10.1213/01.ane.0000248224.42707.48
33. Tas Tuna A, Palabiyik O, Orhan M, Sonbahar T, Sayhan H, Tomak Y. Does Sugammadex Administration Affect Postoperative Nausea and Vomiting After Laparoscopic Cholecystectomy: A Prospective, Double-Blind, Randomized Study. Surg Laparosc Endosc Percutan Tech. 2017;27(4):237-40. https://doi.org/10.1097/SLE.0000000000000439
34. Togioka BM, Yanez D, Aziz MF, Higgins JR, Tekkali P, Treggiari MM. Randomised controlled trial of Sugammadex or neostigmine for reversal of neuromuscular block on the incidence of pulmonary complications in older adults undergoing prolonged surgery. Br J Anaesth. 2020;124(5):553-61. https://doi.org/10.1016/j.bja.2020.01.016
35. Wu X, Oerding H, Liu J, Vanacker B, Yao S, Dahl V, et al. Rocuronium blockade reversal with Sugammadex vs. neostigmine: randomized study in Chinese and Caucasian subjects. BMC Anesthesiol. 2014;14:53. https://doi.org/10.1186/1471-2253-14-53
36. Ghoneim AA, El Beltagy MA. Comparative study between sugammadex and neostigmine in neurosurgical anesthesia in pediatric patients. Saudi J Anaesth. 2015;9(3):247-52. https://doi.org/10.4103/1658-354X.154696
37. Zaini RHM, Tevaraj JMP, Wan Hassan WN, Iberahim MI, Shukeri WFWM. Abstract PR253: comparison between the efficacy of neostigmine versus sugammadex for reversal of rocuronium induced neuromuscular blockade in paediatric patients. Anesth Analg. 2016;123(3S):329. https://doi.org/10.1213/01.ane.0000492650.20862.e4
38. Koç F, Turan G, Subaşı D, Ekinci O. Comparison of Sugammadex and neostigmine in short term surgery Kısa süreli cerrahide sugammadeks ile neostigminin karşılaştırılması. Clin Anal Med. 2015;6(1):41-5. https://doi.org/10.4328/JCAM.1694
39. Herring WJ, Mukai Y, Wang A, Lutkiewicz J, Lombard JF, Lin L, et al. A randomized trial evaluating the safety profile of Sugammadex in high surgical risk ASA physical class 3 or 4 participants. BMC Anesthesiol. 2021;21(1):259. https://doi.org/10.1186/s12871-021-01477-5
40. Voss T, Wang A, Angelis M, Speek M, Saldien V, Hammer GB, et al. Sugammadex for reversal of neuromuscular blockade in pediatric patients: Results from a phase IV randomized study. Paediatr Anaesth. 2022;32(3):436-45. https://doi.org/10.1111/pan.14370
41. An J, Noh H, Kim E, Lee J, Woo K, Kim H. Neuromuscular blockade reversal with sugammadex versus pyridostigmine/glycopyrrolate in laparoscopic cholecystectomy: a randomized trial of effects on postoperative gastrointestinal motility. Korean J Anesthesiol. 2020;73(2):137-44. https://doi.org/10.4097/kja.19360
42. Alsaeed A, Bamehriz F, Eldin S, Alzahrani T, Alharbi A, Eldawlatly A.et al. Sugammadex versus two doses of neostigmine for reversal of rocuronium in gastric sleeve surgery. Saudi J Anaesth. 2017;11(3):309-11. https://doi.org/10.4103/sja.SJA_113_17
43. Batistaki C, Riga M, Zafeiropoulou F, Lyrakos G, KostopanIGAotou G, Matsota P. Effect of Sugammadex versus neostigmine/atropine combination on postoperative cognitive dysfunction after elective surgery. Anaesth Intensive Care. 2017;45(5):581-8. https://doi.org/10.1177/0310057X1704500508
44. Boggett S, Chahal R, Griffiths J, Lin J, Wang D, Williams Z, et al. A randomised controlled trial comparing deep neuromuscular blockade reversed with Sugammadex with moderate neuromuscular block reversed with neostigmine. Anaesthesia. 2020;75(9):1153-63. https://doi.org/10.1111/anae.15094
45. Choi ES, Oh AY, Koo BW, Hwang JW, Han JW, Seo KS, et al. Comparison of reversal with neostigmine of low-dose rocuronium vs. reversal with Sugammadex of high-dose rocuronium for a short procedure. Anaesthesia. 2017;72(10):1185-90. https://doi.org/10.1111/anae.13894

46. Farag E, Rivas E, Bravo M, Hussain S, Argalious M, Khanna S, et al. Sugammadex versus neostigmine for reversal of rocuronium neuromuscular block in patients having catheter-based neurointerventional procedures: a randomized trial. Anesth Analg. 2021;132(6):1666-76. https://doi.org/10.1213/ANE.0000000000005533

47. Han J, Oh AY, Jeon YT, Koo BW, Kim BY, Kim D, et al. Quality of recovery after laparoscopic cholecystectomy following neuromuscular blockade reversal with neostigmine or Sugammadex: a prospective, randomized, controlled trial. J Clin Med. 2021;10(5):938. https://doi.org/10.3390/jcm10050938

48. Jones RK, Caldwell JE, Brull SJ, Soto RG. Reversal of profound rocuronium-induced blockade with Sugammadex: a randomized comparison with neostigmine. Anesthesiology. 2008;109(5):816-24. https://doi.org/10.1097/ALN.0b013e31818a3fee

49. Kim NY, Koh JC, Lee KY, Kim SS, Hong JH, Nam HJ, et al. Influence of reversal of neuromuscular blockade with Sugammadex or neostigmine on postoperative quality of recovery following a single bolus dose of rocuronium: A prospective, randomized, double-blinded, controlled study. J Clin Anesth. 2019;57:97-102. https://doi.org/10.1016/j.jclinane.2019.02.014

50. Koo BW, Oh AY, Na HS, Lee HJ, Kang SB, Kim DW, et al. Effects of depth of neuromuscular block on surgical conditions during laparoscopic colorectal surgery: a randomised controlled trial. Anaesthesia. 2018;73(9):1090-96. https://doi.org/10.1111/anae.14304

51. Niu L, Wang Y, Yao C, Sun Y, Yao S, Lin Y. Efficacy and safety of neuromuscular blockade in overweight patients undergoing nasopharyngeal surgery. Med Sci Monit. 2020;26:e926452. https://doi.org/10.12659/MSM.926452

52. Putz L, Dransart C, Jamart J, Marotta ML, Delnooz G, Dubois PE. Operating room discharge after deep neuromuscular block reversed with Sugammadex compared with shallow block reversed with neostigmine: a randomized controlled trial. J Clin Anesth. 2016;35:107-13. https://doi.org/10.1016/j.jclinane.2016.07.030

53. Schepens T, Janssens K, Maes S, Wildemeersch D, Vellinga J, Jorens PG, et al. Sugammadex-enhanced recovery of neuromuscular blockade: a double blind prospective randomized controlled trial. BMC Anesthesiol. 2019;19(1):187. https://doi.org/10.1186/s12871-019-0863-y

54. Sen A, Erdivanli B, Tomak Y, Pergel A. Reversal of neuromuscular blockade with Sugammadex or neostigmine/atropine: effect on postoperative gastrointestinal motility. J Clin Anesth. 2016;32:208-13. https://doi.org/10.1016/j.jclinane.2016.03.010

55. Stourac P, Adamus M, Seidlova D, Pavlik T, Janku P, Krikava I, et al. Low-dose or high-dose rocuronium reversed with neostigmine or sugammadex for cesarean delivery anesthesia: a randomized controlled noninferiority trial of time to tracheal intubation and extubation. Anesth Analg. 2016;122(5):1536-45. https://doi.org/10.1213/ANE.0000000000001197

56. Williams WH 3rd, Cata JP, Lasala JD, Navai N, Feng L, Gottumukkala V. Effect of reversal of deep neuromuscular block with Sugammadex or moderate block by neostigmine on shoulder pain in elderly patients undergoing robotic prostatectomy. Br J Anaesth. 2020;124(2):164-72. https://doi.org/10.1016/j.bja.2019.09.043

57. Mathur D, Ithnin FB, Han NLR, Sultana R, Sia ATH, Sng BL, et al. Sugammadex vs neostigmine for post-op nausea after lap-gynae surgery. Acta Anaesthesiol Scand. 2019 [cited on Sep 1, 2019];63:8(e15). Available from: https://www.embase.com/search/results?subaction=viewrecord&id=L629085904&from=export

58. Yamashita Y, Takasusuki T, Kimura Y, Komatsuzaki M, Yamaguchi S. Effects of neostigmine and sugammadex for reversal of neuromuscular blockade on QT dispersion under propofol anesthesia: a randomized controlled trial. Cardiol Ther. 2018;7(2):163-72. https://doi.org/10.1007/s40119-018-0119-9

59. Jackson C, Hambidge O, Royan N, Knoblanche G. A randomized double blinded trial comparing Sugammadex and neostigmine in the recovery of cognitive function after volatile anaesthesia. Anaesth Intensive Care. 2017 [cited on Sep 1, 2017];45:5(640). Available from: https://www.embase.com/search/results?subaction=viewrecord&id=L633276920&from=export

60. Kheterpal S, Vaughn MT, Dubovoy TZ, Shah NJ, Bash LD, Colquhoun DA, et al. Sugammadex versus Neostigmine for Reversal of Neuromuscular Blockade and Postoperative Pulmonary Complications (STRONGER): A Multicenter Matched Cohort Analysis. Anesthesiology. 2020;132(6):1371-81. https://doi.org/10.1097/ALN.0000000000003256

61. Carron M, Zarantonello F, Tellaroli P, Ori C. Efficacy and safety of sugammadex compared to neostigmine for reversal of neuromuscular blockade: a meta-analysis of randomized controlled trials. J Clin Anesth. 2016;35:1-12. https://doi.org/10.1016/j.jclinane.2016.06.018

62. Hristovska AM, Duch P, Allingstrup M, Afshari A. Efficacy and safety of Sugammadex versus neostigmine in reversing neuromuscular blockade in adults. Cochrane Database Syst Rev. 2017;8(8):CD012763. https://doi.org/10.1002/14651858.CD012763

APPENDIX 1

Characteristics of the studies

Abdulafit 2018[10]

Adult patients with liver resection with or without cirrhosis, being randomized (60); sugammadex 2 mg/kg (30) × neostigmine 50 μg/kg + atropine 20 μg/kg (30), being evaluated the recovery time (TOF 0.9), length of stay in recovery, and postoperative recurarization, with follow-up time being the time to reach TOF.

Abola 2019[11]

Randomized clinical trial in adult patients for surgery requiring neuromuscular block, endotracheal intubation and extubation at recovery (n=62), sugammadex 2–4 mg/kg (n=31) × neostigmine 70 μg/kg + glycopyrrolate 10 μg/kg were evaluated (n=31). The outcomes evaluated were block reversal by spirometry, handshake, sit down, and sedation level (RASS); follow-up time was recovery time 30, 60, and 120 min.

Alday 2019[12]

Adults who underwent major abdominal surgery (n=130) were randomized comparing sugammadex 4 mg/kg (n=65) and neostigmine 40 μg/kg + atropine 10 μg/kg (n=65), being evaluated as an outcome reversal of the spirometry block, hypoxemia, nausea, and vomiting. Follow-up time was 60 min.

Ammar 2017[13]

Pediatric patients who underwent surgery on the lower abdomen (60), randomized comparing: sugammadex 4 mg/kg (30) versus neostigmine 35 μg/kg + atropine 2 μg/kg (30). Outcomes evaluated: time to recovery (TOF 0.9), extubation time, length of stay in recovery, and adverse events. Follow-up time: time to outcome.

An Jihyun 2020[14]

Children with entropion surgery randomized (n=60), comparing sugammadex 2 mg/kg (n=30) and pyridostigmine 20 μg/kg + glycopyrrolate 1 μg/kg (n=30). Outcomes evaluated: time to recovery (TOF 0.9); extubation time; adverse events. Follow-up done was time for the outcome.

Blobner 2010[15]

Adult patients randomized (n=98) to elective surgical procedure under general anesthesia with ASA I to III classification and any body weight. Divided into sugammadex group with 49 patients and neostigmine with 49 patients. In the reversal of neuromuscular blockade, in the sugammadex group, medication at a dose of 2.0 mg kg IV, and in the neostigmine group, medication at a dose of 50 and 10 mg/kg IV glycopyrrolate, in an alveolar concentration of sevoflurane less than 1.5 in the administration of the reverser. Outcomes evaluated were neuromuscular monitoring until recovery of TOF at 0.9 (T2), heart rate (HR) and blood pressure (BP) were recorded before and 2, 5, 10, and 30 min after medication. Oxygen saturation rate, patients' levels of consciousness, and muscle weakness were also monitored.

Brueckmann B 2015[16]

Randomized clinical trial that studied 154 adult patients for elective laparoscopic or open abdominal surgery, under general anesthesia with rocuronium-induced neuromuscular blockade (NMB). Included ASA class I to III patients. In the sugammadex group, the reversal of deep NMB was performed with a dose of 4 mg/kg, and in moderate, it was with a dose of 2 mg/kg (n=76). In the neostigmine/glycopyrrolate group in NMB reversal, a maximum dose of 5 mg/kg was used (n=78). Primary end point was the presence of residual neuromuscular block, defined by TOF<0.9 on arrival at the PACU. Secondary outcome was the time interval from initiation of medication to being ready to be discharged from the operating room with clinical observance of regular breathing pattern, oxygen saturation, and hemodynamic stability.

Cappellini I, 2020[17]

In this RCT, 59 patients aged between 18 and 80 years with ASA I and II undergoing laryngeal microsurgery with deep NMB with rocuronium were included. Patients with a history of liver disease or renal disease (glomerular filtration <50 ml/min), alcoholism, allergy or hypersensitivity to CNS medications or medications, neurological disease, diaphragmatic paralysis, pregnancy, breastfeeding, or arrhythmic disease were excluded. SUG group with 30 patients received 2 mg/kg of sugammadex IV in identical syringes, and in the NEO group, 29 patients received 50 mg/kg neostigmine and 15 mg/kg atropine IV in identical syringes. Primary outcome was to assess residual neuromuscular blockade at 30 min after administration of reversal drugs.

Castro DS Jr[18]

A total of 88 adult obese patients were randomized to elective laparoscopic video gastroplasty surgery under general anesthesia with neuromuscular blockade (NMB). Patients with chronic pain and those already enrolled in another study of anterior laparoscopy surgery were excluded due to a lack of consent. The reversal of NMB in the sugammadex group with 44 patients was with 2 mg/kg correcting the body weight (CBW) of the medication. The NMB reversal in the neostigmine group with 44 patients was used 0.05 mg/kg (CBW) + atropine 0.02 mg/kg (CBW) of the medication. Main outcome evaluated was extubation in TOF-T2 (>0.9). Pain was assessed using the VAS scale on arrival at RPA, at 30 and 60 min after arrival. Assessed by the Aldrete Scale, a score greater than 9 defined high RPA and nausea and vomiting postoperative omits (PONV).

Dean 2020[19]

This is an unblinded randomized clinical trial with patients undergoing liver transplantation with the primary objective of evaluating the recovery time of neuromuscular transmission obtained with sugammadex versus neostigmine after rocuronium-induced neuromuscular blockade. NMB reversal in the sugammadex group was used 2 mg/kg based on actual body mass index (BMI) with 26 patients and in the neostigmine group with 50 mcg/kg (BMI) adjusted + 10 mcg/kg atropine with 23 patients. The primary end point assessed was the time interval from agent administration to reversal on three consecutive measurements with TOFR≥0.9. Secondary outcome was to analyze the main possible correlations between factors that may have influenced the recovery time of sugammadex and neostigmine.

Gaszynski 2011[20]

Randomized clinical trial that studied 70 morbidly obese adult patients (BMI=0.40 kg/m²) for elective surgical procedure for bariatric surgery. Exclusion criteria were lack of consent, muscle diseases, and severe cardiovascular diseases. NMB reversal in the sugammadex group, 2 mg/kg (CBW) of the medication was used with 35 patients and in the neostigmine group with 35 patients, 0.05 mg/kg CBW + atropine 0.02 mg/kg (CBW) was used. Outcome assessed was the mean time to reach 90% in TOF T2 (>0.9).

Geldner 2012[21]

Randomized, multicenter, active controlled clinical trial, blinded assessor, protocol assessment, 140 patients undergoing scheduled laparoscopic cholecystectomy or appendectomy under general anesthesia, >18 years, ASA I–III, sugammadex 4 mg/kg (n=70) and neostigmine 50 μg/kg in combination with atropine 10 μg/kg (n=70), with the primary efficacy end point being the time from initiation of sugammadex or neostigmine administration to recovery of the TOF to 0.9. Secondary outcome parameters included safety and length of stay in the operating room and postanesthesia care unit following study drug administration. Safety was assessed by adverse events, vital signs, and physical examination.

Ghoneim 2021[22]

Pediatric patients undergoing elective craniotomy scheduled for posterior fossa tumor excision, ASA I–III, 7–18 years (n=40), sugammadex 4 mg/kg (n=20), and neostigmine 0.04 mg/kg combined with atropine 0.02 mg/kg (n=20). The study's primary end point was the time from administration of sugammadex or neostigmine to recovery of the TOF ratio to 90% after rocuronium-induced neuromuscular blockade.

Intraoperative heart rate and blood pressure during administration of reversal agents were considered secondary outcomes, as well as any incidence of adverse events in the first 24 h after surgery.

Hakimoğlu 2016[23]

Randomized clinical trial, analysis by intention to treat arthroscopic surgery under general anesthesia.
Patients aged 18–65 years (n=60), sugammadex (4.0 mg/kg) (n=30) versus neostigmine (50 mg/kg) plus atropine (15 mg/kg) (n=30). The primary efficacy end point for extubation was the time from administration of sugammadex or neostigmine to recovery of the TOF ratio to 0.9. Operating time (time from skin incision to end of surgery) and adverse events (choking, nausea, vomiting, breath holding, laryngospasm, and tremors).
Hemodynamic parameters (heart rate, mean arterial pressure, peripheral arterial oxygen saturation) were measured before induction and 30 s, 2 min, 10 min, and 30 min after extubation; IOPs were measured before induction and 30 s, 2 min, and 10 min after extubation. Those with a baseline IOP of >30 mmHg were excluded. The Tono-Pen XL applanation tonometer (Medtronic Solan, Jacksonville, FL, USA) was used to measure IOP.

illman 2011[24]

Randomized, double-blind clinical trial, with sample and power calculation, performed in elective surgery with general anesthesia, adult patients (18–70 years), ASA I–IV, BMI <32.5 (n=50), sugammadex 2.0 mg/kg (n=25) versus neostigmine 50 μg/kg + glycopyrrolate 10 μg/kg (n=25).
Primary end point was the time interval between the loss of visual fading to the return of a TOF ratio of 0.90. Secondary end points were times to return of TOF ratio to 0.70, 0.80, and 0.90 after reversal, TOF ratio at loss of visual fading, and time of tracheal extubation. The times from loss of visual fade to return of a TOF ratio of 0.70 and 0.80 and the time from tracheal extubation to return of a TOF ratio of 0.9, follow-up until hospital discharge were also recorded.

Kara 2014[25]

Randomized, double-blind clinical trial of elective outpatient surgery, such as lower abdominal or urogenital surgery in ASA I children (n=80), comparing sugammadex 2 mg/kg (n=40) and atropine 0.01 mg/kg and neostigmine 0.03 mg/kg.
Reversal time was evaluated o since last neuromuscular blocker (NMB) administration (min), extubation time since last NMB administration (min), TOF ratio before reversal, TOF ratio during extubation.

Khuenl-Brady 201026

Randomized clinical trial with 93 patients aged ≥18 years, ASA 1–3, comparing sugammadex (2 mg/kg) with neostigmine (50 μg/kg) + glycopyrrolate (10 μg/kg). The following were evaluated: time to recovery to TOF index=0.9, time to recovery to TOF index=0.7 and 0.8, and signs of recovery (level of consciousness, head elevation test, generalized muscle weakness). And the follow-up was for 7 days of adverse effects.

Koyuncu 2015 -2014[27]

In this study, 100 adult patients, ASA 1/2 with extremity surgery compare sugammadex (2 mg/kg) with neostigmine (70 μg/kg) + atropine (0.4 mg/kg). The outcomes evaluated were PONV scale, clinical recovery, time to extubation, eye opening, head raising, flatus elimination, oral intake and ambulation, side effects, and amount of anti-emetics used in 24 h.

Ledowski T, 2021[28]

A total of 180 adult patients were evaluated, comparing sugammadex (2 mg/kg) to neostigmine (0.05 mg/kg) + atropine (0.015 mg/kg), with the following outcomes: pulmonary outcome score, clinical recovery (time to extubation), acute postoperative complications (desaturation, aspiration, signs of muscle weakness, and PONV score), length of hospital stay, and 30-day mortality.

Lee TY 2020[29]

A total of 93 patients aged ≥18 years, undergoing video-assisted lobectomy, ASA 1–3, were randomized evaluating sugammadex (2 mg/kg) and neostigmine (0.05 mg/kg) + atropine (0.02 mg/kg). Outcomes evaluated: incidence of postoperative pulmonary complications (presence of prolonged air fistula, pneumonia, atelectasis, desaturation, and reintubation), length of hospital stay, and length of stay in the ICU in 10 days.

Lemmens 2010[6]

Randomized trial with 81 patients ≥18 years, ASA 1–4, sugammadex (4 mg/kg) compared to neostigmine (70 μg/kg) + glycopyrrolate (14 μg/kg), the outcomes being time to recovery up to TOF=0, 9, time to recovery to TOF index=0.7 and 0.8, and signs of recovery (level of consciousness, head lift test, generalized muscle weakness), as well as adverse effects.

Moon 2020[30]

Comparative trial of sugammadex 2 mg/kg (maximum 200 mg) with neostigmine 40 μg/kg (maximum 5 mg) + glycopyrronium 400 μg. The primary end point was cumulative incidence of PONV from awakening to 6 h after surgery. Follow-up: time to completion.

Paech MJ 2018[31]

Randomized, blinded, controlled clinical trial, whose participants were 304 women aged 18–70 years undergoing general anesthesia for laparoscopic gynecological surgery; we compared the characteristics of postoperative recovery with the use of sugammadex and neostigmine/glycopyrrolate in the reversal of neuromuscular blockade. Nausea and vomiting in the first 6 h postoperatively, the intensity of such symptoms as well as the quality of postoperative recovery were evaluated.

Pişkin Ö, 2016[8]

Prospective, randomized study (sealed envelope method), double-blind and controlled; included 87 patients aged 18–60 years who underwent general anesthesia for abdominal surgery, upper extremity orthopedic interventions, gynecological, plastic, urological, otolaryngological, and spinal surgery lasting approximately 60 min. By comparing the effect of sugammadex against neostigmine, the study aimed to assess whether faster awakening from general anesthesia would influence cognitive functions in the immediate postoperative period. The information contained in the study clarifies the time required to reach the TOF 90% and time to recovery.

Quang TL, 2019[5]

Randomized controlled study composed of 70 patients between 18 and 70 years of age, ASA I–III, donor candidates for nephrectomy and under general anesthesia. We compared the action of sugammadex in relation to the combination of neostigmine + atropine sulfate on neuromuscular blockade along with the side effects presented. The time required for neuromuscular block reversal was analyzed according to TOF >0.9 and postoperative side effects such as cardiovascular changes, headache, nausea, bronchial secretion, and xerostomia.

Sacan O 2007[32]

Randomized trial, 60 adult patients, ASA I–III, elective surgical procedures requiring intubation using neostigmine (70 μg/kg) with glycopyrrolate (14 μg/kg) or edrophonium (1 mg/kg) with atropine (10 μg/kg) versus sugammadex (4 mg/kg). Outcomes assessed: TOF time 0.7, 0.8, and 0.9, heart rate, medial blood pressure, change in MAP (%) in 2 min, dry mouth, muscle weakness, and head elevation.

Taş N, 2017[33]

Randomized, double-blind clinical trial that studied 80 patients aged 18–65 years who underwent laparoscopic cholecystectomy under anesthesia. General care (anesthesiologist was blinded) and neuromuscular blockade with rocuronium 0.6 mg/kg. Patients with wing greater than or equal to III, age below or above 65 years, BMI >30 kg/m^2, and hypersensitivity to any one were excluded from study, such as drugs, history of PONV, high risk for PONV (Apfel score greater than II), patients who were pregnant or menstruating, and those who had taken antiemetic medication in the last 24 h. In the sugammadex group, NMB reversal was performed at a dose of 2 mg/kg. In the neostigmine group, NMB reversal was performed with a dose of 0.04 mg/kg and 0.015 mg of atropine. All patients were extubated with a TOF ratio >90%. The primary end point was the assessment of nausea and vomiting (PONV) from 0 to 24 h postoperatively.

Togioka BM, 2020[34]

This study is an RCT, randomized, evaluator blinded, envelope allocation, anesthetist blinded, IT analysis. We studied 200 patients with eligibility criteria of age over 70 years, scheduled surgery lasting 3 h or more and without contraindications for NMB.

Exclusion criteria included significant kidney disease (stage 4 kidney disease or greater), significant liver disease (aspartate aminotransferase [AST] or alanine aminotransferase [ALT] greater than twice the upper limit of institutional normal), allergies to study drugs, and refusal of consent. Written informed consent was obtained from all enrolled subjects.
The primary outcome measure was to assess postoperative complications from lung surgery. Secondary end points included residual paralysis (train-of-four ratio=0.9) and recovery from Phase 1 (time to pain control stable respiratory, hemodynamic, and neurological status). Additional end points were length of hospital stay, proportion of patients with hospital readmission within 30 days; and proportion of patients diagnosed with a respiratory disease complication, as defined by the National Surgical Quality Improvement Program (postoperative pneumonia, unplanned intubation, ventilator dependence >48 h).
Residual neuromuscular blockade is associated with airway obstruction, hypoxemia, atelectasis, and pneumonia. Furthermore, even low levels of neuromuscular blockade (sequence rate of four [TOF] <0.9 or 0.95) in healthy volunteers not exposed to anesthesia or surgery were associated with pharyngeal-laryngeal dysfunction and depressed hypoxic ventilatory drive. Reducing residual neuromuscular blockade may decrease postoperative pulmonary complications.

Woo T 2015[37]

RCT, randomized, evaluator blinded, analysis by IT that studied 118 Korean patients, over 18 years of age and wing 1,2,3. All patients were of Korean descent, born in Korea, never having left Korea and with a Korean home address. Exclusion criteria were any anatomic malformation that could cause difficult intubation; any patient transferred to the intensive care unit after surgery; neuromuscular disorders that can affect NMB; significant renal or hepatic dysfunction; requirement for a pneumatic tourniquet during surgery; (family) history of malignant hyperthermia; allergy to opioids/opiates, cyclodextrins including sugammadex, muscle relaxants and their excipients, or other drugs used during general anesthesia; administration of toremifene and/or fusidic acid within 24 h of study drug administration (or plan to administer these drugs within 24 h of study drug administration); any condition against the indication of neostigmine and/or glycopyrrolate; pregnant women; participation in a previous study of sugammadex; participation in another clinical drug study within 30 days, including after signing consent for the current study; or a member of or related to the investigation team or the sponsor's team.
Undergoing nose, ear, and larynx surgery, gynecological and digestive system surgeries; under general anesthesia and use of NMB rocuronium at a dose of 0.6 mg/kg for OTI and 0.1–0.2 mg/kg for maintenance. The anesthesiologist was not blinded, compromising allocation, randomization, and double blinding. In the sugammadex group, NMB reversal was performed with a dosage of 2 mg/kg IV after the end of the surgery. In the neostigmine group, NMB reversal was performed at a dose of 50 mcg/kg (total dose should not exceed 5 mg) combined with glycopyrrolate at a dose of 10 mg/kg IV after the end of surgery.
The primary end point is the measure of time of NMB reversal from initiation of drug administration to recovery. (T4/T1=0.9.), evaluating efficacy in Korean patients. Secondary end points included time to recovery from the TOF ratio to 0.7 and 0.8. The timing of T2 reappearance after the last dose of rocuronium was also evaluated. Effect adverse events such as nausea and vomiting, as well as others were evaluated. Previous work with Caucasian populations was compared with the results of this work.

Wu X. 2014[35]

This work is an RCT, multicenter, blinded evaluator, analysis by IT. A total of 308 patients were studied, 247 Chinese and 61 Caucasian aged between 18 and 64 years and ASA I/III. All Chinese were from China, never emigrated out of China, and had domestic addresses in China. The same criteria were extended to Caucasians in relation to Europe. Patients with anatomic malformations that could lead to difficult tracheal intubation, neuromuscular disorders affecting NMB, significant renal/hepatic dysfunction (as determined by the investigator), (family) history of malignant hyperthermia, and allergy to anesthetic medications were excluded from the study. In general, contraindication to study drugs, or a clinically significant condition that may interfere with the trial (as determined by the investigator).
The groups were randomized using a central randomization system. A computer-generated randomization schedule with block treatment codes, using a validated SAS-based application. The schedule associated each treatment code with a PAC number, and patients were randomized in a 1:1 ratio to receive sugammadex 2 mg/kg or neostigmine 50 μg/kg with atropine 10–20 μg/kg.
After induction of anesthesia, but before administration of rocuronium, neuromuscular monitoring was performed using continuous acceleromyography on the adductor thumb muscle using the TOF-Watch® SX.

The primary end point was the time from initiation of sugammadex or neostigmine/atropine administration to recovery from the TOF index to 0.9. The secondary end point included time to recovery from the TOF ratio to 0.7 and 0.8. Studies of adverse effects such as nausea, vomiting, bradycardia, hypotension, and cardiac complications were performed.

Yagan O 2017[9]

This prospective, randomized, controlled, double-blind study was performed with 98 patients, ASA I and II, aged between 18 and 65 years, scheduled for elective surgery with general anesthesia and endotracheal intubation. Envelope allocation compromised randomization. Exclusion criteria were: neurosurgery; laparoscopy; oncological, gynecological and breast surgery; strabismus and middle ear surgery; history of drug and alcohol abuse; body mass index (BMI) >30 kg/m^2; use of analgesics, sedatives or antiemetics in the 24 h before surgery; psychiatric and neurological diseases; allergy or contraindication to study drugs. Patients who underwent surgery longer than 2 h were also excluded.

At the end of the surgery, the administration of the anesthetic agent was suspended and the patient was manually ventilated with 100% oxygen. In accordance with the randomization procedure, reversal of neuromuscular blockade was provided with intravenous administration of neostigmine (0.05 mg/kg) and atropine (0.02 mg/kg) for patients in Group N and sugammadex (2 mg/kg) for patients in Group S, at the reappearance of the second contraction (T2) in the TOF. The patients were extubated after aspiration of secretions from the oropharynx, with a recovery of 90% of the TOF value. Additional IV administration of neostigmine (0.025 mg/kg) and atropine (0.01 mg/kg) in Group N and sugammadex (2 mg/kg) in Group S was planned, if necessary (TOF value below 90% after 5 min).

The primary outcome of our study was that using sugammadex to antagonize the effects of neuromuscular blocking agents would reduce nausea and vomiting compared with neostigmine. Adverse effects such as hypertension, bradycardia, respiratory depression, and others were evaluated.

Ghoneim A.A 2015[36]

A total of 40 pediatric patients were randomly enrolled in this study at Children Cancer Hospital Egypt (CCHE) and those selected with physical status ASA I–III between 7 and 18 years for elective craniotomy and posterior fossa tumor excision. They were randomly allocated to one of two groups (20 patients each): neostigmine and sugammadex group – group in which muscle relaxation was reversed at the end of surgery using neostigmine 0.04 mg/kg combined with atropine 0.02 mg/kg or sugammadex 4 mg/kg only, respectively. The primary study end point was the time from administration of sugammadex or neostigmine to recovery of the TOF ratio to 90% (0.9) after rocuronium-induced neuromuscular blockade.

Mohamad Zaini R.H. 2016[37]

The purpose of this study is to compare recovery time, hemodynamic stability, and complications between two reversal agents, i.e. sugammadex and neostigmine, in antagonizing the effects of rocuronium in the pediatric population. A double-blind, randomized, controlled trial involving 80 children aged 2–12 years for elective surgery under general anesthesia and neuromuscular block rocuronium uromuscular They were randomized into two groups by reversal with neostigmine or sugammadex. Pre- and post-reversion hemodynamic parameters were documented. Patients were reversed according to allocated group – 0.05 mg/kg neostigmine with 0.02 mg/kg atropine or 2 mg/kg sugammadex. A neuromuscular recovery time for TOF ratio of 0.9 has been documented. Patients were extubated at TOF 0.9, any complications observed after extubation were also documented. Results were reported.

Koç 2015[38]

Abstract work where 33 patients aged between 18 and 65 years were evaluated, randomly distributed, ASA I–III, submitted to short-term surgery comparing sugammadex 2 mg/kg (n=16) versus neostigmine 50 g/kg with atropine 20 g/kg (n=17).

Herring WJ 2021[39]

Randomized, active-controlled trial, double-blind safety study, multiple sites, parallel group, conducted at 27 sites in 4 countries from December 2017 to September 2019. Included were men and women aged 18 years or older, more with BMI <40 m²/kg, and ASA 3 or 4 for elective surgeries involving moderate or deep block with rocuronium or vencuronium. Participants were randomized into treatment groups. Moderate neuromuscular blockade and reversal with sugammadex 2 mg/kg; moderate neuromuscular

blockade and reversal with neostigmine (50 µg/kg up to 5 mg maximum dose) plus glycopyrrolate (10 µg/kg up to 1 mg maximum dose). Primary end points included incidences of treatment-emergent sinus bradycardia (TE), sinus tachycardia (TE), and other cardiac arrhythmias (TE).

Voss 2021[40]

Randomized clinical trial, phase IV, with patients aged 2–<17 years, ASA I–III, 288 patients were divided into three groups: (1) moderate block and reversal with sugammadex 2 mg/kg (N=51); (2) moderate block and reversal with neostigmine methyl sulfate 50 µg/kg plus glycopyrrolate 5–15 µg/kg or atropine sulfate 10–30 µg/kg (active control – N=34), or (3) deep block and reversal with sugammadex 4 mg/kg (N=191). The primary end point was TOF recovery time ≥0.9, and clinically relevant bradycardia, hypersensitivity, and anaphylaxis were also assessed.

APPENDIX 2

Risk of bias and quality of evidence

Table 1. Analysis of the risk of bias of the included works.

Author/year	Randomi-zation	Allocation sold	Double blind	Evaluator blinding	Losses	Characteristics prognosis	Outcomes	AIT	Sample calculation	Early INTERRUPTION
Abdulafit 2018										
Abola 2019										
Alday 2019										
Alseed 2017										
Ammar2017										
An Jihyun 2020										
Batistaki 2017										
Blobner 2010										
Brueckmann B 2015										
Cappellini I 2020										
Castro DS, 2014										
Deana 2020										
Gaszynski 2011										
Geldner 2012										
Ghoneim 2021										
Hakimoğlu 2016										
Ilmann 2011										
Kara 2014										
Khuenl-Brady 2010										
Koyuncu 2014										
Ledowski T, 2021										
Lee TY 2020										
Lemmens 2010										
Moon 2020										
Paech 2017										
Piskin 2014										
Quang 2019										
Sacan 2007										
Sen 20										
Stourac 2015										
TAS N 2017										
TOGIOKA BM 2020										
Woo T 2013										
Wu X 2014										
YAGAN O 2017										
Ghoneim A.A 2015										
Mohamad Z R.H. 2016										
Herring WJ 2021										
Koç 2015										
Voss 2021										

AIT: analysis by intention of treatment.

NO BIAS
ABSENCE OF INFORMATION
PRESENCE OF VIES

APPENDIX 3

Author(s):

Question: Sugammadex × neostigmine compared to placebo for anesthesia general

Setting:

Bibliography: Sugammadex versus neostigmine for anestesia geral. Base de Dados de Revisões Sistemáticas da Cochrane [Year], Número [Issue].

Certainty assessment							№ of patients		Effect		Certainty	Importance
N° of studies	Study design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	Sugammadex × neostigmine	placebo	Relative (95%CI)	Absolute (95%CI)		
Extubation time												
12	Randomized trials	Very serious[a,b,c]	Not serious	Serious[c]	Not serious	None	699	708	-	MD **3.67 lower** (5.24 lower to 2.11 lower)	⊕◯◯◯ Very low	
Extubation time – small size												
3	Randomized trials	Very serious[a,b,c]	Not serious	Serious[c]	Not serious	None	96	97	-	MD **2.72 lower** (4.93 lower to 0.51 lower)	⊕◯◯◯ Very low	
Extubation time – midsize												
8	Randomized trials	Very serious[a,b,c]	Not serious	Serious[c]	Not serious	None	568	576	-	MD **4.11 lower** (6.73 lower to 1.49 lower)	⊕◯◯◯ Very low	
Extubation time – large size												
1	Randomized trials	Very serious[a,b,c]	Not serious	Serious[c]	Not serious	None	35	35	-	MD **3.5 lower** (4.45 lower to 2.55 lower)	⊕◯◯◯ Very low	
1.1 Recovery time to reach TOF 90% (0.9)												
20	Randomized trials	Very serious[a,b,c]	Not serious	Serious[c]	Not serious	None	801	777	-	MD **12.98 lower** (15.63 lower to 10.33 lower)	⊕◯◯◯ Very low	
1.1 Recovery time to reach TOF 90% (0.9) – small size												
2	Randomized trials	Very serious[a,b]	Not serious	Serious[c]	Not serious	None	46	46	-	MD **8.58 lower** (10.18 lower to 6.97 lower)	⊕◯◯◯ Very low	
1.1 Recovery time to reach TOF 90% (0.9) – midsize												
11	Randomized trials	Very serious[a,b,c]	Not serious	Serious[c]	Not serious	None	548	534	-	MD **8.63 lower** (10.88 lower to 6.39 lower)	⊕◯◯◯ Very low	
1.1 T Recovery time to reach TOF 90% (0.9) – large size												
7	Randomized trials	Very serious[a,b,c]	Not serious	Serious[c]	Not serious	None	207	197	-	MD **22.16 lower** (29.87 lower to 14.44 lower)	⊕◯◯◯ Very low	
Length of stay in recovery												
6	Randomized trials	Very serious[b,c,d]	Not serious	Serious[c]	Serious[d]	None	364	370	-	MD **9.91 lower** (15.66 lower to 4.16 lower)	⊕◯◯◯ Very low	

Certainty assessment							№ of patients		Effect		Certainty	Importance
N° of studies	Study design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	Sugammadex × neostigmine	placebo	Relative (95%CI)	Absolute (95%CI)		
Length of stay in recovery – midsize												
3	Randomized trials	Very serious[b,c,d]	Not serious	Serious[c]	Serious[d]	None	176	178	-	MD **15.33 lower** (25.83 lower to 4.83 lower)	⊕◯◯◯ Very low	
Length of stay in recovery – large size												
3	Randomized trials	Very serious[b,c,d]	Not serious	Serious[c]	Serious[d]	None	188	192	-	MD **5.87 lower** (12.65 lower to 0.91 higher)	⊕◯◯◯ Very low	
Nausea												
14	Randomized trials	Very serious[b,c,e]	Not serious	Serious[c]	Not serious	None	131/819 (16.0%)	140/800 (17.5%)	Not estimable	**20 more per 1.000** (from 10 fewer to 50 more)	⊕◯◯◯ Very low	
Nausea – midsize												
12	Randomized trials	Very serious[b,d,e]	Not serious	Not serious	Serious[d]	None	106/738 (14.4%)	120/729 (16.5%)	Not estimable	**20 more per 1.000** (from 10 fewer to 40 more)	⊕◯◯◯ Very low	
Nausea – large size												
2	Randomized trials	Very serious[b,c,e]	Not serious	Serious[c]	Not serious	None	25/81 (30.9%)	20/71 (28.2%)	Not estimable	**10 more per 1.000** (from 400 fewer to 430 more)	⊕◯◯◯ Very low	
Vomit												
12	Randomized trials	Very serious[b,c,d,e]	Not serious	Serious[c]	Serious[d]	None	77/720 (10.7%)	66/620 (10.6%)	Not estimable	**10 more per 1.000** (from 30 fewer to 50 more)	⊕◯◯◯ Very low	
Vomit – midsize												
10	Randomized trials	Very serious[b,c,d,e]	Not serious	Serious[c]	Serious[d]	NONE	66/654 (10.1%)	58/564 (10.3%)	Not estimable	**10 more per 1.000** (from 30 fewer to 50 more)	⊕◯◯◯ Very low	
Vomit – large size												
2	Randomized trials	Very serious[b,c,d,e]	Not serious	Serious[c]	Serious[d]	None	11/66 (16.7%)	8/56 (14.3%)	Not estimable	**10 fewer per 1.000** (from 190 fewer to 170 more)	⊕◯◯◯ Very low	
Hypoxemia												
5	Randomized trials	Very serious[a,b,c,e]	Not serious	Serious[c]	Not serious	None	97/388 (25.0%)	86/395 (21.8%)	**OR 1.21** (0.68 to 2.15)	**34 more per 1.000** (from 59 fewer to 157 more)	⊕◯◯◯ Very low	
Hypoxemia – midsize												
2	Randomized trials	Very serious[a,b,e]	Not serious	Serious[c]	Not serious	None	63/236 (26.7%)	54/236 (22.9%)	**OR 1.25** (0.81 to 1.91)	**42 more per 1.000** (from 35 fewer to 133 more)	⊕◯◯◯ Very low	
Hypoxemia – large size												
3	Randomized trials	Very serious[a,b,c,d,e]	Not serious	Serious[c]	Serious[d]	None	34/152 (22.4%)	32/159 (20.1%)	**OR 1.60** (0.36 to 7.02)	**86 more per 1.000** (from 118 fewer to 438 more)	⊕◯◯◯ Very low	

Certainty assessment							№ of patients		Effect		Certainty	Importance
N° of studies	Study design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	Sugammadex × neostigmine	placebo	Relative (95%CI)	Absolute (95%CI)		
Hypotensive												
2	Randomized trials	Serious[b,e]	Not serious	Not serious	Not serious	None	4/126 (3.2%)	6/128 (4.7%)	Not estimable	**0 fewer per 1.000** (from 30 fewer to 40 more)	⊕⊕⊕◯ Moderate	
Bradycardia												
10	Randomized trials	Very serious[a,b,e]	Not serious	Not serious	Not serious	None	7/621 (1.1%)	57/563 (10.1%)	**HR 0.14** (0.07 to 0.29)	**86 fewer per 1.000** (from 94 fewer to 71 fewer)	⊕⊕◯◯ Low	
Bradycardia – small size												
2	Randomized trials	Very serious[a,b,e]	Not serious	Not serious	Not serious	None	1/80 (1.3%)	7/80 (8.8%)	**HR 0.13** (0.01 to 1.06)	**76 fewer per 1.000** (from 87 fewer to 5 more)	⊕⊕◯◯ Low	
Bradycardia – midsize												
7	Randomized trials	[a,b,e]	Not serious	Not serious	Not serious	None	6/506 (1.2%)	40/448 (8.9%)	**HR 0.15** (0.07 to 0.33)	**75 fewer per 1.000** (from 83 fewer to 59 fewer)	-	
Bradycardia – large size												
1	Randomized trials	Very serious[a,b,d,e]	Not serious	Not serious	Serious[d]	None	0/35 (0.0%)	10/35 (28.6%)	**HR 0.03** (0.00 to 0.61)	**276 fewer per 1.000** (from 100 fewer to --)	⊕◯◯◯ Very low	
Hypertension												
3	Randomized trials	Very serious[b,d,e]	Not serious	Not serious	Serious[d]	None	15/174 (8.6%)	4/174 (2.3%)	**HR 3.69** (1.27 to 10.75)	**59 more per 1.000** (from 6 more to 198 more)	⊕◯◯◯ Very low	

CI: confidence interval; HR: hazard ratio; MD: mean difference; OR: odds ratio

Explanations

[a]No analysis of intention to treat.

[b]Absence of double blind.

[c]High heterogeneity.

[d]Long confidence interval.

[e]Absence of sample calculation.

APPENDIX IV

MEANING OF TOF (TRAIN OF FOUR)

Neuromuscular blockade can be monitored with different forms of electrostimulation. The TOF consists of performing a sequence of four stimuli at a frequency of 2 Hz with an interval of 10 s between them. The degree of block will be evaluated through the difference in contraction amplitude between the first and fourth sequence of stimuli. It will be considered the existence of muscle block when there is a decrease in the amplitude of response between the stimuli and the existence of anesthetic recovery if all four responses are the same; or according to the T4/T1 ratio.

1. T4/T1>0.7: recovery of diaphragm blockage, but insufficient to prevent aspiration of gastric contents
2. T4/T1>0.8: represents the patient's ability to generate 90% of his tidal volume
3. T4/T1>0.9: desirable and safer value in clinical practice with disappearance of swallowing difficulties

Source: Tardelli MA. Monitoring Neuromuscular Blockade. In: Brazilian Society of Anesthesiology. Distance Education Course in Anesthesiology. Sao Paulo: Office; 2002. p. 177-90.

https://doi.org/10.1590/1806-9282.20220423

Serum endocan levels in patients with beta-thalassemia minor may be affected by age and gender

Yanping Qiao[1]*

Dear Editor,

We were very pleased to read the study by Khanmammadov N[1] and his colleagues in which they revealed that there was no change in endocan level in beta-thalassemia minor and serum endocan levels may be altered secondarily to decreased beta-globin chain, increased sympathetic activity due to anemia, or platelet dysfunction induced by oxidative stress in beta-thalassemia minor. In my opinion, however, some concerns should be raised.

The main problem of the study was that age and gender may correct the relationships between serum endocan levels and beta-thalassemia minor. The study found no statistically significant differences in age or sex between the two groups. As this study did not estimate the sample size, we could not judge whether the study had enough sample size. However, from the experimental results, the two groups showed a trend of age difference. No matter in normal subjects or in patients with beta-thalassemia minor, serum endocan levels showed a trend of difference between the two groups. If the sample size is large, we speculate that the difference should be statistically significant.

Overall, it is necessary to calculate the power so that we can exclude the influence of age and sex on the experimental results.

REFERENCE

1. Khanmammadov N, Zorlu M, Ozer OF, Karatoprak C, Kiskac M, Cakirca M. Assessment of serum endocan levels in patients with beta-thalassemia minor. Rev Assoc Med Bras (1992).2022;68(2):147-51. https://doi.org/10.1590/1806-9282.20210753

[1]Weihai Central Hospital – Shandong, China.
*Corresponding author: qiaoyanpingweihai@163.com

Conflicts of interest: the authors declare there is no conflicts of interest. Funding: none.
Received on March 19, 2022. Accepted on May 08, 2022.

https://doi.org/10.1590/1806-9282.20220616

Comment on: "Effect of group hope therapy on self-efficacy of adolescents with type 1 diabetes"

Jiahao Jin[1], Lingling Zhou[1*]

Dear editor,

We are honored to read the high-level article by Nasim Nikbakhtan Esfahani et al.[1], entitled "Effect of group hope therapy on self-efficacy of adolescents with type 1 diabetes". This study found that hope therapy had a significant impact on self-efficacy of adolescents with type 1 diabetes, but had no effect on academic self-efficacy and self-efficacy in blood glucose management. However, according to our opinion, there are some issues that are worth exploring.

First, general self-efficacy did not change glycemic control in diabetic patients. The duration of the disease is the only variable that affects glycemic control in diabetic individuals. A sample of 46 patients was randomly allocated to the intervention group or the control group. Different patients have different diseases, different blood sugar levels, and different treatments, and this study did not establish the standard drug treatment regimen. These factors may bias the self-efficacy of diabetes management.

Second, if the sample size is calculated haphazardly and the sample does not include a well-defined population, the results of the survey should not be extrapolated to the overall situation. How the authors assure that adolescent patients have never obtained the relevant section. In contrast, have sample size estimates been produced? Whether the inconsistency with previous research results is caused by the small sample size? All these concerns are not discussed in this study.

The authors did not explain whether the missing demographic descriptions are associated with the missing values in the tables. Finally, the criteria for the p-value specified in the table are also not discussed.

AUTHORS' CONTRIBUTION

JJH: Conceptualization, Data curation, Funding acquisition, Investigation, Methodology, Project administration, Resources, Software, Supervision, Validation, Visualization, Writing – original draft. **ZLL:** Conceptualization, Data curation, Funding acquisition, Investigation, Methodology, Project administration, Resources, Software, Supervision, Validation, Visualization, Writing – review & editing.

REFERENCE

1. Esfahani NN, Talakoub S, Jafari-Mianaei S, Mostofizadeh N. Effect of group hope therapy on self-efficacy of adolescents with type 1 diabetes. Rev Assoc Med Bras (1992). 2021;67(12):1816-20. https://doi.org/10.1590/1806-9282.20210750

[1]Taizhou University, School of Medicine – Zhejiang, China.
*Corresponding author: 45686662@qq.com

Conflicts of interest: the authors declare there is no conflicts of interest. Funding: none.
Received on April 21, 2022. Accepted on June 17, 2022.

SHORT COMMUNICATION

https://doi.org/10.1590/1806-9282.20220724

Quality of life and psychological comorbidities in patients with migraine and hypertension

Thamires Sales Ribeiro[1], Luciana Salles Branco de Almeida[1], Vandilson Pinheiro Rodrigues[1], Caio Marcio Barros de Oliveira[1], Ed Carlos Rey Moura[1], Luciana Maia Moura Naves[1], Lidio Gonçalves Lima Neto[2], Leonardo Victor Galvão Moreira[1], Emanuel Cabral Pereira[2], Plínio da Cunha Leal[1]*

INTRODUCTION

Migraine is one of the most common headache subtypes and most affects the quality of life of the affected population and has several pathophysiological mechanisms that have not yet been appropriately clarified[1,2]. The relationship between migraine and systemic arterial hypertension (SAH) is causal to common risk factors such as family history, anxiety, and depression[3]. Also, neuropsychological comorbidities and sleep disturbances are factors that are intrinsically related to migraine and hypertension[4-6].

Evidence has suggested that stress may be a risk factor for SAH and exacerbating migraine symptoms[7,8]. Some studies further point to anxiety and depression being associated with migraine and hypertension[9-11]. However, these previous studies have not considered the effect of various confounding factors in analyzing the relationship between migraine and hypertension.

This study aimed to assess the occurrence and severity of psychological comorbidities (such as depression, anxiety, stress, and sleep disturbance) with migraine and SAH.

METHODS

This case-control study was conducted on outpatients of both sexes aged over 18 years, hypertensive, and non-hypertensive, with or without a diagnosis of migraine, screened at the University Hospital of Federal University of Maranhão, São Luís, Brazil, Maranhão, between December 2017 and July 2019. The research project was approved by the hospital's Research Ethics Committee (CAAE: 61420016.5.0000.5086). The participants were informed about the objectives and procedures involved in the study, and after indicating their complete understanding, they signed the informed consent form.

Patients diagnosed or had received treatment for any rheumatic, musculoskeletal, otorhinolaryngologic, malignant or benign neoplastic diseases, psychiatric disorder, had taken in the past 6 months or were taking anxiolytics, or any psychotropic or centrally acting analgesic, steroid, or alcohol and tobacco >15 days per month were excluded from this study.

The diagnosis of hypertension was made according to the American Heart Association criteria.

The General Health Questionnaire (GHQ-12) was used to evaluate the participants' general mental health condition, and The Depression, Anxiety and Stress Scale-21 (DASS-21) was used to evaluate depression, anxiety, and stress levels. The Pittsburg Sleep Quality Index (PSQI) was used to assess sleep quality. Patients were interviewed individually after recruitment to fill in the scales used.

The data were analyzed using SPSS version 28 (IBM, Chicago, Illinois, USA). Data related to descriptive analysis were expressed as percentages, means, standard deviation, medians, and interquartile ranges (IQR). The Kruskal-Wallis test was used to calculate the effect sizes (eta squared, η^2), followed by Dunn's multiple comparisons test for comparative analyses. Multiple linear regression was used to investigate the effect of migraine and hypertension on the psychometric scores, adjusted for age, sex, and body mass index. The D'Agostino-Pearson omnibus test was used to test the normality of residuals. A 5% significance level was adopted for all analyses.

RESULTS

In all, 124 patients were screened, and 54 were excluded based on eligibility criteria. A sample of 70 patients (47 females and

[1]Universidade Federal do Maranhão – São Luís (MA), Brazil.
[2]Universidade CEUMA – São Luís (MA), Brazil.
*Corresponding author: pliniocunhaleal@hotmail.com

Conflicts of interest: the authors declare there is no conflicts of interest. Funding: Fundação de Amparo à Pesquisa e ao Desenvolvimento Científico e Tecnológico do Maranhão, grant number UNIVERSAL-01350/17 and financed by Coordenação de Aperfeiçoamento de Pessoal de Nível Superior (CAPES).
Received on June 13, 2022. Accepted on June 15, 2022.

23 males), with a mean age of 46.7±16.3 years, was included in this study. The frequency of migraine was 41.4% (Table 1). The assessment of Migraine Disability Assessment revealed that most patients had mild migraine (37.9%), and the median of this value was 7 (4–10). A value of 7 (3–12) was the median number of headache episodes in the last 3 months in patients with migraine.

The negative GHQ-12 showed significant differences between groups (p=0.001, effect size statistic η^2=0.190). The score was significantly higher in the migraine groups than in the nonmigraine group with hypertension (p<0.05). The DASS depression score was higher in the groups with migraine than in the groups without migraine and hypertension (p<0.05). The DASS anxiety score showed significant differences between groups (p<0.001, effect size statistic η^2=0.319). The migraine and hypertension group had higher anxiety scores than the other groups; in addition, the score of the group with migraine but without hypertension was higher than that of the group without both conditions. The DASS stress score was higher in the two groups with migraine than in the two groups without migraine. The PSQI score was not significantly different between the groups (p=0.124, effect size statistic η^2=0.042) (Table 2).

The adjusted effects of migraine and hypertension on psychometrics are shown in Table 3. The residuals of models 1, 3, and 4 showed an approximately normal distribution. Model 2 showed a significant departure from the normality assumption (statistics=5.234, p<0.001). The adjusted coefficients showed that migraine had a significant effect on the increment of GHQ-12 (beta=0.46, SE=0.12, p=0.001), DASS-21 anxiety score (beta=5.77, SE=1.07, p<0.001), and DASS-21 stress score (beta=8.18, SE=1.54, p<0.001).

DISCUSSION

Several studies have attempted to identify an association between migraine and hypertension[12-14]. However, none have been correlated with specific signs and symptoms associated with these comorbidities. Comparing patients with migraine and hypertension and those without migraine and hypertension, clear associations with psychological comorbidities could promote new therapeutic avenues for these diseases and, consequently, improve the quality of life of this population.

In this study, those with migraine in combination with SAH had higher levels of unfavorable overall health quality when compared to the group without migraine. This result corroborates that both migraine and SAH negatively influence the quality of life and, when associated, may further worsen it[14,15].

In the participants of this study, the presence of migraine, especially when combined with SAH, was accompanied by a higher frequency of depression and higher degrees of stress severity and anxiety symptoms. This relationship between depression and migraine is bidirectional, as shown by another study[16] based on a dose-response effect between migraine and depression and anxiety. The number of migraine attacks may increase the prevalence of mental disorders[4-7,17], due to the pathophysiological mechanisms involved, such as the attack on the serotonergic system, the influence of gonadotropins, and an increase in pro-inflammatory cytokines, and the presence of a family history[5].

Table 1. Comparative analysis on general health, neck pain, low back pain, depression, anxiety, stress, and sleep quality according to migraine and hypertension diagnosis.

	Migraine		No migraine		p-value
	Hypertension (n=9)	No hypertension (n=20)	Hypertension (n=21)	No hypertension (n=20)	
	Med (IQR)	Med (IQR)	Med (IQR)	Med (IQR)	
GHQ-12					
Positive score	2.1 (1.3–2.1)	2.0 (1.3–2.5)	1.8 (1.5–2.0)	1.6 (1.2–2.0)	0.522
Negative score	2.7 (1.3–2.1)[a]	2.0 (1.5–2.5)[a]	1.3 (1.1–1.5)[b]	1.5 (1.3–2.0)[a,b]	0.001
DASS-21					
Depression score	4 (2–6)[a]	2 (0–8)[a]	0 (0–2)[a,b]	0 (0–1)[b]	0.003
Anxiety score	14 (6–16)[a]	4 (2–8)[b]	2 (0–6)[b,c]	0 (0–2)[c]	<0.001
Stress score	14 (4–24)[a]	7 (4–16)[a]	2 (0–4)[b]	2 (0–3)[b]	<0.001
PSQI total score	2 (1–2)	2 (2–3)	2 (1–2)	2 (1–2)	0.124

Med: median; IQR: interquartile range (1st quartile – 3rd quartile); GHQ-12: general health questionnaire-12; DASS-21: depression, anxiety and stress scale-21; PSQI: Pittsburgh sleep quality index. After a Kruskal-Wallis test, different superscript letters indicate a significant difference by Dunn's multiple comparison post-test (p<0.05).

Stress is intrinsically related to SAH, and it can be both a risk factor and a consequence of this comorbidity[7], because there is an interconnection between these pathological pathways, with endothelial dysfunction being one of these elements, and stress may be a consequence or cause of an alteration in systemic blood pressure[17].

Moreover, studies show that stress has a bidirectional relationship with chronic migraine and may be a possible enhancer of other psychological comorbidities. In this context, serotonin is part of this association because it increases stress and participates in the central nucleus of pain, working as a pain stimulus[2,8].

Table 2. Multiple linear regression analysis of migraine and hypertension on health scores and salivary biomarkers levels.

Outcomes/factors	Multiple linear regression models[a]			
	R^2	Intercept	Beta	p-value
Outcome: GHQ-12 negative score	0.231	1.954		
Migraine			0.46	0.001*
Hypertension			-0.21	0.186
Outcome: DASS-21 depression	0.158	-0.622		
Migraine			3.54	0.002*
Hypertension			0.90	0.505
Outcome: DASS-21 anxiety	0.354	-2.581		
Migraine			5.74	<0.001*
Hypertension			3.36	0.014*
Outcome: DASS-21 stress	0.374	2.236		
Migraine			8.17	<0.001*
Hypertension			4.34	0.028*

R^2: determination coefficient; Beta: regression coefficient, GHQ-12: general health questionnaire-12; DASS-21: depression, anxiety and stress scale-21. [a]Multiple linear regression models adjusted by migraine, hypertension, age, female sex, and body mass index. *Statistically significant factor (p<0.05).

Table 3. Multiple linear regression analysis of migraine and hypertension on psychometric outcomes.

Outcomes/factors	Multiple linear regression models[a]				Normality of residuals of regression models	
	R^2	Beta	SE	p	Statistics	p
Model 1 Outcome: GHQ–12 Negative score	0.225				3.223	0.199
Migraine		0.46	0.12	0.001*		
Hypertension		-0.22	0.15	0.150		
Model 2 Outcome: DASS–21 depression	0.151				5.234	<0.001
Migraine		3.54	1.08	0.001*		
Hypertension		0.90	1.33	0.437		
Model 3 Outcome: DASS–21 anxiety	0.350				5.662	0.061
Migraine		5.77	1.07	<0.001*		
Hypertension		3.49	1.32	0.010*		
Model 4 Outcome: DASS–21 stress	0.374				3.566	0.168
Migraine		8.18	1.54	<0.001*		
Hypertension		4.40	1.89	0.023*		

R^2: determination coefficient; SE: standard error. Beta: regression coefficient. [a]Multiple linear regression models adjusted by migraine, hypertension, age, female sex and body mass index. *Statistically significant factor (p<0.05).

Serotonin is also present in physiopathological mechanisms related to poor-quality sleep. Experimental studies have demonstrated the association between serotonin, waking up at night, and migraine[18,19]. However, the results of those studies did not show differences between the groups. Relatedly, one study found that this causal relationship can reach a stage of stability when the frequency of headache attacks exceeds 9 days per month[20], which also occurred in most of our patients affected by migraine.

Some sleep disorders, such as obstructive sleep apnea and chronic insomnia, are associated with a higher risk of SAH[21-23]. However, research explained these associations with comorbidities such as obesity and depression, which are risk factors for increased blood pressure and poor sleep quality[24]. These confounding risk factors may have influenced the results related to SAH in the present study.

The study's limitations include the difficulty in finding individuals with SHA combined with migraine, since medications to treat hypertension end up helping to prevent migraine.

Patients with migraine had higher scores for overall negative health quality, anxiety, depression, and stress. Such scores were more evident in those with migraine and hypertension, although only anxiety had this combined effect statistically significant, demonstrating that these two conditions are more detrimental to physical and mental health.

ACKNOWLEDGMENTS

All procedures performed in studies involving human participants followed the ethical standards of the institutional and national research committee and with the 1964 Helsinki Declaration and its later amendments or comparable ethical standards. Informed consent was obtained from all individual participants included in the study.

The Ethics Committee of the Federal University of Maranhão approved the study (CAAE: 61420016.5.0000.5086).

This study was supported by the Fundação de Amparo à Pesquisa e ao Desenvolvimento Científico e Tecnológico do Maranhão, grant number UNIVERSAL-01350/17 and financed by Coordenação de Aperfeiçoamento de Pessoal de Nível Superior (CAPES). The funders had no role in study design, data collection and analysis, decision to publish, or preparation of the manuscript.

AUTHORS' CONTRIBUTIONS

TSR: Conceptualization, Methodology, Formal Analysis, Investigation, Supervision, Writing – original draft, Writing – review & editing. **LSBA:** Conceptualization, Methodology, Formal Analysis, Investigation, Supervision, Writing – original draft, Writing – review & editing. **VPR:** Conceptualization, Methodology, Formal Analysis, Investigation, Supervision, Writing – original draft, Writing – review & editing. **CMBO**: Conceptualization, Methodology, Formal Analysis, Investigation, Supervision, Writing – original draft, Writing – review & editing. **ECRM** Conceptualization, Methodology, Formal Analysis, Investigation, Supervision, Writing – original draft, Writing – review & editing. **LMMN:** Conceptualization, Methodology, Formal Analysis, Investigation, Supervision, Writing – original draft, Writing – review & editing. **LGLN**: Conceptualization, Methodology, Formal Analysis, Investigation, Supervision, Writing – original draft, Writing – review & editing. **LVGM:** Conceptualization, Methodology, Formal Analysis, Investigation, Supervision, Writing – original draft, Writing – review & editing. **ECPPCL:** Conceptualization, Methodology, Formal Analysis, Investigation, Supervision, Writing – original draft, Writing – review & editing.

REFERENCES

1. Shi X, Di W, Wieczorek A. Basic and clinical advances in the diagnosis and management of migraine. Pain Res Manag. 2020;2020:8958143. https://doi.org/10.1155/2020/8958143
2. Buse DC, Reed ML, Fanning KM, Bostic R, Dodick DW, Schwedt TJ, et al. Comorbid and co-occurring conditions in migraine and associated risk of increasing headache pain intensity and headache frequency: results of the migraine in America symptoms and treatment (MAST) study. J Headache Pain. 2020;21(1):23. https://doi.org/10.1186/s10194-020-1084-y
3. Hagen K, Stovner LJ, Zwart JA. Time trends of major headache diagnoses and predictive factors. Data from three Nord-Trøndelag health surveys. J Headache Pain. 2020;21(1):24. https://doi.org/10.1186/s10194-020-01095-5
4. Dresler T, Caratozzolo S, Guldolf K, Huhn JI, Loiacono C, Niiberg-Pikksööt T, et al. Understanding the nature of psychiatric comorbidity in migraine: a systematic review focused on interactions and treatment implications. J Headache Pain. 2019;20(1):51. https://doi.org/10.1186/s10194-019-0988-x
5. Maatouk I, Herzog W, Böhlen F, Quinzler R, Löwe B, Saum KU, et al. Association of hypertension with depression and generalized anxiety symptoms in a large population-based sample of older adults. J Hypertens. 2016;34(9):1711-20. https://doi.org/10.1097/HJH.0000000000001006
6. Dich N, Rod NH, Doan SN. Both High and Low Levels of Negative Emotions Are Associated with Higher Blood Pressure: Evidence from Whitehall II Cohort Study. Int J Behav Med. 2020;27(2):170-8. https://doi.org/10.1007/s12529-019-09844-w

7. Liu MY, Li N, Li WA, Khan H. Association between psychosocial stress and hypertension: a systematic review and meta-analysis. Neurol Res. 2017;39(6):573-80. https://doi.org/10.1080/01616412.2017.1317904
8. Cha MJ, Kim BK, Moon HS, Ahn JY, Oh K, Kim JY, et al. Stress is associated with poor outcome of acute treatment for chronic migraine: a multicenter study. Pain Med. 2018;19(9):1832-8. https://doi.org/10.1093/pm/pnx269
9. Bougea A, Spantideas N, Galanis P, Katsika P, Boufidou F, Voskou P, et al. Salivary inflammatory markers in tension type headache and migraine: the SalHead cohort study. Neurol Sci. 2020;41(4):877-84. https://doi.org/10.1007/s10072-019-04151-4
10. Peres MFP, Mercante JPP, Tobo PR, Kamei H, Bigal ME. Anxiety and depression symptoms and migraine: a symptom-based approach research. J Headache Pain. 2017;18(1):37. https://doi.org/10.1186/s10194-017-0742-1
11. Gray CA, Sims OT, Oh H. Prevalence and predictors of co-occurring hypertension and depression among community-dwelling older adults. J Racial Ethn Health Disparities. 2020;7(2):365-73. https://doi.org/10.1007/s40615-019-00665-x
12. Gudmundsson LS, Thorgeirsson G, Sigfusson N, Sigvaldason H, Johannsson M. Migraine patients have lower systolic but higher diastolic blood pressure compared with controls in a population-based study of 21,537 subjects. The Reykjavik Study. Cephalalgia. 2006;26(4):436-44. https://doi.org/10.1111/j.1468-2982.2005.01057.x
13. Lima GS, Laurentino IMS, Silva VNC, Leite AFB, Valença MM, Santos ERR. Interactive between headache, systemic arterial hypertension and stoke: a integrative review. HM [Internet]. 2018;9(4):199-204. https://doi.org/10.48208/HeadacheMed.2018.23
14. Burch RC, Buse DC, Lipton RB. Migraine: Epidemiology, burden, and comorbidity. Neurol Clin. 2019;37(4):631-49. https://doi.org/10.1016/j.ncl.2019.06.001
15. Plesh O, Adams SH, Gansky SA. Self-reported comorbid pains in severe headaches or migraines in a US national sample. Headache. 2012;52(6):946-56.https://doi.org/10.1111/j.1526-4610.2012.02155.x
16. Breslau N, Davis GC, Schultz LR, Paterson EL. Migraine and major depression: a longitudinal study. Headache. 1994;34(7):387-93. https://doi.org/10.1111/j.1526-4610.1994.hed3407387.x
17. Vgontzas A, Pavlović JM. Sleep Disorders and Migraine: Review of Literature and Potential Pathophysiology Mechanisms. Headache. 2018;58(7):1030-9. https://doi.org/10.1111/head.13358
18. Ushakov AV, Ivanchenko VS, Gagarina AA. Psychological stress in pathogenesis of essential hypertension. Curr Hypertens Rev. 2016;12(3):203-14.https://doi.org/10.2174/1573402112666161230121622
19. Ferini-Strambi L, Galbiati A, Combi R. Sleep disorder-related headaches. Neurol Sci. 2019;40(Suppl 1):107-13. https://doi.org/10.1007/s10072-019-03837-z
20. Buse DC, Rains JC, Pavlovic JM, Fanning KM, Reed ML, Manack Adams A, et al. Sleep disorders among people with migraine: results from the chronic migraine epidemiology and outcomes (CaMEO) study. Headache. 2019;59(1):32-45. https://doi.org/10.1111/head.13435
21. Hein M, Lanquart JP, Loas G, Hubain P, Linkowski P. Risk of high blood pressure associated with objective insomnia and self-reported insomnia complaints in major depression: a study on 703 individuals. Clin Exp Hypertens. 2019;41(6):538-47. https://doi.org/10.1080/10641963.2018.1516775
22. Jarrin DC, Alvaro PK, Bouchard MA, Jarrin SD, Drake CL, Morin CM. Insomnia and hypertension: a systematic review. Sleep Med Rev. 2018;41:3-38. https://doi.org/10.1016/j.smrv.2018.02.003
23. Carnethon MR, Johnson DA. Sleep and Resistant Hypertension. Curr Hypertens Rep. 2019;21(5):34. https://doi.org/10.1007/s11906-019-0941-z
24. Mansukhani MP, Covassin N, Somers VK. Apneic sleep, insufficient sleep, and hypertension. Hypertension. 2019;73(4):744-56. https://doi.org/10.1161/HYPERTENSIONAHA.118.11780

ORIGINAL ARTICLE

https://doi.org/10.1590/1806-9282.20210368

Quantification of cell-free circulating mitochondrial DNA copy number variation in hepatocellular carcinoma

Burhanettin Yalçınkaya[1*], Didem Tastekin[2], Fatih Güzelbulut[3], Muslum Akgoz[1], Sadrettin Pençe[4]

SUMMARY

OBJECTIVE: Hepatocellular carcinoma is the most common primary malignant liver tumor. Mitochondrial DNA copy number has been shown to be associated with various malignancies. However, there has not been any study on the absolute quantification of mtDNA copy number in hepatocellular carcinoma. The aim of this study was to develop a new method for absolute quantification of mtDNA copy number and to relatively quantify the variations in the mtDNA copy number in hepatocellular carcinoma patients in comparison with healthy individuals.

METHODS: Venous blood samples were collected from both hepatocellular carcinoma patients (34) and healthy individuals (34). Circulating cell-free DNAs were isolated and the relative quantification of mtDNA copy number variation was determined using quantitative polymerase chain reaction and digital polymerase chain reaction.

RESULTS: It was found that the relative mtDNA copy number was significantly decreased in hepatocellular carcinoma patients in comparison with the control group ($p<0.05$). The median (range) and average of relative mtDNA/β-actin gene of the patients were determined as 42.8 cp/μL (11.1–88.5) and 45.1 cp/μL, respectively, while the median (range) and average relative mtDNA/β-actin gene of the control group were determined as 102.8 cp/μL (55.1–291.8) and 138.7 cp/μL, respectively ($p<0.05$). When quantitative polymerase chain reaction and digital polymerase chain reaction were compared, mtDNA/β-actin gene copy number ratio of digital polymerase chain reaction results was found to be 1.76-fold more than that of quantitative polymerase chain reaction results.

CONCLUSION: Circulating mtDNA copy number was decreased in hepatocellular carcinoma patients in comparison with healthy individuals, and we suggest that it can be used as a noninvasive biomarker for hepatocellular carcinoma diagnosis in the future.

KEYWORDS: Mitochondria. CfDNA. HCC. dPCR.

INTRODUCTION

Hepatocellular carcinoma (HCC) is the most common primary malignant liver tumor and constitutes 80–90% of all primary malignant liver tumors. It is the fifth most common cancer in adult men and eighth most common cancer in adult women. Also, HCC is ranked the sixth in cancer-related deaths and is the leading cause of liver-related mortality in patients with chronic hepatitis and cirrhosis[1,2].

Mitochondria produce energy through ATP synthesis via the citric acid cycle and oxidative phosphorylation. Since the mtDNA does not have histones and has limited proofreading activity, the mutation rate is about 10 times higher than in the nuclear genome. The noncoded D-loop region of mtDNA region shows a high degree of polymorphism, and mutations in this region lead to changes in the number of mtDNA copies and suppression of mitochondrial gene expression[3,4].

Many clinical, histological, genetic, and biochemical diseases have been associated with mutations in mitochondria[5]. In the literature, the mtDNA copy number alterations have been reported in some malignancies. It has also been published that the number of mtDNA copies were decreased in HCC, but the mechanism has not yet been fully explored[6-9]. There has not been any study on the absolute quantification of mtDNA copy number in HCC, although a few studies were reported on other malignancies.

The aim of this study was to develop a novel method for absolute quantification of mtDNA copy number and to relatively quantify the variations in the mtDNA copy number in HCC patients in comparison with healthy individuals.

METHODS

Human serum samples collection

Serum samples were collected from 34 newly diagnosed HCC patients who were admitted to the Istanbul University Oncology

[1]TUBITAK National Metrology Institute – Kocaeli, Turkey.
[2]Istanbul University, Institute of Oncology – Istanbul, Turkey.
[3]University of Health Sciences, Haydarpaşa Numune Training and Research Hospital – Istanbul, Turkey.
[4]Istanbul Medeniyet University, Faculty of Medicine – Istanbul, Turkey.
*Corresponding author: burhanettin.yalcinkaya@tubitak.gov.tr; burhanettinyalcinkaya@gmail.com
Conflicts of interest: the authors declare there is no conflicts of interest. Funding: This work was supported by TUBITAK UME National Metrology Institute.
Received on April 03, 2022. Accepted on May 16, 2022.

Institute and Gastroenterology Outpatient Clinic, Haydarpasa Numune Training and Research Hospital.

The patients who had received radiotherapy and chemotherapy, have confirmed infection and chronic inflammatory diseases, as well as those with tumors in other organs and used antibiotics, anti-inflammatory drugs, or corticosteroids were not included in the study.

As a control group, serum samples were obtained from 34 healthy individuals. Epidemiologic variables and clinical data were collected by physicians. The presence of chronic hepatitis B and C and cirrhosis were recorded according to the laboratory and radiological test results (Table 1). The study was approved by the Ethics Committee of the Istanbul University (Document number 2016/1297).

Cell-free DNAs were isolated using Norgen Plasma/Serum Cell-Free Circulating DNA Purification Kit (Catalog No. 55100) according to the kit's protocol from 500 µL serum samples. The concentration and purity of the isolated DNA was determined using NanoDrop Spectrometer.

Quantitative analysis of cell-free mtDNA

The relative quantification of mtDNA copy number was determined using quantitative real-time PCR (qPCR), and absolute quantification of mtDNA copy number was performed by QuantStudio 3D Digital PCR (dPCR) System using a slightly modified protocol as described previously[10,11]. Briefly, for the amplification of the short segment inside the 7S region of the mtDNA, 2′ Mastermix (SensiFast Probe No-ROX Kit, Bioline) with 900 nM primer each together with 250 nM TaqMan probe and 5 µL DNA were used (Table 2).

As an endogenous gene control, the nuclear low copy gene β-actin (GenBank accession number NM_001101) was used. The qPCR and dPCR conditions of both genes are as follows: an initial denaturation at 95°C for 10 min, denaturation at °C for 15 s, annealing at 64°C for 60 s, and a total of 40 and 39 cycles of PCR, respectively. All samples were measured in duplicate using qPCR and dPCR. Human genomic DNA (sonicated) Hybridime (Cambio Cat No. CA-972-06) was used as a positive PCR control.

For relative quantification of mtDNA by qPCR, ΔC_t method was used as the cycle threshold (C_t) values were obtained from the Light Cycler® 480 Software. After dPCR, mtDNA and β-actin genes of patient and control group samples were analyzed using QuantStudio™ 3D Analysis Suite™ Cloud Software.

Statistical analysis

All data were analyzed using the IBM SPSS statistics v21 package. For the determination of skewness and kurtosis of all data, values were calculated using the Kolmogorov-Smirnov test. Then, all data were analyzed using Mann-Whitney U test as nonparametric statistics. The threshold $p<0.05$ was considered statistically significant.

RESULTS

Epidemiologic data of the patients and healthy individuals are summarized in Table 1. In total, 24 (71%) patients were male with a mean age of 51±9 years. Fourteen had chronic hepatitis B and 11 had chronic hepatitis C. Eight of them were smokers and seven of them were drinkers. As expected,

Table 1. Epidemiologic variation of patients and healthy individuals.

Variables	Patients (n=34, %)	Control (n=34, %)	p-value
Age (years) (mean±SD)	51±9	48±10	>0.05
Male/female	24 (71)/10 (29)	20 (59)/14 (41)	>0.05
Chronic hepatitis B	14 (41)	–	
Chronic hepatitis C	11 (32)	–	
Smoking status			
Never	26 (76)	23 (68)	>0.05
Ever	8 (24)	11 (32)	>0.05
Drinking status			
Never	27 (79)	30 (88)	>0.05
Ever	7 (21)	4 (12)	>0.05
Cirrhosis			
Yes	24 (71)	–	
Family history of cancer			
Yes	11 (32)	4 (12)	<0.05

most of the patients had cirrhosis. In all, 11 patients had a family history of cancer. None of the healthy individuals had cirrhosis. Four of the healthy individuals had a family history of cancer.

There were no significant differences between patients and healthy individuals with respect to gender, age, smoking, and drinking status (all p>0.05). More HCC patients had a family history of cancer than in healthy individuals (p<0.05).

Relative quantification of mtDNA copy number

The mtDNA copy number alteration was determined by qPCR using mtDNA-specific and β-actin gene-specific primers and probes. Then, the ΔC_t analysis of the qPCR data showed that relative mtDNA copy number was significantly decreased in HCC patients in comparison with the control group (p<0.05). The median ratios of mtDNA to β-actin gene in HCC patients and control group individuals were 3.73±0.94 and 4.53±0.54, respectively (p<0.05).

Absolute quantification of mtDNA copy number

For the successful determination of the alterations in the mtDNA copy number, the ratio of mtDNA to β-actin gene was measured using dPCR. The ratio of mtDNA to β-actin gene was decreased in HCC patients in comparison with that of control group (p<0.05). The median (range) and average of the patient relative mtDNA/β-actin gene were 42.8 cp/μL (11.1–88.5) and 45.1 cp/μL, while the median (range) and average of the control group relative mtDNA/β-actin gene were 102.8 cp/μL (55.1–291.8) and 138.7 cp/μL, respectively (p<0.05).

When dPCR results were compared, the mtDNA/β-actin gene ratio of some HCC patients was much less than that of other status of patients (Table 3). Also, when chronic hepatitis B was evaluated with drinkers and smokers, drinkers and smokers had much less cell-free mtDNA copy numbers than in other HCC patients.

Quantitative polymerase chain reaction (qPCR) and dPCR results were also compared and it was shown that mtDNA/β-actin gene copy number ratio of dPCR results was 1.8-fold more than that of qPCR results.

DISCUSSION

In recent years, tumor markers were discovered and utilized from the blood (liquid biopsy specimens) of the patients. The biggest advantage of these markers is that they contain genetic information that may represent tumor tissue in a liquid biopsy specimen taken without the need for surgery[12,13]. In this study, we investigated the mtDNA copy number alterations in liquid biopsy samples of HCC patients. In the literature, it has been reported that the number of mtDNA copies has been increased in some malignancies such as breast cancer, lung cancer, endometrial adenocarcinoma, and colorectal cancer[14-16]. In contrast, the number of mtDNA copies has decreased in some malignancies such as ovarian cancer, gastric cancer, Ewing sarcoma, and HCC[6-9]. It is believed that this decrease is due to point mutations that may occur in the noncoding D-loop region that regulates mitochondrial genome replication. mtDNA copy number has also decreased in HBV-related HCC patients[17].

For clinical and diagnostic approach, precise and accurate nucleic-acid quantification is required to prevent incorrect diagnosis. Digital PCR is considered the reference method for absolute nucleic-acid copy-number detection[18,19].

In this study, mtDNA was quantified for the first time by dPCR in HCC patients. Using qPCR, it was found that mtDNA copy number decreased 1.7-fold in newly diagnosed HCC patients (p<0.05). The mtDNA/β-actin gene ratio was found to be decreased 1.8-fold using dPCR measurements. Since dPCR is considered the reference measurement system, we consider that dPCR gives higher accuracy in results.

A survey including smoking status, drinking status, and family history of cancer was filled by patients during serum collection from the patients and healthy individuals. The dPCR data showed that the mtDNA copy number was significantly lower in both smokers and drinkers than in other patients. It was reported that consuming more than two portions of alcoholic beverages per day was significantly associated with 2-fold higher risk of developing HCC[20,21]. Also, currents or past smokers have been significantly associated with HCC[22]. It has been reported that smoking decreases mtDNA copy number, proving that it may also be associated with mitochondrial dysfunction[23].

Table 2. Primer and probe sequences of β-actin and mtDNA gene for quantitative polymerase chain reaction and digital polymerase chain reaction.

	Primer/probe	Sequence	PCR product size (bp)
β-actin	Forward	5′-GGCACCACACCTTCTACAATGAG-3′	104
	Reverse	5′-GGTCATCTTCTCGCGGTTGG-3′	
	Probe	HEX 5′-TGCTGCTGACCGAGGCCCCC-3′ BHQ1	
mtDNA	Forward	5′-CATAAAGCCTAAATAGCCCACACG-3′	85
	Reverse	5′-CCGTGAGTGGTTAATAGGGTGATA-3′	
	Probe	FAM 5′-AGACATCACGATGGATCACAGGTCT-3′ BHQ1	

Table 3. mtDNA/β-actin gene ratio in hepatocellular carcinoma patients.

	Female	Male	Hepatitis B	Hepatitis C	Smoking	Alcohol	Cirrhosis	Family hist. of cancer
	Average (n) Median Range	Average (n) Median Range	Average (n) Median Range	Average (n) Median Range	Average (n) Median Range	Average (n) Median Range	Average (n) Median Range	Average (n) Median Range
Gender	53.0 10 55.6 16.6–82.1	41.6 24 41.4 11.2–88.5						
Hepatitis B	73.1 3 74.9 62.4–82.1	39.6 11 39.3 16.2–73.8	47.3 14 44.1 16.2–82.1					
Hepatitis C	52.5 5 50.9 26.9–74.9	32.6 6 36.3 11.7–44.5	47.2 5 44.1 30.9–74.9	41 11 41.8 11.7–74.9				
Smoking	54.5 2 54.5 40.7–68.3	28.3 6 23.3 11.2–63.3	27.8 3 30.4 16.2–36.8	40.3 4 40.7 11.7–68.3	34.8 8 33.6 11.2–68.3			
Alcohol	–	32.7 7 30.4 11.7–69.6	32 4 33.6 16.2–44.5	28.1 2 28.1 44.5–18.7	23.8 4 23.3 11.7–36.8	32.7 7 30.4 11.7–69.6		
Cirrhosis	71.6 5 71.6 68.3–71.9	39.7 19 42.9 16.7–73.8	50.9 17 44.5 24.3–74.9	48.4 15 44.3 16.7–74.9	–	32.2 6 32.2 19.9–44.5	46.1 24 44.3 16.7–74.9	
Family hist. of cancer	52.7 4 54.5 26.9–74.9	40 7 30.9 19.9–69.6	40.4 5 30.9 24.3–74.9	47.3 6 41.8 26.9–74.9	50.7 4 52 30.4–.68.3	39.9 3 30.4 19.9–69.6	45.8 5 41.8 19.9–74.9	44.6 11 40.7 19.9–74.9

The decreased mtDNA copy numbers in HCC patients who were smokers and drinkers may be associated with the chemicals that target the mtDNA.

This study has some limitations. First of all, the study population was relatively small. Moreover, this study involved patients only from two medical centers from Istanbul, Turkey. However, our new and successful technique renders our study interesting and favorable.

CONCLUSIONS

This is the first study that performs absolute quantification of cell-free mtDNA to β-actin gene ratio in HCC patients using qPCR in addition to dPCR. Although mtDNA/β-actin gene ratio was found to be decreased in both platforms, there was about 1.8-fold difference in them. Since dPCR is considered the reference measurement system, we have higher confidence in the results of dPCR than in qPCR. It was shown that circulating mtDNA copy number was decreased in HCC patients using both platforms. Thus, dPCR has the potential to be used as a noninvasive biomarker for HCC diagnosis in the future.

AUTHORS' CONTRIBUTIONS

BY: Conceptualization, Data curation, Formal Analysis, Investigation, Methodology, Project administration, Writing – original draft, Writing – review & editing. **DT:** Formal Analysis, Investigation, Resources. **FG:** Formal Analysis, Investigation, Resources, Writing – original draft. **MA:** Project administration, Supervision. **SP:** Project administration, Supervision.

REFERENCES

1. Balogh J, Victor D, Asham EH, Burroughs SG, Boktour M, Saharia A, et al. Hepatocellular carcinoma: a review. J Hepatocell Carcinoma. 2016;3:41-53. https://doi.org/10.2147/JHC.S61146
2. Yalçinkaya B, Güzel Tanoğlu E, Taştekın D, Pençe S. Role of mir-33a, mir-203b, mir361-3p, and mir-424 in hepatocellular carcinoma. Turkish J Med Sci. 2021;51(2):638-43. https://doi.org/10.3906/sag-2004-214
3. Mansouri A, Gattolliat C-H, Asselah T. Mitochondrial dysfunction and signaling in chronic liver diseases. Gastroenterology. 2018;155(3):629-47. https://doi.org/10.1053/j.gastro.2018.06.083
4. Wang J, Xu J, Xia M, Yang Y, Shen Z, Chen G, et al. Correlation between hepatic oxidative damage and clinical severity and mitochondrial gene sequencing results in biliary atresia. Hepatol Res. 2019;49(6):695-704. https://doi.org/10.1111/hepr.13324
5. Wei W, Keogh MJ, Wilson I, Coxhead J, Ryan S, Rollinson S, et al. Mitochondrial DNA point mutations and relative copy number in 1363 disease and control human brains. Acta Neuropathol Commun. 2017;5(1):13. https://doi.org/10.1186/s40478-016-0404-6
6. Wang Y, Liu VWS, Xue WC, Cheung ANY, Ngan HYS. Association of decreased mitochondrial DNA content with ovarian cancer progression. Br J Cancer. 2006;95(8):1087-91. https://doi.org/10.1038/sj.bjc.6603377
7. Pyle A, Anugrha H, Kurzawa-Akanbi M, Yarnall A, Burn D, Hudson G. Reduced mitochondrial DNA copy number is a biomarker of Parkinson's disease. Neurobiol Aging. 2016;38:216.e7-10. https://doi.org/10.1016/j.neurobiolaging.2015.10.033
8. Hu L, Yao X, Shen Y. Altered mitochondrial DNA copy number contributes to human cancer risk: evidence from an updated meta-analysis. Sci Rep. 2016;6:35859. https://doi.org/10.1038/srep35859
9. Lindqvist D, Wolkowitz O, Picard M, Ohlsson L, Bersani FS, Fernström J, et al. Circulating cell-free mitochondrial DNA-a novel marker of mitochondrial stress associated with suicidality and major depressive disorder. Biol Psychiatry. 2018;83(9):S25-6. https://doi.org/10.1016/j.biopsych.2018.02.079
10. Zsurka G, Baron M, Stewart JD, Kornblum C, Bös M, Sassen R, et al. Clonally expanded mitochondrial DNA mutations in epileptic individuals with mutated DNA polymerase γ. J Neuropathol Exp Neurol. 2008;67(9):857-66. https://doi.org/10.1097/NEN.0b013e3181839b2d
11. Kornblum C, Nicholls TJ, Haack TB, Schöler S, Peeva V, Danhauser K, et al. Loss-of-function mutations in MGME1 impair mtDNA replication and cause multisystemic mitochondrial disease. Nat Genet. 2013;45(2):214-9. https://doi.org/10.1038/ng.2501
12. Yalçinkaya B, Coşkun K, Akgoz M, Pence S. A simple silica based DNA isolation method for cell-free DNA analysis from liquid biopsy. Turkish J Biochem. 2020;45(6):701-5. https://doi.org/10.1515/tjb-2020-0253
13. Cisneros-Villanueva M, Hidalgo-Pérez L, Rios-Romero M, Cedro-Tanda A, Ruiz-Villavicencio CA, Page K, et al. Cell-free DNA analysis in current cancer clinical trials: a review. Br J Cancer. 2022;126(4809):391-400. https://doi.org/10.1038/s41416-021-01696-0
14. Sun X, Zhan L, Chen Y, Wang G, He L, Wang Q, et al. Increased mtDNA copy number promotes cancer progression by enhancing mitochondrial oxidative phosphorylation in microsatellite-stable colorectal cancer. Signal Transduct Target Ther. 2018;3(1):8. https://doi.org/10.1038/s41392-018-0011-z
15. Kopinski PK, Singh LN, Zhang S, Lott MT, Wallace DC. Mitochondrial DNA variation and cancer. Nat Rev Cancer. 2021;21(7):431-45. https://doi.org/10.1038/s41568-021-00358-w
16. Rai NK, Panjwani G, Ghosh AK, Haque R, Sharma LK. Analysis of mitochondrial DNA copy number variation in blood and tissue samples of metastatic breast cancer patients (A pilot study). Biochem Biophys Rep. 2021;26:100931. https://doi.org/10.1016/j.bbrep.2021.100931
17. Li L, Hann H-W, Wan S, Hann RS, Wang C, Lai Y, et al. Cell-free circulating mitochondrial DNA content and risk of hepatocellular carcinoma in patients with chronic HBV infection. Sci Rep. 2016;6(1):23992. https://doi.org/10.1038/srep23992
18. Košir AB, Divieto C, Pavšič J, Pavarelli S, Dobnik D, Dreo T, et al. Droplet volume variability as a critical factor for accuracy of absolute quantification using droplet digital PCR. Anal Bioanal Chem. 2017;409(28):6689-97. https://doi.org/10.1007/s00216-017-0625-y
19. Zhang H, Yan Z, Wang X, Gaňová M, Korabečná M, Zahradník P, et al. Digital PCR system development accelerator—A methodology to emulate dPCR results. Sensors Actuators B Chem. 2022;358:131527. https://doi.org/10.1016/j.snb.2022.131527
20. Koh W-P, Robien K, Wang R, Govindarajan S, Yuan J-M, Yu MC. Smoking as an independent risk factor for hepatocellular carcinoma: the Singapore Chinese Health Study. Br J Cancer. 2011;105(9):1430-5. https://doi.org/10.1038/bjc.2011.360
21. Petrick JL, Campbell PT, Koshiol J, Thistle JE, Andreotti G, Beane-Freeman LE, et al. Tobacco, alcohol use and risk of hepatocellular carcinoma and intrahepatic cholangiocarcinoma: the liver cancer pooling project. Br J Cancer. 2018;118(7):1005-12. https://doi.org/10.1038/s41416-018-0007-z
22. Chiang C-H, Lu C-W, Han H-C, Hung S-H, Lee Y-H, Yang K-C, et al. The relationship of diabetes and smoking status to hepatocellular carcinoma mortality. Medicine (Baltimore). 2016;95(6):e2699. https://doi.org/10.1097/MD.0000000000002699
23. Bouhours-Nouet N, May-Panloup P, Coutant R, de Casson FB, Descamps P, Douay O, et al. Maternal smoking is associated with mitochondrial DNA depletion and respiratory chain complex III deficiency in placenta. Am J Physiol Metab. 2005;288(1):E171-7. https://doi.org/10.1152/ajpendo.00260.2003

ORIGINAL ARTICLE

https://doi.org/10.1590/1806-9282.20210696

Dexmedetomidine potential in attenuating postoperative delirium in elderly patients after total hip joint replacement

Yuqin Lv[1*], Lilei Gu[2]

SUMMARY

OBJECTIVE: This study aims to evaluate the effectiveness of dexmedetomidine in reducing the occurrence of postoperative delirium in elderly patients after total hip joint replacement.

METHODS: Patients who have undergone total hip joint replacement and who were admitted to the hospital from August 1, 2017, to August 1, 2020, were included in this study. After initial screening, 327 out of 385 patients were selected and randomly assigned to either dexmedetomidine (0.1 μg/kg/h, n=163) or placebo (n=164) groups. The occurrence of delirium was examined twice a day for one week by using the Confusion Assessment Method. Furthermore, 30-day all-cause mortality, hospitalization duration and costs, and the presence of any postoperative complications were also evaluated.

RESULTS: The postoperative delirium incidence was significantly lower in the dexmedetomidine group compared to that in the placebo group (13.8 vs. 29.3%, p<0.01). The hospitalization duration (17.2±6.3 vs. 15.6±4.2, p=0.006) and cost (4.5±0.9 vs. 4.9±1.1, p=0.001) in the dexmedetomidine group were also lower than those in the placebo group. Meanwhile, no significant difference between the 30-day all-cause mortality of the two groups was observed (p=0.60). In terms of safety, no significant differences between the occurrence of hypotension and bradycardia were also observed.

CONCLUSION: Our findings show that the dexmedetomidine medication can reduce the postoperative delirium incidence in older total hip joint replacement patients and can subsequently decrease the related hospitalization duration and cost of these patients.

KEYWORDS: Dexmedetomidine. Joint Replacement. Delirium.

INTRODUCTION

Postoperative delirium (POD) is a life-threatening clinical complication that is prevalent in elderly patients. It is associated with a higher risk of dementia and mortality[1]. In most cases, POD often leads to prolonged treatment duration and high costs due to cognitive impairment and disability[2]. Interestingly, a previous study has reported that POD has an incidence of around 11–51% in elderly patients who have received total hip arthroplasty (THA)[3]. In a similar study, it has been found that 23.33% of elderly patients undergoing THA due to hip fracture will develop POD[4]. Furthermore, POD can manifest in 60–80% of hospitalized elderly patients[5]. Alarmingly, in the United States, an 85% increase in total knee arthroplasty (TKA) procedure growth rate was observed within the last 14 years, and it is anticipated that THA procedures will increase to 71% by 2030[6]. Thus, it is important to prevent the development of POD to improve long-term outcomes and decrease the hospitalization duration and cost of affected patients. Currently, there is no effective preventive drug against POD as well as proof from randomized controlled studies in post-THA elderly patients that has been reported yet.

Dexmedetomidine (DEX) is a highly selective agonist of the α-2-adrenergic receptor that causes adequate sedation with minimal respiratory depression[7]. Recent studies are increasingly providing evidence on the protective effects of DEX administration on various organ injuries[7,8] and delirium[2,9]. A previous study has also reported that DEX can potentially slow the course of delirium in critically ill patients[10]. Currently, there are no reports of any randomized controlled trials done to demonstrate the potency of DEX in preventing the development of POD in elderly patients following THA. Thus, the anti-delirium effectiveness of DEX has remained unclear and controversial. To bridge this knowledge gap, this study aims to explore the effectiveness of acute DEX treatment in reducing POD and improving post-THA operation clinical outcomes.

[1]The 904th Hospital of Joint Logistic Support Force, Department of drug distribution center – Wuxi, China.
[2]The 904th Hospital of Joint Logistic Support Force, Department of oncology – Wuxi, China.
*Corresponding author: lvyuqin@21cn.com

Conflicts of interest: the authors declare there is no conflicts of interest. Funding: none.
Received on April 06, 2022. Accepted on June 17, 2022.

METHODS

Study design and patient screening

A total of 385 patients who were admitted to the hospital from August 1, 2017 to August 1, 2020 were recruited for this study. Elderly patients who were scheduled for THA surgery were considered eligible to be included in the trial based on the following inclusion criteria:

1. over 60 years old,
2. amenable to a random treatment of DEX or placebo 72 h postsurgery, and
3. received general anesthetization for the surgery and was admitted in the Intensive Care Unit (ICU) after surgery.

In contrast, patients were excluded from the trial if they met any of the following criteria:

1. identified as probably unsalvageable at admission,
2. diagnosed with diabetes combined with high cholesterol levels, or
3. any history of brain injury, neurosurgery, severe sinus bradycardia, neurological disease, rhabdomyolysis, myopathy, mental illness, epilepsy, severe lung disease, and multiple organ dysfunction.

Using these criteria, 58 patients were excluded, while 327 patients were randomly assigned (1:1) to either the treatment or placebo group. The treatment group was treated with 0.1 μg/kg/h DEX, while the placebo group was administered with an equal amount of normal saline solution intravenously within 72 h following THA surgery. Assessment of delirium was performed twice a day for one week using the Confusion Assessment Method (CAM). One month after surgery, a final visit was conducted as a 30-day follow-up.

Randomization and masking

All patients and investigators involved in treatment delivery, data collection, or outcome assessment were kept blinded to the randomization detail. As previously discussed, the recruited subjects were randomly assigned to either the DEX or the placebo group. The drug appearance and packages of medical envelopes were all identical, and medications were delivered by a nurse adhering to the randomization sequence. To ensure that the safety of patients was maintained, two on-call experts or pharmacists were authorized to decide whether the grouping details could be revealed in any incidence of severe adverse events or unexpected deterioration in the patient's clinical status. All situations were documented in the case report forms.

Procedures

All patients were assigned to a subgroup based on the American Society of Anesthesiologists (ASA) classification following the evaluation of their medical comorbidities. In addition, they received no premedication, along with a standard preoperative evaluation and the same general anesthesia protocol using IV midazolam (1–2 mg) and fentanyl (50–100 mg) for preoperative sedation, and 3–6 mg/kg IV fentanyl for maintaining anesthesia. Electrocardiography, noninvasive blood pressure, pulse oximetry (SpO_2), and bispectral index were monitored routinely. Radial arterial pressure and central venous pressure were monitored as necessary.

Outcome assessment

As previously mentioned, all investigators were blinded to treatment allocation and were trained before the study. Those involved in data collection and outcome assessment did not participate in the treatment procedures. The POD incidence was evaluated postsurgery as the primary endpoint, with the first examination performed almost 24 h after surgery and continued twice a day during the first week[9]. POD assessment was conducted using CAM for the detection of four main features:

1. an acute change or a fluctuation in mental status,
2. inattention,
3. disorganization in thinking, and
4. alteration in consciousness levels.

Patients displaying features 1 and 2 with either 3 or 4 were diagnosed as developing delirium[9]. In case of death or discharge within the 1-week postsurgery period, the last delirium assessment was missing[9]. The 30-day all-cause mortality, hospital costs, and length of stay, as well as the occurrence of any nondelirium postoperative complications, were defined as the secondary endpoints.

Assessment of Dexmedetomidine-related adverse events

All related adverse events were subjected to evaluation. Hypotension and bradycardia were the most frequent adverse events. Patients were informed of their conditions when necessary.

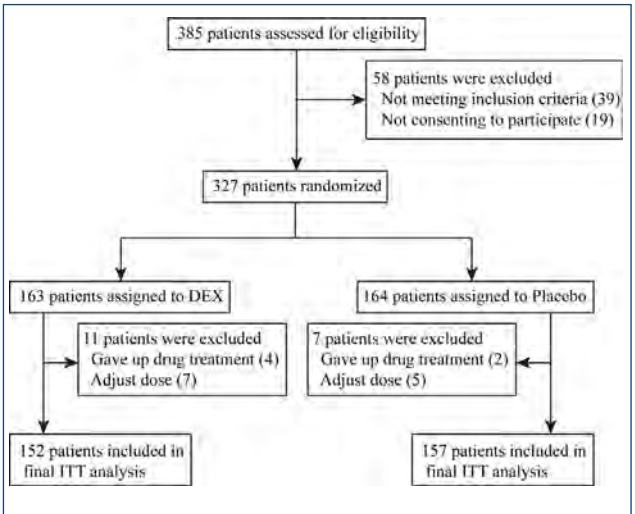
Statistical analysis

To estimate the minimum appropriate sample size to be used in this study, an assumption of a 40% rate of POD for the DEX group and a 25% rate for the placebo group was made based on our preliminary trial. With these, we estimated that a sample size of 298 patients would be required for this study (80% power and 2-sided, α=0.05, a 10% loss to follow-up),

and to account for our estimate, at least 300 patients were enrolled in our experimental design. The incidence and relative risk reduction of dichotomous variables were described for the DEX-treated group and were compared to the placebo group (95%CI). Normally distributed continuous data (mean±SD) and non-normally distributed data were analyzed using the unpaired t-test and independent-samples Mann-Whitney U test, respectively. In addition, the χ^2 test or continuity correction χ^2 test was used to compare the categorical data. Mean differences or risk ratios were calculated with two-sided 95%CI, considering a $p<0.05$ as statistically significant. Statistical analyses were conducted using the SPSS statistics software (version 18, IBM, Chicago, IL). No interim analysis was included in the assessments. Data overseeing was performed by the Clinical Research Ethics Committee from the 904th Hospital of Joint Logistic Support Force of PLA.

RESULTS

Out of the 385 initially assessed patients, 327 patients were recognized as eligible to be included in the study. The enrolled patients were randomly assigned to either the DEX (n=163) or placebo (n=164) groups (Figure 1). No patient withdrew their consent; however, four patients in the DEX group and two patients in the control group gave up the treatment. Furthermore, seven patients from the DEX group and five patients from the placebo group had to adjust their doses as shedding cases. Therefore, a total of 309 patients were ultimately included in the final intention-to-treat analysis (Figure 1), with all patients completing the 30-day follow-up.



DEX: dexmedetomidine; ITT: intention-to-treat.

Figure 1. Trial profile.

Comparison of the baseline patient characteristics between the Dexmedetomidine and placebo groups

The baseline patient characteristics of 152 DEX-treated patients and 157 placebo-treated patients were compared at the end of the intervention period. The demographics, characteristics, and postoperative medication and management of patients were similar between the two groups (Table 1).

Postoperative delirium incidence

A lower POD incidence was observed in the DEX (21 cases; 13.8% of total) group compared to that in the placebo (46 cases; 29.3% of total) group ($p<0.01$; Table 2).

Secondary endpoint parameters

A lower 30-day all-cause mortality of 3.3% (n=5 out of 152) was observed in the DEX group compared to 4.5% (n=7 out of 157) in the placebo group (p=0.60; Table 2). Meanwhile, hospitalization duration in the placebo group was significantly higher than that in the DEX group (17.2±6.3 vs. 15.6±4.2; p=0.006; Table 2). Similarly, the hospitalization costs in the placebo group were also significantly higher than that in the DEX group (4.9±1.1 vs. 4.5±0.9; p=0.001; Table 2).

Safety evaluation

The occurrence of hypotension and bradycardia were evaluated as drug-related complications. Signs of hypotension were observed in 8.3% of the placebo group and 14.5% of the DEX group, while bradycardia was observed in 5.7% of the placebo group and 10.5% of the DEX group. However, no significant difference in the occurrence of these complications was seen in both groups (Table 2). Nonetheless, a relative increase in the incidence of postoperative complications was observed in the DEX group compared to the placebo group, which requires attention to minimize the development of serious complications.

DISCUSSION

Based on our findings, DEX treatment can significantly decrease POD in elderly patients who have undergone THA surgery. Furthermore, the use of DEX can also reduce hospitalization duration and costs. However, the 30-day all-cause mortality rates were not improved by the DEX administration. There was also no significant difference in the occurrence of postoperative complications, such as hypotension and bradycardia, between the treatment and placebo groups.

The incidence of POD following a THA operation was 29.3% in the DEX group and 13.8% in the placebo group.

Table 1. Demographic and baseline characteristics of the study population in the two groups.

	Placebo (%)	DEX (%)	p-value
Number	157	152	
Age			0.50
Mean±SD	68.4±6.6	67.9±5.9	
Sex			0.88
Male	74 (47.1)	73 (48.0)	
Female	83 (52.9)	79 (52.0)	
BMI	20.14±0.89	20.25±0.92	0.29
Weight	63.4±10.9	64.8±11.3	0.27
Type 2 DM			0.56
Yes	23 (14.6)	26 (17.1)	
No	134 (85.4)	126 (82.9)	
History of hypertension			0.75
Yes	51 (32.5)	52 (34.2)	
No	106 (67.5)	100 (65.8)	
Smoking history			0.23
Yes	41 (26.1)	31 (20.4)	
No	116 (73.9)	121 (79.6)	
Duration of operation (min)	2.3±0.4	2.3±0.3	0.45
Blood transfusion			0.40
Yes	12 (7.6)	8 (5.3)	
No	145 (92.4)	144 (94.7.0)	
Bleeding (mL)	435±108	382±93	0.07
ICU stays (day)	2.2±1.4	2.2±1.5	0.96
Intraoperative medication			>0.05
Midazolam	81 (51.6)	77 (50.7)	
Fentanyl	157 (100)	152 (100)	
Propofol	157 (100)	152 (100)	
Atropine	22 (14.0)	18 (11.8)	
Analgesic (within 7 days)			>0.05
Diclofenac sodium	55 (35.0)	49 (32.2)	
Diclofenac sodium dose (mg)	284±92	229±113	
Morphine	40 (25.5)	34 (22.4)	
Morphine dose (mg)	24.4±5.8	23.12±9.4	
Midazolam	13 (8.3)	9 (5.9)	
Midazolam (mg)	37.3±9.5	36.1±8.2	

DEX: dexmedetomidine; Mean±SD: Mean±Standart Deviation; BMI: Body mass index; DM: diabetes.

These results are consistent with the findings of previous studies[4,11]. In one study, an overall POD incidence of 44% was observed in 144 patients undergoing major abdominal, thoracic, and vascular operations with an average onset time of 2.1±0.9 days and a mean duration of 4.0±5.1 days[12]. Another recent study has shown that delirium in elderly patients undergoing major thoracic and abdominal surgeries decreased by one-third upon using a combined epidural and general anesthesia procedure[13]. Similarly, our findings indicated that POD increases hospitalization duration and costs, which emphasizes efficient medications as the major therapy. In relation to this, treatment with haloperidol or ziprasidone did not elicit any significant change in the POD duration in ICU patients with acute respiratory failure or shock, as well as in the presence of hypoactive or hyperactive delirium in these patients[14]. Another similar trial showed that treatment with simvastatin did not reduce the incidence nor the duration of delirium in treated patients[15]. Hence, it is necessary to explore new drugs that can be beneficial for ameliorating delirium.

Delirium is a multifactorial disorder that can be induced or aggravated by many factors, such as the use of sedatives or hypnotic drugs, sleep deprivation, brain trauma, and coma[1]. The pathophysiologic underlying mechanisms of delirium are extremely complicated and can include systemic neuroinflammation and micro-thrombosis processes, oxidative stress and endothelial damage, various neurotransmitters, cerebral hypoperfusion, and an injured blood-brain barrier[1,16]. Previous studies have reported elevated expression levels of C-reactive protein, interleukins (IL) 1, 6, 8, and 10, as well as tumor necrosis

Table 2. The results between two groups.

	Placebo (%)	DEX (%)	p-value
Number	157	152	
POD	21 (13.8)	46 (29.3)	<0.01
All-cause 30-day mortality	5 (3.3)	7 (4.5)	0.60
Hospitalization duration	17.2±6.3	15.6±4.2	0.006
Hospitalization costs	4.5±0.9	4.9±1.1	0.001
Hypotension			0.086
Yes	13 (8.3)	52 (14.5)	
No	144 (91.7)	100 (85.5)	
Bradycardia			0.122
Yes	9 (5.7)	16 (10.5)	
No	148 (94.3)	136 (89.5)	

DEX: dexmedetomidine; POD: postoperative delirium.

factor-alpha (TNF-α) in patients developing delirium during acute medical hospitalizations[17]. Interestingly, DEX treatment has been shown to significantly increase the neurological score and suppress the expression of other factors such as IL-1β, IL-6, and TNF-α in patients, which suggests that DEX can alleviate neuroinflammation[18].

DEX is frequently used as an adjuvant in general anesthesia because of its potency and specific affinity to α-2-adrenergic receptors. It also serves as a sedation agent against delirium for ICU patients receiving mechanical ventilation[9,19]. It has been shown that the effects of DEX on POD were dose-dependent, as low doses could significantly decrease POD with no enhancement in the risk of adverse events[9,20]. We also observed that a low dose of DEX was safe and did not aggravate drug-related complications, such as hypotension and bradycardia. Consistent with our findings, previous studies have reported that intraoperative DEX treatment can reduce the delirium risk in elderly patients following a major noncardiac surgery[21]. To our knowledge, no evidence-based medical investigation has been done to determine the effectiveness of DEX in THA patients. This is the first large-sample randomized, double-blind, placebo-controlled trial that explored the effectiveness of low-dose DEX in elderly patients who received THA. Because of the limitations in the availability of treatment options for established delirium, risk assessment and perioperative risk reduction have been suggested to be the most effective approaches to managing POD[22,23].

CONCLUSION

Postoperative DEX administration has the potential to reduce the incidence of POD in elderly patients who have undergone THA. Furthermore, although we have not observed any benefit of the DEX treatment in reducing the 30-day all-cause mortality rate, our analyses showed that it can decrease the length of ICU stay and hospital costs for patients. Moving forward, we recommend that a larger population of elderly patients who have undergone THA surgery should be investigated using a variety of DEX doses to achieve a more comprehensive understanding of its potential for preventing POD.

AUTHORS' CONTRIBUTIONS

YL: Conceptualization, Data curation, Formal analysis, Writing – original draft, Writing – review & editing. **LG:** Data curation, Writing – original draft .

REFERENCES

1. Chen J, Wang Y, Hu X, Li M, Xiong K, Zhang Z, et al. The role of statins in the management of delirium: recent advances. CNS Neurol Disord Drug Targets. 2021;20(3):203-15. https://doi.org/10.2174/1871527319666200720111318
2. Inouye SK, Westendorp RG, Saczynski JS. Delirium in elderly people. Lancet. 2014;383(9920):911-22. https://doi.org/10.1016/S0140-6736(13)60688-1
3. Girard TD, Jackson JC, Pandharipande PP, Pun BT, Thompson JL, Shintani AK, et al. Delirium as a predictor of long-term cognitive impairment in survivors of critical illness. Crit Care Med. 2010;38(7):1513-20. https://doi.org/10.1097/CCM.0b013e3181e47be1
4. Redelmeier DA, Manzoor F, Thiruchelvam D. Association Between Statin Use and Risk of Dementia After a Concussion. JAMA Neurol. 2019;76(8):887-96. https://doi.org/10.1001/jamaneurol.2019.1148
5. Sloan M, Premkumar A, Sheth NP. Projected Volume of Primary Total Joint Arthroplasty in the U.S., 2014 to 2030. J Bone Joint Surg Am. 2018;100(17):1455-60. https://doi.org/10.2106/JBJS.17.01617
6. He R, Wang F, Shen H, Zeng Y, Lijuan Zhang. Association between increased neutrophil-to-lymphocyte ratio and postoperative delirium in elderly patients with total hip arthroplasty for hip fracture. BMC Psychiatry. 2020;20(1):496. https://doi.org/10.1186/s12888-020-02908-2
7. Yang T, Feng X, Zhao Y, Zhang H, Cui H, Wei M, et al. Dexmedetomidine enhances autophagy via α2-AR/AMPK/mTOR pathway to inhibit the activation of nlrp3 inflammasome and subsequently alleviates lipopolysaccharide-induced acute kidney injury. Front Pharmacol. 2020;11:790. https://doi.org/10.3389/fphar.2020.00790
8. Li H, Lu C, Yao W, Xu L, Zhou J, Zheng B. Dexmedetomidine inhibits inflammatory response and autophagy through the circLrp1b/miR-27a-3p/Dram2 pathway in a rat model of traumatic brain injury. Aging (Albany NY). 2020;12(21):21687-705. https://doi.org/10.18632/aging.103975
9. Su X, Meng ZT, Wu XH, Cui F, Li HL, Wang DX, et al. Dexmedetomidine for prevention of delirium in elderly patients after non-cardiac surgery: a randomised, double-blind, placebo-controlled trial. Lancet. 2016;388(10054):1893-902. https://doi.org/10.1016/S0140-6736(16)30580-3
10. Riker RR, Shehabi Y, Bokesch PM, Ceraso D, Wisemandle W, Koura F, et al. Dexmedetomidine vs midazolam for sedation of critically ill patients: a randomized trial. JAMA. 2009;301(5):489-99. https://doi.org/10.1001/jama.2009.56
11. O'Gara BP, Mueller A, Gasangwa DVI, Patxot M, Shaefi S, Khabbaz K, et al. Prevention of Early Postoperative Decline: A Randomized, Controlled Feasibility Trial of Perioperative Cognitive Training. Anesth Analg. 2020;130(3):586-95. https://doi.org/10.1213/ANE.0000000000004469
12. Robinson TN, Raeburn CD, Tran ZV, Angles EM, Brenner LA, Moss M. Postoperative delirium in the elderly: risk factors and outcomes. Ann Surg. 2009;249(1):173-8. https://doi.org/10.1097/SLA.0b013e31818e4776
13. Li YW, Li HJ, Li HJ, Zhao BJ, Guo XY, Feng Y, et al. Delirium in Older Patients after Combined Epidural-General Anesthesia or General Anesthesia for Major Surgery: A Randomized Trial. Anesthesiology. 2021;135(2):218-32. https://doi.org/10.1097/ALN.0000000000003834
14. Girard TD, Exline MC, Carson SS, Hough CL, Rock P, Gong MN, et al. Haloperidol and Ziprasidone for Treatment of Delirium in

Critical Illness. N Engl J Med. 2018;379(26):2506-16. https://doi.org/10.1056/NEJMoa1808217

15. Page VJ, Casarin A, Ely EW, Zhao XB, McDowell C, Murphy L, et al. Evaluation of early administration of simvastatin in the prevention and treatment of delirium in critically ill patients undergoing mechanical ventilation (MoDUS): a randomised, double-blind, placebo-controlled trial. Lancet Respir Med. 2017;5(9):727-37. https://doi.org/10.1016/S2213-2600(17)30234-5
16. Alam A, Hana Z, Jin Z, Suen KC, Ma D. Surgery, neuroinflammation and cognitive impairment. EBioMedicine. 2018;37:547-56. https://doi.org/10.1016/j.ebiom.2018.10.021
17. Maldonado JR. Neuropathogenesis of delirium: review of current etiologic theories and common pathways. Am J Geriatr Psychiatry. 2013;21(12):1190-222. https://doi.org/10.1016/j.jagp.2013.09.005
18. Feng X, Ma W, Zhu J, Jiao W, Wang Y. Dexmedetomidine alleviates early brain injury following traumatic brain injury by inhibiting autophagy and neuroinflammation through the ROS/Nrf2 signaling pathway. Mol Med Rep. 2021;24(3):661. https://doi.org/10.3892/mmr.2021.12300
19. Alexopoulou C, Kondili E, Diamantaki E, Psarologakis C, Kokkini S, Bolaki M, et al. Effects of dexmedetomidine on sleep quality in critically ill patients: a pilot study. Anesthesiology. 2014;121(4):801-7. https://doi.org/10.1097/ALN.0000000000000361
20. Maldonado JR, Wysong A, van der Starre PJ, Block T, Miller C, Reitz BA. Dexmedetomidine and the reduction of postoperative delirium after cardiac surgery. Psychosomatics. 2009;50(3):206-17. https://doi.org/10.1176/appi.psy.50.3.206
21. Li CJ, Wang BJ, Mu DL, Hu J, Guo C, Li XY, et al. Randomized clinical trial of intraoperative dexmedetomidine to prevent delirium in the elderly undergoing major non-cardiac surgery. Br J Surg. 2020;107(2):e123-32. https://doi.org/10.1002/bjs.11354
22. Alam A, Ma D. Is it time to Assess Neurological Status Before Surgery to Improve Postoperative Outcomes? Ann Surg. 2022;275(4):644-5. https://doi.org/10.1097/sla.0000000000005287
23. Jin Z, Hu J, Ma D. Postoperative delirium: perioperative assessment, risk reduction, and management. Br J Anaesth. 2020;125(4):492-504. https://doi.org/10.1016/j.bja.2020.06.063

ORIGINAL ARTICLE

https://doi.org/10.1590/1806-9282.20211092

Behavioural intention of hand hygiene compliance in an average Ecuadorian hospital

Pía Escudero[1*], Mireia Urrea Ayala[2,3], Natalia Romero[1,3], Cintia Pullas[1], Domenica Reina[1], Edison Daniel Miranda Brazales[1], María José Ayora Pérez[1], Ignacio Peñaherrera Suárez[1], Emily Granadillo[1,3], Miguel Martín[2,4]

SUMMARY

OBJECTIVE: This study aimed to characterize hand hygiene behavioural intention by hospital services clusters in a medium-sized hospital in an Ecuadorian city.

METHODS: This is a cross-sectional study based on the World Health Organization Hand Hygiene Knowledge Questionnaire for Health-Care Workers. The responses on hand hygiene behavioural intention for the Five Moments for hand hygiene according to the World Health Organization were recorded in three categories: before patient contact, before and after sterile technique and management of body fluids, and after contact with the environment of the patient. The variables were the knowledge regarding the source of germs causing nosocomial infections, the optimal time to achieve disinfection with alcohol, hospital services clusters (clinical medicine, surgery, and therapeutic services), and history of previous formal hand hygiene training. The variables in each moment were analysed using a saturated log-linear model.

RESULTS: The average age of participants was 34 years (Q_1 32.1–Q_3 36.4). Of them, 62% belonged to the clinic cluster and 87.6% had previous formal hand hygiene training. The incorrect response rates for before and after sterile technique and management of body fluids, before patient contact, and after contact with the environment of the patient were 30.2, 88.4, and 99.2%, respectively. In before patient contact, the incorrect responses for optimal time depended on the department (worse surgery cluster situation), and in before and after sterile technique and management of body fluids and after contact with the environment of the patient, the incorrect responses for source of germs depended on the previous formal hand hygiene training and the department (worse surgery and clinic clusters).

CONCLUSION: The incorrect answer related to hand hygiene behavioural intention was high compared to other reports, and the worse situation was found in after contact with the environment of the patient and before patient contact. These data suggest the need of strengthening permanently the hand hygiene programme.

KEYWORDS: Hand hygiene. Hospital medicine. Health education.

INTRODUCTION

In 1846, Ignaz Semmelweis demonstrated that the hands of health personnel transmitted puerperal fever[1], and 150 years later (2009), the World Health Organization (WHO) published the "Guidelines on Hand Hygiene in Health Care." The WHO defines hand hygiene (HH) as any standard adopted for a hand cleaning procedure that applies hand scrubbing with an alcoholic base or handwashing with soap and water to eliminate or decrease germ colonization on hands and contribute to achieving a correct HH[2].

Healthcare personnel should perform HH in "Five Moments" according to the WHO multimodal strategy in patient-centred settings[3-5]. Although the implementation of strategy was successful worldwide and across all categories of health workers, hospitals, wards, and hospital departments, it is advisable to adapt the strategy to local resources, maintain training, and evaluate compliance[6].

Lack of HH leads to an increased risk of healthcare-related infections, disability and mortality in patients, and high expense for the healthcare system[7-9]. Knowledge of the source of germs that cause nosocomial infections and the time required for an alcoholic disinfectant to act constitute two of the essential factors for achieving optimal HH; however, healthcare personnel have observed a significant gap between knowledge and practice of this technique[10].

[1]International University of Ecuador, School of Medicine – Quito, Ecuador.
[2]Hospital Sant Joan de Déu Barcelona 2020 – Barcelona, Spain.
[3]The Network Grups de Recerca d'Amèrica i Àfrica Llatines – Barcelona, Spain.
[4]Universitat Autònoma de Barcelona, Facultat de Medicina, Unitat de Bioestadística – Barcelona, Spain.
*Corresponding author: piescuderobu@uide.edu.ec

Conflicts of interest: the authors declare there is no conflicts of interest. Funding: Universidad Internacional del Ecuador (UIDE-DGIP-MAT-PROY-17-033).
Received on February 24, 2022. Accepted on June 02, 2022.

In contrast, several questionnaires have been applied to measure hand hygiene behavioural intention (HHBI). The WHO Hand Hygiene Knowledge Questionnaires for Health-Care Workers (WHO-Q), revised in 2009, is previously validated and published in a Spanish version; correct answers were provided by WHO and the questionnaire items and domains are administered independently[11]. This questionnaire is used in cross-sectional studies, clinical trials, and results comparison. Another advantage is that it allows for unit, services, or ward analysis of a hospital.

In Ecuador, there are no data on the rate of HHBI by hospital services. With this background, we set out to characterize the HHBI compliance considering services clusters of a medium-sized hospital in a sizeable Ecuadorian city to better understand inappropriate HHBI and generate strategies to improve it.

METHODS

Context

The participating hospital has a level 2 complexity. It offers 81 beds, various medical specialties services, and outpatient consultation. For this study, we organized the services into three clusters: clinical medicine cluster (paediatric and internal medicine department, outpatient clinics, emergency department, and an intermediate care unit with 7 beds), surgery cluster (five operating theatres and gynaecology and obstetrics ward), and therapeutic services cluster (physiotherapy and respiratory therapy). The hospital has hand-rub dispensers according to the WHO standards.

Participants

Resident doctors, nurses, nursing assistants, therapists, and cleaning staff with a full-time contract in the hospital at least 3 months before the study, and final-year medical students with a stay of not less than 3 months participated. Each of the participants worked in a specific hospital service in the 3 months before the survey. Of the 96 health workers, all comply with rotating shift work. Although shift work time was a maximum of 8 h for nurses, assistants, and therapeutic services department personnel, it was not possible to confirm if any participant was working a double shift at the time of the survey. For resident doctors and students, it was a maximum of 24 h. In addition, the 33 visiting medical specialists who do not have fixed hours were included. Of the 131 participants, 129 completed the questionnaire.

Variables

We used the following WHO-Q questions: the identification of the source of the germs causing infections (SG) in two categories: germs in the hospital environment (correct response) and germs in the water or the patients; to point out that 20 s is the optimal time needed for an alcoholic disinfectant to eliminate most hand germs (OT), the fact of having received HH training at some point in their professional career (pT), and three services clusters (clinical medicine, surgery, and support). The survey was applied by three trained interviewers, keeping confidentiality and privacy and in the break time of the participants' working hours. The application took approximately 20 min. The data were collected from 4 May to 30 June 2019.

Response variables

Hand hygiene behavioural intention was defined for each moment of HH in three categories, and the basis was the WHO-Q available in Spanish. Table 1 presents the questions

Table 1. General characteristics of the 129 participants.

Variable	n (%)
Cluster	
Clinical medicine	80 (62.0)
Surgery	41 (31.8)
Therapeutic services	8 (6.2)
Did you ever receive hand hygiene training during professional practice?	
Yes	113 (87.6)
No	16 (12.4)
Source of germs causing nosocomial infections	
Germs in the hospital environment	30 (23.3)
Germs from hospital water or present in the patient	99 (76.7)
Minimum time required for an alcoholic disinfectant to remove most germs from the hands	
20 s	86 (66.7)
Other than 20 s	43 (33.3)
BPC	
Complies	15 (11.6)
Fails	114 (88.4)
BAMF	
Complies	90 (69.8)
Fails	39 (30.2)
ACEP	
Complies	1 (0.8)
Fails	128 (99.2)

BPC: before patient contact; BAMF: before and after antiseptic technique and management of body fluids; ACEP: after contact and environment of the patient.

that feed each of these three moments: "before patient contact" (BPC), "before and after antiseptic technique and management of body fluids" (BAMF), and "after contact with the environment of the patient" (ACEP). The questions that were considered for the construction of the category "compliance of HH activities" in each moment were defined using the nominal group technique[12]. Based on the results of four rounds of the questionnaire sent to a panel of three experts, the identified responses were aggregated and shared with the experts after each round. The experts could adjust their answers in three subsequent rounds, based on how they interpret the compliance with HH activities in each moment.

Pilot study

A pilot study was carried out in the last week of April 2019 to ensure understanding of the questions, apply the nominal group technique, and record the questionnaire application time. On average, participants' time was 20 min per survey (SD 5).

Statistical analysis

Differences in proportions between study factors and incorrect responses of the HH methods in each moment were analysed with the χ^2 statistic. Due to all the variables' categorical nature and to analyse the interdependence between them, a multivariable descriptive analysis was carried out using a saturated log-linear model of the multidimensional table formed by all the variables considered for each moment. In the use of a single adjustment, the relationships between the variables were analysed, between two variables, as well as the orders of three dimensions (interactions) and higher orders. A p-value of 0.05 was considered the cut-off point for statistical significance.

Ethics statement

All necessary permits were obtained from a Bioethics Committee of the International University of Ecuador and the hospital authorities (UIDE-DGIP-MAT-PROY-17-033).

RESULTS

Descriptive analysis

The average age of the participants was 34 years (Q1 32.1-Q3 36.4). Notably, 62% belonged to the clinic cluster. pT was recorded in 114 (87.6%) participants, of which 99 (79.7%) did not have a correct knowledge of SG. Table 2 presents the general characteristics of the study variables.

Description of the moments and associated variables

In the BPC moment, 114 (88.4%) participants gave incorrect answers, while in BAMF, they were 39 (30.2%), and in ACEP, they were 128 (99.2%). The lowest incorrect response rates (12.5–39.5%) were found in BAMF compared to those of the other two moments (81.3–99.2%). Table 3 presents the factors related to non-compliance with the HH procedure in each study setting.

Table 4 shows the results of the saturated log-linear model between non-compliance with the HH procedure in each moment and the variables. In BPC and ACEP, the knowledge of SG depends on the pT (χ^2 4.69, p-value 0.03; χ^2 4.71, p-value 0.03, respectively), adjusted for other factors, and in BAMF, it depends on the department (χ^2 4.47, p-value 0.04) and pT (χ^2 6.40, p-value 0.04).

DISCUSSION

From our literature review, this is one of the first works focusing on the analysis of HHBI in services considered as clusters and not in health professionals themselves[13-15]. The work at a hospital is assured when it is proposed to do so as a team, which leads to effective and efficient practices that offer the best possible patient care[16]. In this context, we found high rates of unawareness of HHBI in the services clusters (clinic, surgery, and therapeutic services). This lack of knowledge was equally high for the BPC and ACEP moments (81.3–99.2%, in both) and improvement for the BAMF moment (12.5–39.5%). The literature has not described ranges of HH unawareness before and after patient contact as high as that found in this study, suggesting the need to evaluate the strategy and reinforce on-going training of health care staff.

Studies outside Latin America that have analysed health professionals' command of WHO-Q knowledge have also shown worrying data. A study carried out in 105 healthcare providers from private clinics in Pakistan revealed high rates of inadequate knowledge of the standard guidelines for HH[17]. Studies that analysed all dimensions of WHO-Q in hospitals in the Republic of Korea and Iran showed different levels of knowledge overall, and all had serious weaknesses in knowledge[14,18]. In a university hospital in Cairo, the assessment in different departments showed that the highest mean score was in the neonatal intensive care unit paediatric department[19]. In 2136, tests provided by Spanish nurses during their accreditation processes in 5 years, those with the highest accreditation level had the highest average number of correct answers[18].

Table 2. Factors related to non-compliance with the hand hygiene procedure in each studied environment.

Environment	Study factor	n (%)*	χ^2	p-value
BPC (n=114)	Cluster		2.71	0.26
	Clinical medicine	68 (85.0)		
	Surgery	39 (95.1)		
	Therapeutic services	7 (87.5)		
	Received training		0.90	0.34
	Yes	101 (89.4)		
	No	13 (81.3)		
	Germ source		0.10	0.75
	Hospital environment	27 (90.0)		
	Water and patient	87 (87.9)		
	Disinfecting time		1.36	0.24
	20 s	78 (90.7)		
	Other than 20 s	36 (83.7)		
BAMF (n=39)	Cluster		2.98	0.23
	Clinical medicine	22 (27.5)		
	Surgery	16 (39.0)		
	Therapeutic services	1 (12.5)		
	Received training		0.46	
	Yes	33 (29.2)		
	No	6 (37.5)		
	Germ source		0.24	0.63
	Hospital environment	8 (26.7)		
	Water and patient	31 (31.3)		
	Disinfecting time		2.65	0.10
	20 s	22 (25.6)		
	Other than 20 s	17 (39.5)		
ACEP (n=128)	Cluster		0.62	0.73
	Clinical medicine	79 (98.8)		
	Surgery	41 (100.0)		
	Therapeutic services	8 (100.0)		
	Received training		0.14	0.71
	Yes	112 (99.1)		
	No	16 (100.0)		
	Germ source		0.31	0.58
	Hospital environment	30 (100.0)		
	Water and patient	98 (99.0)		
	Disinfecting time		2.02	0.16
	20 s	86 (100.0)		
	Other than 20 s	42 (97.7)		

BPC: before patient contact; BAMF: before and after antiseptic technique and management of body fluids; ACEP: after contact and environment of the patient.
*All the percentages express the total of the category.

Table 3. Results of the saturated log-linear model between non-compliance with the hand hygiene procedure in each moment and the study factors.

Environment	Interactions	χ^2	p-value
BPC	Incorrect answers for the moment × Disinfecting time × Cluster	6.10	0.05
	Germ source × Cluster	5.65	0.06
	Germ source × Received training	4.69	0.03
	Disinfectant time × Cluster	0.27	0.88
	Incorrect answers for the environment × Disinfecting time	2.34	0.13
	Incorrect answers for the environment × Cluster	1.47	0.48
BAMF	Germ source × Cluster	6.40	0.04
	Germ source × Received training	4.47	0.04
ACEP	Germ source × Received training	4.71	0.03

BPC: before patient contact; BAMF before and after antiseptic technique and management of body fluids; ACEP after contact and environment of the patient.

The scope of the unawareness also includes healthcare students in training. A high percentage of medical and nursing students in Spanish universities reported always or almost always not carrying out HH at BPC or BAMF[20]. A study in 69 nursing students in Nigeria revealed that HHBI was lowest in the 1st year of study[21]. A study carried out in 2018 showed that 15.2% of healthcare personnel in Islamabad private clinics had inadequate knowledge about the OT[17], and Soon's study showed serious weaknesses in knowledge of the question "What is the most frequent SG?"[14]. In our study, we also found that the analysis of the associations between the variables revealed the participants' lack of knowledge about the analysed indicators of HH knowledge, despite claiming to have received training.

The correct performance of the HH is an individual and collective responsibility[22]. It is important to emphasize that knowledge about the SG, the OT, and the technique to be used for HH, by itself, does not guarantee the adherence and effectiveness of HH in health personnel in the different hospital areas[23], but the application of an HH educational plan, based on a standardized multimodal HH strategy, proved to be effective in improving HH compliance[24].

Finally, in this study, we recognize the following limitations. (1) This study did not include the evaluation of patients' knowledge, an aspect that, according to Srigley et al. is essential for an overview of HH knowledge and educational interventions[25]. (2) It was not possible to confirm if the work shift influenced the knowledge of the activities to ensure HH. (3) This study concentrated on the characterization of HHBI in the three defined moments at the hospital departments (as clusters); the analysis focused on participants or professions could vary the results. (4) We did not have the authorization to analyse by individuals. (5) We did not consider the role of each participant (i.e., senior, junior, and student).

CONCLUSIONS

The general proportion of incorrect answers about HHBI among hospital services clusters in a medium-sized hospital in a sizeable Ecuadorian city is high. The worst situation is in the BPC and ACEP moments. The results highlight areas for improvement and the need to reinforce the WHO multimodal strategy in patient-centred settings.

ACKNOWLEDGMENTS

This research was supported by International University of Ecuador Research grant 2017.

AUTHORS' CONTRIBUTIONS

PE: Conceptualization, Funding acquisition, Methodology, Project administration, Visualization, Writing – original draft, Writing – review & editing. **MU:** Conceptualization, Methodology, Writing – review & editing. **NR-S:** Conceptualization, Formal Analysis, Funding acquisition, Methodology, Writing – original draft. **CP:** Data curation, Formal Analysis, Writing – original draft. **MM:** Data curation, Formal Analysis, Methodology. **DR:** Writing – original draft. **EG:** Writing – original draft.

REFERENCES

1. Miranda CM, Navarrete TL. Semmelweis y su aporte científico a la medicina: un lavado de manos salva vidas. Rev Chil Infectol. 2008;25(1):54-7. PMID: 18273526
2. WHO. WHO guidelines on hand hygiene in health care: first global patient safety challenge: clean care is safer care. Geneva: World Health Organization, Patient Safety; 2009.
3. Martínez LL, Leyva AMG, Pérez MR, Fernández KC, Pupo LL. Efectividad de Intervención educativa en el conocimiento del personal de salud sobre el lavado de manos. Rev Cuba Enferm. 2020;36(1):1-13. Available from: http://www.revenfermeria.sld.cu/index.php/enf/article/view/1684
4. Løyland B, Peveri AM, Hessevaagbakke E, Taasen I, Lindeflaten K. Students' observations of hand hygiene in nursing homes using the five moments of hand hygiene. J Clin Nurs. 2020;29(5-6):821-30. https://doi.org/10.1111/jocn.15136
5. Ye L, Zhang X, Lai X. Does hospital ownership influence hand hygiene compliance? Curr Med Sci. 2017;37(5):787-94. https://doi.org/10.1007/s11596-017-1806-9
6. Vermeil T, Peters A, Kilpatrick C, Pires D, Allegranzi B, Pittet D. Hand hygiene in hospitals: anatomy of a revolution. J Hosp Infect. 2019;101(4):383-92. https://doi.org/10.1016/j.jhin.2018.09.003
7. Allegranzi B, Bagheri Nejad S, Combescure C, Graafmans W, Attar H, Donaldson L, et al. Burden of endemic health-care-associated infection in developing countries: systematic review and meta-analysis. Lancet. 2011;377(9761):228-41. https://doi.org/10.1016/S0140-6736(10)61458-4
8. Loftus MJ, Guitart C, Tartari E, Stewardson AJ, Amer F, Bellissimo-Rodrigues F, et al. Hand hygiene in low- and middle-income countries. Int J Infect Dis. 2019;86:25-30. https://doi.org/10.1016/j.ijid.2019.06.002
9. Allegranzi B, Gayet-Ageron A, Damani N, Bengaly L, McLaws M-L, Moro M-L, et al. Global implementation of WHO's multimodal strategy for improvement of hand hygiene: a quasi-experimental study. Lancet Infect Dis. 2013;13(10):843-51. https://doi.org/10.1016/S1473-3099(13)70163-4
10. Ahmed J, Malik F, Memon ZA, Bin Arif T, Ali A, Nasim S, et al. Compliance and knowledge of healthcare workers regarding hand hygiene and use of disinfectants: a study based in Karachi. Cureus. 2020;12(2):e7036. https://doi.org/10.7759/cureus.7036
11. World Health Organization. Hand hygiene knowledge questionnaire for health-care workers. WHO; 2017. Available from: https://cdn.who.int/media/docs/default-source/integrated-health-services-(ihs)/hand-hygiene/monitoring/surveyform/hand-hygiene-knowledge-questionnaire.doc?sfvrsn=dbb4da65_2
12. Dekker M, Caris MG, Van Gunsteren AM, Van Mansfeld R, Lucas C, Vandenbroucke-Grauls CMJE. Effectiveness of a behavioral approach to improve healthcare worker compliance with hospital dress code. Infect Control Hosp Epidemiol. 2017;38(12):1435-40. https://doi.org/10.1017/ice.2017.233
13. Cambil-Martin J, Fernandez-Prada M, Gonzalez-Cabrera J, Rodriguez-Lopez C, Almaraz-Gomez A, Lana-Perez A, et al. Comparison of knowledge, attitudes and hand hygiene behavioral intention in medical and nursing students. J Prev Med Hyg. 2020;61(1):E9-14. https://doi.org/10.15167/2421-4248/jpmh2020.61.1.741
14. Oh HS. Knowledge, perceptions, and self-reported performance of hand hygiene among registered nurses at community-based hospitals in the Republic of Korea: a cross-sectional multi-center study. J Prev Med Pub Health. 2018;51(3):121-9. https://doi.org/10.3961/jpmph.17.188
15. Fernandez Sierra MA, Rodriguez del Aguila MdM, Navarro Espigares JL, Enriquez Maroto MF. Effect of patient safety strategies on the incidence of adverse events. J Eval Clin Pract. 2014;20(2):184-90. https://doi.org/10.1111/jep.12105
16. Vazquez CE. Successful work cultures: recommendations for leaders in healthcare. Leadersh Health Serv Bradf Engl. 2019;32(2):296-308. https://doi.org/10.1108/LHS-08-2018-0038
17. Bangash S, ul Haq MI, Hassan U, Rahim SK, Qadeer AA. Assessment of hand hygiene knowledge and practices among the health care providers working at private clinics in Islamabad, Pakistan. Rawal Med J. 2019;44(4): 856-60. Available from: https://www.researchgate.net/publication/337719585_Assessment_of_hand_hygiene_knowledge_and_practices_among_the_Health_care_providers_working_at_private_clinics_in_Islamabad
18. Nabavi M, Alavi-Moghaddam M, Gachkar L, Moeinian M. Knowledge, attitudes, and practices study on hand hygiene among Imam Hossein Hospital's residents in 2013. Iran Red Crescent Med J. 2015;17(10):e19606. https://doi.org/10.5812/ircmj.19606
19. Elsheikh RM, El-Belbasy RM. Assessment of knowledge, attitude and practice of hand washing among healthcare workers in Al-Azhar University hospitals in Cairo. Life Sci J. 2018;15(2). Available from: http://www.lifesciencesite.com/lsj/life150218/07_33346lsj150218_53_60.pdf
20. Brea Rivero P, Rojas de Mora Figueroa A, Julián Carrión J, Salguero Cabalgante R, Herrera Usagre M. Buenas prácticas en higiene de manos de las enfermeras que han acreditado su competencia profesional. Metas Enferm. 2017;20(3):20-8. https://doi.org/10.35667/MetasEnf.2019.20.1003081048
21. Oyapero A, Oyapero O. An assessment of hand hygiene perception and practices among undergraduate nursing students in Lagos State: a pilot study. J Educ Health Promot. 2018;7:150. https://doi.org/10.4103/jehp.jehp_56_17
22. Beyamo A, Dodicho T, Facha W. Compliance with standard precaution practices and associated factors among health care workers in Dawuro Zone, South West Ethiopia, cross sectional study. BMC Health Serv Res. 2019;19(1):381. https://doi.org/10.1186/s12913-019-4172-4
23. Lotfinejad N, Peters A, Tartari E, Fankhauser-Rodriguez C, Pires D, Pittet D. Hand hygiene in health care: 20 years of ongoing advances and perspectives. Lancet Infect Dis. 2021;21(8):e209-21. https://doi.org/10.1016/S1473-3099(21)00383-2
24. Saad AE, Al-Natig A-WT, Sadek MM, Afifi RM. A quasi experiment to implement multimodal strategy to improve hand hygiene behavior in a healthcare facility in central Saudi Arabia. Adv Infect Dis. 2019;9(1):49. https://doi.org/10.4236/aid.2019.91005
25. Srigley JA, Cho SM, O'Neill C, Bialachowski A, Ali RA, Lee C, et al. Hand hygiene knowledge, attitudes, and practices among hospital inpatients: a descriptive study. Am J Infect Control. 2019;48(5):507-10. https://doi.org/10.1016/j.ajic.2019.11.020

ORIGINAL ARTICLE

https://doi.org/10.1590/1806-9282.20220069

Importance of epicardial adipose tissue as a predictor of heart failure with preserved ejection fraction

Kenan Ateş[1], Muhammed Demir[2*]

SUMMARY

OBJECTIVE: Epicardial adipose tissue is a special form of visceral fat surrounding the heart. It is associated with cardiac and metabolic diseases. Epicardial adipose tissue is associated with risk factors for heart failure with preserved ejection fraction, such as obesity, metabolic syndrome, hypertension, and diabetes. In this study, we examined the importance of Epicardial adipose tissue as a predictor of heart failure with preserved ejection fraction.

METHODS: Patients who were admitted to the Dicle University Medicine Faculty Heart Hospital between November 2013 and August 2014 were recruited for the study. The heart failure group consisted of 30 patients who were admitted to the cardiac intensive care unit, and the control group consisted of 30 patients who were admitted to cardiology polyclinics. We care about patients' demographic and clinical features to be similar. Heart failure was diagnosed according to the European Cardiology Society 2012 heart failure guidelines. Epicardial adipose tissue was measured with a transthoracic parasternal long axis with an echocardiography device (GE Vivid S6). We compared the Epicardial adipose tissue measurements between the two groups.

RESULTS: Epicardial adipose tissue was higher in patients with heart failure with preserved ejection fraction than in the control group (9.21±0.82 and 7.13±1.39 mm, respectively; p<0.001). Echocardiographic findings associated with left ventricular hypertrophy were intact ventricular septum (13.03±0.57 and 12.11±2.22 mm, respectively; p=0.013) and left ventricular mass index (131.13±18.00 and 117.90±20.30 g/m^2, respectively; p=0.010). Findings associated with left ventricular diastolic dysfunction were as follows: left atrial volume index (60.71±21.53 and 44.92±9.93 mL/m^2, respectively; p<0.001) and E/è (13.87±3.88 and 10.12±2.44, respectively; p<0.001) were higher in patients with heart failure with preserved ejection fraction than in the control group. Body mass index was not a significant indicator of obesity (p=0.097), but waist circumference was a significant indicator of visceral obesity (p<0.001). Logistic regression analyses indicated that Epicardial adipose tissue, age, left atrial volume index, left ventricular mass index, waist circumference, and E/é were significant in the Heart failure group; Epicardial adipose tissue was significant (p=0.012), and waist circumference significance was borderline (p=0.045).

CONCLUSIONS: Epicardial adipose tissue was higher in patients with HF than in the control group, and Epicardial adipose tissue was a predictor of heart failure with preserved ejection fraction. In patients with heart failure with preserved ejection fraction, increased Epicardial adipose tissue means that Epicardial adipose tissue can be used as a biomarker of inflammation in the pathophysiology of heart failure with preserved ejection fraction.

KEYWORDS: Adipose tissue. Diastolic heart failure. Comorbidities. Obesity. Inflammation.

INTRODUCTION

Heart failure is a common disease. It is seen in approximately 1–2% of the adult population in developed countries, and this rate rises to 10% in individuals aged 70 and over. Heart failure with preserved ejection fraction (HFpEF) constitutes approximately half of these cases[1,2]. HFpEF is associated with significant morbidity and mortality, and, so far, no treatment has been clearly demonstrated to improve the outcomes of HFpEF (in contrast to the efficacy of treatment for heart failure with reduced ejection fraction [HFrEF])[3]. In recent years, many studies have been performed with the goal of reducing the morbidity and mortality associated with HFpEF. The EMPEROR-Preserved trial[4] is a popular study on this subject. In that study, empagliflozin reduced the combined risk of cardiovascular death and hospitalization for heart failure in patients with HFpEF, regardless of the presence or absence of diabetes. In addition, another study evaluated the efficacy of spironolactone treatment for HFpEF. Treatment with spironolactone did not significantly reduce the incidence of the primary composite outcome of death from cardiovascular causes, aborted cardiac arrest, and hospitalization in patients with HFpEF[5].

Epicardial adipose tissue (EAT) is a special form of visceral adipose tissue stored around the heart. EAT has been shown to be associated with cardiac diseases and metabolic diseases[6]. The relationships between EAT and obesity, metabolic syndrome,

[1]Baglar Private Hospital, Department of Cardiology – Diyarbakir, Turkey.
[2]Dicle University, School of Medicine, Department of Cardiology – Diyarbakir, Turkey.
*Corresponding author: drmdemirr@gmail.com.
Conflicts of interest: the authors declare there is no conflicts of interest. Funding: none.
Received on March 20, 2022. Accepted on June 12, 2022.

diabetes, hypertension, coronary artery disease, and atherosclerosis have been the subjects of many studies[6-8].

As EAT is associated with obesity, metabolic syndrome, diabetes, and hypertension, which constitute risk factors for HFpEF, this study was conducted to investigate the importance of EAT in the early diagnosis and treatment of HFpEF.

METHODS

Study population

The study included a total of 60 patients who required outpatient follow-up due to mild symptoms and signs of heart failure or who required coronary intensive care unit hospitalization due to severe symptoms and signs of heart failure between November 2013 and August 2014. Patients who declined to participate or whose information could not be obtained were excluded from the study. Patients with severe valvular disease, HFrEF, chronic lung diseases, anemia, chronic liver disease, chronic renal failure, malignancy, a history of severe trauma before a month, or a history of surgery were also excluded.

The patients included in the study were examined according to the 2012 heart failure guidelines of the European Society of Cardiology (9). Routine tests, such as hemogram and biochemistry, as well as N-terminal pro-brain natriuretic peptide (NT-proBNP), electrocardiography (ECG), and echocardiography tests, were performed to diagnose HFpEF. Approval for this study was obtained from the University Ethics Committee (approval date: 05/08/2014; number: 313). Information about the study was provided both orally and in written form to the patients or their trustees. All patients were informed about the study in accordance with the ethical principles of human research, as reported in the second Helsinki Declaration, and their written informed consent was obtained.

Definitions and laboratory parameters

The following demographic and clinical data were recorded for all patients: age; gender; body mass index (BMI) (kg/m^2); waist circumference (cm); smoking status; dietary approaches to stop hypertension; known hypertension treated with antihypertensive drugs, or two times blood pressure measurement above 140/90 mmHg; diabetes mellitus (known diabetes treated with diet or medication, or fasting serum glucose level above 126 mg/dL); heart valve diseases (natural or prosthetic valve diseases, including mild-moderate stenosis and/or regurgitation); history of ischemic heart disease (history of myocardial infarction, percutaneous coronary intervention, coronary artery bypass surgery, or diagnosis of coronary artery disease by invasive or noninvasive tests); atrial fibrillation (AF); and history of previous ischemic stroke or transient ischemic attack.

Blood samples were taken from all patients, and the following analyses were performed: hemogram; WBC (white blood cell), HGB (hemoglobin), HCT (hematocrit), PLT (platelet), biochemical parameters; fasting blood sugar, urea, creatinine, ALT (alanine aminotransferase), AST (aspartate aminotransferase), and lipid profile; total cholesterol, LDL (low-density lipoprotein), HDL (high-density lipoprotein), triglyceride, and NT-proBNP were studied. In addition, GFR (glomerular filtration rate) was calculated with the Cockroft-Gault formula.

Electrocardiography and echocardiography

The 12-lead ECG recordings were taken with a 12-channel ECG device at a speed of 25 mm/s and a calibration of 10 mm/mV. According to the European Society of Echocardiography[9], transthoracic echocardiographic evaluation was performed using a standard two-dimensional and M-mode recording echocardiography device (Vivid S6 General Electric Vingmed ultrasound Horten, Norway) using a 2.5–3.25 MHz transducer. Left ventricular ejection fraction (LVEF>50%), left ventricular mass index (LVMI over 95 g/m^2 in women, 115 g/m^2 in men), left ventricular end-diastolic volume index (LVEDVI>97 mL/m^2), left atrial volume index (LAVI>34 mL/m^2), diastolic dysfunction grades (stages 1, 2, 3, and 4), diastolic parameters (E, A, Dt, and E/é), and tricuspid annular systolic excursion (TAPSE) as an indicator of right ventricular systolic function, systolic pulmonary arterial pressure and interventricular septum (IVS), left ventricular systolic and diastolic diameters, left atrium diameter, and right ventricle and right atrium diameter were evaluated. EAT was measured above the free wall of the right ventricle from the parasternal long axis view in the left lateral position by echocardiography (Figure 1A).

Statistical analysis

Data were analyzed using the SPSS for Windows version 25.0 (Armonk, NY: IBM Corp.). The Kolmogorov-Smirnov test was used to confirm the normality of the distribution of continuous variables. Continuous variables were defined as mean±standard deviation or median (interquartile range); categorical variables were given as percentages. Parametric continuous variables were compared using the Student's t-test, and nonparametric continuous variables were compared using the Mann-Whitney U test. Chi-square test and Fisher's exact test were used to compare categorical variables. Univariate and multivariate logistic regression was performed to examine the association between EAT and HFpEF after adjusting for all confounders. The variables resulting from the univariate analysis with a p-value <0.05

were entered as covariates in the multivariate regression model. The level of significance was interpreted using the "p"-value. A p-value of <0.05 was considered significant.

RESULTS

A total of 60 patients were included in our study; 30 of them were HFpEF patients and 30 were in the control group. The mean age of the individuals was 71.60±6.70 years in the heart failure group and 63.70±9.02 years in the control group (p<0.001). In all, 54 (90%) of the participants were female, and 6 (10%) were male. Clinical characteristics, medications, and demographic data of both groups are shown in Table 1. The age, waist circumference, New York Heart Association (NYHA) class, AF incidence, use of diuretics, beta blockers, and statins were significantly higher in the HFpEF group compared to the control group (Table 1). The antiaggregants, anticoagulants, digoxin, and spironolactone were not compared between groups due to not being applicable in the control group (Table 1).

The echocardiographic findings of the patients are shown in Table 1. Left atrial diameter, IVS thickness, LVMI, LAVI, E/é, and systolic pulmonary arterial pressure (SPAP) were found to be statistically significantly higher in the heart failure group than in the control group, but the ejection fraction was found to be lower (Table 1).

Laboratory parameters such as HGB, NT-proBNP, GFR, and creatinine were statistically different between the two groups. There was no difference in other parameters. While NT-proBNP was found to be higher in the HF group, HGB, creatine, and GFR were found to be lower (Table 1).

In the multivariate regression analysis, EAT was an independent predictor of HFpEF (OR 3.890; 95%CI 1.345–11.252; p=0.012), together with waist circumference (OR 1.117; 95%CI 1.002–1.245; p=0.045, Table 2). At a cutoff value of 8.1 mm, the EAT thickness predicted HFpEF with a sensitivity of 86% and a specificity of 80% (Figure 1B).

DISCUSSION

In this study, we examined the relationship between EAT and HFpEF. There are two main findings in this study. First, EAT was significantly higher in the HFpEF group. Second, parameters leading to HFpEF by causing left ventricular concentric remodeling – IVS and LVMI – were found to be increased in the HF group, and parameters associated with diastolic dysfunction – LA diameter, LAVI, E/é, and AF – were also found to be increased in the HF group. Furthermore, EAT was an independent predictor of HFpEF together with waist circumference.

Heart failure is a common disease and is seen in approximately 1–2% of the adult population in developed countries, and this rate increases up to 10% in individuals aged 70 and over. HFpEF constitutes approximately half of these patients[1]. In studies conducted so far, no treatment has been proved to reduce mortality due to HFpEF. Therefore, it is more important to predict HFpEF.

Structural and functional changes associated with LV concentric remodeling and LV diastolic dysfunction are the basic pathophysiological mechanisms in HFpEF[10,11]. Comorbid diseases and especially obesity produce a systemic pro-inflammatory state. Inflammation causes coronary microvascular

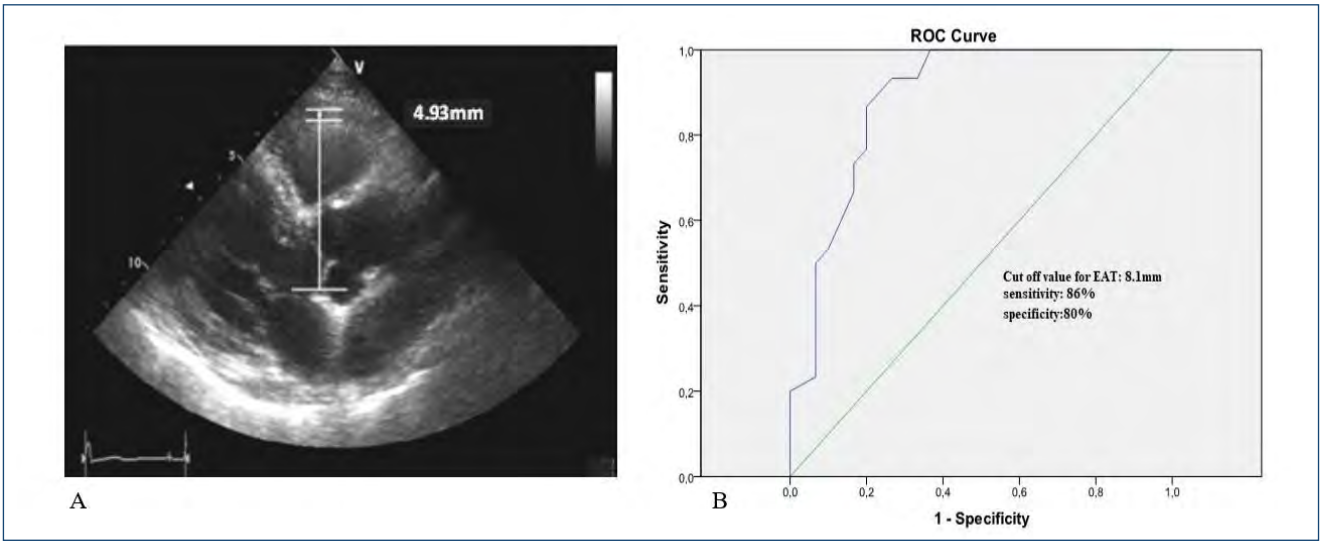


Figure 1. (A) Measurement of epicardial adipose tissue from the anterior wall of the right ventricle in the parasternal long axis by transthoracic echocardiography. (B) Receiver operating characteristic of Epicardial adipose tissue to determine sensitivity and specificity.

Table 1. Demographic, clinical characteristics, laboratory findings, and echocardiography parameters of patients

Demographic and clinical characteristics		Heart failure N=30	Control N=30	p-value
Age mean (year)		71.60±6.70	63.70±9.02	**<0.001**
Sex	Female (%)	26 (87)	28 (93)	0.335
	Male (%)	4 (13)	2 (7)	
BMI (kg/m^2)		32.79±4.72	30.86±4.01	0.097
Waist circumference (cm)		103.33±8.95	93.06±10.2	**<0.001**
Smoking (%)		3 (10)	4 (13)	0.5
Diet (%)		8 (27)	14 (47)	0.090
NYHA	Class 1 (%)	0	27 (90)	**<0.001**
	Class 2 (%)	2 (6)	3 (10)	
	Class 3 (%)	14 (47)	0	
	Class 4 (%)	14 (47)	0	
Ischemic heart disease (%)		18 (60)	8 (27)	**0.009**
Hypertension (%)		28 (93)	30 (100)	0.246
Diabetes mellitus (%)		13 (43)	10 (33)	0.298
Stroke (%)		1 (3)	4 (13)	0.161
Atrial fibrillation (%)		10 (33)	3 (10)	**0.028**
Diuretics		27 (90)	16 (53)	**0.002**
ACE/ARB		25 (83)	20 (67)	0.136
Beta Blockers		22 (73)	12 (40)	**0.009**
CCB		9 (30)	5 (17)	0.222
Statins		11 (37)	4 (13)	**0.037**
Antiaggregants		21 (70)	10 (33)	**0.004**
Anticoagulants		6 (20)	0	**N/A**
Digoxin		5 (17)	0	**N/A**
Spironolactone		4 (13)	0	**N/A**
Laboratory findings of patients				
White blood cell count (×10^3 µl)		8.11±2.49	10.95±3.053	0.362
Hemoglobin (g/dL)		11.21±1.16	12.81±0.95	**<0.001**
Platelets (×10^3 µL)		248±82.91	268±101.06	0.420
NT-proBNP (pg/dL)		542.26±361.33	74.93±19.35	**<0.001**
GFR (ml/min/1.73 m^2)		61.12±24.68	76.30±22.32	**0.015**
Creatine (mg/dL)		1.20±0.55	0.91±0.43	**0.028**
ALT (U/L)		24.13±30.22	17.56±5.85	0.247
AST (U/L)		24.43±11.57	22.90±8.86	0.567
Total cholesterol (mg/dL)		177.10±57.56	198.26±44.02	0.115
LDL (mg/dL)		132.37±105.52	116.03±38.21	0.429
HDL (mg/dL)		43.83±40.76	45.43±29.37	0.862
Triglyceride (mg/dL)		159.80±90.48	167.50±68.31	0.711

Continue...

Table 1. Continuation.

Demographic and clinical characteristics	Heart failure N=30	Control N=30	p-value
Echocardiography parameters of patients			
LVEF (%)	58.73±4.11	60.96±3.70	**0.031**
EAT (mm)	9.21±0.82	7.13±1.39	**<0.001**
LA (mm)	40.30±10.92	35.57±6.50	**0.047**
IVS (mm)	13.03±0.57	12.11±2.22	**0.013**
LVMI (g/m^2)	131.13±18.00	117.90±20.30	**0.010**
LVEDVI (mL/m^2)	44.39±10.42	40.20±6.24	0.064
LAVI (mL/m^2)	60.71±21.53	44.92±9.93	**<0.001**
E/é	13.87±3.88	10.12±2.44	**<0.001**
Diastolic dysfunction Stage 1 (%)	11 (58)	19 (70)	0.531
Stage 2 (%)	8 (42)	8 (30)	
TAPSE (cm)	2.71±3.30	2.74±0.37	0.961
SPAP (mmHg)	32.66±6.67	26.20±3.75	**<0.001**

Data are expressed as mean±standard deviation (SD) or frequencies (percentages) as appropriate. BMI: body mass index; NYHA: New York Heart Association; ACE/ARB: angiotensin converting enzyme inhibitors/angiotensin receptor blockers; CCB: calcium channel blockers; NT-proBNP: n-terminal pro-brain natriuretic peptide; GFR: glomerular filtration rate; ALT: alanine aminotransferase; AST: aspartate aminotransferase; LDL: low-density lipoprotein; HDL: high-density lipoprotein; LVEF: left ventricular ejection fraction; EAT: epicardial adipose tissue; LA: left atrium; IVS: interventricular septum; LVMI: left ventricular mass index (LVMI over 95 g/m^2 in women, 115 g/m^2 in men); LVEDVI: left ventricular end-diastolic volume index; LAVI: left atrial volume index (LAVI>34 mL/m^2); TAPSE: tricuspid annular systolic excursion; SPAP: systolic pulmonary arterial pressure. The statistically significant p-values has shown with bold characters.

Table 2. Univariate and multivariable logistic regression analysis to determine independent predictors of Heart failure with preserved ejection fraction.

	Univariate			Multivariate		
	OR	95%CI	p-value	OR	95%CI	p-value
Age	1.127	1.048–1.213	**0.001**	1.082	0.970–1.207	0.157
EAT	4.523	2.148–9.523	**<0.001**	3.890	1.345–11.252	**0.012**
LVMI	1.038	1.007–1.070	**0.016**	0.993	0.944–1.046	0.799
Waist circumference	1.118	1.047–1.195	**0.001**	1.117	1.002–1.245	**0.045**
LAVI	1.089	1.030–1.151	**0.003**	1.033	0.943–1.131	0.488
E/é	1.450	1.180–1.782	**<0.001**	1.132	0.895–1.431	0.302

EAT: epicardial adipose tissue; LVMI: left ventricular mass index; LAVI: left atrial volume index; OR: odds ratio; CI: confidence interval. The statistically significant p-values has shown with bold characters.

endothelial cells to produce free oxygen radicals and reduces the bioavailability of nitric oxide (NO) in cardiomyocytes. Protein kinase G (PKG) activity in cardiomyocytes is reduced due to damaged NO bioavailability. Decreased PKG activity causes hypophosphorylation of the giant cytoskeletal protein titin and triggers LV concentric remodeling and cardiomyocyte stiffness. Cardiomyocyte stiffness and collagen deposition by myofibroblasts cause diastolic dysfunction, which is the main functional impairment in HFpEF. Ather et al.[12] found the prevalence of comorbid diseases that cause systemic inflammatory status to be higher in the HFrEF group than in the HFpEF group.

In visceral obesity, macrophages infiltrate the adipose tissue, release pro-inflammatory cytokines, and cause a systemic inflammatory state[13]. Jelic et al.[14] found that obstructive sleep apnea disease and obesity cause endothelial dysfunction, inflammation, and oxidative stress. Similarly, the relationship between obesity and HFpEF was investigated in the I-PRESERVE study, and more clinical adverse outcomes were found in patients with

a high BMI[15]. Kalogeropoulos et al.[16] investigated the relationship between heart failure and inflammation in elderly patients and concluded that systemic inflammatory conditions caused by comorbid diseases may be a predictor of HFpEF.

The fact that obesity causes a systemic inflammatory condition and there is a reciprocal relationship between obesity and HFpEF makes obesity an important issue to be investigated in patients with HFpEF. Obesity is also part of metabolic syndrome. BMI is used as an objective indicator of obesity. Metabolic syndrome, which is seen as a risk factor for cardiovascular diseases, is associated with visceral obesity. Abdominal fat is a part of visceral obesity and is determined by measuring waist circumference. Therefore, waist circumference is one of the diagnostic criteria for metabolic syndrome, and increased waist circumference is a risk factor for cardiovascular diseases. EAT forms another part of visceral obesity and can be measured using various imaging methods.

In studies on EAT, Corradi et al.[17] found a relationship between the amount of epicardial fat and ventricular mass. Iacobellis et al.[18] found a positive correlation between the amount of epicardial fat and ventricular myocardial mass. These two studies also support that obesity causes a systemic inflammatory state and causes LV concentric remodeling as a result of a series of pathophysiological mechanisms[19]. Mohammed et al.[20] found that comorbid diseases cause more myocardial structure and dysfunction than arterial hypertension.

Marchington et al.[21,22] could not find a relationship between EAT and the total amount of adipose tissue in other fat stores of the body in various animals. This finding is in line with echocardiographic, magnetic resonance imaging, and autopsy findings in humans, suggesting that the amount of epicardial fat is related to the amount of visceral fat rather than the amount of total fat[17,22-26].

Considering that BMI is used as an obesity indicator and waist circumference is used for visceral obesity, in our study, BMI did not cause a significant difference between the two groups, and the waist circumference was significantly increased in the HF group, which was consistent with the literature[22,23].

As with any study, certain design limitations are inherent. First, this was a single-center study and had a relatively small sample size. Second, heart function was assessed only by using transthoracic echocardiography. Other imaging methods such as cardiac computed tomography, 3D echocardiography, and heart catheterization that can quantitatively show EAT, left atrial functions, and filling pressures were not used. Finally, the study consisted predominantly of female population, so further studies with an equally distributed gender population are needed.

CONCLUSIONS

We found increased EAT in the heart failure group and determined EAT as a predictor for HFpEF. The EAT could be used as an easy and practical inflammatory indicator to identify HFpEF patients. Further multi-center and larger-scale investigations are warranted for clinical assessment of HFpEF.

AUTHORS' CONTRIBUTIONS

KA: Conceptualization, Data curation, Formal Analysis, Writing – original draft. **MD:** Conceptualization, Data curation, Formal Analysis, Writing – original draft.

REFERENCES

1. Dickstein K, Cohen-Solal A, Filippatos G, McMurray JJ, Ponikowski P, Poole-Wilson PA, et al. ESC guidelines for the diagnosis and treatment of acute and chronic heart failure 2008: the Task Force for the diagnosis and treatment of acute and chronic heart failure 2008 of the European Society of Cardiology. Developed in collaboration with the Heart Failure Association of the ESC (HFA) and endorsed by the European Society of Intensive Care Medicine (ESICM). Eur J Heart Fail. 2008;10(10):933-89. https://doi.org/10.1016/j.ejheart.2008.08.005
2. Mosterd A, Hoes AW. Clinical epidemiology of heart failure. Heart. 2007;93(9):1137-46. https://doi.org/10.1136/hrt.2003.025270
3. Iliescu AM, Hodorogea AS. Treatment of Heart Failure with Preserved Ejection Fraction. Adv Exp Med Biol. 2018;1067:67-87. https://doi.org/10.1007/5584_2018_149
4. Anker SD, Butler J, Filippatos G, Ferreira JP, Bocchi E, Böhm M, et al. Empagliflozin in Heart Failure with a Preserved Ejection Fraction. N Engl J Med. 2021;385(16):1451-61. https://doi.org/10.1056/NEJMoa2107038
5. Pitt B, Pfeffer MA, Assmann SF, Boineau R, Anand IS, Claggett B, et al. Spironolactone for heart failure with preserved ejection fraction. N Engl J Med. 2014;370(15):1383-92. https://doi.org/10.1056/NEJMoa1313731
6. Le Jemtel TH, Samson R, Ayinapudi K, Singh T, Oparil S. Epicardial adipose tissue and cardiovascular disease. Curr Hypertens Rep. 2019;21(5):36. https://doi.org/10.1007/s11906-019-0939-6
7. Iacobellis G, Sharma AM. Epicardial adipose tissue as new cardiometabolic risk marker and potential therapeutic target in the metabolic syndrome. Curr Pharm Des. 2007;13(21):2180-4. https://doi.org/10.2174/138161207781039670
8. Patel VB, Shah S, Verma S, Oudit GY. Epicardial adipose tissue as a metabolic transducer: role in heart failure and coronary artery disease. Heart Fail Rev. 2017;22(6):889-902. https://doi.org/10.1007/s10741-017-9644-1
9. McMurray JJ, Adamopoulos S, Anker SD, Auricchio A, Böhm M, Dickstein K, et al. ESC Guidelines for the diagnosis and treatment of acute and chronic heart failure 2012: the task force for the diagnosis and treatment of acute and chronic heart failure 2012

of the European Society of Cardiology. Developed in collaboration with the Heart Failure Association (HFA) of the ESC. Eur Heart J. 2012;33(14):1787-847. https://doi.org/10.1093/eurheartj/ehs104

10. Zile MR, Gottdiener JS, Hetzel SJ, McMurray JJ, Komajda M, McKelvie R, et al. Prevalence and significance of alterations in cardiac structure and function in patients with heart failure and a preserved ejection fraction. Circulation. 2011;124(23):2491-501. https://doi.org/10.1161/CIRCULATIONAHA.110.011031
11. Zile MR, Baicu CF, Gaasch WH. Diastolic heart failure--abnormalities in active relaxation and passive stiffness of the left ventricle. N Engl J Med. 2004;350(19):1953-9. https://doi.org/10.1056/NEJMoa032566
12. Ather S, Chan W, Bozkurt B, Aguilar D, Ramasubbu K, Zachariah AA, et al. Impact of noncardiac comorbidities on morbidity and mortality in a predominantly male population with heart failure and preserved versus reduced ejection fraction. J Am Coll Cardiol. 2012;59(11):998-1005. https://doi.org/10.1016/j.jacc.2011.11.040
13. Taube A, Schlich R, Sell H, Eckardt K, Eckel J. Inflammation and metabolic dysfunction: links to cardiovascular diseases. Am J Physiol Heart Circ Physiol. 2012;302(11):H2148-65. https://doi.org/10.1152/ajpheart.00907.2011
14. Jelic S, Lederer DJ, Adams T, Padeletti M, Colombo PC, Factor PH, et al. Vascular inflammation in obesity and sleep apnea. Circulation. 2010;121(8):1014-21. https://doi.org/10.1161/CIRCULATIONAHA.109.900357
15. Haass M, Kitzman DW, Anand IS, Miller A, Zile MR, Massie BM, et al. Body mass index and adverse cardiovascular outcomes in heart failure patients with preserved ejection fraction: results from the Irbesartan in Heart Failure with Preserved Ejection Fraction (I-PRESERVE) trial. Circ Heart Fail. 2011;4(3):324-31. https://doi.org/10.1161/CIRCHEARTFAILURE.110.959890
16. Kalogeropoulos A, Georgiopoulou V, Psaty BM, Rodondi N, Smith AL, Harrison DG, et al. Inflammatory markers and incident heart failure risk in older adults: the ,health ABC (Health, Aging, and Body Composition) study. J Am Coll Cardiol. 2010;55(19):2129-37. https://doi.org/10.1016/j.jacc.2009.12.045
17. Corradi D, Maestri R, Callegari S, Pastori P, Goldoni M, Luong TV, et al. The ventricular epicardial fat is related to the myocardial mass in normal, ischemic and hypertrophic hearts. Cardiovasc Pathol. 2004;13(6):313-6. https://doi.org/10.1016/j.carpath.2004.08.005
18. Iacobellis G, Ribaudo MC, Zappaterreno A, Iannucci CV, Leonetti F. Relation between epicardial adipose tissue and left ventricular mass. Am J Cardiol. 2004;94(8):1084-7. https://doi.org/10.1016/j.amjcard.2004.06.075
19. Paulus WJ, Tschöpe C. A novel paradigm for heart failure with preserved ejection fraction: comorbidities drive myocardial dysfunction and remodeling through coronary microvascular endothelial inflammation. J Am Coll Cardiol. 2013;62(4):263-71. https://doi.org/10.1016/j.jacc.2013.02.092
20. Mohammed SF, Borlaug BA, Roger VL, Mirzoyev SA, Rodeheffer RJ, Chirinos JA, et al. Comorbidity and ventricular and vascular structure and function in heart failure with preserved ejection fraction: a community-based study. Circ Heart Fail. 2012;5(6):710-9. https://doi.org/10.1161/CIRCHEARTFAILURE.112.968594
21. Marchington JM, Pond CM. Site-specific properties of pericardial and epicardial adipose tissue: the effects of insulin and high-fat feeding on lipogenesis and the incorporation of fatty acids in vitro. Int J Obes. 1990;14(12):1013-22. PMID: 2086494
22. Iacobellis G, Assael F, Ribaudo MC, Zappaterreno A, Alessi G, Di Mario U, et al. Epicardial fat from echocardiography: a new method for visceral adipose tissue prediction. Obes Res. 2003;11(2):304-10. https://doi.org/10.1038/oby.2003.45
23. Iacobellis G, Ribaudo MC, Assael F, Vecci E, Tiberti C, Zappaterreno A, et al. Echocardiographic epicardial adipose tissue is related to anthropometric and clinical parameters of metabolic syndrome: a new indicator of cardiovascular risk. J Clin Endocrinol Metab. 2003;88(11):5163-8. https://doi.org/10.1210/jc.2003-030698
24. Iacobellis G, Leonetti F, Di Mario U. Images in cardiology: massive epicardial adipose tissue indicating severe visceral obesity. Clin Cardiol. 2003;26(5):237. https://doi.org/10.1002/clc.4960260508
25. Sironi AM, Gastaldelli A, Mari A, Ciociaro D, Positano V, Buzzigoli E, et al. Visceral fat in hypertension: influence on insulin resistance and beta-cell function. Hypertension. 2004;44(2):127-33. https://doi.org/10.1161/01.HYP.0000137982.10191.0a
26. Olivetti G, Giordano G, Corradi D, Melissari M, Lagrasta C, Gambert SR, et al. Gender differences and aging: effects on the human heart. J Am Coll Cardiol. 1995;26(4):1068-79. https://doi.org/10.1016/0735-1097(95)00282-8

ORIGINAL ARTICLE

https://doi.org/10.1590/1806-9282.20220140

The importance of inflammatory parameters in predicting deep sternal wound infections after open heart surgery

Kemal Parla[1], Ahmet Burak Tatli[2*], Arda Aybars Pala[2], Mehmet Tugrul Goncu[2]

SUMMARY

OBJECTIVE: The aim of this study was to investigate the relationship between the development of deep sternal wound infection after open heart surgery and inflammatory parameters obtained from routine biochemical tests.

METHODS: A total of 280 patients who underwent cardiac surgery with median sternotomy between January 2015 and January 2020 were examined retrospectively. Patients who developed deep sternal wound infection were identified as "Group 1," and those who did not develop deep sternal wound infection were identified as "Group 2."

RESULTS: There were 70 patients with a mean age of 61.6±9.9 years in Group 1 and 210 patients with a mean age of 62.7±9.8 years in Group 2. As a result of the analysis, it was found that the presence of concomitant chronic obstructive pulmonary disease, concomitant diabetes mellitus, blood and blood product transfusion, postoperative 2nd day C-reactive protein, postoperative 1st day neutrophil-to-lymphocyte ratio, and delta neutrophil-to-lymphocyte ratio was found as independent predictive factors of postoperative deep sternal wound infection development (p=0.043, p=0.012, p=0.029, p=0.009, p=0.002, and p<0.001; respectively). As a predictor of deep sternal wound infections development, postoperative 1st day neutrophil-to-lymphocyte ratio cutoff value was 11.2 (area under the curve [AUC] 0.598; p=0.014; 60% sensitivity, and 65.2% specificity), and delta neutrophil-to-lymphocyte ratio cutoff value was 9.6 (AUC 0.716; p<0.001; 57.1% sensitivity, and 73.8% specificity).

CONCLUSIONS: Deep sternal wound infection development can be predicted with inflammatory parameters such as neutrophil-to-lymphocyte ratio and C-reactive protein that are obtained from cheap and easily available routine biochemical tests.

KEYWORDS: Cardiac surgery. C-reactive protein. Inflammation. Sternum. Postoperative wound infections.

INTRODUCTION

One of the significant unwanted complications after open heart surgery is sternum wound infections. This infection is basically divided into two — deep and superficial infections. In superficial infections, the skin and subcutaneous soft tissues are involved, and the muscle and bone structures are involved in deep sternal wound infections (DSWI). Hospitalization is longer and the treatment costs are increasing in both cases[1-3]. Thanks to the early detection of postoperative sternal wound site infections with clinical and laboratory data, it is of vital importance to apply preventive treatments, proper antibiotherapy, and early surgical treatments[4].

The inflammatory response that occurs as the natural defense mechanism of the body against surgical processes is an important factor in postoperative morbidity and mortality. The preoperative inflammatory status of the patient also affects the inflammatory response to surgery and thus postoperative results[5,6]. The aim of this study was to investigate whether inflammatory parameters obtained from routine biochemical tests are predictors for the development of DSWI, which is one of the complications that increase morbidity and morbidity after open heart surgery.

METHODS

Study design and patient selection

The patients who underwent cardiac surgery by the same surgical team between January 2015 and January 2020 at the University of Health Sciences, Bursa Yuksek Ihtisas Training and Research Hospital, and Cardiovascular Surgery Clinic were scanned retrospectively. A total of 280 patients who underwent elective cardiac surgery with cardiopulmonary bypass (CPB) and median sternotomy were included in our study. The local ethics committee approval was obtained (approval number: 2011-KAEK-25 2020/05-01).

In our study, the patients we considered as DSWI consisted of patients in whom the wound infection passed through the skin and subcutaneous tissues and the muscles in the sternal region were involved or the infection spread to the mediastinum,

[1]University of Health Sciences, Van Training and Research Hospital, Department of Cardiovascular Surgery – Van, Turkey.
[2]University of Health Sciences, Bursa Yuksek Ihtisas Training and Research Hospital, Department of Cardiovascular Surgery – Bursa, Turkey.
*Corresponding author: ahmetburaktatli@gmail.com
Conflicts of interest: the authors declare there is no conflicts of interest. Funding: none.
Received on March 29, 2022. Accepted on June 12, 2022.

and 70 patients were included in the study as "Group 1." For the control group, among the patients who did not develop DSWI, 210 patients were randomly selected in the computer environment according to the protocol numbers using the random number table by looking at the data in the similar literature (to show the significant difference with 80% power and 5% Type-1 error) and included in the study as "Group 2." Patients with a history of emergency surgery or cardiac surgery, who were not in the age range between 18 and 80, who had only superficial sternum wound site infection, who had undergone off-pump surgery, chronic inflammatory disease, hematological disease, or who received steroid treatment were excluded from the study.

Laboratory measurements

Blood samples were obtained from the peripheral venous structures of all patients. Complete blood count and biochemical measurements were made with automatic analyzers (Coulter LH780, USA, and Coulter AU5800, USA). The preoperative, postoperative 1st day (Po1), and postoperative 2nd day (Po2) neutrophil-to-lymphocyte ratio (NLR) values were calculated. Delta NLR values were calculated by subtracting the preoperative NLR value from the highest NLR value of Po1 and Po2.

Preoperative preparation and postoperative follow-up

All the body shaves were made with a shaving machine one day before the surgery and bathed with chlorhexidine solutions. In the perioperative process, the skin of patients was stained with 10% polyvinylpyrrolidone iodine (Batticon^{R}). Perioperative surgical prophylaxis was initiated with 1–2 g of IV cefazolin. On the first 2 postoperative days, 1–2 g of IV cefazolin was applied at 6-h intervals. Unless the specialist for infection diseases had any additional recommendations, cefazolin prophylaxis was discontinued on the Po2. The surgical wound dressing was performed using 10% polyvinylpyrrolidone iodine (Batticon^{R}), and if there were no other conditions, wound sites were left open on the Po2 and later.

Statistical method

SPSS 21.0 was used for the analysis of the data. Mean and standard deviation values were calculated using descriptive methods for continuous and ordinal data. The Shapiro-Wilk test was used for the normality distribution. The Student's t-test was used for data showing normal distribution, and the Mann-Whitney U test was used for data that did not meet the normal distribution. Frequency and percentage analyses were performed for nominal data. After comparing the data, the chi-Square test was used. A multivariate logistics regression analysis was conducted to analyze predictors of postoperative DSWI development (in univariate analysis, variables with a p-value below 0.100 were included). A p-value below 0.05 was deemed statistically significant. The receiver operating characteristic (ROC) analysis was performed for Po1-NLR and delta NLR values to predict DSWI development.

RESULTS

A total of 280 patients were included in this study. Group 1 had 70 patients with a mean age of 61.6±9.9 years, and there were 210 patients in Group 2 with a mean age of 62.7±9.8 years. In the evaluation of the preoperative characteristics of the groups, the number of patients with diabetes mellitus (DM), chronic obstructive pulmonary disease (COPD), and body mass index >30 kg/m^2 were significantly higher in Group 1 ($p<0.001$, $p=0.021$, and $p=0.039$, respectively) (Table 1).

When the laboratory parameters were compared, the preoperative NLR value was found to be significantly higher in Group 1 ($p=0.044$). While the neutrophil, CRP, and NLR values in Po1 were significantly higher in Group 1 ($p=0.014$, $p=0.021$, and $p<0.001$, respectively), lymphocyte values were significantly lower ($p=0.005$). NLR and CRP values in Po2 were found to be significantly higher in Group 1 ($p=0.003$ and $p<0.001$, respectively). During this period, lymphocyte values were significantly lower in Group 1 ($p=0.014$). The delta NLR value was found to be significantly higher in Group 1 ($p<0.001$) (Table 2).

The comparison of perioperative and postoperative characteristics of the patient groups is presented in Table 1. Blood and blood product transfusion amount, mechanical ventilation need for more than 48 h, and hospitalization times were significantly higher in Group 1 ($p=0.005$, $p=0.017$, and $p<0.001$, respectively).

Multivariate logistic regression analysis was performed to predict postoperative DSWI development (Table 3). In the analysis performed, COPD, DM, blood and blood product transfusion, Po2-CRP, Po1-NLR, and delta NLR were identified as independent predictors of postoperative DSWI development ($p=0.043$, $p=0.012$, $p=0.029$, $p=0.009$, $p=0.002$, and $p<0.001$, respectively). In the ROC analysis, the cutoff value for Po1-NLR was found to be 11.2 (AUC 0.598, 95%CI 0.518–0.687; $p=0.014$, 60% sensitivity, and 65.2% specificity), and the cutoff value for delta NLR was 9.6 (AUC 0.716; 95%CI 0.648–0.784; $p<0.001$; 57.1% sensitivity, and 73.8% specificity).

Table 1. Demographic, preoperative, perioperative, and postoperative clinical characteristics of the patients.

Preoperative variables	Group 1 (n=70)	Group 2 (n=210)	p-value
	n mean±SD/median (IQR) (%)	n mean±SD/median (IQR) (%)	
Age (years)	61.6 9.9	62.7±9.8	0.294[b]
Gender (female)	17 (24.3)	68 (32.3)	0.260[a]
Hypertension	39 (55.7)	126 (60)	0.528[a]
Hyperlipidemia	20 (28.5)	68 (32.3)	0.671[a]
COPD	20 (28.5)	28 (13.3)	0.021[a]
Diabetes mellitus	32 (45.7)	41 (19.5)	<0.001[a]
Smoking	35 (50)	85 (40.4)	0.163[a]
BMI (>30 kg/m^2)	24 (34.2)	42 (20)	0.039[a]
Ejection fraction (%)	51.5±9.8	50±10.1	0.407[b]
EuroSCORE II	1.9 (0.5–5.4)	1.5 (0.5–4.9)	0.214[c]
Perioperative and postoperative variables			
CPB time (min)	83 (36–126)	78 (44–158)	0.318[c]
CABG	44 (62.8)	138 (65.7)	0.497[a]
AVR or MVR or MRA or AVR+MVR	6 (8.5)	24 (11.4)	0.503[a]
Combined surgery	20 (28.5)	48 (22.8)	0.747[a]
Blood and blood product transfusion (unit)	7 (5–18)	5 (4–9)	0.005[c]
Inotropic support	20 (28.5)	38 (18)	0.071[a]
Prolonged mechanical ventilation (>48 h)	19 (27.1)	29 (13.8)	0.017[a]
Length of hospital stay (day)	18 (15–78)	7 (6–21)	<0.001[c]
Length of stay in the ICU (day)	2 (2–7)	2 (2–5)	0.317[c]

Bold indicates statistically significant values. a: χ^2 test; b: Student's t-test; c: Mann-Whitney U test. SD: standard deviation; IQR: 25–75th percentile; COPD: chronic obstructive pulmonary disease; BMI: body mass index; CPB: cardiopulmonary bypass; CABG: coronary artery bypass grafting; AVR: aortic valve replacement; MVR: mitral valve replacement; MRA: mitral ring annuloplasty; ICU: intensive care unit.

DISCUSSION

In our study, we evaluated the relationship between inflammatory parameters and the development of postoperative DSWI in patients who underwent open heart surgery. As a result of the analysis, it was found that COPD, DM, blood and blood product transfusion, Po2-CRP, Po1-NLR, and delta NLR were found to be independent predictive factors for postoperative DSWI development. Among the inflammatory parameters, which were evaluated as the priority targets of our study, a one-unit increase in the Po2-CRP variable increased the risk of DSWI development 1.675 times, a one-unit increase in the Po1-NLR variable increased the risk of DSWI development 1.779 times, and a one-unit increase in the delta NLR variable increased the risk of DSWI development 3.192 times.

The DSWI is a serious and life-threatening complication that can be observed after open heart surgery with median sternotomy. It was reported that the incidence is 0.5–6% and the 1-year mortality associated with DSWI is 25.4%[2,7]. Inflammatory processes play a role in the pathogenesis and progression of DSWI. NLR is an inflammatory biomarker and is also deemed to be an indicator of subclinical inflammation. It is known that neutrophil numbers in the circulation increase, and there is a decrease in the numbers of lymphocytes in the presence of systemic inflammation or inflammatory response, and therefore, NLR also increases[8-10]. There are studies in the literature investigating the relationship between preoperatively evaluated NLR and postoperative complications. Gurbuz et al. conducted a study on 751 elective coronary artery bypass grafting (CABG) patients and reported that preoperative NLR was an independent predictive factor for the postoperative long-term major adverse cardiac and cerebrovascular event[9]. In our study, preoperative NLR levels were found to be significantly higher in our patient group who developed DSWI, but it was not found to be a predictive factor for DSWI development.

An acute inflammatory response is induced during surgical procedures, which may cause complications in the postoperative period[11,12]. Especially, this inflammatory response

Table 2. Laboratory variables of the patients.

Variables	Group 1 (n=70)	Group 2 (n=210)	p-value
	Median (IQR)	Median (IQR)	
Pre-WBC ($10^3/\mu L$)	7.4 (4.1–11.2)	7.2 (3.8–10.2)	0.347[c]
Pre-hemoglobin (g/dL)	12.7 (10.1–16.5)	12.5 (10.7–16.8)	0.545[c]
Pre-platelet ($10^3/\mu L$)	234 (148–477)	242 (144–476)	0.298[c]
Pre-neutrophil ($10^3/\mu L$)	4.7 (2.7–8)	4.4 (2.2–7.6)	0.196[c]
Pre-lymphocyte ($10^3/\mu L$)	1.4 (1–4.2)	1.8 (1.1–4.4)	0.098[c]
Pre-creatinine (mg/dL)	1 (0.6–1.9)	1.2 (0.6–2)	0.214[c]
Pre-urea (mg/dL)	19 (10–46)	17 (11–38)	0.474[c]
Pre-CRP (mg/dL)	9.5 (3.2–41.3)	8.9 (2.9–42)	0.320[c]
Pre-NLR	3.4 (0.7–6.5)	2.9 (0.8–6.1)	**0.044[c]**
Po1-WBC ($10^3/\mu L$)	10.8 (6–16)	10.2 (5.3–17.4)	0.271[c]
Po1-hemoglobin (g/dL)	9.4 (8.4–11.2)	8.9 (7.9–12)	0.118[c]
Po1-neutrophil ($10^3/\mu L$)	8.3 (5.4–12.9)	7.8 (5.1–11.4)	**0.014[c]**
Po1-lymphocyte ($10^3/\mu L$)	0.7 (0.2–1.7)	0.9 (0.4–2.4)	**0.005[c]**
Po1-CRP (mg/dL)	48.5 (12–150)	43.9 (9–138)	**0.021[c]**
Po1-NLR	11.9 (4.8–27.2)	9.9 (4.4–25.1)	**<0.001[c]**
Po2-WBC ($10^3/\mu L$)	11.5 (7.7–17.1)	11.1 (7.3–16.9)	0.211[c]
Po2-hemoglobin (g/dL)	10.1 (8.9–12.3)	9.6 (8.5–12.9)	0.490[c]
Po2-neutrophil ($10^3/\mu L$)	9.7 (5.4–14.8)	9.2 (5.3–13.7)	0.094[c]
Po2-lymphocyte ($10^3/\mu L$)	1 (0.5–2.3)	1.2 (0.6–2.7)	**0.014[c]**
Po2-CRP (mg/dL)	102.5 (34–311)	89.9 (29–294)	**<0.001[c]**
Po2-NLR	9.8 (3.5–21.6)	8.9 (3.4–19.2)	**0.003[c]**
Delta NLR	9.8 (4.2–25.2)	7.8 (2.8–21.8)	**<0.001[c]**

Bold indicates statistically significant values. c: Mann-Whitney U test. IQR: 25–75th percentile; Pre: preoperative; Po1: postoperative 1st day; Po2: postoperative 2nd day; WBC: white blood cell; CRP: C-reactive protein; NLR: neutrophil-to-lymphocyte ratio.

Table 3. Multivariate logistic regression analysis to determine predictors of postoperative DSWI development.

Variables	Multivariate analysis		
	p-value	OR	95%CI Lower-upper
BMI (>30 kg/m^2)	0.124	0.657	0.495–1.022
COPD	**0.043**	0.593	0.456–0.798
Diabetes mellitus	**0.012**	1.184	1.032–1.446
Inotropic support	0.156	0.778	0.456–1.114
Blood and blood product transfusion	**0.029**	0.798	0.659–0.991
Prolonged mechanical ventilation (>48 h)	0.057	0.865	0.691–1.138
Po1-CRP	0.217	0.797	0.544–1.009
Po2-CRP	**0.009**	1.675	1.214–2.229
Pre-NLR	0.239	0.796	0.654–1.002
Po1-NLR	**0.002**	1.779	1.554–3.191
Po2-NLR	0.071	0.983	0.697–1.598
Delta NLR	**<0.001**	3.192	2.997–7.734

Bold indicates statistically significant values. OR: odds ratio; CI: confidence interval; BMI: body mass index; COPD: chronic obstructive pulmonary disease; Pre: preoperative; Po1: postoperative 1st day; Po2: postoperative 2nd day; CRP: C-reactive protein; NLR: neutrophil-to-lymphocyte ratio.

occurs in cardiac surgery due to CPB[13]. This may cause surgical site infections and sepsis. It was shown in previous studies that postoperative NLR value, as well as preoperative NLR value, may be a predictor of complications, which may also develop. In their study, Kim et al. found that the NLR value evaluated immediately after open heart surgery and the NLR value evaluated on the Po1 were associated with postoperative mortality due to all reasons throughout one year[14]. In our study, we investigated the effects of Po1-NLR and Po2-NLR values and found that both NLR values were significantly higher in the patient group developing DSWI. However, we found that only the Po1-NLR value was a predictor in the multivariate analysis.

In the light of all these evaluations, studies have been carried out on the delta NLR value obtained from the difference between the NLR value after surgical operations or interventional procedures and the NLR value in the preoperative period[15]. Rich et al. included 1019 hepatocellular patients in their study and reported that the delta NLR value, which they described as the difference between the NLR values before and after the treatment, was the independent predictor of mortality[16]. In a study by Li et al., delta NLR was associated with major adverse cardiovascular events independently after percutaneous coronary interventions[17]. In our study, the delta NLR value was found to be a predictive factor of DSWI development.

There have been studies in the literature examining CRP levels and the development of postoperative complications[12]. In their study on 185 off-pump CABG patients, Kim et al. reported that there was a significant relationship between elevated preoperative CRP and the development of major postoperative complications, including the development of DSWI[5]. In our study, the Po1-CRP and Po2-CRP levels were significantly higher in our DSWI developing patient group, and the Po2-CRP variable was a predictor of DSWI development.

The comorbidities of the patients affect surgical field infections. DM affects wound healing negatively depending on the changes in the microvascular area[18,19]. DM was significantly higher in the patient group with DSWI in our study, and it was a predictor of DSWI development. In various studies, COPD has been shown to be a risk factor for DSWI development. This is often associated with tissue hypoxia due to COPD[3]. We also found that having concomitant COPD is an independent predictor of DSWI development. It is already known that increased blood and blood product transfusion may cause many complications in the perioperative and postoperative periods[20]. We found that increased blood and blood product transfusion was a predictor of DSWI development.

The primary limitations of our study were the retrospective design and being a single-centered study. It had a relatively small sample size to make strong and generalizable interpretations. Preoperative length of stay is known as a modifiable risk factor for DSWI development in open heart surgery[21]. In this respect, it is another limitation that the preoperative length of stay status of the patients was not added to the analyses.

CONCLUSIONS

The DSWI, which develops after open heart surgery with a median sternotomy, is a rare but feared complication. It is important that the predictors of this complication are known, risky patients are detected early, and preventive treatments are applied for the treatment of this complication. Our analysis performed for this purpose showed that COPD, DM, blood and blood product transfusion, Po2-CRP, Po1-NLR, and delta NLR are independent predictive factors for DSWI development after open heart surgery.

AUTHORS' CONTRIBUTIONS

KP: Conceptualization, Data curation, Formal analysis, Writing – original draft, Writing – review & editing. **ABT:** Conceptualization, Data curation, Formal analysis, Writing – original draft, Writing – review & editing. **AAP:** Conceptualization, Formal analysis, Writing – original draft, Writing – review & editing. **MTG:** Conceptualization, Formal analysis, Writing – original draft, Writing – review & editing.

REFERENCES

1. Kubota H, Miyata H, Motomura N, Ono M, Takamoto S, Harii K, et al. Deep sternal wound infection after cardiac surgery. J Cardiothorac Surg. 2013;8:132. https://doi.org/10.1186/1749-8090-8-132
2. Hever P, Singh P, Eiben I, Eiben P, Nikkhah D. The management of deep sternal wound infection: Literature review and reconstructive algorithm. JPRAS Open. 2021;28:77-89. https://doi.org/10.1016/j.jpra.2021.02.007
3. Hämäläinen E, Laurikka J, Huhtala H, Järvinen O. Vacuum assistance therapy as compared to early reconstructive treatment in deep sternal wound infection. Scand J Surg. 2021;110(2):248-53. https://doi.org/10.1177/1457496920979289
4. Lazar HL, Salm TV, Engelman R, Orgill D, Gordon S. Prevention and management of sternal wound infections. J Thorac Cardiovasc Surg. 2016;152(4):962-72. https://doi.org/10.1016/j.jtcvs.2016.01.060
5. Kim DH, Shim JK, Hong SW, Cho KR, Kang SY, Kwak YL. Predictive value of C-reactive protein for major postoperative complications

following off-pump coronary artery bypass surgery: prospective and observational trial. Circ J. 2009;73(5):872-7. https://doi.org/10.1253/circj.cj-08-1010

6. Badawy MA, Shammari FA, Aleinati T, Eldin MS, Tarazi R, Alfadli J. Deep sternal wound infection after coronary artery bypass: how to manage? Asian Cardiovasc Thorac Ann. 2014;22(6):649-54. https://doi.org/10.1177/0218492314536106
7. Segers P, Jong AP, Kloek JJ, Mol BA. Poststernotomy mediastinitis: comparison of two treatment modalities. Interact Cardiovasc Thorac Surg. 2005;4(6):555-60. https://doi.org/10.1510/icvts.2005.112714
8. Abanoz M, Engin M. The effect of the relationship between post-cardiotomy neutrophil/lymphocyte ratio and platelet counts on early major adverse events after isolated coronary artery bypass grafting. Turk Gogus Kalp Damar Cerrahisi Derg. 2021;29(1):36-44. https://doi.org/10.5606/tgkdc.dergisi.2021.20873
9. Gurbuz O, Kumtepe G, Ozkan H, Karal IH, Velioglu Y, Ercan A, et al. Predictive Value of Neutrophil-Lymphocyte Ratio for Long-Term Cardiovascular Event Following Coronary Artery Bypass Grafting. Braz J Cardiovasc Surg. 2020;35(3):274-84. https://doi.org/10.21470/1678-9741-2018-0362
10. Mohri Y, Tanaka K, Toiyama Y, Ohi M, Yasuda H, Inoue Y, et al. Impact of preoperative neutrophil to lymphocyte ratio and postoperative infectious complications on survival after curative gastrectomy for gastric cancer: a single institutional cohort study. Medicine (Baltimore). 2016;95(11):e3125. https://doi.org/10.1097/MD.0000000000003125
11. Forget P, Dinant V, Kock M. Is the Neutrophil-to-Lymphocyte Ratio more correlated than C-reactive protein with postoperative complications after major abdominal surgery? PeerJ. 2015;3:e713. https://doi.org/10.7717/peerj.713
12. Inose H, Kobayashi Y, Yuasa M, Hirai T, Yoshii T, Okawa A. Postoperative lymphocyte percentage and neutrophil-lymphocyte ratio are useful markers for the early prediction of surgical site infection in spinal decompression surgery. J Orthop Surg (Hong Kong). 2020;28(2):2309499020918402. https://doi.org/10.1177/2309499020918402
13. Pala AA, Urcun YS. Is the Mean Platelet Volume a Predictive Factor for Atrial Fibrillation Developing After Coronary Artery Bypass Grafting in Elderly Patients? Heart Surg Forum. 2020;23(6):E809-14. https://doi.org/10.1532/hsf.3201
14. Kim WH, Park JY, Ok SH, Shin IW, Sohn JT. Association between the neutrophil/lymphocyte ratio and acute kidney injury after cardiovascular surgery: a retrospective observational study. Medicine (Baltimore). 2015;94(43):e1867. https://doi.org/10.1097/MD.0000000000001867
15. Seong YW, Han SJ, Jung W, Jeon JH, Cho S, Jheon S, et al. Perioperative change in neutrophil-to-lymphocyte ratio (NLR) is a prognostic factor in patients with completely resected primary pulmonary sarcomatoid carcinoma. J Thorac Dis. 2019;11(3):819-26. https://doi.org/10.21037/jtd.2019.02.02
16. Rich NE, Parvathaneni A, Sen A, Odewole M, Arroyo A, Mufti AR, et al. High neutrophil-lymphocyte ratio and delta neutrophil-lymphocyte ratio are associated with increased mortality in patients with hepatocellular cancer. Dig Dis Sci. 2022;67(6):2666-76. https://doi.org/10.1007/s10620-021-07001-6
17. Li C, Zhang F, Shen Y, Xu R, Chen Z, Dai Y, et al. Impact of neutrophil to lymphocyte ratio (NLR) index and its periprocedural change (NLRΔ) for percutaneous coronary intervention in patients with chronic total occlusion. Angiology. 2017;68(7):640-6. https://doi.org/10.1177/0003319716649112
18. Furnary AP, Zerr KJ, Grunkemeier GL, Starr A. Continuous intravenous insulin infusion reduces the incidence of deep sternal wound infection in diabetic patients after cardiac surgical procedures. Ann Thorac Surg. 1999;67(2):352-60;discussion360-2. https://doi.org/10.1016/s0003-4975(99)00014-4
19. Ledur P, Almeida L, Pellanda LC, Schaan BD. Predictors of infection in post-coronary artery bypass graft surgery. Rev Bras Cir Cardiovasc. 2011;26(2):190-6. PMID: 21894408
20. Horvath KA, Acker MA, Chang H, Bagiella E, Smith PK, Iribarne A, et al. Blood transfusion and infection after cardiac surgery. Ann Thorac Surg. 2013;95(6):2194-201. https://doi.org/10.1016/j.athoracsur.2012.11.078
21. Storey A, MacDonald B, Rahman MA. The association between preoperative length of hospital stay and deep sternal wound infection: a scoping review. Aust Crit Care. 2021;34(6):620-33. https://doi.org/10.1016/j.aucc.2020.12.010

ORIGINAL ARTICLE

https://doi.org/10.1590/1806-9282.20220178

Mutagenic damage among bronchiectasis patients attending in the pulmonology sector of a hospital in southern Brazil

Daniel Wenceslau Votto Olmedo[1,2], Katheryne Benini Martins[1,2], Milene Machado Paz[1,2], Caroline Lopes Feijo Fernandes[1,3], Flavio Manoel Rodrigues da Silva Júnior[1,3], Daniela Fernandes Ramos[1,2*]

SUMMARY

OBJECTIVE: Bronchiectasis is a chronic respiratory disease characterized by inflammation, irreversible dilation of the bronchi, and recurrent pulmonary infections, with a high morbidity and mortality rate, but is less studied from the point of view of its prevalence and associated factors not directly related to respiratory prognosis. As it is a disease related to the exacerbation of the inflammatory process and oxidative stress, this study searched to investigate the micronucleus frequency in patients with and without bronchiectasis treated at a specialized pulmonology service in a hospital in the extreme south of Brazil.

METHODS: Patients with a confirmed tomographic diagnosis of bronchiectasis were defined as cases. Mutagenicity was evaluated by the micronucleus test in patients' oral mucosa cells. Data collection was performed through a questionnaire containing socioeconomic, demographic, lifestyle, and health condition information.

RESULTS: Of the 95 patients involved in this study, 21 (22.1%) were diagnosed with bronchiectasis aged between 12 and 89 years. There was no significant difference in the frequency of micronucleus between patients with and without bronchiectasis. There was a significant positive association between age and frequency of micronucleus among patients with bronchiectasis, but this association does not occur among patients without the disease.

CONCLUSION: This is the first study to investigate data on the prevalence and clinical and epidemiological aspects of this chronic disease in Brazil, especially those related to the genotoxicity outcome.

KEYWORDS: Fibrosis. Mutagenesis. Bronchiectasis. Morbidity.

INTRODUCTION

Chronic respiratory diseases (CRDs) affect hundreds of millions of people around the world, and their worsening is increasingly recognized as one of the main causes of loss of quality of life and mortality associated with the disease[1].

CRD affects both the upper and lower airways, with the most common morbidities being allergic rhinitis, chronic obstructive pulmonary disease (COPD), asthma[2], and bronchiectasis. The latter has been shown to be a more frequent pathology than previously considered but with few studies[3].

Bronchiectasis is characterized by an abnormal and irreversible dilation of the bronchi that results in bacterial colonization, impaired mucociliary clearance, and chronic inflammation of the bronchial mucosa with the consequent gradual destruction of lung tissue[4,5]. This inflammatory process is progressive and results in a cycle of worsening lung injury[6].

The biological mechanism for the epidemiological association of chronic respiratory diseases and the subsequent development of lung cancer remains unclear. However, the lungs are in direct contact with high concentrations of oxygen and pollutants[7]. In addition to these factors, an important component of lung disease is inflammation and activation of inflammatory cells that produce reactive oxygen species and can lead to oxidative stress[7-9], being this, one of the main factors responsible for direct damage, enhancing other participating mechanisms such as inflammation, changes in the balance between proteases and antiproteases in the lungs and apoptosis[10,11]. Thus, lung cancer can be attributed to chronic inflammation and recurrent infection of bronchial trees that can activate multiple oncogenic pathways and facilitate the development of tumors[12].

Considering that the evolution of bronchiectasis and many other chronic lung diseases involves a vicious cycle consisting of

[1]Universidade Federal do Rio Grande, Faculty of Medicine, Postgraduate Program in Health Sciences – Rio Grande (RS), Brazil.
[2]Universidade Federal do Rio Grande, Faculty of Medicine, New Drug Development Center – Rio Grande (RS), Brazil.
[3]Universidade Federal do Rio Grande, Institute of Biological Sciences, Laboratory of Pharmacological and Toxicological Tests – Rio Grande (RS), Brazil.
*Corresponding author: danielaramos@furg.br

Conflicts of interest: the authors declare there is no conflicts of interest. Funding: This study was supported by the Coordenação de Aperfeiçoamento de Pessoal de Nível Superior – Brasil (CAPES) and Fundação de Amparo à Pesquisa do Estado do Rio Grande do Sul (FAPERGS) – Finance Code 001.
Received on May 04, 2022. Accepted on June 02, 2022.

bronchial changes, which predispose to lower lung clearance, leading to recurrent infections and increasing the inflammatory process and genomic instability, and in turn, could act as a critical step for the worsening of the clinical picture of these patients and even induce mutations or epigenetic alterations that may be associated with irreversible damages such as the appearance of lung cancer[13,14].

Studies have shown that there is a significant association between the increased frequency of chromosomal damage measured by the micronucleus (MN) test and other chronic lung diseases such as COPD, highlighting this technique as a noninvasive, robust, and low-cost method to early predict phenotypic and biological changes in individuals at high risk of developing lung cancer[15].

Pathologies with similar conditions in terms of the inflammatory process and oxidative stress have been associated with the occurrence of mutagenesis, and among the most widely chosen biomarkers for the study is the MN test. Given the scarcity of information on bronchiectasis and triggering factors, this study aimed to investigate the frequency of micronuclei in patients treated at a pulmonology clinic in the extreme south of Brazil, in addition to studying possible factors associated with increased mutagenic damage.

METHODS

Study population

This is a prospective and observational study with a quantitative approach developed from July 2018 to August 2018, having as the study population all adult patients treated at a specialized outpatient clinic at the Doctor Miguel Riet Corrêa Junior University Hospital (HU-FURG), in Southern Brazil (Rio Grande/RS).

Patients with high-resolution computed tomography confirmed diagnosis and clinical history consistent with bronchiectasis were defined as cases, and the other subjects were considered to study controls.

Ethical aspects

This observational study was approved by the Research Ethics Committee in the Health Area of the Federal University of Rio Grande (CEP/FURG), process 23116.006049-2018-10.

Human samples

A smear of buccal cells (for MN assay) and the oropharyngeal (for the bacterial colonization) were collected from 95 patients, using a cytobrush and swab, respectively.

Micronucleus test

Mutagenicity was evaluated via the MN test in cells of the oral mucosa of the patients. Smears were made on the slides, and these were stained with eosin-methylene blue according to Leishman; the total number of cells were counted by two analyzers using an optical microscope at 400´ and 1,000´ magnifications; and the frequency of MN was expressed as the number of MN in 1000 cells[16]. All slide readings were performed blindly.

Microbiological evaluation

The oropharyngeal samples were made on a slide smear with the oropharyngeal samples and were stained with Gram coloration, classifying the microorganisms into Gram-positive and/or Gram-negative.

Data analysis

The volunteers who agreed to participate in this study signed an informed consent form and were asked to answer a semi-structured questionnaire for data collection containing information on socioeconomic, demographic, lifestyle, and health conditions.

Comparison of the frequency of MN between groups (with and without chronic diseases or bronchiectasis) was performed using the Mann-Whitney test, and the association between age and frequency of MN was tested using simple linear regression analysis. For both analyses, a critical p-value of 5% was considered.

The association between the MN frequencies in buccal cells and different confounding factors was investigated using multiple Poisson regressions (multivariate and bivariate) with a robust estimate. For this, individuals who had a micronuclei frequency ≤ 2.5 micronuclei in 1000 cells were considered "without risk" (Holland et al., 2008). Regression analysis was conducted from hierarchical levels: first level (age, ethnicity, gender, marital status, and income *per capita*); second level (living and working conditions); and third level (life habit: smoking, drinking, and drug use and clinical conditions: pulmonary function and oropharynx colonization). The goodness of fit was checked using the deviance statistics. The variables with a p-value < 0.2 remained in the model but were considered significant only if the p-value was <0.05. Data analyses were performed using the SPSS software.

The sample power was calculated using the website http://powerandsamplesize.com/, by comparing the means and standard deviations of each parameter in the groups (with or without non-cystic fibrosis bronchiectasis), considering a level of significance of 5% in the ANOVA model.

RESULTS

A total of 95 patients seen at the HU-FURG during the study period were included (Table 1), with a 22.1% prevalence of bronchiectasis (21/95). Most patients were female (68.4%), white (80%), non-smoker (72%), with a mean age of 59.91±15.9 years (from 12–89 years). Regarding respiratory compromise, as evidenced by respiratory disorders during spirometry, approximately half of the patients included in this study had the ratio between forced expiratory volume in one second (FEV1) and forced vital capacity (FVC) below 70%, with the frequency of airflow limitation of 57 vs. 42.9% in patients with non-cystic fibrosis bronchiectasis (NFB) when compared with controls, respectively.

Chronic bacterial colonization of the oropharynx in NFB has been an important predictive factor with regard to the prognosis of these patients, and 66.3% of patients (63/95) had bacterial colonization, with *Staphylococcus aureus* being the pathogen most frequently isolated.

Regarding the evaluation of mutagenesis in the oral mucosa of these patients, the frequency range of MN was between 0–3‰, and only samples from older individuals (over 59 years) had frequencies equal to or greater than 2.5 ‰. There was no statistically significant difference in the frequency of MN between patients with a history of chronic respiratory disease, as well as no difference in the frequency of MN between patients with and without bronchiectasis (Figure 1), and the power of the sample was 0.33.

Considering age as an important factor associated with MN, Figure 2 shows a significant positive association between age and frequency of MN among patients with bronchiectasis, but this association does not occur among patients without the disease. There is also no association between age and frequency of MN when considering patients with and without any chronic respiratory disease.

Comparing the results of MN frequency between men and women diagnosed or not diagnosed with NFB (Figure 3), there was no significant difference between the two groups. Furthermore, regardless of sex, age seems to remain a pillar in the increase in MN in patients with NFB (Figure 4).

The analysis of associated factors using Poisson regression analysis with robust variance did not show any significantly associated variable in both bivariate and multivariate analyses (Table 2).

DISCUSSION

The prevalence of NFB in Brazil has not been well characterized since this disease has been considered an orphan from an epidemiological point of view, which has remained underdiagnosed,

Table 1. Baseline characteristics of study population.

	Frequency (%)
Age (years)	
Average age (years)	59.91±15.9
Above 59	58.9
30–59	34.8
Up to 29	6.3
Gender	
Female	68.4
Male	31.6
Marital status	
Married	47.7
Single	12.8
Other	39.5
Skin color	
White	80
Non-white	20
Average family income*	2,123.97±1,876.59
Income >2 salaries	41.5
Between 1 and 2 salaries	29.8
Income ±1 salary	28.7
Average people residing in the house	2.91±1.99
Above 1	77.7
Up to 1	22.3
Average number of rooms in the house	5.16±1.74
More than 3	69.9
Between 2 and 3	9.7
1 room	4.3
Work	
Yes	89.5
Not	10.5
Cigarette	
Smoker	16.3
Ex-smoker	54.3
Non-smoking	29.3
Alcohol	
Addict	22.3
Do not drink anymore	22.3
Never drank	55.3
Drug user	
Already used	4.3
Never used	95.7
Altered pulmonary function**	
Not	44.9
Yes	55.1
Bacterial colonization	
Multicolonized (GPC+GNB)	16.8
Gram-Positive Cocci (GPC)	69.5
Gram-Negative Bacilli (GNB)	6.3
There was no bacterial growth	7.4

*Minimum Salary: R$954.00; **Altered spirometry if forced expiratory volume in one second/forced vital capacity (%) below 70%. GPC: Gram-positive cocci; GNB: Gram-negartive bacilli.

especially in developing countries[3,17,18]. Even with the high variability between different populations[19], some studies conducted in Europe and the United States of America reveal an increase in the prevalence of the disease in these locations[20-22].

Considering the scarcity of national studies and high variability in mortality rates related to this chronic disease (ranging from 2–35%), there seems to be an underestimation of Brazilian data. In this study, the prevalence of NFB found in

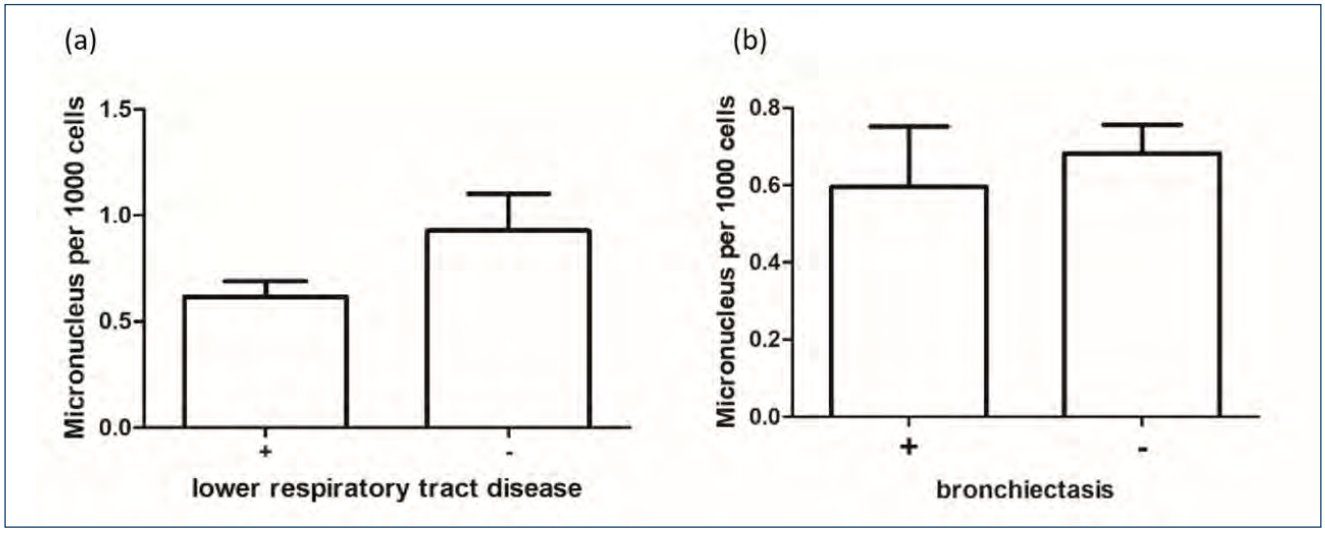


Figure 1. Frequency of micronucleus/1000 cells in patients (A) with and without a diagnosis of lower respiratory tract diseases (asthma, bronchitis, rhinitis, sinusitis, tuberculosis, emphysema, and cystic fibrosis) and (B) with or without non-cystic fibrosis bronchiectasis.

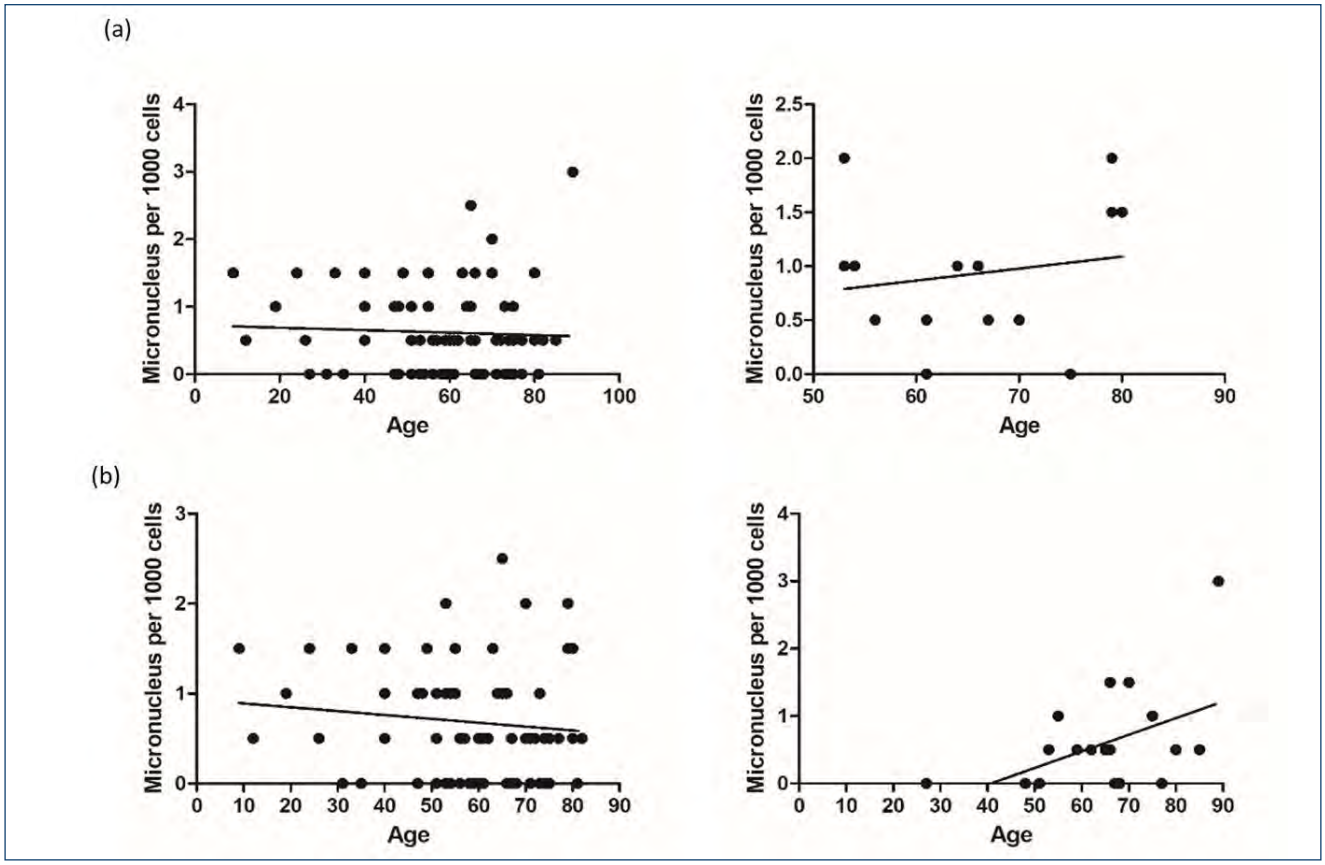


Figure 2. Association between age and micronucleus frequency (‰) in oral mucosa samples from patients (A) with (r^2=0.002; p=0.68) and without (r^2=0.03; p=0.53) diagnosis of respiratory diseases and (B) with (r^2=0.22; p=0.03) or without (r^2=0.01; p=0.35) diagnosis of non-cystic fibrosis bronchiectasis.

outpatients seen in a single month of 2018 at the regional reference center for pulmonology in the far south of the country was 22.1%. This prevalence tends to be higher proportionally to the increase in age of patients, corroborating other studies[23].

The data showed an association between age and frequency of MN among patients diagnosed with bronchiectasis, and this association did not exist between patients without the disease and patients with another chronic respiratory disease. Age has been identified as a factor related to mutagenesis, and even studies with healthy subjects have shown an increase in the frequency of age-related mutagenic damage[24]. In addition, the prognostic data from the NFB itself have highlighted age as an important factor for the increase in the prevalence of this disease, as well as an increase in hospitalization and mortality rates in this population[3,25].

The frequency of micronuclei has been widely studied in several pathologies. However, to date, no studies have been found that have shown the frequency of MN in elderly people with bronchiectasis as a possible biomarker for the evaluation of mutagenesis and cancer in these patients.

Studies have shown that bronchiectasis increases systemic inflammation and arterial stiffness and causes bone thinning, and the inflammatory response plays an essential role in tissue genotoxicity and consequently in tumorogenesis[5,26]. On the other hand, some authors have proposed that there is an intimate relationship between NFB and cancer, including proposing the tracking and follow-up of these patients in longitudinal studies[12,23]. In this sense, this is the first study that evaluates mutagenesis through the quantification of MN in mouth epithelial samples of individuals with NFB in Brazil, in order to validate this tool as a possible prognostic marker to be considered in the routine evaluations of these patients.

Although the frequency of MN in patients with bronchiectasis was similar to that in patients without the disease, this association reveals a scenario that highlights the need for additional patient care beyond those listed in the diagnostic and therapeutic management in order to prevent disease progression respiratory, indicating that the aging of the population with NFB associated with other risk factors, such as occupational exposure, constant imaging tests, exposure to chemicals, and

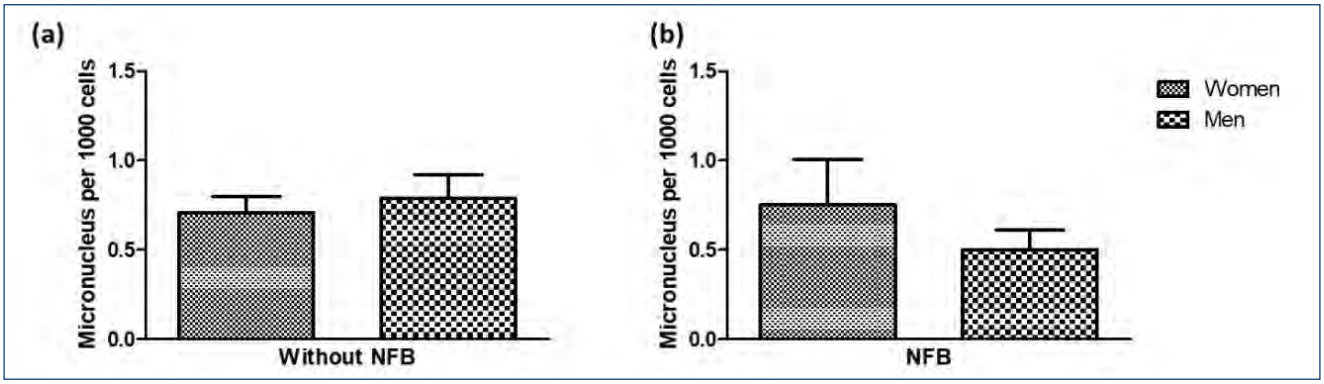


Figure 3. Frequency of micronucleus/1000 cells in men and women (A) without non-cystic fibrosis bronchiectasis (NFB) and (B) with non-cystic fibrosis bronchiectasis.

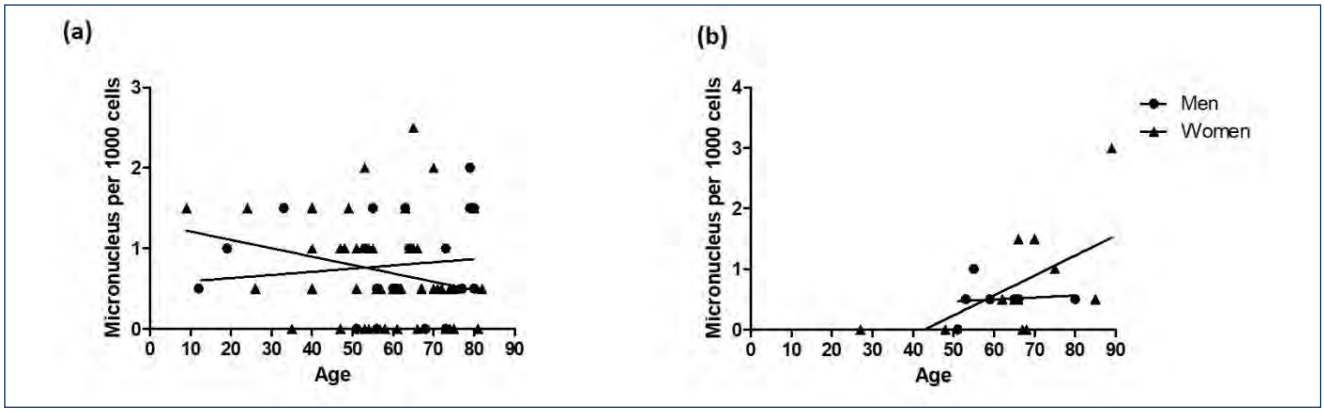


Figure 4. Association between age and micronucleus frequency (‰) in oral mucosa samples of (A) of men (r^2=0.014; p=0.60) and women (r^2=0.06; p=0.08) without diagnosis of non-cystic fibrosis bronchiectasis and (B) men (r^2=0.01; p=0.81) and women (r^2=0.35; p=0.04) with diagnosis of non-cystic fibrosis bronchiectasis.

Table 2. Bi- and multivariate analysis of associated factors using Poisson regression.

Level		Bivariate		Multivariate	
		95%CI	p-value	95%CI	p-value
1	Age (years)		0.95		0.71
	Over 59	1		1	
	30–59	0.86 (0.36–2.09)		0.84 (0.37–1.90)	
	Up to 29	0.95 (0.15–5.89)		0.47 (0.07–3.01)	
1	Gender		1.00		0.68
	Female	1		1	
	Male	1.00 (0.42–2.38)		1.22 (0.48–3.12)	
1	Marital Status		0.61		0.39
	Married	1		1	
	Single	1.24 (0.55–2.80)		1.39 (0.66–2.90)	
1	Skin Color		0.33		0.21
	White	1		1	
	Non-white	2.60 (0.38–17.8)		3.22 (0.51–20.27)	
1	Family income		0.30		0.26
	Above 2 minimum salary	1		1	
	Between 1 and 2 minimum salary	1.43 (0.61–3.35)		1.55 (0.71–3.35)	
	Below 1 minimum salary	0.56 (0.16–1.91)		0.58 (0.17–1.98)	
1	Education		0.55		0.55
	8 or more years	1		1	
	Up to 8 years old	0.46 (0.21–1.02)		0.46 (0.21–1.02)	
2	People per part of the house		0.07		0.09
	Above 1	1		1	
	Below 1	2.27 (0.93–5.50)		2.26 (0.89–5.73)	
2	Working time		0.64		0.80
		0.99 (0.96–1.03)		1.00 (0.97–1.04)	
3	Cigarette consumption		0.51		0.95
	Smoker	1		1	
	Ex smoker	0.57 (0.22–1.50)		0.81 (0.22–2.95)	
	Non-smoking	0.68 (0.24–1.90)		0.87 (0.25–3.07)	
3	Alcohol		0.71		
	Use	1			
	Don't drink anymore	1.14 (0.12–10.7)			
	Never drank	1.75 (0.26–11.53)			
3	Drug user		0.79		0.43
	Aready used	1		1	
	Never used	0.79 (0.14–4.54)		0.51 (0.10–2.70)	
3	Use of medications		0.38		0.53
	Use	1		1	
	Do not use	0.54 (0.14–2.12)		0.69 (0.22–2.17)	
3	Altered pulmonary function*		0.15		0.08
	Not	1		1	
	Yes	1.81 (0.80–4.09)		2.06 (0.91–4.65)	
3	Bacterial colonization		0.17		0.34
	GPC+GNB	1		1	
	GPC	0.40 (0.17–0.95)		0.46 (0.18–1.17)	
	GNB	0.89 (0.24–3.25)		0.95 (0.24–3.68)	
	NG	0.38 (0.56–2.60)		0.42 (0.06–2.96)	

*Altered spirometry if forced expiratory volume in one second/ forced vital capacity(%) below 70%. GPC: Gram-positive cocci; GNB: Gram-negartive bacilli; NG: No microbial growth.

comorbidities, and hospitalizations associated with recurrent infections due to the clinical condition of NFB may favor the increase in events genotoxic up to 4 times[27].

Advanced age appears to be associated with an increase in genomic instability resulting from reduced DNA damage repair capacity[28]. In addition, studies have shown that bronchiectasis seems to be directly related to the emergence of cancers, at a frequency ranging from 0.2–16%, and that age helps to increase these rates among bronchiectasis[23,29].

It should be noted that the MN test could be used as a biomarker as a screening method for genotoxicity in patients with chronic lung diseases such as bronchiectasis, even considering one of its main limitations: the background MN frequency in buccal cells is relatively low (approximately 0.1%)[27,30], which can influence the individual variability of the evaluated sample and, consequently, interfere in the statistical power found.

CONCLUSION

Therefore, this is the first study to investigate data on the prevalence and clinical and epidemiological aspects of this chronic disease in Brazil, especially those related to the genotoxicity outcome. We also emphasize that it was only in 2019 that the first Brazilian consensus was published[3] for the management of NFB and that due to the high impact of chronic lung diseases on human morbidity and mortality rates, and the severity and prognosis of these patients have emerged as an important point of clinical evaluation, having proposed several scores based on infection markers, the clinical status of patients, tissue involvement, and access to hospitalization services. However, mutagenesis markers that may predispose to lung cancer, for example, are not among the aspects evaluated to estimate the severity and prognosis of these patients. Therefore, using simple, easy-to-perform, and inexpensive tools for the early screening of genotoxic events in these patients could facilitate diagnostic and therapeutic management, including avoiding the negative outcome associated with the appearance of carcinogenic events and increasing the quality of life of patients.

ACKNOWLEDGMENT

The authors thank the Coordenação de Aperfeiçoamento de Pessoal de Nível Superior, CAPES and CNPq (Research Productivity Grant 310856/2020-5) – Flavio Manoel Rodrigues da Silva Júnior and CNPq (Research Productivity, Grant 305921/2019-3 – Daniela Fernandes Ramos) and Fundação de Amparo à Pesquisa do Estado do Rio Grande do Sul (FAPERGS).

AUTHORS' CONTRIBUITION

DWVO: Visualization, Investigation, Writing – original draft. **KBM:** visualization, investigation, and writing – original draft preparation. **MMP:** Visualization, Investigation, Methodology. **CLFF:** Visualization, Investigation, Methodology. **FMRSJ:** Conceptualization, Data curation, Writing – review & editing. **DFR:** Conceptualization, Data curation, Writing – review & editing.

REFERENCES

1. Kreuter M, Cottin V. The threat in chronic lung diseases: acute exacerbations. Eur Respir Rev. 2017;26(145):170075. https://doi.org/10.1183/16000617.0075-2017
2. Brasil. Cadernos de Atenção Básica: doenças respiratórias crônicas. Brasília: Ministério da Saúde; 2010. 160p.
3. Pereira MC, Athanazio RA, Dalcin PTR, Figueiredo MRF, Gomes M, Freitas CG, et al. Brazilian consensus on non-cystic fibrosis bronchiectasis. J Bras Pneumol. 2019;45(4):e20190122. https://doi.org/10.1590/1806-3713/e20190122
4. Chalmers JD, Sethi S. Raising awareness of bronchiectasis in primary care: overview of diagnosis and management strategies in adults. NPJ Prim Care Respir Med. 2017;27(1):18. https://doi.org/10.1038/s41533-017-0019-9
5. Flume PA, Chalmers JD, Olivier KN. Advances in bronchiectasis: endotyping, genetics, microbiome, and disease heterogeneity. Lancet. 2018;392(10150):880-90. https://doi.org/10.1016/S0140-6736(18)31767-7
6. Polverino E, Dimakou K, Hurst J, Martinez-Garcia MA, Miravitlles M, Paggiaro P, et al. The overlap between bronchiectasis and chronic airway diseases: state of the art and future directions. Eur Respir J. 2018;52(3):1800328. https://doi.org/10.1183/13993003.00328-2018
7. Kinnula VL, Crapo JD. Superoxide dismutases in the lung and human lung diseases. Am J Respir Crit Care Med. 2003;167(12):1600-19. https://doi.org/10.1164/rccm.200212-1479SO
8. Alessandri AL, Sousa LP, Lucas CD, Rossi AG, Pinho V, Teixeira MM. Resolution of inflammation: mechanisms and opportunity for drug development. Pharmacol Ther. 2013;139(2):189-212. https://doi.org/10.1016/j.pharmthera.2013.04.006
9. Rajendrasozhan S, Yang SR, Edirisinghe I, Yao H, Adenuga D, Rahman I. Deacetylases and NF-kappaB in redox regulation of cigarette smoke-induced lung inflammation: epigenetics in pathogenesis of COPD. Antioxid Redox Signal. 2008;10(4):799-811. https://doi.org/10.1089/ars.2007.1938
10. Barnes PJ, Shapiro SD, Pauwels RA. Chronic obstructive pulmonary disease: molecular and cellular mechanisms. Eur Respir J. 2003;22(4):672-88. https://doi.org/10.1183/09031936.03.00040703
11. Demedts IK, Demoor T, Bracke KR, Joos GF, Brusselle GG. Role of apoptosis in the pathogenesis of COPD and pulmonary emphysema. Respir Res. 2006;7(1):53. https://doi.org/10.1186/1465-9921-7-53

12. Chung WS, Lin CL, Hsu WH, Kao CH. Increased risk of lung cancer among patients with bronchiectasis: a nationwide cohort study. QJM. 2016;109(1):17-25. https://doi.org/10.1093/qjmed/hcu237
13. Amati F, Simonetta E, Gramegna A, Tarsia P, Contarini M, Blasi F, et al. The biology of pulmonary exacerbations in bronchiectasis. Eur Respir Rev. 2019;28(154):190055. https://doi.org/10.1183/16000617.0055-2019
14. Jeggo PA, Pearl LH, Carr AM. DNA repair, genome stability and cancer: a historical perspective. Nat Rev Cancer. 2016;16(1):35-42. https://doi.org/10.1038/nrc.2015.4
15. Asanov M, Bonassi S, Proietti S, Minina VI, Tomino C, El-Zein R. Genomic instability in chronic obstructive pulmonary disease and lung cancer: a systematic review and meta-analysis of studies using the micronucleus assay. Mutat Res Rev Mutat Res. 2021;787:108344. https://doi.org/10.1016/j.mrrev.2020.108344
16. Tolbert PE, Shy CM, Allen JW. Micronuclei and other nuclear anomalies in buccal smears: methods development. Mutat Res. 1992;271(1):69-77. https://doi.org/10.1016/0165-1161(92)90033-i
17. Cardoso AP, Polisseni N, Loivos LPP. Bronquiectasias – uma doença órfã. Pulmão RJ. 2014;23(3):3-7.
18. Imam JS, Duarte AG. Non-CF bronchiectasis: orphan disease no longer. Respir Med. 2020;166:105940. https://doi.org/10.1016/j.rmed.2020.105940
19. King P, Holdsworth S, Freezer N, Holmes P. Bronchiectasis. Intern Med J. 2006;36(11):729-37. https://doi.org/10.1111/j.1445-5994.2006.01219.x
20. Quint JK, Millett ER, Joshi M, Navaratnam V, Thomas SL, Hurst JR, et al. Changes in the incidence, prevalence and mortality of bronchiectasis in the UK from 2004 to 2013: a population-based cohort study. Eur Respir J. 2016;47(1):186-93. https://doi.org/10.1183/13993003.01033-2015
21. Ringshausen FC, Roux A, Diel R, Hohmann D, Welte T, Rademacher J. Bronchiectasis in Germany: a population-based estimation of disease prevalence. Eur Respir J. 2015;46(6):1805-7. https://doi.org/10.1183/13993003.00954-2015
22. Seitz AE, Olivier KN, Adjemian J, Holland SM, Prevots DR. Trends in bronchiectasis among medicare beneficiaries in the United States, 2000 to 2007. Chest. 2012;142(2):432-9. https://doi.org/10.1378/chest.11-2209
23. Chung WS, Lin CL, Lin CL, Kao CH. Bronchiectasis and the risk of cancer: a nationwide retrospective cohort study. Int J Clin Pract. 2015;69(6):682-8. https://doi.org/10.1111/ijcp.12599
24. Cavalcante DNC, Crispim BDA, Grisolia BB, Viana LF, Maran NH, Solórzano JCJ, et al. Effects of age, sex, medication, and environmental conditions on genetic alterations in oral mucosa cells. Heliyon. 2019;5(6):e01840. https://doi.org/10.1016/j.heliyon.2019.e01840
25. Quinn TM, Hill AT. Non-cystic fibrosis bronchiectasis in the elderly: current perspectives. Clin Interv Aging. 2018;13:1649-56. https://doi.org/10.2147/CIA.S143139
26. Maluf SW, Mergener M, Dalcanale L, Costa CC, Pollo T, Kayser M, et al. DNA damage in peripheral blood of patients with chronic obstructive pulmonary disease (COPD). Mutat Res. 2007;626(1-2):180-4. https://doi.org/10.1016/j.mrgentox.2006.10.002
27. Holland N, Bolognesi C, Kirsch-Volders M, Bonassi S, Zeiger E, Knasmueller S, et al. The micronucleus assay in human buccal cells as a tool for biomonitoring DNA damage: the HUMN project perspective on current status and knowledge gaps. Mutat Res. 2008;659(1-2):93-108. https://doi.org/10.1016/j.mrrev.2008.03.007
28. Trzeciak AR, Barnes J, Ejiogu N, Foster K, Brant LJ, Zonderman AB, et al. Age, sex, and race influence single-strand break repair capacity in a human population. Free Radic Biol Med. 2008;45(12):1631-41. https://doi.org/10.1016/j.freeradbiomed.2008.08.031
29. A Sanchez-Carpintero Abad M, Sanchez-Salcedo P, de-Torres JP, Alcaide AB, Seijo LM, Pueyo J, et al. Prevalence and burden of bronchiectasis in a lung cancer screening program. PLoS One. 2020;15(4):e0231204. https://doi.org/10.1371/journal.pone.0231204
30. Ceppi M, Biasotti B, Fenech M, Bonassi S. Human population studies with the exfoliated buccal micronucleus assay: statistical and epidemiological issues. Mutat Res. 2010;705(1):11-9. https://doi.org/10.1016/j.mrrev.2009.11.001

ORIGINAL ARTICLE

https://doi.org/10.1590/1806-9282.20220196

Adjunctive corticosteroid therapy in patients with pulmonary tuberculosis

Carolina Xavier Lemos[1], Camila Anton[1], Felipe Dominguez Machado[1], Rafaela Manzoni Bernardi[1], Alana Ambos Freitas[2], Denise Rossato Silva[1,2,3*]

SUMMARY

OBJECTIVES: In tuberculosis treatment, corticosteroids are used as adjuvants, especially in meningeal/pericardial tuberculosis. In other forms of the disease, especially in severe tuberculosis requiring mechanical ventilation, its use is controversial. The aim of the present study is to assess whether the use of corticosteroids in the treatment of pulmonary tuberculosis patients in mechanical ventilation is associated with in-hospital mortality.

METHODS: This is a retrospective cohort study. Tuberculosis patients >18 years requiring mechanical ventilation, admitted to the emergency department or intensive care unit, were included. Data on corticosteroid use and mortality were collected.

RESULTS: In total, 467 patients were included in the analysis; 399 used corticosteroids and 68 were noncorticosteroid users. The mortality rate was higher among corticosteroid users (59.9%) than in noncorticosteroid users (41.2%) (p=0.010). The total dose of corticosteroid in prednisone equivalents was not different between survivors and nonsurvivors (median [interquartile range]: 80 mg [5–56.6 mg] vs. 80 mg [50–135 mg]; p=0.881).

CONCLUSIONS: Tuberculosis patients in mechanical ventilation who used corticosteroids had a higher mortality rate than those who did not use corticosteroids. The role of corticosteroids in pulmonary tuberculosis, especially in critically ill patients, remains unclear and needs further evaluation in prospective studies.

KEYWORDS: Tuberculosis. Respiration, artificial. Respiratory insufficiency. Glucocorticoid. Critical care.

INTRODUCTION

A significant portion of tuberculosis (TB) patients, especially severe cases, are still being hospitalized, with estimates ranging from 2 to 12%. In addition, patients required mechanical ventilation (MV) in many cases[1,2]. In a study conducted in Brazil, ICU admission was necessary in 8.5% of cases[3]. In another study at a university hospital, 16.7% of the 311 cases of TB were admitted to the ICU and 15.4% required MV[4]. Besides, in-hospital mortality of patients with TB remains high, particularly among patients requiring MV. TB associated with acute respiratory failure has been associated with mortality rates of up to 81.0%[5-9].

Several factors have been identified as predictive of mortality among TB patients, such as delay in diagnosis, irregular treatment, human immunodeficiency virus infection, malnutrition, and multidrug-resistant TB[4,10-13]. In a study[10] that evaluated 311 patients with TB, MV and negative sputum smear were predictors of in-hospital death in multivariate analysis. In another retrospective cohort study[4] with 67 patients requiring intensive care, ventilator-associated pneumonia and early intensive care unit admission were risk factors for in-hospital mortality. In addition, serum levels of albumin, reflecting the nutritional status, were associated with higher mortality in ICU patients with TB and respiratory failure[14,15].

In the treatment of TB, corticosteroids are used as adjuvants, especially in meningeal and pericardial TB. Corticosteroids can allow anti-TB drugs to penetrate granulomas, undoing their formation. Moreover, they inhibit the release of cytokines and lymphokines[16,17]. In other forms of the disease, especially in severe TB, its use is controversial[16,18-22]. Therefore, the aim of the present study is to assess whether the use of corticosteroids in the treatment of pulmonary TB patients in MV is associated with in-hospital mortality.

[1]Universidade Federal do Rio Grande do Sul, Graduate Program in Pulmonology Sciences – Porto Alegre (RS), Brazil.
[2]Universidade Federal do Rio Grande do Sul, School of Medicine – Porto Alegre (RS), Brazil.
[3]Hospital de Clínicas de Porto Alegre, Department of Pulmonology – Porto Alegre (RS), Brazil.
*Corresponding author: denise.rossato@terra.com.br
Conflicts of interest: the authors declare there is no conflicts of interest. Funding: none.
Received on May 10, 2022. Accepted on May 23, 2022.

METHODS

Study design and location

The study was conducted at the Hospital de Clínicas de Porto Alegre (HCPA). This was a retrospective cohort study, with data collection from January 2010 to December 2019. The study was approved by the HCPA's Ethics Committee (2013-0024), and all research was performed in accordance with relevant guidelines/regulations. Informed consent has been waived by the Ethics Committee of HCPA, but patient confidentiality has been maintained.

Patients and data collection

Tuberculosis (TB) patients >18 years, requiring MV, admitted to the intensive care unit, were included in the study. The TB diagnosis was based on consensus criteria[23]. There is no protocol to guide the administration of corticosteroids in our hospital; it is at the discretion of the attending physician. The following information was collected: demographic data, alcoholism, smoking status, prior anti-TB therapy, comorbidities, Acute Physiologic and Chronic Health Evaluation (APACHE) II and Sequential Organ Failure Assessment scores, vasopressor use, and hospitalization outcome (death or discharge).

Statistical analysis

Data analysis was performed using IBM SPSS 22.0 (Statistical Package for the Social Sciences, Armonk, NY). Chi-square test using Yates's correction if indicated or Fisher's exact test was used for categorical comparisons. The t-test or Wilcoxon test was used to compare continuous variables. A multivariate logistic regression analysis was performed to evaluate if the use of corticosteroids is independently associated with mortality. The Hosmer-Lemeshow test was used to assess the goodness of fit of the multiple logistic regression models. Odds ratios (ORs) and nominal 95% confidence intervals (CIs) were presented, and a p-value <0.05 was considered significant[24].

A previous study[18] was used for the calculation of the sample size, in which the percentage of use of corticosteroids in the nonsurviving group was 37.8% and in the surviving group, it was 61.9%. Thus, it would be necessary to include at least 128 patients (at least 64 per group), with an alpha error of 0.05 and a beta error of 0.20.

RESULTS

In total, 467 patients were included in the analysis; 399 used corticosteroids and 68 were noncorticosteroid users (Table 1). Patients using corticosteroids were younger (46.5±14.9 years) than those not using corticosteroids (51.3±16.4 years) (p=0.017). HIV infection was more frequent in corticosteroid users (53.6%) compared to noncorticosteroid users (36.8%) (p=0.010). Vasopressor use was also more common among corticosteroid users. On the other hand, diabetes was more frequent in noncorticosteroid users (25.0%) as compared to corticosteroid users (14.5%) (p=0.030). There were no drug-resistant TB cases included in the study.

Table 1. Characteristics of patients according to the use of corticosteroids.

Characteristic	Corticosteroid users (n=399)	Noncorticosteroid users (n=68)	p-value
Age	46.5±14.9	51.3±16.4	0.017
Male sex	252 (63.2)	46 (67.6)	0.476
BMI	22.3±4.8	21.1±4.4	0.073
Smoking	186 (46.6)	37 (54.4)	0.234
Alcohol abuse	111 (27.8)	23 (33.8)	0.312
HIV	214 (53.6)	25 (36.8)	0.010
Diabetes	58 (14.5)	17 (25.0)	0.030
Neoplasia	29 (7.3)	3 (4.4)	0.547
Liver failure	113 (28.3)	13 (19.1)	0.114
Smear-positive TB	114 (28.6)	19 (27.9)	0.915
Prior anti-TB therapy	123 (30.8)	23 (33.8)	0.622
Vasopressor use	318 (79.7)	44 (64.7)	0.006
APACHE II score	22.3±8.1	22.1±8.2	0.864
SOFA score	6.8±3.6	6.3±3.5	0.270
Death	231 (57.9)	28 (41.2)	0.010

Data are presented as mean ±SD, or n/N (%): number of cases with characteristic/total number of cases (percentage).

The mortality was higher among corticosteroid users (59.9%) than in noncorticosteroid users (41.2%) (p=0.010). In a multivariate analysis, the best model included the variables: age, diabetes, HIV, vasopressor use, and death. Only death was independently associated with corticosteroid use (Table 2). The total dose of corticosteroid in prednisone equivalents was not different between survivors and nonsurvivors (median [interquartile range]: 80 mg [56.6–146.7 mg] vs. 80 mg [50–135 mg]; p=0.881). In addition, the total time of corticosteroid use was shorter in nonsurvivors than that in survivors (median [interquartile range]: 12 days [5–25 days] vs. 21 days [8.8–36.2 days]; p<0.0001), but the length of hospital stay was also shorter in nonsurvivors as compared to that in survivors (median [interquartile range]: 23 days [11–43 days] vs. 42 days [28–58 days]; p<0.0001).

DISCUSSION

In this retrospective study, we demonstrated, in TB patients in MV, higher mortality rate among corticosteroid users (59.9%) as compared to noncorticosteroid users (41.2%). In addition, the total dose of corticosteroids in prednisone equivalents was not different between survivors and nonsurvivors.

The use of corticosteroids is recommended in the meningeal TB treatment with a moderate degree of evidence and is considered in the treatment of pericardial TB, with a low degree of evidence[25]. In pleural TB, the use of corticosteroids would be associated with a faster recovery of symptoms, although it has no impact on the outcome[26]. However, the role of corticosteroids in the pulmonary TB treatment is still uncertain and, although it has been evaluated in several studies, some of them were conducted more than 20 years ago, before the introduction of therapies with rifampicin and combinations of drugs.

One of the first studies[16] that described the adjunctive use of corticosteroids in pulmonary TB, 12 cases were reported in which 20–60 mg of prednisone was used daily, for an average of 20.1±9 days. During this period, the patients' appetites, weight, and serum albumin were increased, and no deaths were reported. Kim et al.[18] demonstrated that among TB pneumonia patients, the use of corticosteroids was associated with a lower mean mortality rate, but in the miliary TB group, those receiving corticosteroids did not have a better survival rate. In both studies[16,18] the mean daily dosage of prednisone equivalents was lower than that used in our study, which may explain some of the different results.

Several studies have shown no benefit in reducing mortality with the use of corticosteroids in pulmonary TB patients. A meta-analysis[20] that evaluated the use of corticosteroids in patients with pulmonary TB showed that after excluding studies with a high risk of bias, there was no difference in mortality between the groups that used and that did not use corticosteroids. Another meta-analysis[21], which included 18 studies, also demonstrated that the use of corticosteroids did not show a reduction in all-cause mortality when compared to placebo or no steroid. Also, Yang et al.[22] investigated the 90-day mortality rate in patients with pulmonary TB requiring intensive care and using corticosteroids. They studied retrospectively 124 patients and found that the corticosteroid used had no effect on the 90-day mortality rate. In addition, in a more recent meta-analysis[19], from 2018, 35 studies were included to assess the outcomes of patients with TB who required ICU admission. The most common indications for the use of corticosteroids were miliary TB, respiratory failure, acute respiratory discomfort syndrome, and shock. The use of corticosteroids in this group of patients did not demonstrate a reduction in mortality.

This study has some methodological limitations. First, we recruited patients from a single tertiary care hospital. However, we believe the results may apply to other settings. Second, retrospective analysis is also a limitation, since the data collected are dependent on medical records, often incomplete or insufficient, and some information is not widely accessible, such as adherence to TB and HIV treatment or duration of illness (HIV). Third, we cannot exclude a selection bias once that is quite probably that the most severe cases (of lung involvement) were candidates who receive the corticosteroids; nevertheless, we performed a multivariate analysis to evaluate if the use of corticosteroids was independently associated with mortality, minimizing the possible selection bias. Despite these concerns,

Table 2. Multivariate analysis of factors associated with corticosteroid use.

Characteristic	β	SE	Wald	OR (95%CI)	p-value
Age	-0.016	0.010	2.532	0.984 (0.965–1.004)	0.112
Diabetes	-0.271	0.352	0.591	0.763 (0.382–1.522)	0.442
HIV infection	0.370	0.314	1.389	1.448 (0.782–2.680)	0.238
Vasopressor use	0.553	0.308	3.221	1.738 (0.950–3.179)	0.073
Death	0.589	0.291	4.104	1.803 (1.019–3.188)	0.043

we showed that the use of corticosteroids in patients with pulmonary TB is associated with higher mortality.

CONCLUSIONS

In this study, we identified that TB patients in MV who used corticosteroids had a higher mortality rate than those who did not use corticosteroids. The role of corticosteroids in pulmonary TB, especially in critically ill patients, remains unclear and needs further evaluation in prospective studies.

AUTHORS' CONTRIBUTIONS

CXL: Conceptualization, Methodology, Investigation, Data curation, Project administration, Writing – original draft. **CA:** Conceptualization, Methodology, Investigation, Writing – review & editing. **FDM:** Conceptualization, Methodology, Investigation, Writing – review & editing. **RMB:** Conceptualization, Methodology, Investigation, Writing – review & editing. **AAF:** Conceptualization, Methodology, Investigation, Writing – review & editing. **DRS:** Conceptualization, Methodology, Investigation, Data curation, Project administration, Supervision, Writing – original draft.

REFERENCES

1. Greenaway C, Menzies D, Fanning A, Grewal R, Yuan L, Mark Fitzgerald J. Delay in diagnosis among hospitalized patients with active tuberculosis – Predictors and outcomes. Am J Respir Crit Care Med. 2002;165(7):927-33. https://doi.org/10.1164/ajrccm.165.7.2107040
2. Rao VK, Iademarco EP, Fraser VJ, Kollef MH. The impact of comorbidity on mortality following in-hospital diagnosis of tuberculosis. Chest. 1998;114(5):1244-52. https://doi.org/10.1378/chest.114.5.1244. Available from: https://pubmed.ncbi.nlm.nih.gov/9823996/
3. Ribeiro SA, Matsui TN. Hospitalização por tuberculose em hospital universitário. J Pneumol. 2003;29(1). Available from: https://docplayer.com.br/32848146-Hospitalizacao-por-tuberculose-em-hospital-universitario.html
4. Silva DR, Menegotto DM, Schulz LF, Gazzana MB, Dalcin PTR. Mortality among patients with tuberculosis requiring intensive care: a retrospective cohort study. BMC Infect Dis. 2010;10:54. https://doi.org/10.1186/1471-2334-10-54
5. Lee PL, Jerng JS, Chang YL, Chen CF, Hsueh PR, Yu CJ, et al. Patient mortality of active pulmonary tuberculosis requiring mechanical ventilation. Eur Respir J. 2003;22(1):141-7. https://doi.org/10.1183/09031936.03.00038703
6. Penner C, Roberts D, Kunimoto D, Manfreda J, Long R. Tuberculosis as a primary cause of respiratory failure requiring mechanical ventilation. Am J Respir Crit Care Med. 1995;151(3I):867-72. https://doi.org/10.1164/ajrccm/151.3_Pt_1.867
7. Erbes R, Oettel K, Raffenberg M, Mauch H, Schmidt-Ioanas M, Lode H. Characteristics and outcome of patients with active pulmonary tuberculosis requiring intensive care. Eur Respir J. 2006;27(6):1223-8. https://doi.org/10.1183/09031936.06.00088105
8. Silva DR, Menegotto DM, Schulz LF, Gazzana MB, Dalcin PTR. Mortality among patients with tuberculosis requiring intensive care: a retrospective cohort study. BMC Infect Dis. 2010;10:54. https://doi.org/10.1186/1471-2334-10-54
9. Frame RN, Johnson MC, Eichenhorn MS, Bower GC, Popovich J. Active tuberculosis in the medical intensive care unit. Crit Care Med. 1987;15(11):1012-4. https://doi.org/10.1097/00003246-198711000-00005
10. Silva DR, Menegotto DM, Schulz LF, Gazzana MB, Dalcin PDTR. Factors associated with mortality in hospitalized patients with newly diagnosed tuberculosis. Lung. 2010;188(1):33-41. https://doi.org/10.1007/s00408-009-9224-9
11. Hansel NN, Merriman B, Haponik EF, Diette GB. Hospitalizations for tuberculosis in the United States in 2000: predictors of in-hospital mortality. Chest. 2004;126(4):1079-86. https://doi.org/10.1378/chest.126.4.1079
12. Falques Casanovas M, Langohr K, Gomez Melis G, Garcia de Olalla Rizo P, Jansa Lopez del Vallado JM, Cayla Buqueras JA. Survival of patients with HIV-related tuberculosis. Study of mortality during the first 9 months of treatment. Rev Esp Salud Publica. 1999;73(5):549-62. PMID: 10650746
13. Pablos-Méndez A, Sterling TR, Frieden TR. The relationship between delayed or incomplete treatment and all-cause mortality in patients with tuberculosis. JAMA. 1996;276(15):1223-8. https://doi.org/10.1001/jama.1996.03540150025026
14. Mehta JB, Fields CL, Byrd RP Jr, Roy T. Nutritional status and mortality in respiratory failure caused by tuberculosis. Tenn Med. 1996;89(10):369-71. Available from: https://pubmed.ncbi.nlm.nih.gov/8870488/
15. Silva DR, Gazzana MB, De Tarso P, Dalcin R. Severe tuberculosis requiring ICU admission. J Bras Pneumol. 2012;38(3):386-94. https://doi.org/10.1590/s1806-37132012000300015
16. Muthuswamy P, Hu TC, Carasso B, Antonio M, Dandamudi N. Prednisone as adjunctive therapy in the management of pulmonary tuberculosis: report of 12 cases and review of the literature. Chest. 1995;107(6):1621-30. https://doi.org/10.1378/chest.107.6.1621
17. Wallis RS. Reconsidering adjuvant immunotherapy for tuberculosis. Clin Infect Dis. 2005;41(2):201-8. https://doi.org/10.1086/430914
18. Kim YJ, Pack KM, Jeong E, Na JO, Oh YM, Lee SD, et al. Pulmonary tuberculosis with acute respiratory failure. Eur Respir J. 2008;32(6):1625-30. https://doi.org/10.1183/09031936.00070907
19. Muthu V, Agarwal R, Dhooria S, Aggarwal AN, Behera D, Sehgal IS. Outcome of critically ill subjects with tuberculosis: systematic review and meta-analysis. Respir Care. 2018;63(12):1541-54. https://doi.org/10.4187/respcare.06190
20. Critchley JA, Young F, Orton L, Garner P. Corticosteroids for prevention of tuberculosis mortality – Authors' reply. Lancet Infect Dis. 2013;13(11):916-7. Available from: https://www.academia.edu/13706798/Corticosteroids_for_prevention_of_tuberculosis_mortality_Authors_reply
21. Critchley JA, Orton LC, Pearson F. Adjunctive steroid therapy for managing pulmonary tuberculosis. Cochrane Database Syst Rev. 2014;2014(11):CD011370. https://doi.org/10.1002/14651858.CD011370
22. Yang JY, Han M, Koh Y, Kim W-S, Song J-W, Oh Y-M, et al. Effects of corticosteroids on critically Ill pulmonary tuberculosis patients with acute respiratory failure: a propensity analysis of mortality. Clin Infect Dis. 2016;63(11):1449-55. https://doi.org/10.1093/cid/ciw616

23. Silva DR, Rabahi MF, Sant'Anna CC, da Silva-Junior JLR, Capone D, Bombarda S, et al. Diagnosis of tuberculosis: a consensus statement from the Brazilian Thoracic Association. J Bras Pneumol. 2021;47(2):e20210054. https://doi.org/10.36416/1806-3756/e20210054

24. Pereira GR, Barbosa MS, Dias NJD, De Almeida CPB, Silva DR. Impact of introduction of Xpert MTB/RIF test on tuberculosis (TB) diagnosis in a city with high TB incidence in Brazil. PLoS One. 2018;13(3):e0193988. https://doi.org/10.1371/journal.pone.0193988

25. Schutz C, Davis AG, Sossen B, Lai RPJ, Ntsekhe M, Harley YXR, et al. Corticosteroids as an adjunct to tuberculosis therapy. Expert Rev Respir Med. 2018;12(10):881-91. https://doi.org/10.1080/17476348.2018.1515628

26. Singh S, Tiwari K. Use of corticosteroids in tuberculosis. J Assoc Chest Physicians. 2017;5(2):70. Available from: http://www.jacpjournal.org/text.asp?2017/5/2/70/206131

ORIGINAL ARTICLE

https://doi.org/10.1590/1806-9282.20220200

Characteristics and outcomes of COVID-19 patients assisted by intensivists and nonintensivists

Sergio Henrique Loss[1*], Deise Cappelletti Luce[2], Giovana Capellari[2]

SUMMARY

OBJECTIVE: The aim of this study was to assess the outcomes of critically ill patients with COVID-19 in an intensive care unit seen by a care team formed by intensive and nonintensive physicians and treatment guided by processes and protocols linked to the "choosing wisely" concept, comparing them with similar data recently published.

METHODS: An observational cohort including adult patients with COVID-19 admitted to the intensive care unit of Hospital Independence between August 2020 and August 2021. Inclusion criteria were 18 years of age or older and there were no exclusion criteria.

RESULTS: The study included 449 patients, of which 64.1% were referred from the ward, 21.6% from emergency rooms, and 14.2% from another hospital (continuity of attendance). The overall mortality was 48.5%, occurring mainly in the elderly and or those undergoing mechanical ventilation. We did not find any associations between different strata of body mass index and mortality. In the multivariate analysis, the time elapsed between the onset of symptoms and hospital admission, mechanical ventilation, C-reactive protein value at the end of the first week in the intensive care unit, and renal failure were independently associated with mortality. Vaccinated people comprised 8.8% of the sample, with no differences in mortality among the different vaccines, and 13.4% of patients underwent palliative treatment.

CONCLUSIONS: Patients admitted for acute respiratory syndrome due to SARS-CoV-2 are severe and have a high mortality rate, mainly if submitted to invasive mechanical ventilation. The emergence of acute renal failure marks an especially severe subgroup with increased mortality. Processes and protocols linked to the "choosing-wisely" concept seemed to significantly benefit our intensive care unit since it had a large contingent of nonspecialist physicians.

KEYWORDS: Critical care. COVID-19. Mechanical ventilation.

INTRODUCTION

Severe acute respiratory syndrome by Coronavirus 2 (SARS-CoV-2), which belongs to the Coronaviridae family, is responsible for the current Coronavirus 2019 (COVID-19) outbreak and has been devastating worldwide[1,2]. This infection constitutes a flu-like illness similar to severe acute respiratory syndrome by coronavirus (SARS-CoV) and Middle East respiratory syndrome by coronavirus (MERS-CoV), which occurred in 2002 and 2012, respectively. It has a broad spectrum of signs and symptoms so that most infections (80%) are mild, and 6–10% will require transfer to the intensive care unit (ICU)[3-5].

Critically ill patients who are transferred to the ICU usually develop ventilatory failure and the need for noninvasive or invasive ventilatory support, in addition to multiorgan dysfunctions, secondary to a combination of exacerbated inflammatory and thrombogenic activity[1]. The mortality of critically ill patients due to COVID-19 is high, with reports ranging between 50 and 90%[6]. An observational study found that mortality in Brazil varied by region (higher in the north and northeast) and changed with aspects related to the need for invasive ventilatory support or age[7].

This study aims to describe the epidemiological profile, clinical behavior, and outcomes of critically ill patients seen by a care team formed by intensive and nonintensive physicians, comparing them with similar data recently published.

METHODS

Design and patients

This observational study included adult patients with COVID-19 admitted to the ICU of Hospital Independence. Inclusion criteria were 18 years of age or older. There were no exclusion criteria. The Research Ethics Committee approved the study at our institution.

[1]Hospital Independência, Intensive Care Physician – Porto Alegre (RS), Brazil.
[2]Hospital Independência, Intensive Care Nurse – Porto Alegre (RS), Brazil.
*Corresponding author: sergio.loss@gmail.com
Conflicts of interest: the authors declare there is no conflicts of interest. Funding: none.
Received on February 17, 2022. Accepted on June 12, 2022.

Institutional protocol for the treatment of critically ill patients with COVID-19

Patients admitted to the ICU undergo the institutional protocol for the treatment of critically ill patients with COVID-19, which is summarized as follows:

a) Noninvasive ventilatory support if feasible (noninvasive ventilation, high-flow oxygen cannula); self-prone position.
b) Invasive ventilatory support in the event of failure or when (a) is not feasible. Preferentially adjusted volume-controlled regimen within current ventilation assumptions for patients with acute respiratory distress syndrome – protective ventilation strategy; prone ventilation in refractory hypoxemia.
c) Hemodynamic support according to the institution's usual protocol: a fluid challenge in patients with dysoxia and volume responders (pulse pressure variation – delta PP, ultrasound indicators); use of vasopressors (noradrenaline and/or vasopressin).
d) Use of antimicrobial drugs only if the bacterial infection diagnosis is confirmed or if there is a strong possibility of associated bacterial contamination.
e) Preferentially enteral and early nutritional support (started within the first 24–48 h after hemodynamic stability, caloric and protein target adjusted for the first 3 and 7 days).
f) Nonuse of "labeled" drugs as early therapy for COVID (e.g., chloroquine, ivermectin, azithromycin, and zinc).
g) Use of dexamethasone 6 mg daily for 10 days.
h) Anticoagulation in cases of vascular thrombosis.
i) Daily rounds with an intensive care specialist.

Data and collection tools

Data collection took place over 13 months (August 2020 to August 2021). Data were obtained by consulting medical records. The information collected was recorded in an electronic spreadsheet: age, gender, morbidities (e.g., hypertension, diabetes, heart disease, lung disease, and cancer), duration of mechanical ventilation (MV), length of stay in the ICU and hospital, body mass index (BMI), SAPs-3 score, and outcome (hospital discharge or death). Morbidities were assumed to be present based on data from medical records with a demonstration or confirmatory tests that allowed the diagnosis to be confirmed.

Statistical analysis

Sample for convenience. Descriptive analysis used frequencies and percentages, means and standard deviations (SDs), or medians and interquartile ranges (IQRs). Comparisons were performed using χ^2 or Fisher's exact tests for qualitative variables and using t-tests or nonparametric Wilcoxon tests for quantitative variables. Binary logistic regression models were used to compare in-hospital courses and clinical outcomes between the groups. The number of independent variables followed the rule of including one variable for every 10 results. A p-value <0.05 was considered statistically significant. Data were analyzed using the statistical software package Microsoft Excel version 16.5, StatPlus version v7, and IMB SPSS-23.0.

RESULTS

Data were collected between August 2020 and August 2021 and totaled 449 patients. The admissions came from 64.1% by referral from the ward, 21.6% by referral from emergencies or emergency care units in the state of Rio Grande do Sul (UPA), and 14.2% by referral from another hospital (continuity of attendance). When previously admitted to the ward and later transferred to the ICU, the average transfer time was 1 [0–2] day. Table 1 summarizes the epidemiological profile of the sample, stratified for mortality.

The standardized mortality ratio (SMR), using the prediction of mortality from the score of the SAPS-3 score, was 1.25 (if we consider the hospital mortality of the patient admitted to the ICU, we have an SMR of 1.3). The time (in days) elapsed between the onset of symptoms and hospitalization and the time to perform tracheotomy between our patients and patients transferred from another institution for continuity of care in our ICU did not show a significant difference (9 [7–12] vs. 9.5 [6.75–12]; p=0.705 and 22 [18-27] vs. 23 [19–27]; p=0.923, respectively). As for invasive ventilatory support, we observed that when we stratified patients by age (over and under 60 years), mortality was found to be 81.1 and 51.4%. Mortality was even higher in older ventilated patients. Individuals who were invasively ventilated and aged 75 years and 80 years or older had mortality rates of 97.5 and 100%, respectively. Table 2 compares the observed mortality of different age groups in this study with reports from other studies.

We found no association between different BMI strata (less than 20 kg/m^2, between 20 and 30 kg/m^2, between 30 and 40 kg/m^2, and greater than 40 kg/m^2; p=0.458) and outcomes. Patients with a BMI of <20 kg/m^2 represented 1.8% of the population, between 20 and 30 kg/m^2 enrolled 48.3%, and greater than 30 kg/m^2 comprised 49.9% of patients. All patients received oral/enteral nutritional support following the institutional protocol (we did not observe cases of parenteral nutrition).

Table 1. Epidemiological profile of critically ill patients with COVID-19.

	All 449	Outcomes		p-value
		Survival 231 (51.45%)	Nonsurvival 218 (48.55%)	
Age (years)	60 [50–70]	56 [45–73]	65 [56–73]	<0.001
Male (%)	52.11	51.71	48.29	0.907
Time between OS and H (days)	9 [7–12]	10 [8–11]	9 [7–11]	0.001
Time between H and ICU (days)	1 [0–2]	1 [0–2]	1 [0–2]	0.531
Previous morbidities				
Diabetes mellitus (%)	28.5	46.9	53.1	0.220
Arterial hypertension (%)	52.6	44.1	55.9	0.001
Ischemic heart disease (%)	8.2	37.8	62.9	0.083
Cardiac insufficiency (%)	3.6	37.5	62.5	0.255
Chronic kidney failure (%)	4.5	50	50	0.894
Cancer (%)	4.0	27.8	72.2	0.042
AIDS (%)	2.2	60	40	0.584
COPD (%)	7.6	17.6	82.4	<0.001
Asthma (%)	5.8	53.8	46.2	0.800
Absence of known morbidities (%)	28.7	59.6	40.4	0.001
SAPS-3	53 [47–61]	50 [47–66]	58 [52–66]	<0.001
BMI (kg/m^2)	29.8 [26.1–34.2]	30.3 [26.3–33.4]	29.3 [25.6–33.4]	0.114
CRP initial (mg/dL)	19 [7.2–26.5]	17.8 [6.15–28.4]	20.8 [9.5–28.4]	0.004
CRP final (mg/dL)	7.2 [3.9–21.3]	4.5 [2.3–27.67]	15 [6.2–27.6]	<0.001
CRP variation (%)	-45.9 [-78.4–9.5]	-72.1 [-86.6–32.6]	-20.6 [-66–32.6]	<0.001
Mechanical ventilation (%)	68.5	32.9	67.1	<0.001
Time to MV (days)	13 [8–20]	13 [9–18]	13 [7–18]	0.152
Tracheotomy (total %)	15.4	50.3	49.7	0.896
Tracheotomy at IND (%)	8.4	48.6	51.4	0.744
Time to tracheotomy (days)	22 [18–28.5]	21 [18–27]	22.5 [18.2–27]	0.505
Acute kidney failure (%)	41.4	22	78	<0.001
Hemodialysis (%)	22.3	16	84	<0.001
CCI (%)	34	46.8	56.2	0.002
Vaccinated (2 doses %)*	8.8	39.3	60.7	0.190
Palliative care (%)	13.4	10	90	<0.001
ICU LOS (days)	11 [6–18]	9 [6–19]	14 [8–19]	<0.001
Hospital LOS (days)	17 [11–24]	18 [12–22]	16 [10–22]	<0.001

OS: onset of symptoms; H: hospitalization; ICU: intensive care unit; AIDS: acquired immunodeficiency syndrome; COPD: chronic obstructive pulmonary disease; SAPS-3: Simplified Acute Physiology Score 3; BMI: body mass index; CRP: C-reactive protein (Initial and final PCR over the first week); MV: mechanical ventilation; IND: Hospital Independência; CCI: chronic critical illness; LOS: length of stay. *Related to hospitalization after vaccination campaign (28 vaccinated out 319 admissions).

A multivariate model was constructed using the univariate analyses most significantly associated with mortality (Table 3).

Regarding admissions of previously vaccinated patients, we have 6.2% (28 patients) fully vaccinated, if we consider the entire collection period. If we consider the admissions that took place after the start of vaccination, the percentage rises to 8.8%. The partially vaccinated group totaled 16 patients, corresponding to 3.5 and 5%, respectively, of the total number of patients admitted during the entire collection period or only after the start of vaccination. Of those fully vaccinated,

Table 2. Comparative mortality data with other studies.

	Ranzani (Ref 7)		Al Mutair (Ref 12)	IND
	Brazil	South (Brazil)		
MV	47.8	54.3	29.0	33.7
Deaths in the ICU	59.0	55.5	41.8	46.4
Deaths in MV	79.7	72.2	65.3	67.3
Deaths in MV <60 years	67.8	54.6		51.4
Deaths in MV ≥60 years	87.3	82.1		81.1
Age <60 years	41.6	35.8		34.8
Age ≥60 years	71.7	68.6		61.1

Data are reported in percentages. IND: Hospital Independência; MV: mechanical ventilation; ICU: intensive care unit.

Table 3. Multivariate analysis of parameters associated with mortality.

	RR (95%CI)	p-value
Age	1.013 (0.967–1.061)	0.578
SAPS-3	1.099 (1.017–1.188)	0.016
Time between OS and H	0.887 (0.794–0.991)	0.034
Mechanical ventilation	36.489 (2.645–503.385)	0.007
CRP initial	0.997 (0.992–1.001)	0.219
CRP final	1.010 (1.004–1.016)	<0.001
CRP variation percentage	0.934 (0.809–1.080)	0.361
Arterial hypertension	0.380 (0.085–1.701)	0.206
COPD	7.792 (0.582–104.262)	0.120
Absence of known morbidities	0.331 (0.074–1.469)	0.146
Acute kidney failure	7.516 (2.969–19.024)	<0.001
Critical chronic illness	0.634 (0.245–1.642)	0.348

RR: relative risk; CI: confidence interval; SAPS-3: Simplified Acute Physiology Score 3; OS: onset of symptoms; H: hospitalization; CRP: C-reactive protein (in the beginning and at the end of first week); COPD: chronic obstructive pulmonary disease.

89.3% received CoronaVac, 7.1% AstraZeneca, and 3.5% Pfizer. The age of patients who received CoronaVac was higher but not statistically significant compared to those vaccinated with AstraZeneca (73 [66–77] years vs. 68 [62.5–77] years; p=0.713 – only one patient vaccinated with Pfizer, 56 years old). Mortality in this group was 60.7%, all CoronaVac (nonsignificant difference, p=0.055). Analyzing the partially vaccinated in the same way, we observed that 37.5% received one dose of CoronaVac, and 62.5% received one AstraZeneca dose. Their ages also did not vary significantly (CoronaVac 58.5 [43–62.5] years; AstraZeneca 55 [48.75–62.5]; p=0.872). Mortality in this group was 31.2%, 20% of whom received the CoronaVac vaccine, and 80% AstraZeneca (nonsignificant difference, p=0.329).

Our team defined a palliative treatment strategy for 13.4% of patients. Mortality in the ICU was 80% and in-hospital was 90%.

DISCUSSION

Due to the pandemic caused by SARS-CoV-2 and unlike other hospitals in the city, we set up an inexperienced medical group of nonspecialists in intensive care medicine. To this end, we review our protocols and guide decisions within the recommendations of "choosing wisely"[8-10], in addition to highlighting medical leadership specialized in intensive care medicine and aligned with these recommendations.

Our retrospective cohort showed that 71.3% of patients admitted by COVID-19 to our ICU had some prior morbidity and that this was significantly associated with mortality (58.9%; p=0.001). The morbidities that were significantly associated with death were arterial hypertension and chronic obstructive pulmonary disease. Obesity (BMI≥30 kg/m^2) was prevalent, representing 59.9% of the enrolled population.

According to our study, mortality in the ICU was 46.4% and in-hospital was 48.5%. The SMR demonstrated an excess of mortality in the order of 30%. However, SAPS-3 seems to underestimate the mortality of critically ill patients with COVID-19, with the need to calibrate the tool to parameterize outcomes in this context[11]. The SAPS-3 score probably should receive a calibration for COVID-19.

In the univariate analyses, the time elapsed between the onset of symptoms caused by SARS-CoV-2 infection, older age, SAPS-3 mortality score, highest C-reactive protein (CRP) (in the beginning and at the end of first week), renal failure, high blood pressure, cancer, and chronic obstructive pulmonary disease were significantly associated with mortality. Except for the behavior of CRP and the occurrence of renal failure, our data agree with the study by Al Mutair et al[12]. They carried out a similar analysis in Asia. Also, in agreement with this study, we could not demonstrate that BMI strata are associated with mortality (which surprised us). Regarding CRP, we understand that this biomarker that measures inflammation was much more related to the secondary infectious complications in the course of patients than viral pneumonia per se, because, as suggested by the increased time lag between symptom onset and hospital admission (Table 1), the possibility of previous asymptomatic hypoxia[13] cannot be disregarded, so that the CRP measurement in the first week of ICU stay is probably no longer related to the viral infection at this time. Thus, the variation in CRP in the

first 7–10 days says much more about the control of the secondary bacterial infection than the control of the virus disease itself. The disagreement regarding the impact of renal failure and the need for renal replacement therapy between our study and the Asian cohort must be due to different epidemiological contexts. Other studies have linked renal dysfunction to worse outcomes in critically ill patients[14,15].

The association between older age and the need for invasive MV seemed essential to determine death, especially in individuals aged over 60 years. These data do not differ from the Brazilian case series that included more than 250,000 patients[7], demonstrating the devastating consequences of severe coronavirus pneumonia in the elderly.

In the multivariate analysis, the time elapsed between symptom onset and hospital admission, MV, CRP value at the end of the first week in the ICU, and renal failure were independently associated with mortality, notably the need for invasive ventilatory and renal support. These data can support us in the elaboration of an earlier prognosis for critically ill patients with COVID-19. Chronic critical illness (CCI), according to our expectations, had a high incidence in our ICU. We defined CCI according to consensus published over the past decade[16-18], mainly based on prolonged dependence on MV (longer than 14 days), associated with evident muscle weakness acquired in the ICU. As expected, it constituted a fragile population, manifesting the usual range of signs/symptoms that characterize the syndrome.

Our study failed to identify the clear superiority of one vaccine over another among those hospitalized after vaccination. It is important to emphasize that the number of vaccination constituted a small portion of our total population, making us analyze the data with extreme caution.

The choice for palliative treatment resulted from the assessment of the multidisciplinary care group when there was agreement that therapeutic tenacity generated futility from a certain point onward and would increase dysthanasia and the suffering of the patient and their families. In this context, two worlds were always associated, CCI and the need for palliative treatment. At this moment, the decision-making process was done in the best interest of the patients. Advance directives were respected, although it is an uncommon condition in our reality[19].

Our study has limitations. It is an observational study, and as such, we cannot determine causality. Our study was carried out in a single center so that generalizations should not be made without caution and contextualization. We did not analyze aspects potentially related to organizing pneumonia because we do not have images of all patients with this suspicion. In addition, the patients did not undergo a formal organizing pneumonia protocol.

CONCLUSIONS

Patients admitted for acute respiratory syndrome due to SARS-CoV-2 are severe and have a high mortality rate, mainly if submitted to invasive MV. The emergence of acute renal failure marks an especially severe subgroup with increased mortality. Our results are similar to the best results published to date and demonstrate that the consolidation of processes and application of protocols linked to the "choosing-wisely" concept seemed to significantly benefit our ICU since a large contingent of non-specialist physicians.

ACKNOWLEDGMENT

The authors thank Dr. Ana Carolina Peçanha Antonio for her guidance and suggestions and Dr Angelo Giuliani Chaves for all his support.

AUTHORS' CONTRIBUTIONS

SHL: Conceptualization, Data curation, Formal analysis, Writing – original draft, Writing – review & editing. **DCL:** Formal analysis, Data curation, Writing – original draft, Writing – review & editing. **GC:** Formal analysis, Writing – original draft, Writing – review & editing.

REFERENCES

1. LaFond E, Weidman K, Lief L. Care of the postcoronavirus disease 2019 patient. Curr Opin Pulm Med. 2021;27(3):199-204. https://doi.org/10.1097/MCP.0000000000000767
2. Bouadma L, Lescure FX, Lucet JC, Yazdanpanah Y, Timsit JF. Severe SARS-CoV-2 infections: practical considerations and management strategy for intensivists. Intensive Care Med. 2020;46(4):579-82. https://doi.org/10.1007/s00134-020-05967-x
3. Mendes JJ, Silva MJ, Miguel LS, Gonçalves MA, Oliveira MJ, Oliveira CDL, et al. Sociedade Portuguesa de Cuidados Intensivos guidelines for stress ulcer prophylaxis in the intensive care unit. Rev Bras Ter Intensiva. 2019;31(1):5-14. https://doi.org/10.5935/0103-507X.20190002
4. Loss SH, Nunes DL, Franzosi OS, Teixeira C. A pragmatic approach and treatment of coronavirus disease 2019 (COVID-19) in intensive care unit. Rev Assoc Med Bras (1992). 2020;66(8):1157-63. https://doi.org/10.1590/1806-9282.66.8.1157

5. Synowiec A, Szczepański A, Barreto-Duran E, Lie LK, Pyrc K. Severe Acute Respiratory Syndrome Coronavirus 2 (SARS-CoV-2): a Systemic Infection. Clin Microbiol Rev. 2021;34(2):e00133-20. https://doi.org/10.1128/CMR.00133-20
6. Phua J, Weng L, Ling L, Egi M, Lim CM, Divatia JV, et al. Intensive care management of coronavirus disease 2019 (COVID-19): challenges and recommendations. Lancet Respir Med. 2020;8(5):506-17. https://doi.org/10.1016/S2213-2600(20)30161-2
7. Ranzani OT, Bastos LSL, Gelli JGM, Marchesi JF, Baião F, Hamacher S, et al. Characterisation of the first 250,000 hospital admissions for COVID-19 in Brazil: a retrospective analysis of nationwide data. Lancet Respir Med. 2021;9(4):407-18. https://doi.org/10.1016/S2213-2600(20)30560-9
8. Cassel CK, Guest JA. Choosing wisely: helping physicians and patients make smart decisions about their care. JAMA. 2012;307(17):1801-2. https://doi.org/10.1001/jama.2012.476
9. Lobo SM, Mendes CL, Rezende E. Choosing Wisely in intensive care medicine. Rev Bras Ter Intensiva. 2020;32(1):11-3. https://doi.org/10.5935/0103-507X.20200003
10. Zimmerman JJ, Harmon LA, Smithburger PL, Chaykosky D, Heffner AC, Hravnak M, et al. Choosing wisely for critical care: the next five. Crit Care Med. 2021;49(3):472-81. https://doi.org/10.1097/CCM.0000000000004876
11. Kurtz P, Bastos LSL, Salluh JIF, Bozza FA, Soares M. SAPS-3 performance for hospital mortality prediction in 30,571 patients with COVID-19 admitted to ICUs in Brazil. Intensive Care Med. 2021;47(9):1047-9. https://doi.org/10.1007/s00134-021-06474-3
12. Al Mutair A, Elhazmi A, Alhumaid S, Ahmad GY, Rabaan AA, Alghdeer MA, et al. Examining the Clinical Prognosis of Critically Ill Patients with COVID-19 Admitted to Intensive Care Units: A Nationwide Saudi Study. Medicina (Kaunas). 2021;57(9):878. https://doi.org/10.3390/medicina57090878
13. Dhont S, Derom E, Van Braeckel E, Depuydt P, Lambrecht BN. The pathophysiology of 'happy' hypoxemia in COVID-19. Respir Res. 2020;21(1):198. https://doi.org/10.1186/s12931-020-01462-5
14. Luo M, Yang Y, Xu J, Cheng W, Li XW, Tang MM, et al. A new scoring model for the prediction of mortality in patients with acute kidney injury. Sci Rep. 2017;7(1):7862. https://doi.org/10.1038/s41598-017-08440-w
15. Hoste EA, Bagshaw SM, Bellomo R, Cely CM, Colman R, Cruz DN, et al. Epidemiology of acute kidney injury in critically ill patients: the multinational AKI-EPI study. Intensive Care Med. 2015;41(8):1411-23. https://doi.org/10.1007/s00134-015-3934-7
16. Loss SH, Marchese CB, Boniatti MM, Wawrzeniak IC, Oliveira RP, Nunes LN, et al. Prediction of chronic critical illness in a general intensive care unit. Rev Assoc Med Bras (1992). 2013;59:241-7. https://doi.org/10.1016/j.ramb.2012.12.002
17. Mira JC, Gentile LF, Mathias BJ, Efron PA, Brakenridge SC, Mohr AM, et al. Sepsis Pathophysiology, Chronic Critical Illness, and Persistent Inflammation-Immunosuppression and Catabolism Syndrome. Crit Care Med. 2017;45(2):253-62. https://doi.org/10.1097/CCM.0000000000002074
18. Nelson JE, Cox CE, Hope AA, Carson SS. Chronic critical illness. Am J Respir Crit Care Med. 2010;182(4):446-54. https://doi.org/10.1164/rccm.201002-0210CI
19. Madrid RA, McGee W. Value, Chronic Critical Illness, and Choosing Wisely. J Intensive Care Med. 2019;34(8):609-14. https://doi.org/10.1177/0885066618790942

ORIGINAL ARTICLE

https://doi.org/10.1590/1806-9282.20220232

Sexual function in Brazilian female adolescents and young adults: a cross-sectional study

Mariana Negri[1], Eduardo de Souza[1], Maria Regina Torloni[2], Meireluci Costa Ribeiro[3], Edward Araujo Júnior[1*], Cristina Aparecida Falbo Guazzelli[1]

SUMMARY

OBJECTIVE: The aim of this study was to investigate and compare the sexual function of Brazilian adolescents and young women who were using popular contraceptive methods.

METHODS: This cross-sectional study took place in 2012–2014 in a free family planning clinic of a tertiary teaching hospital in Brazil. Participants were female adolescents (10–19 years) and young adults (20–24 years) who were using barrier (condom) or hormonal contraceptive methods. The Female Sexual Function Index questionnaire was used to assess the sexual function in the last 4 weeks.

RESULTS: A total of 199 women (128 adolescents and 71 young adults) were included. There were no significant differences in the mean total Female Sexual Function Index scores of adolescents and young adults (26.6±5.7 versus 27.6±6.2, respectively, p=0.264). Compared to young adults, adolescents had significantly lower mean scores for orgasm (3.9±1.5 versus 4.4±1.4, p=0.020) and dyspareunia (4.4±1.6 versus 5.2±1.5, p=0.001; lower scores indicate more dyspareunia). There were no significant differences in the proportion of adolescents versus adults classified as being at risk for sexual dysfunction (38.3 versus 42.3%, p=0.651) or at risk of low desire (18.0 versus 21.1%, p=0.579).

CONCLUSION: Nearly 40% of Brazilian female adolescents and young adults are at risk for sexual dysfunctional symptoms and 19% have low desire, without significant differences between the two age groups.

KEYWORDS: Sexuality. Sexual behavior. Women health. Contraception. Adolescent.

INTRODUCTION

Adolescents, defined by the World Health Organization as individuals between 10 and 19 years of age, represent almost one-fifth of the world population[1]. Adolescence is a period of many physical, cognitive, emotional, and behavioral changes associated with a desire for autonomy and new behaviors. Along with experimentation of alcohol, drugs, and tobacco use, many adolescents also start sexual activity, a behavior that can expose them to sexual and reproductive risks including infections and unplanned pregnancy[2]. The experience of sexual activity also exposes vulnerable young people to personal and emotional conflicts[3,4].

In Latin America, 22% of adolescents report to have had their first sexual intercourse before 15 years of age, not always consciously and safely[5]. This first experience, in most cases, is associated with anxiety due to fear of not responding to the expectations of the sexual partner, insecurity, social pressure, and the choice of a meeting place that is often inadequate[5,6]. Adolescent girls from less affluent families, and with an older first partner, are more likely to report negative feelings regarding their first intercourse experience[7]. In young girls, negative feelings about the first sexual intercourse have been associated with a worse quality of life[8].

Some studies have reported an increase in the use of contraceptive methods at first sexual intercourse, but many young individuals do not use any contraception and continue to have unsafe sex[9]. Condoms and oral hormonal contraceptives are the most frequent contraceptive methods used by young people[9,10].

The existing evidence suggests that many adolescents may have difficulties in sexual experiences that can be related to a lack of knowledge about human sexuality[3,5,7-10]. There are few studies on the prevalence of sexual dysfunction in adolescents and none in Brazil[4].

[1]Universidade Federal de São Paulo, Paulista School of Medicine, Department of Obstetrics – São Paulo (SP), Brazil.
[2]Universidade Federal de São Paulo, Paulista School of Medicine, Department of Internal Medicine – São Paulo (SP), Brazil.
[3]Centro Universitário Salesiano de São Paulo, Postgraduate Program in Sex Therapy – São Paulo (SP), Brazil.
*Corresponding author: araujojred@terra.com.br
Conflicts of interest: the authors declare there is no conflicts of interest. Funding: none.
Received on April 25, 2022. Accepted on May 23, 2022.

The aim of this study was to investigate and compare the sexual function of Brazilian adolescents and young adults who were using popular contraceptive methods. We hypothesized that adolescents would have worse female sexual function scores than young adults.

METHODS

This cross-sectional study involved female adolescents and young adults managed at a large public family planning clinic in Brazil. Recruitment occurred for 18 months (October 2012–April 2014). All participants gave written informed consent, and the study was approved by the Ethics Committee of Federal University of São Paulo, Process no. 97.969, on September 14, 2012.

Potential participants were approached by the main investigator while waiting for their regular visits at the Family Planning Clinic. Inclusion criteria were: adolescents (10–19 years) and young adults (20–24 years), users of combined hormonal (oral or injectable) or barrier (male condom) contraceptive methods. Only adolescents and young women having an exclusive sexual partner in the last month were eligible to participate. Information about the purpose and procedures of the study was explained to each participant, and written informed consent was signed by the participants and legal guardians. Confidentiality and anonymity of data were ensured. We excluded non-native Portuguese speakers, women with visual or auditory deficiencies, or unable to read a written questionnaire due to low literacy. Those who fulfilled the selection criteria and agreed to participate received two written questionnaires to be answered individually and anonymously. The first questionnaire included personal data, socioeconomic status, and gynecological characteristics. The second questionnaire was the Brazilian version of the Female Sexual Function Index (FSFI) that was used to assess female sexual function[11]. They filled out the questionnaires in the waiting room of the clinic with the first author available for questions in a nearby corridor. The completed questionnaires were placed in individual unidentified envelopes and returned to the main investigator.

The FSFI is a self-responsive questionnaire with 19 multiple-choice questions divided into 6 main domains. The Brazilian version of this questionnaire has good internal consistency (Cronbach's alpha 0.791–0.914)[11]. The FSFI evaluates phases of the sexual cycle (desire, arousal, and orgasm), sexual satisfaction, and dyspareunia in the last 4 weeks[11]. Individual scores for each question vary from 0 to 5, except for desire that varies from 1 to 5. Domain scores are obtained by adding individual question scores and multiplying these by a specific factor. Higher domain scores indicate better performance in the specific area, except for the dyspareunia domain where higher scores indicate less dyspareunia. The six domain scores are added to obtain a total FSFI score which ranges from 2 to 36, with higher scores indicating a better sexual function. A total score ≤26 suggests a risk for sexual dysfunction. Only the desire domain has an established cutoff; it is scored on a 10-point scale, with final score ≤5 indicating sexual desire dysfunction symptoms. The FSFI is accepted as a valid tool to measure female sexual function and has previously been used in studies involving young women[12].

Participant characteristics were presented descriptively and compared between groups (adolescents and young adults) using two-tailed Student's t-test or chi-square test. Differences in mean FSFI total and domain scores between the two age groups were assessed using the Student's t-test. Differences in the prevalence of women at risk for sexual dysfunction in adolescents versus young adults were assessed using the chi-square test; $p<0.05$ were considered significant. Statistical analyses were performed using Stata, version 12 (Stata Corp., College Station, TX, USA).

RESULTS

A total of 211 women were invited and agreed to participate in the study, but 12 were excluded because they were not with an exclusive sexual partner during the last month. Therefore, the study included 199 participants (128 adolescents and 71 young adults). The mean age was 19.7 years, with 17.4±1.5 years for adolescents and 22±1.6 years for young adults. Most were Catholic, single, of mixed race, unemployed, and had at least 8 years of formal education. Over 75% of the participants had no children and lived in households with three or more persons. Adolescents were more likely to be single, less educated, unemployed, nulliparous, and live in households with more inhabitants than young adults (Table 1).

Adolescents had a significantly lower mean age at menarche and at sexual initiation than young adults. Adolescents also had significantly fewer sexual partners, less time of sexual activity with their current partner, and less time of current contraceptive use than young adults. Over two-thirds (68.8%) of the adolescents and over three-fourths (76.1%) of the young adults used hormonal contraceptives (Table 2).

There were no significant differences in the mean total (±standard deviation) FSFI scores of adolescents and young adults (26.6±5.7 versus 27.6±6.2, respectively, p=0.264). Adolescents had significantly lower mean orgasm (3.9±1.5 versus 4.4±1.4, p=0.02) and dyspareunia scores (4.4±1.6 versus

5.2±1.5, p=0.001) than young adults. Lower dyspareunia scores indicate more dyspareunia. The domain with the lowest mean score among adolescents was orgasm (3.9). Among young adult women, the lowest mean score was in the desired domain (4.2) (Table 3).

A total of 79 participants (39.7%) were at risk for sexual dysfunction symptoms (total FSFI score ≤26), and 38 participants (19.1%) had scores indicative of low desire (desire domain score <5). There were no significant differences in the proportion of adolescents versus adults classified as being at risk for sexual dysfunction (total FSFI ≤26) (38.3 versus 42.3%, p=0.651) or at risk of low desire (18.0 versus 21.1%, p=0.579). The prevalence of these disorders did not differ significantly according to the contraceptive method used (Table S1).

The contraceptive method was evaluated in relation to the six domains of sexual function, both in adolescents and young adults, and there was no statistically significant result (Table S2).

DISCUSSION

We found that nearly 40% of young Brazilian female adults and adolescents were at risk for sexual dysfunction according to Wiegel's classification[13], without significant differences between the two age groups. Similarly, 41.6% of 144 Canadian

Table 1. Main characteristics of the included participants.

Variable	Adolescents N=128	Young adults N=71	p-value
Age (mean, SD)	17.4±1.5	22.0±1.6	<0.0001*
Religion			
Catholic	59 (46,1)	37 (52,1)	0.265†
Protestant	37 (28,9)	13 (18,3)	
Other/none	32 (25.0)	21 (29.6)	
Marital status			
Single	103 (80.5)	46 (64.8)	0.017†
Married/common law marriage	25 (19.5)	25 (35.2)	
Race			
Black	23 (18.0)	9 (12.6)	0.253†
Mixed	64 (50.0)	31 (43.7)	
White	41 (32.0)	31 (43.7)	
Employment			
Employed	37 (28.9)	38 (53.5)	0.001†
Unemployed	91 (71.1)	33 (46.5)	
Education (years)			
≤8	9 (7.0)	3 (4.2)	<0.0001†
8<12	109 (85.2)	41 (57.7)	
≥12	10 (7.8)	27 (38.1)	
Parity			
0	109 (85.1)	47 (66.2)	0.002†
1	17 (13.3)	17 (23.9)	
2 or more	2 (1.6)	7 (9.9)	
Total number of persons living at home			
1	1 (0.8)	6 (8.5)	0.007†
2	24 (18.7)	18 (25.4)	
3 or more	103 (80.5)	47 (66.1)	

*Student's t-test. †Fisher's exact test. Values presented as N (%) or mean ± standard deviation (SD).

Table 2. Gynecological characteristics of the included participants.

Variable	Adolescents N=128	Young adults N=71	p-value
Menarche (years)	11.8±1.4	12.4±1.3	0.003*
Age at initiation of sexual activity (years)	14.8±2.0	16.2±2.2	<0.0001*
Time of sexual relationship with current partner (months)	14.8±14.6	25.1±21.0	0.0004*
Median	12	24	
Minimum–maximum	1–60	1–81	
Time of use of current contraceptive method (months)	18.1±17.7	48.5±35.4	<0.0001*
Median	12	48	
Minimum–maximum value	1–96	1–132	
Number of sexual partners			
1	63 (49.2)	21 (29.6)	0.006†
2	25 (19.5)	12 (16.9)	
≥3	40 (31.3)	38 (53.5)	
Current contraceptive method			
Oral hormonal contraceptives	51 (39.8)	39 (55.0)	
Monthly injectable contraceptive	37 (28.9)	15 (21.1)	
Condom	40 (31.3)	17 (23.9)	0.132†

*Student's t-test. †Fisher's exact test. Values presented as N (%) or mean ±standard deviation (SD).

Table 3. Sexual function of adolescents and young adults according to the Female Sexual Function Index questionnaire.

Domain	Adolescents N=128	Young adults N=71	p-value*
Desire†	4.1±0.9	4.2±1.1	0.514
Arousal‡	4.5±8	4.8±4.8	0.673
Lubrication‡	4.1±1.6	4.5±1.5	0.081
Orgasm‡	3.9±1.5	4.4±1.4	0.020
Satisfaction§	5.1±1.1	4.9±1.3	0.275
Dyspareunia‡	4.4±1.6	5.2±1.5	0.001
Total score¶	26.6±5.7	27.6±6.2	0.264

*Student's t-test. †Scores range from 1.2 to 6. ‡Scores range from 0 to 6. §Scores range from 0.8 to 6. ¶Scores range from 2 to 36; total score ≤26 suggest risk for sexual dysfunction [14]. All values express mean ±standard deviation. FSFI, female sexual function index.

female adolescents had sexual dysfunction symptoms, that is, total FSFI scores ≤26[4].

Almost one in five of our participants had scores indicative of low desire, with no significant differences between adolescents and young adult women. Similar results were also reported by O'Sullivan et al.[4] in 229 Canadian female adolescents and young adults. The authors report that 22.2% of the adolescents had desire scores indicative of low desire. Although the prevalence of low desire varies throughout a woman's life, in general, at least one in every three women will experience low sexual desire and impaired arousal during her reproductive age period[14].

The most common sexual problems among our participants were difficulties with orgasm among adolescents and low desire among young adults. These findings are similar to those reported in the study involving female Canadian adolescents[4]. Wallwiener et al.[15] investigated the sexual function of 1086 young German women who used contraceptive methods (78.8% <26 years) and also reported that orgasm and desire were the domains with the lowest FSFI scores. Another study also reported that the lowest FSFI score in 413 young Italian women was in the desire domain[16]. Similarly, Mitchell et al.[17] also reported that the most common problems among young British women were lack of interest in sex and difficulty in reaching climax.

Possible causes for the high prevalence of sexual problems among adolescents and young women include the fact that these women are at the beginning of their sexual lives, going through the body and sexual changes that are often associated with insecurities[18], anxiety, fears, myths, guilt, shame[19], difficulties with image and body satisfaction[20], and negative feelings regarding the first sexual activity[7,8].

Although mean total FSFI scores were similar, adolescent participants had significantly lower scores for orgasm and dyspareunia (more dyspareunia) than those in young adult women. These difficulties are probably more frequent in adolescents because they are still going through an identity crisis and may not feel ready to establish intimacy with their sexual partners[21]. According to the Erikson's theory of psychosocial development, an individual enters the stage when he is able to establish intimacy only after the age of 20[21]. In human sexuality, intimacy is a determining factor for women, in the different stages of their lives, to feel confident and comfortable to have satisfactory sexual experiences, and according to some authors, stronger emotional intimacy with a partner is associated with less feelings of sexual inadequacy[22].

Partnered sexual behaviors become prominent only during mid- and late adolescence[18]. As reported in other Latin American studies, our participants' mean age at first sexual activity was approximately 15 years[3]. This underscores the need for interventions to provide education and contraception to young adolescents to prevent the consequences of unsafe sex, including unintended pregnancy, unsafe abortions, pregnancy-related mortality and morbidity, and sexually transmitted infections, including HIV[3,23].

We did not find significant differences in the sexual function of adolescent versus young adult participants who used the same contraceptive method. Several studies have analyzed the effect of contraceptive methods on female sexual function and reported contradictory findings[24,25]. This could be attributed, in part, to the fact that sexuality is influenced by many other factors besides contraceptive methods.

This study has several strengths, starting with its originality. To the best of our knowledge, this is the first study to assess the female sexual function of Latin American female adolescents and young adults according to the contraceptive method used. Another strong point of the study was the use of a validated questionnaire that has been previously used to assess the sexual function of adolescents and young women in several other countries[4,16].

CONCLUSION

In summary, our findings suggest that the sexual function of Brazilian female adolescents is similar to that of young women who are using the same contraceptive methods. In both age groups, there were high prevalence of women at risk for sexual dysfunction symptoms and a low desire. These data show the importance of practices in the care of female sexual health, a well-being described by the World Health Organization, as a guarantee of human being. Additional studies, involving a larger number of participants of different socioeconomic strata, including women who are not using any contraceptive methods, are necessary to confirm the results of this study.

AUTHORS' CONTRIBUTIONS

MCR: Conceptualization, Methodology, Validation, Visualization. **MN**: Data curation, Visualization, Writing – original draft. **MRT**: Formal Analysis, Visualization. **CAFG**: Funding acquisition, Project administration, Supervision, Visualization. **ES**: Investigation, Resources, Visualization. **EAJ**: Visualization, Writing – review & editing.

REFERENCES

1. World Health Organization. Adolescence: a period needing special attention. Age--not the whole story. Available from: http://apps.who.int/adolescent/second-decade/section2/page2/age-not-the-whole-story.html
2. Daiane de Peder L, Mesquita da Silva C, Nascimento BL, Malizan JA, Madeira HS, Horvath JD, et al. Prevalence of sexually transmitted infections and risk factors among young people in a Public Health Center in Brazil: a cross-sectional study. J Pediatr Adolesc Gynecol. 2020;33(4):1-20. https://doi.org/10.1016/j.jpag.2020.02.008
3. Chandra-Mouli V, McCarraher DR, Phillips SJ, Williamson NE, Hainsworth G. Contraception for adolescents in low and middle income countries: needs, barriers, and access. Reprod Health. 2014;11(1):1. https://doi.org/10.1186/1742-4755-11-1
4. O'Sullivan LF, Brotto LA, Byers ES, Majerovich JA, Wuest JA. Prevalence and characteristics of sexual functioning among sexually experienced middle to late adolescents. J Sex Med. 2014;11(3):630-41. https://doi.org/10.1111/jsm.12419
5. Teixeira AM, Knauth DR, Fachel JM, Leal AF. Teenagers and condom use: choices by young Brazilians from three Brazilian State capitals in their first and last sexual intercourse. Cad Saude Publica. 2006;22(7):1385-96. https://doi.org/10.1590/s0102-311x2006000700004
6. Liang M, Simelane S, Fortuny Fillo G, Chalasani S, Weny K, Salazar Canelos P, et al. The state of adolescent sexual and reproductive health. J Adolesc Health. 2019;65(6S):S3-15. https://doi.org/10.1016/j.jadohealth.2019.09.015
7. Moreau N, Kolto A, Young H, Maillochon F, Godeau E. Negative feelings about the timing of first sexual intercourse: findings from the Health Behaviour in School-aged Children study. Int J Public Health. 2019;64(2):219-27. https://doi.org/10.1007/s00038-018-1170-y
8. Rouche M, Castetbon K, Dujeu M, Meroc E, Lebacq T, Pedroni C, et al. Feelings about the timing of first sexual intercourse and health-related quality of life among adolescents. BMC Public Health. 2019;19(1):408. https://doi.org/10.1186/s12889-019-6728-y

9. Abma JC, Martinez GM. Sexual activity and contraceptive use among teenagers in the United States, 2011–2015. Natl Health Stat Report. 2017(104):1-23. PMID: 2869620
10. Ott MA, Sucato GS. Committee on adolescence. contraception for adolescents. Pediatrics. 2014;134(4):e1257-81. Available from: https://publications.aap.org/pediatrics/article/134/4/e1257/33010/Contraception-for-Adolescents?autologincheck=redirected
11. Leite AP, Moura EA, Campos AA, Mattar R, Souza E, Camano L. Validation of the female sexual function index in Brazilian pregnant women. Rev Bras Ginecol Obstet. 2007;29(8):414-9. https://doi.org/10.1590/S0100-72032007000800003
12. Bezerra KC, Feitoza SR, Vasconcelos CTM, Karbage SAL, Saboia DM, Oria MOB. Sexual function of undergraduate women: a comparative study between Brazil and Italy. Rev Bras Enferm. 2018;71(suppl 3):1428-34. https://doi.org/10.1590/0034-7167-2016-0669
13. Wiegel M, Meston C, Rosen R. The female sexual function index (FSFI): cross-validation and development of clinical cutoff scores. J Sex Marital Ther. 2005;31(1):1-20. https://doi.org/10.1080/00926230590475206
14. Brotto LA, Petkau AJ, Labrie F, Basson R. Predictors of sexual desire disorders in women. J Sex Med. 2011;8(3):742-53. https://doi.org/10.1111/j.1743-6109.2010.02146.x
15. Wallwiener CW, Wallwiener LM, Seeger H, Muck AO, Bitzer J, Wallwiener M. Prevalence of sexual dysfunction and impact of contraception in female German medical students. J Sex Med. 2010;7(6):2139-48. https://doi.org/10.1111/j.1743-6109.2010.01742.x
16. Guida M, Troisi J, Saccone G, Sarno L, Caiazza M, Vivone I, et al. Contraceptive use and sexual function: a comparison of Italian female medical students and women attending family planning services. Eur J Contracept Reprod Health Care. 2019;24(6):430-7. https://doi.org/10.1080/13625187.2019.1663500
17. Mitchell KR, Geary R, Graham C, Clifton S, Mercer CH, Lewis R, et al. Sexual function in 16- to 21-Year-Olds in Britain. J Adolesc Health. 2016;59(4):422-8. https://doi.org/10.1016/j.jadohealth.2016.05.017
18. Fortenberry JD. Puberty and adolescent sexuality. Horm Behav. 2013;64(2):280-7. https://doi.org/10.1016/j.yhbeh.2013.03.007
19. Hall KS, Morhe E, Manu A, Harris LH, Ela E, Loll D, et al. Factors associated with sexual and reproductive health stigma among adolescent girls in Ghana. PLoS One. 2018;13(4):e0195163. https://doi.org/10.1371/journal.pone.0195163
20. Jimenez Flores P, Jimenez Cruz A, Bacardi Gascon M. Body-image dissatisfaction in children and adolescents: a systematic review. Nutr Hosp. 2017;34(2):479-89. https://doi.org/10.20960/nh.455
21. Widick C, Parker CA, Knefelkamp L. Erik Erikson and psychosocial development. New Dir Stud Serv. 1978;(4):1-17. https://doi.org/10.1002/ss.37119780403
22. Bancroft J, Loftus J, Long JS. Distress about sex: a national survey of women in heterosexual relationships. Arch Sex Behav. 2003;32(3):193-208. https://doi.org/10.1023/a:1023420431760
23. Committee on Adolescent Health Care. Pregnancy, contraception and sexual activity. Obstet Gynecol. 2017;129(5):142-9. https://doi.org/10.1097/AOG.0000000000002045
24. Burrows LJ, Basha M, Goldstein AT. The effects of hormonal contraceptives on female sexuality: a review. J Sex Med. 2012;9(9):2213-23. https://doi.org/10.1111/j.1743-6109.2012.02848.x
25. Casey PM, MacLaughlin KL, Faubion SS. Impact of contraception on female sexual function. J Womens Health (Larchmt). 2017;26(3):207-13. https://doi.org/10.1089/jwh.2015.5703

ORIGINAL ARTICLE

https://doi.org/10.1590/1806-9282.20220240

Nutritional profile and outcomes of noncritical hospitalized patients with COVID-19 in a large tertiary hospital in southern Brazil

Emeline Caldana Nunes[1], Sabrina Marcon[1], Paula Elisa de Oliveira[1], Sergio Henrique Loss[2*]

SUMMARY

INTRODUCTION: Patients with chronic diseases, such as diabetes and cardiovascular diseases, and old age, which are associated with a high risk of malnutrition and worse outcomes, are at a higher risk for developing the severe presentation of COVID-19.

METHODS: This is an observational and cross-sectional study with a sample defined by convenience. Data were collected in adult inpatient units through information obtained via telephone contact with the patient/companion, records collected by the nursing staff, and medical records, tabulating demographics, body composition, previous illnesses, nutritional diagnoses, diet acceptance, and hospitalization outcomes. The following symptoms were observed: inappetence, smell, dysgeusia, odynophagia, nausea, vomiting, and diarrhea.

RESULTS: Most deaths occurred after transfer to the intensive care unit (79.6%). Patients with the worst outcome had lower food intake with a cutoff point of 60% for diet acceptance, which seems to be an adequate discriminator between those who survived and those who did not. Gastrointestinal symptoms were significantly associated with food consumption below 60% of the planned goal. The symptoms most associated with lower energy intake were inappetence, dysgeusia, and nausea/vomiting.

CONCLUSIONS: Reduced caloric intake and the presence of nutritional risk or its appearance during hospitalization seemed to be associated with mortality in patients with COVID-19 admitted outside the intensive care unit.

KEYWORDS: Coronavirus infections. COVID-19. Nutritional status. Nutritional support.

INTRODUCTION

Infections of the new coronavirus (called COVID-19, i.e., coronavirus disease 2019) are caused by SARS-CoV-2 (severe acute respiratory syndrome coronavirus 2). They are flu-like infections similar to the severe acute respiratory syndrome coronavirus (SARS-CoV) and Middle East respiratory syndrome coronavirus (MERS-CoV) in 2002 and 2012, respectively. Most conditions (80%) are mild. However, approximately 20% of cases will require hospitalization, of which 6–10% will require transfer to the intensive care unit (ICU)[1]. Among noncritical hospitalized patients, nutritional therapy appears to be associated with reduced complications[2].

Patients with chronic diseases, such as diabetes and cardiovascular diseases, and old age, associated with a high risk of malnutrition and worse outcomes, are at a higher risk of developing the severe presentation of COVID-19. Thus, assessing nutritional risk and body composition takes on additional importance since combining these morbidities increases the chance of malnutrition, immunosuppression, and unfavorable outcomes[2-4]. Recent data suggest that nutritional risk, accessed by the NRS-2002, is associated with higher mortality[5]. A series of cases indicated that these patients are hypercatabolic[6], which determines a more significant concern on the part of the care team in avoiding the establishment of a negative energy balance. In this context, COVID-19 is associated with malnutrition. Diarrhea, abdominal pain, nausea, vomiting, lack of appetite, and other symptoms are commonly reported and related to COVID-19. Cachexia can be related to feeding difficulties and malnutrition in this population[7].

Our objective was to recognize whether a given level of caloric intake, body mass index (BMI), or the presence of nutritional risk is associated with outcomes in this population (noncritical patients with COVID-19) and to identify factors related to this level of intake.

METHODS

Study, patients, and data: This is a cross-sectional observational study with a convenience sample. Patients were selected in the emergency room and adult inpatient units of the Moinhos de

[1]Hospital Moinhos de Vento, Intensive Care Dietitian – Porto Alegre (RS), Brazil.
[2]Hospital Moinhos de Vento, Intensive Care Physician – Porto Alegre (RS), Brazil.
*Corresponding author: sergio.loss@gmail.com
Conflicts of interest: the authors declare there is no conflicts of interest. Funding: none.
Received on April 20, 2022. Accepted on June 20, 2022.

Vento Hospital, a tertiary clinical-surgical hospital reference for COVID-19 treatment. Inclusion criteria included age equal to or above 18 years, and presenting COVID-19 and needing hospitalization outside the ICU. The only exclusion criterion was to remain hospitalized for less than 24 h. Data collection took place over 5 months (from March 25, 2020 to August 31, 2020). Data were obtained through the information obtained during nutritional screening, nutritional assessment, and care via telephone contact with the patient or family/caregiver. The following data were collected by the nursing team and medical record data and tabulated in an electronic spreadsheet: age, arterial hypertension, diabetes, heart disease, lung diseases, neoplasms, date of patient assessment, the result of nutritional screening (Nutritional Risk Score, 2002), BMI, nutritional diagnosis, the results of Subjective Global Assessment and patient-generated Subjective Global Assessment if pertinent, nutritional therapy route, percentage of oral diet acceptance, use of nutritional supplementation, length of stay in the inpatient unit before being transferred to the ICU, length of stay in ICU, and the total length of stay and outcome (hospital discharge or death). The following symptoms were also observed: loss of appetite, smell, dysgeusia, odynophagia, nausea, vomiting, and diarrhea.

Protocol: The first nutritional screening was carried out in the first 24 h of hospitalization and was repeated every 24 (patients at risk) or 48–72 h (no-risk patients). Patients with oral feeding were monitored for the number of calories consumed and received either high protein supplements or enteral nutrition when their intake was less than 60% of the predicted. Once submitted to enteral nutrition, the target for calories was 25–30 kcal/kg/day and protein was 1.5–2 g/kg/day, both to be achieved over 3 days.

Statistical analysis: The variables were expressed as percentile, mean (and standard deviation), or median (and interquartile range) and compared with Student's t-test, Mann-Whitney U test, or χ^2. A multivariate binary logistic regression model was used to assess the determinants of the outcomes. The number of independent variables followed the rule of one variable for every 10 outcomes. The data were analyzed using the IMB SPSS-23.0 statistical software package. A p-value of less than 0.05 was adopted for the significance level in all analyses.

RESULTS

The sample comprised 526 patients. The characteristics of the population enrolled, stratified by mortality, are described in Table 1. Most deaths happened after ICU transference (79.6%). Patients who did not survive significantly received less energy intake, and the 60% cutoff seemed to be an adequate discriminator between those who survived and those who did not.

Considering the specificity and sensitivity of BMI related to mortality, values between 26.5 and 33 kg/m^2 seem to be

Table 1. Characteristics of the patients who survived and died during hospitalization

Characteristics	All patients (n=526)	Survivors (n=485)	Nonsurvivors (n=31)	p-value
Age	59.5 (46–72)	58.5 (44–77)	85 (82–90)	<0.001
BMI	28.2 (24.7–30.8)	27.4 (24.8–30.9)	25.3 (22.9–28.7)	0.004
Obesity (BMI>29.9 kg/m^2) (%)	31.1	97.5	2.5	0.019
Female gender (%)	42.4	92.9	7.1	0.069
Nutritional risk (NRS-2002≥3) (%)	20.4	83.1	16.9	<0.001
Change in risk (NRS-2002) (%)	13.3	83.7	17.3	0.027
Diet acceptance (in %)	75 (57–92)	76.5 (59.2–94)	52.5 (39.5–62.7)	<0.001
Reduced intake (<60%)	30.2	36.8	76.3	<0.001
Previous comorbidity (%)	65.1	91.8	8.2	0.003
Hypertension (%) Diabetes (%) Heart disease (%) COPD (%) Cancer (%)	48.3 18.7 15 12.7 8.9	92.7 89.1 81.3 96.9 81.8	7.3 10.9 18.7 3.1 18.2	0.177 0.025 <0.001 0.316 <0.001
GIT symptoms (%)	53.6	95.2	4.8	0.152
Nausea/vomiting (%) Anosmia (%) Dysgeusia (%) Inappetence (%) Diarrhea (%)	15.8 16.7 18.9 36.4 11.1	94.7 99 98.2 95.4 95	5.3 1 1.8 4.6 5	0.767 0.022 0.035 0.275 0.728

BMI: body mass index; NRS: nutritional risk score; COPD: chronic obstructive pulmonary disease; GIT: gastrointestinal tract.

associated with a population with a greater chance of survival. The associations between digestive tract symptoms and calorie consumption are shown in Figure 1. Digestive tract symptoms were significantly associated with energy consumption below 60% of the planned goal (35.2% of the sample, p<0.001). Symptoms related to lower energy intake were inappetence, dysgeusia, and nausea/vomiting.

The most significant parameters in the univariate analysis were analyzed in multivariate logistic regression and are shown in Table 2.

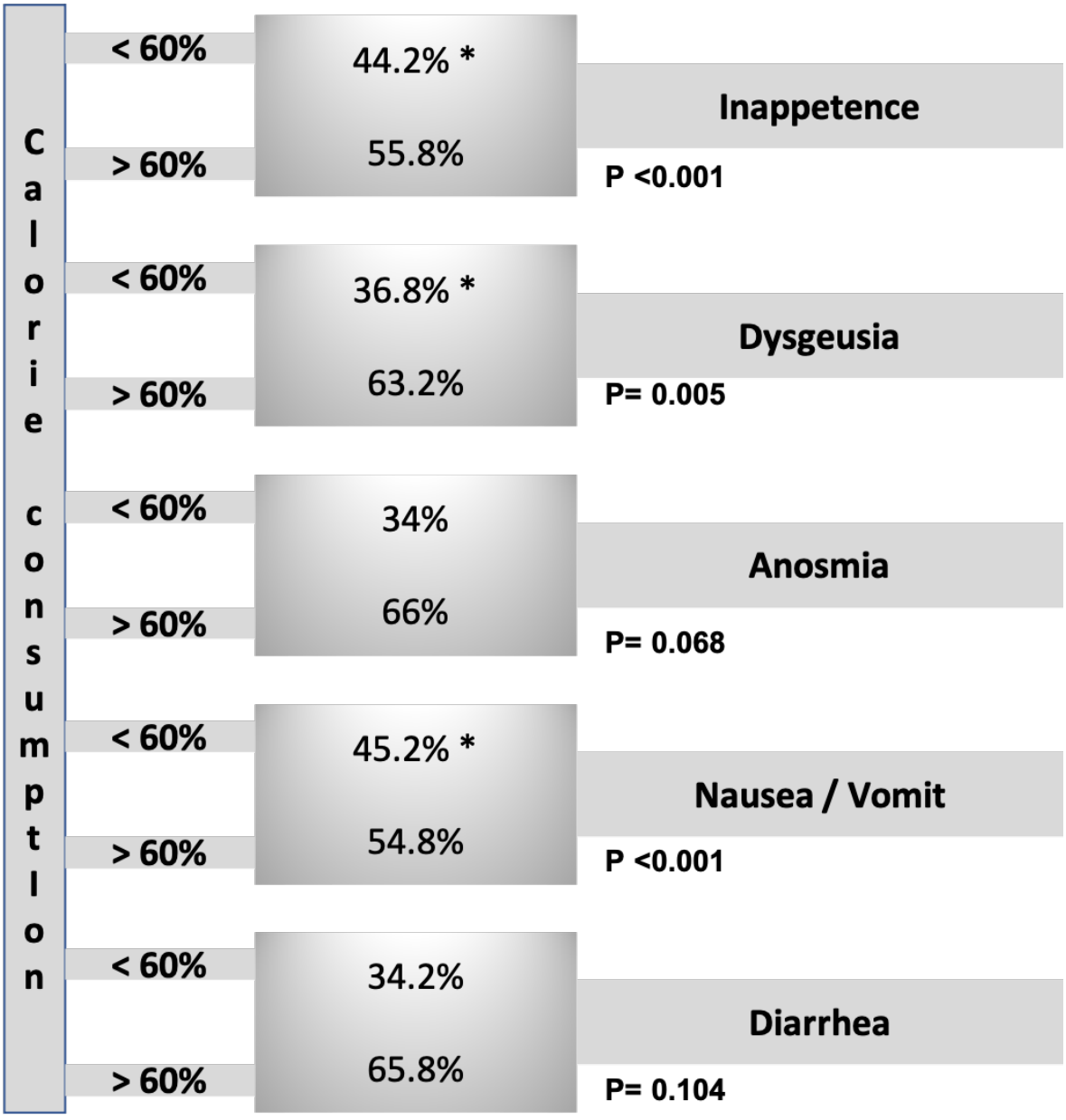
DISCUSSION

This study demonstrates an association between mortality and elderly patients and those who consume less than 60% of the

Table 2. Multivariate analysis of parameters associated with mortality

	RR (95%CI)	p-value
Age	1.133 (1.084–1.184)	<0.001
Nutritional risk (NRS-2002)	0.705 (0.293–1.697)	0.436
Diet acceptance percentage	0.978 (0.959–0.998)	0.032

RR: relative risk; NRS: nutritional risk score.



*Shows the parameter significantly elevated.

Figure 1. Associations between caloric intake and the presence of digestive symptoms.

planned energy supply in COVID-19 hospitalized patients outside the ICU. The mortality of critically ill patients with COVID-19 is high (up to 61.5%)[8], determining that all treatment strategies should be adequately combined to reduce it. Among these strategies, nutritional therapy plays a prominent role. The prevalence of the elderly in intensive care is increasing[9], constituting a fragile population with even higher mortality[10,11]. Thus, it is not surprising that older patients had a worse outcome. Regarding calorie intake, our study echoes others who have linked negative energy balance to worse outcomes[12,13].

The presence of nutritional risk or its appearance during hospitalization seems to mark more severe patients (Table 1), reinforcing the need for nutritional therapy teams to adopt some risk and nutritional assessment tool and use it early on in admission.

Although BMI did not remain an independent variable in the multivariate analysis of survival, patients with higher BMI demonstrated a tendency to survive in the univariate analysis. We cannot argue here about the possibility of parallelism about the debated paradox of obesity in the ICU, but if we consider negative energy balance as a parameter associated with mortality, those with body composition potentially associated with malnutrition (lower BMI) could present a worse outcome. A fact that should be noted is related to the average BMI of the population studied (28.2 kg/m^2 [24.7–30.8]), suggesting that the malnutrition rate in this sample is low, deviating from the pattern most often observed in most Brazilian hospitals. Our hospital is private, which may at least partially explain this finding. Finally, BMI does not appear in the logistic regression (Table 2), because in no regression model, it was proved to be an independently significant variable (due to the total number of deaths, we could not include more than four parameters in the model).

The presence of symptoms that potentially interfere with ingestion (e.g., lack of appetite, nausea, vomiting, changes in taste or smell, and diarrhea) was associated with lower consumption of calories, especially inappetence, dysgeusia, and nausea/vomiting. These complications reinforce the importance of monitoring negative energy balance and implementing strategies to minimize it, such as supplements or inserting a feeding tube. These strategies become more important if, in the background, there is a patient with hypoxemia using some form of ventilatory support (noninvasive ventilation or high-flow cannula) that can compromise ingestion.

This study has limitations. No comorbidity score, such as the Charlson score, was recorded (it would probably improve the comparisons among patients). We do not have indirect calorimetry, which would contribute to an accurate measurement of energy expenditure. Patients were not submitted to computed tomography or dual x-ray absorptiometry to determine their muscle mass.

In summary, reduced caloric intake appears to be associated with mortality in patients with COVID-19 admitted outside the ICU. Nutritional therapy strategies should be implemented in this population. Our findings need to be confirmed by a prospective, randomized, and controlled study.

CONCLUSIONS

Reduced caloric intake appears to be associated with mortality in patients with COVID-19 admitted outside the ICU. Nutritional therapy strategies should be implemented in this population. Our findings need to be confirmed by a prospective, randomized, and controlled study.

AUTHORS' CONTRIBUTIONS

ECN: Conceptualization, Data curation, Formal Analysis, Writing – original draft, Writing – review & editing. **SM:** Conceptualization, Data curation, Formal Analysis, Writing – original draft, Writing – review & editing. **PEO:** Data curation, Formal Analysis, Writing – original draft, Writing – review & editing. **SHL:** Conceptualization, Data curation, Formal Analysis, Writing – review & editing.

REFERENCES

1. Loss SH, Nunes DL, Franzosi OS, Teixeira C. Loss SH, Nunes DL, Franzosi OS, Teixeira C. A pragmatic approach and treatment of coronavirus disease 2019 (COVID-19) in intensive care unit. Rev Assoc Med Bras (1992). 2020;66(8):1157-63. https://doi.org/10.1590/1806-9282.66.8.1157
2. Barazzoni R, Bischoff SC, Breda J, Wickramasinghe K, Krznaric Z, Nitzan D, et al. ESPEN expert statements and practical guidance for nutritional management of individuals with SARS-CoV-2 infection. Clin Nutr. 2020;39(6):1631-8. https://doi.org/10.1016/j.clnu.2020.03.022
3. Gasmi A, Noor S, Tippairote T, Dadar M, Menzel A, Bjørklund G. Individual risk management strategy and potential therapeutic options for the COVID-19 pandemic. Clin Immunol. 2020;215:108409. https://doi.org/10.1016/j.clim.2020.108409
4. Caccialanza R, Laviano A, Lobascio F, Montagna E, Bruno R, Ludovisi S, et al. Early nutritional supplementation in non-critically ill patients hospitalized for the 2019 novel coronavirus disease (COVID-19): Rationale and feasibility of a shared pragmatic protocol. Nutrition. 2020;74:110835. https://doi.org/10.1016/j.nut.2020.110835

5. Zhao X, Li Y, Ge Y, Shi Y, Lv P, Zhang J, et al. Evaluation of Nutrition Risk and Its Association With Mortality Risk in Severely and Critically Ill COVID-19 Patients. JPEN J Parenter Enteral Nutr. 2021;45(1):32-42. https://doi.org/10.1002/jpen.1953
6. Yu PJ, Cassiere H, DeRosa S, Bocchieri K, Yar S, Hartman A. Hypermetabolism and Coronavirus Disease 2019. JPEN J Parenter Enteral Nutr. 2020;44(7):1234-6. https://doi.org/10.1002/jpen.1948
7. Virgens IPA, Santana NM, Lima SCVC, Fayh APT. Can COVID-19 be a risk for cachexia for patients during intensive care? Narrative review and nutritional recommendations. Br J Nutr. 2021;126(4):552-60. https://doi.org/10.1017/S0007114520004420
8. Yang X, Yu Y, Xu J, Shu H, Xia J, Liu H, et al. Clinical course and outcomes of critically ill patients with SARS-CoV-2 pneumonia in Wuhan, China: a single-centered, retrospective, observational study. Lancet Respir Med. 2020;8(5):475-81. https://doi.org/10.1016/S2213-2600(20)30079-5
9. Fuchs L, Chronaki CE, Park S, Novack V, Baumfeld Y, Scott D, et al. ICU admission characteristics and mortality rates among elderly and very elderly patients. Intensive Care Med. 2012;38(10):1654-61. https://doi.org/10.1007/s00134-012-2629-6
10. Silva DJN, Casimiro LGG, Oliveira MIS, Ferreira LBDC, Abelha FJPA. A população cirúrgica muito idosa em cuidados intensivos: características clínicas e desfechos [The very elderly surgical population in a critically ill scenario: clinical characteristics and outcomes]. Braz J Anesthesiol. 2020;70(1):3-8. https://doi.org/10.1016/j.bjan.2019.10.001
11. Guidet B, Vallet H, Boddaert J, Lange DW, Morandi A, Leblanc G, et al. Caring for the critically ill patients over 80: a narrative review. Ann Intensive Care. 2018;8(1):114. https://doi.org/10.1186/s13613-018-0458-7
12. Waitzberg DL, Caiaffa WT, Correia MI. Hospital malnutrition: the Brazilian national survey (IBRANUTRI): a study of 4000 patients. Nutrition. 2001;17(7-8):573-80. https://doi.org/10.1016/s0899-9007(01)00573-1
13. Klipstein-Grobusch K, Reilly JJ, Potter J, Edwards CA, Roberts MA. Energy intake and expenditure in elderly patients admitted to hospital with acute illness. Br J Nutr. 1995;73(2):323-34. https://doi.org/10.1079/bjn19950033

ORIGINAL ARTICLE

https://doi.org/10.1590/1806-9282.20220249

Braden scale has low reliability in different patients under care in intensive care unit

Thalita Pereira Veiga[1], Adriana Sousa Rêgo[1], Widlani Sousa Montenegro[2], Patrícia Rodrigues Ferreira[3], Daniel Santos Rocha[3], Ilana Mírian Almeida Felipe[1], Aldair Darlan Santos-de-Araújo[4], Renata Gonçalves Mendes[4], Rudys Rodolfo de Jesus Tavarez[5], Daniela Bassi-Dibai[1]*

SUMMARY

OBJECTIVE: The aim of this study was to assess the inter-reliability of the Braden scale and its subscales for different patients assisted in the intensive care unit. We hypothesized that the Braden scale has low reliability in different populations.

METHODS: This reliability study involved the Braden scale in intensive care unit of a hospital. A total of 200 patients were admitted to the intensive care unit in four different groups: neurological patients, sepsis, elderly, and adults affected by trauma. The Braden scale is a tool composed of six subscales for patient assessment: sensory perception, humidity, activity, mobility, nutrition, and friction. The total score was also calculated. The Braden scale was applied by two different nurses with an interval of 20–30 min between applications.

RESULTS: For all populations, kappa values considered unsuitable were observed for most categories of the Braden scale, ranging from 0.06–0.25. Only for the total Braden scale score was moderate reliability identified in all groups evaluated, with intraclass correlation coefficient values ranging from 0.48–0.75.

CONCLUSIONS: Braden scale is not a reliable tool to be used in the intensive care unit, and we do not recommend the use of this scale to assess the risk of developing pressure injury.

KEYWORDS: Risk assessment. Validation study. Intensive care unit. Pressure injuries.

INTRODUCTION

At present, pressure injuries (PI) represent a great and growing burden to society[1], especially in the elderly and those with chronic diseases[2]. PI is still considered a major health issue for hospitals, especially in intensive care unit (ICU). Due to technological advances, there are a large number of survivors of ICU admission; however, the ICU can cause other disorders to patients, such as prolonged hospital stay, clinical complications not associated with initial hospitalization, risk of infection, as well as increased costs and expenses[3,4].

Therefore, the risk assessment of developing PI becomes essential, in view of the environmental, psychological, and therapeutic limitations to which patients are submitted to the ICU. Furthermore, through this risk assessment of developing PI, it is possible to detect the patients at an early stage who are at potential risk for acquiring this type of injury. Once the risk is verified, specific prevention measures and interventions must be implemented by the ICU team of professionals[5]. Furthermore, the risk assessment must be adopted in a systematic and applied manner, both on the patient's admission and daily during the physical examination and whenever there is a change in their clinical condition[6].

The risk of PI is usually assessed using scales, among which the most commonly used is the Braden scale (BS)[7,8]. In this context, the BS has been widely used in several hospital services; its validation in the Brazilian Portuguese took place by Paranhos in 1999[9]. It consists of the following six subscales: sensory perception, humidity, activity, mobility, nutrition, and friction and shear. The total score can vary from 6–23 points, where the higher the score, the greater the individual's chance of developing PI[10].

As risk assessment is the first step in preventing this disease, it anticipates the team of health care professionals to gather

[1]Universidade Ceuma, Postgraduate Program in Management and Health Services – São Luís (MA), Brazil.
[2]São Domingos Hospital – São Luís (MA), Brazil.
[3]Universidade Ceuma, Department of Physical Therapy – São Luís (MA), Brazil.
[4]Universidade Federal de São Carlos, Department of Physical Therapy – São Carlos (SP), Brazil.
[5]Universidade Ceuma, Postgraduate Program in Dentistry – São Luís (MA), Brazil.
*Corresponding author: danielabassifisio@gmail.com

Conflicts of interest: the authors declare there is no conflicts of interest. Funding: This study was partially supported by Coordenação de Aperfeiçoamento de Pessoal de Nível Superior (CAPES), finance code 001.
Received on March 29, 2022. Accepted on June 15, 2022.

important information, which will help identify the patients who are more likely to develop PI and later plan the individualized and specific care plan for the same[11].

Furthermore, the BS has been used in several populations with different characteristics of sensory perception, mobility, and skin hydration, among other factors. Although studies show that BS has a good sensitivity for the risk assessment for the development of PI and its prevention, these studies show a small number of individuals without considering different clinical characteristics relevant to a possible development or not of PI[7] or even do retrospective analyses in different sectors such as wards and surgical sectors[8]. Additionally, they did not assess the reliability but only the sensitivity of the scale; it is noteworthy that there are different professionals who work in shifts in ICU, evaluating and taking responsibility for the care of the same patient, and that most of the evaluation methods are instrument-dependent, emphasizing the importance of the study of reliability among evaluators in the use of the scale.

Some previous studies aimed to assess the reliability of the BS in the ICU[7,12]; however, without taking into account the different characteristics, such as sensory characteristics, it is known that different populations in the ICU have different sensory perceptions, nutrition, and hair moisture, which should be considered when screening or assessing the risk of developing PI. In addition, considering only the total score, it can induce an error in the risk assessment of PI, because a subscale with a very low score can be an important factor which raises the risk of PI, even if the total score shows no such risk.

In this context, to the best of our knowledge, there is no approach in the literature that attempted to assess the reliability of the BS and its subscales in different populations that are frequently assisted in ICUs. Thus, the aim of this study was to evaluate the inter-rater reliability of the BS and its subscales in different patients, such as elderly and those with neurological disorders, sepsis, and trauma, commonly assisted in the ICU.

METHODS

Design and ethical aspects of the study

This is a prospective and analytical reliability study. Data collection took place in an adult ICU of a tertiary hospital located in the city of São Luís (MA, Brazil) from February to December 2019. This study was conducted according to the Guidelines for Reporting Reliability and Agreement Studies (GRRAS)[13].

Sample

The sample size was based on measurement property evaluation guidelines, recommending a minimum of 50 participants to assess reliability[14].

A total of 200 individuals were included in the study who were divided into the following four groups:

1. adults with neurological disorders (n=50),
2. adults with sepsis (n=50),
3. elderly (n=50), and
4. adults affected by trauma (n=50).

The anthropometric and sociodemographic data of the patients were collected by means of the electronic medical record used in the ICU of the studied service.

Inclusion and exclusion criteria

The sample of patients in this study included those who were under the care of health care professionals in the ICU, with age over 18 years and of both sexes. The composition of the groups considered the clinical diagnosis of admission to the ICU.

Thus, in the trauma group, individuals affected by various traumas were allocated as the most common polytrauma and head trauma. The elderly group included those specifically aged over 60 years, who were admitted to the ICU, the majority being due to decompensation of the underlying diseases, especially congestive heart failure and chronic obstructive pulmonary disease. In the sepsis group, individuals with a diagnosis of sepsis were included, the majority being urinary tract infection and acute abdomen. Finally, the patients in the neurological group were composed of individuals affected mainly by stroke and encephalitis.

Exclusion criteria were as follows: the presence of injury due to previous pressure or any other problem that makes the application of BS unfeasible.

Initial evaluation

An initial evaluation was undertaken to collect the participants' demographic and personal data, which were extracted from the electronic medical records of the patients participating in the study, such as gender; age; anthropometric and clinical data such as weight, height, BMI, diagnosis, comorbidities, and the Charlson comorbidity index; nutritional data such as protein intake (kg/day) and kcal/day; and risk factors such as smoking, use of vasoactive drugs, and mobility that were collected via medical records of the evolution of physiotherapy assessment through the Functional Status Score for the ICU.

Reliability procedures

The BS was completed on admission of patients to the ICU by two different nurses, previously trained, with an experience of approximately 10 years in completing it. A draw was carried out in order to select which evaluator would start applying the BS. An interval between evaluations of 20 and 30 min was performed in order to ensure that the conditions or characteristics of sensory perception, mobility, and skin hydration of the patients did not change.

Statistical analysis

Reliability was assessed based on an inter-rater model. For the total BS score, the intraclass correlation coefficient ($ICC_{2,1}$) was measured, along with 95% confidence interval (95%CI), standard error of measurement (SEM) in absolute score and percentage, and the minimum detectable change (MDC) in absolute score and percentage. The interpretation of the ICC value was based on the study by Fleiss[15]: for values below 0.40, the reliability will be considered low; between 0.40–0.75, moderate; between 0.75–0.90, substantial; and, finally, for values greater than 0.90, the reliability was considered excellent. The interpretation of the percentage of SEM was based on the study by Ostelo et al.[16]: 5% or less, very good; greater than 5% and less than or equal to 10%, good; greater than 10% and less than or equal to 20%, doubtful; and greater than 20%, negative.

For the reliability of each BS item and the categories resulting from the stratification of the total score (no risk, light, moderate, high, and very high), the kappa value with linear weighting and 95%CI was used, since the possible responses for each BS item are categorical. The interpretation of the kappa value was based on the study by Landis and Koch[17]: <0, null; 0.01–0.19, poor; 0.21–0.39, weak; 0.40–0.59, moderate; 0.60–0.79, substantial; and 0.80–1, almost perfect.

RESULTS

Table 1 shows the sample characterization data. Most patients were lean, nonsmokers, under mechanical ventilation (except neurological patients), and using vasoactive drugs.

Regarding the reliability of the BS subscales, the data are presented in Table 2. We observed that most of the kappa values were below 0.40, ranging from 0.20–0.53 for neurological patients, from 0.04–0.42 for sepsis, from 0.01–0.42 for the elderly, and from 0.04–0.45 for the trauma group. Considering the reliability of the categories generated from the BS stratification (no risk, light, moderate, high, and very high), as shown in Table 3, kappa values below acceptable were observed, varying between 0.06–0.25.

Table 1. Characterization of the individuals according to the clinical condition.

	All (n=200)	Neurological (n=50)	Sepsis (n=50)	Elderly (n=50)	Trauma (n=50)
Age (years)	69.61 (18.91)	68.94 (16.93)	71.18 (16.18)	78.44 (9.35)	59.90 (25.25)
Gender					
Male (%)	92 (46)	19 (38)	17 (34)	29 (58)	27 (54)
Female (%)	108 (54)	31 (62)	33 (66)	21 (42)	23 (46)
Weight (kg)	65.24 (15.67)	64.90 (17)	64.13 (16.11)	63.33 (13.58)	68.58 (15.76)
Height (m)	1.60 (0.10)	1.41 (53.05)	1.59 (0.09)	1.60 (0.09)	1.61 (0.11)
BMI (kg/m^2)	25.25 (5.05)	25.30 (5.08)	25.30 (6.05)	24.46 (4.70)	25.95 (4.23)
Protein supply (kg/day)	91.06 (71.16)	87.98 (24.63)	81.48 (30.61)	89.22 (19.08)	105.55 (135.42)
Protein supply (kcal/day)	1474.51 (297.39)	1390.00 (297.15)	1450.06 (266.24)	1507.82 (291.58)	1550.16 (316.37)
Smoker					
No (%)	164 (82)	39 (78)	45 (90)	41 (82)	39 (78)
Yes (%)	36 (18)	11 (22)	5 (10)	9 (18)	11 (22)
Use of vasoactive drugs					
No (%)	118 (59)	25 (50)	26 (52)	33 (66)	34 (68)
Yes (%)	82 (41)	25 (50)	24 (48)	17 (34)	16 (32)
IMV					
No (%)	108 (54)	20 (40)	25 (50)	32 (64)	31 (62)
Yes (%)	92 (46)	30 (60)	25 (50)	18 (36)	19 (38)
CCI	2.09 (1.95)	2.18 (1.76)	2 (1.78)	2.96 (2.03)	1.24 (1.87)

Data are expressed as mean (standard deviation) or absolute number (percentage). BMI: body mass index; IMV: invasive mechanical ventilation; CCI: Charlson comorbidity index.

Table 2. Inter-examiner reliability of the subscales of the Braden scale for the different samples studied.

Item	Examiner 1	Examiner 2	Kappa (95%CI)
Neurological			
Sensory perception	2.30 (0.99)	2.52 (0.93)	0.53 (0.38–0.68)
Moisture	2.38 (0.67)	2.66 (0.63)	0.24 (0.03–0.45)
Activity	1.12 (0.44)	1.24 (0.69)	0.27 (0.00–0.60)
Mobility	2.28 (0.76)	2.22 (0.84)	0.22 (0.05–0.39)
Nutrition	2.90 (0.30)	2.82 (0.48)	0.20 (0.00–0.51)
Friction and shear	1.56 (0.76)	1.70 (0.68)	0.28 (0.06–0.50)
Sepsis			
Sensory perception	2.40 (0.82)	2.82 (1.00)	0.38 (0.21–0.54)
Moisture	2.36 (0.62)	2.68 (0.59)	0.11 (0.00–0.25)
Activity	1.04 (0.20)	1.12 (0.48)	0.04 (0.00–0.09)
Mobility	2.44 (0.61)	2.40 (0.73)	0.42 (0.22–0.62)
Nutrition	2.96 (0.20)	2.86 (0.45)	0.41 (0.05–0.78)
Friction and shear	1.32 (0.55)	1.82 (0.72)	0.08 (0.00–0.24)
Elderly			
Sensory perception	2.66 (0.75)	2.98 (1.02)	0.38 (0.23–0.52)
Moisture	2.34 (0.59)	2.78 (0.58)	0.01 (0.18–0.21)
Activity	1.30 (0.61)	1.14 (0.45)	0.04 (0.07–0.16)
Mobility	2.62 (0.60)	2.42 (0.73)	0.42 (0.23–0.61)
Nutrition	2.94 (0.24)	2.92 (0.34)	0.05 (0.04–0.09)
Friction and shear	1.34 (0.56)	1.96 (0.64)	0.14 (0.00–0.30)
Trauma			
Sensory perception	2.62 (0.85)	3.04 (0.92)	0.43 (0.26–0.61)
Moisture	2.60 (0.64)	2.96 (0.70)	0.07 (0.00–0.24)
Activity	1.22 (0.68)	1.14 (0.50)	0.05 (0.02–0.08)
Mobility	2.44 (0.67)	2.50 (0.81)	0.45 (0.25–0.66)
Nutrition	2.74 (0.60)	2.80 (0.49)	0.04 (0.00–0.25)
Friction and shear	1.54 (0.68)	1.96 (0.78)	0.31 (0.13–0.49)

CI: confidence interval.

Data on the reliability of the total BS score can be found in Table 3, and the ICC values were moderate (ranging from 0.48–0.75). Regarding the interpretation of the percentage of SEM, unacceptable values (greater than 10%) were observed in patients with sepsis and the elderly. For neurological and trauma patients, acceptable values of the percentage of SEM were observed, but very close to the 10% error limit.

DISCUSSION

The main findings of this study were:

1. BS reliability varies according to the target population of the assessment;
2. BS has a low reliability for most of its items and for the four groups assessed here;
3. the majority of BS subscales do not have acceptable reliability; and
4. total score and moderate ICC values were verified for the four groups and the percentage of adequate SEM (very close to the 10% limit) for neurological and trauma patients.

The use of risk assessment scales for developing PI is important for nurses and other health care professionals, making it possible, through these instruments, to identify vulnerable points and reinforce constant assessment as a means for preventing

Table 3. Reliability of the categories established by stratifying the total score of the Braden scale and reliability of the total Braden score for the different samples evaluated.

Group	Categories	Examiner 1 (%)	Examiner 2 (%)	Kappa (95%CI)
Neurological	Without risk	1 (2)	1 (2)	0.17 (0.00–0.36)
	Light	12 (24)	14 (28)	
	Moderate	5 (10)	13 (26)	
	High	30 (60)	19 (38)	
	Very high	2 (4)	3 (6)	
Sepsis	Without risk	0 (0)	2 (4)	0.10 (0.00–0.32)
	Light	8 (16)	17 (34)	
	Moderate	18 (36)	14 (28)	
	High	21 (42)	14 (28)	
	Very high	3 (6)	3 (6)	
Elderly	Without risk	1 (2)	1 (2)	0.25 (0.03–0.47)
	Light	10 (20)	23 (46)	
	Moderate	22 (44)	12 (24)	
	High	15 (30)	12 (24)	
	Very high	2 (4)	2 (4)	
Trauma	Without risk	1 (2)	3 (6)	0.06 (0.00–0.26)
	Light	11 (22)	20 (40)	
	Moderate	15 (30)	11 (22)	
	High	19 (38)	15 (30)	
	Very high	4 (8)	1 (2)	

Sample	Examiner 1	Examiner 2	ICC (95%CI)	SEM (score)	SEM (%)	MDC (score)	MDC (%)
Neurological	12.54 (2.06)	13.68 (2.57)	0.68 (0.50–0.80)	1.31	9.99	3.63	27.69
Sepsis	13.00 (2.67)	14.22 (2.43)	0.64 (0.45–0.78)	1.53	11.24	4.24	31.16
Elderly	12.54 (2.84)	13.20 (2.84)	0.48 (0.19–0.64)	2.05	15.91	5.68	44.11
Trauma	13.10 (2.60)	14.34 (2.67)	0.75 (0.60–0.85)	1.32	9.60	3.65	26.62

ICC: intraclass correlation coefficient; CI: confidence interval; SEM: standard error measurement; MDC: minimal detectable change.

PI[17]. In addition, BS has proved to be valid for predicting the risk of PI when compared to the simple judgment of the team of health care professionals[18,19]. However, again, inter-examiner reliability has not been achieved. In addition, it is known that reliability is about the ability to reproduce a result consistently in time and space, or from different observers, who will indicate coherence, precision, stability, equivalence, and homogeneity[14]. Thus, this study shows that BS has low reliability in PI prediction in patients who are in the ICU.

A previous study with the secondary objective of verifying inter-examiner reliability in the risk assessment of PI of 87 patients from different sectors (surgical clinic, internal medicine, adult, ICU, and semi-intensive) also found that the subscales of moisture and nutrition showed relatively low kappa values. The authors attribute this result to the insufficient training of the nursing team[6]. However, it is worth mentioning that such subscales also showed low reliability for most of the samples tested in the present study. Thus, the explanation given by the aforementioned authors does not seem convincing, given that the examiners of the present study had a great experience of 10 years in the application of BS.

Hyun et al.[20] conducted a retrospective study, using a 4-year time window and using data from electronic medical records of 7790 patients in order to verify the predictive validity of BS to assess the risk of developing PI in ICU patients. The authors identified that BS has insufficient predictive validity

and low precision in discriminating patients in intensive care who are at risk of developing PI. In addition, they concluded that BS may not sufficiently reflect the characteristics of patients in intensive care. Although it did not discriminate the clinical characteristics of the population, it reinforces the results found in our study, in which BS has low reliability for populations with neurological disorders, sepsis, the elderly, and adults with trauma.

A robust and recent study aimed at investigating the structural validity of BS, using a structural equation model, which has the ability to isolate an observational error from measuring possible variables, such as the risk of pressure ulcers, concluded that BS in its original form has inadequate validity for ICU patients[21]. Still, it indicates that the most important scores of the subscale were sensory perception, mobility, and humidity, concluding that professionals should pay special attention to patients with low scores in one or more of these subscales. In this study, the subscales showed acceptable reliability only for the item mobility in patients with sepsis, trauma, and the elderly; sensory perception in neurological and trauma patients; and nutrition only in elderly patients.

Recently, a study aiming to assess the accuracy of the predictive capacity for the development of pressure ulcers using BS in traumatized and burned patients in the ICU was emphatic in concluding that BS has a median discriminatory capacity among the traumatized and burned population, also suggesting that it generates unnecessary expenditure of time and human resources, which could be concentrated on the prevention of pressure ulcer formation[22]. In our study, in addition to evaluating the accuracy of BS in trauma patients, we evaluated three other populations with different clinical characteristics; however, all of them with intensive care needs, and we found results similar to the study mentioned above. The question is, would these four populations have the same sensory perception, skin moisture, and even friction and shear so that BS would then be used as a useful tool?

Contrary to the results of this study and the aforementioned studies, Sundaram et al.[23] observed positive results, that is, the use of BS was able to predict the risk of PI in hospitalized patients after liver transplantation. However, these authors did not investigate the reliability of BS in this population; they focused only on its predictive aspect.

In this study, we affirm that BS is not a useful clinical tool, that is, it has no reliable applicability for the populations in question, assisted in the ICU. Reinforcing our study, Ranzani et al.[24], with the objective of validating a new version and improving the BS for critically ill patients, added clinical variables to the original scale, since the author reports that BS cannot be considered accurate for critically ill patients. From this view, again, we do not indicate its use, since the majority of patients in the ICU are considered to be serious.

The main limitation of this study is related to the multiple diagnoses or the coexistence of comorbidities in the population. However, one of the strengths of the article was to precisely evaluate four different populations that are most part of the routine of an ICU and conclude that the BS is not a good tool for predicting pressure ulcers in these populations.

The clinical implications conveyed in this study are the nonrecommendation of the use of the BS for ICU and we also encourage the scientific population to address studies that seek to create a more adequate tool that considers intrinsic factors of the diseases.

CONCLUSIONS

We do not recommend the use of this scale and emphasize the need to develop another tool to assess the risk of developing PI in ICU patients.

AUTHORS' CONTRIBUTIONS

TPV: Conceptualization, Data curation, Formal Analysis, Investigation, Methodology, Project administration, Resources, Supervision, Writing – original draft, Writing – review & editing. **ASR:** Conceptualization, Data curation, Formal Analysis, Investigation, Methodology, Project administration, Resources, Supervision, Writing – original draft, Writing – review & editing. **WSM:** Formal Analysis, Methodology, Supervision, Writing – original draft, Writing – review & editing. **PRF:** Formal Analysis, Methodology, Supervision, Writing – original draft, Writing – review & editing. **DSR:** Formal Analysis, Methodology, Supervision, Writing – original draft, Writing – review & editing. **IMAF:** Formal Analysis, Methodology, Supervision, Writing – original draft, Writing – review & editing. **ADSA:** Formal Analysis, Methodology, Supervision, Writing – original draft, Writing – review & editing. **RGM:** Formal Analysis, Methodology, Supervision, Writing – original draft, Writing – review & editing. **RRJT:** Formal Analysis, Methodology, Supervision, Writing – original draft, Writing – review & editing. **DBD:** Conceptualization, Data curation, Formal Analysis, Methodology, Investigation, Project administration, Resources, Supervision, Writing – original draft, Writing – review & editing.

REFERENCES

1. Boyko TV, Longaker MT, Yang GP. Review of the Current Management of Pressure Ulcers. Adv Wound Care (New Rochelle). 2018;7(2):57-67. https://doi.org/10.1089/wound.2016.0697
2. Jaul E, Barron J, Rosenzweig JP, Menczel J. An overview of co-morbidities and the development of pressure ulcers among older adults. BMC Geriatr. 2018;18(1):305. https://doi.org/10.1186/s12877-018-0997-7
3. Chaboyer WP, Thalib L, Harbeck EL, Coyer FM, Blot S, Bull CF, et al. Incidence and prevalence of pressure injuries in adult intensive care patients: a systematic review and meta-analysis. Crit Care Med. 2018;46(11):e1074-81. https://doi.org/10.1097/CCM.0000000000003366
4. Li Z, Lin F, Thalib L, Chaboyer W. Global prevalence and incidence of pressure injuries in hospitalised adult patients: a systematic review and meta-analysis. Int J Nurs Stud. 2020;105:103546. https://doi.org/10.1016/j.ijnurstu.2020.103546
5. Lima-Serrano M, González-Méndez MI, Martín-Castaño C, Alonso-Araujo I, Lima-Rodríguez JS. Predictive validity and reliability of the Braden scale for risk assessment of pressure ulcers in an intensive care unit. Med Intensiva (Engl Ed). 2018;42(2):82-91. https://doi.org/10.1016/j.medin.2016.12.014
6. Rogenski NMB, Kurcgant P. Avaliação da concordância na aplicação da Escala de Braden interobservadores. Acta Paul Enferm. 2012;25(1):24-8. https://doi.org/10.1590/S0103-21002012000100005
7. Gadd MM, Morris SM. Use of the Braden Scale for pressure ulcer risk assessment in a community hospital setting: the role of total score and individual subscale scores in triggering preventive interventions. J Wound Ostomy Continence Nurs. 2014;41(6):535-8. https://doi.org/10.1097/WON.0000000000000066
8. Sardo P, Simões C, Alvarelhão J, Costa C, Simões CJ, Figueira J, et al. Pressure ulcer risk assessment: retrospective analysis of Braden Scale scores in Portuguese hospitalised adult patients. J Clin Nurs. 2015;24(21-22):3165-76. https://doi.org/10.1111/jocn.12927
9. Paranhos WY, Santos VLCG. Avaliação de risco para úlceras de pressão por meio da escala de braden, na lingua portuguesa. Rev Esc Enferm USP. 1999;33(Número especial):191-9.
10. Chou R, Dana T, Bougatsos C, Blazina I, Starmer AJ, Reitel K, et al. Pressure ulcer risk assessment and prevention: a systematic comparative effectiveness review. Ann Intern Med. 2013;159(1):28-38. https://doi.org/10.7326/0003-4819-159-1-201307020-00006
11. Menegon DB, Bercini RR, Santos CT, Lucena AF, Pereira AGS, Scain SF. Análise das subescalas de braden como indicativos de risco para úlcera por pressão. Texto Contexto – Enferm. 2012;21(4):854-61. https://doi.org/10.1590/S0104-07072012000400016
12. Adibelli S, Korkmaz F. Pressure injury risk assessment in intensive care units: Comparison of the reliability and predictive validity of the Braden and Jackson/Cubbin scales. J Clin Nurs. 2019;28(23-24):4595-605. https://doi.org/10.1111/jocn.15054
13. Kottner J, Audigé L, Brorson S, Donner A, Gajewski BJ, Hróbjartsson A, et al. Guidelines for reporting reliability and agreement studies (GRRAS) were proposed. J Clin Epidemiol. 2011;64(1):96-106. https://doi.org/10.1016/j.jclinepi.2010.03.002
14. Terwee CB, Bot SD, Boer MR, van der Windt DA, Knol DL, Dekker J, et al. Quality criteria were proposed for measurement properties of health status questionnaires. J Clin Epidemiol. 2007;60(1):34-42. https://doi.org/10.1016/j.jclinepi.2006.03.012
15. Fleiss JL. The design and analysis of clinical experiments. John Wiley & Sons, Inc.; 1999. https://doi.org/10.1002/9781118032923
16. Ostelo RW, Vet HC, Knol DL, van den Brandt PA. 24-item Roland-Morris disability questionnaire was preferred out of six functional status questionnaires for post-lumbar disc surgery. J Clin Epidemiol. 2004;57(3):268-76. https://doi.org/10.1016/j.jclinepi.2003.09.005
17. Landis JR, Koch GG. The measurement of observer agreement for categorical data. Biometrics. 1977;33(1):159-74. PMID: 843571
18. Wilchesky M, Lungu O. Predictive and concurrent validity of the Braden scale in long-term care: a meta-analysis. Wound Repair Regen. 2015;23(1):44-56. https://doi.org/10.1111/wrr.12261
19. Park SH, Choi YK, Kang CB. Predictive validity of the Braden Scale for pressure ulcer risk in hospitalized patients. J Tissue Viability. 2015;24(3):102-13. https://doi.org/10.1016/j.jtv.2015.05.001
20. Hyun S, Vermillion B, Newton C, Fall M, Li X, Kaewprag P, et al. Predictive validity of the Braden scale for patients in intensive care units. Am J Crit Care. 2013;22(6):514-20. https://doi.org/10.4037/ajcc2013991
21. Marsh HW, Morin AJ, Parker PD, Kaur G. Exploratory structural equation modeling: an integration of the best features of exploratory and confirmatory factor analysis. Annu Rev Clin Psychol. 2014;10:85-110. https://doi.org/10.1146/annurev-clinpsy-032813-153700
22. Griswold LH, Griffin RL, Swain T, Kerby JD. Validity of the Braden Scale in grading pressure ulcers in trauma and burn patients. J Surg Res. 2017;219:151-7. https://doi.org/10.1016/j.jss.2017.05.095
23. Sundaram V, Lim J, Tholey DM, Iriana S, Kim I, Manne V, et al. The Braden Scale, A standard tool for assessing pressure ulcer risk, predicts early outcomes after liver transplantation. Liver Transpl. 2017;23(9):1153-60. https://doi.org/10.1002/lt.24789
24. Ranzani OT, Simpson ES, Japiassú AM, Noritomi DT; Amil Critical Care Group. The Challenge of Predicting Pressure Ulcers in Critically Ill Patients. A Multicenter Cohort Study. Ann Am Thorac Soc. 2016;13(10):1775-83. https://doi.org/10.1513/AnnalsATS.201603-154OC

ORIGINAL ARTICLE

https://doi.org/10.1590/1806-9282.20220253

Message applications in the doctor-patient relationship as a stressor

Melissa Gonzalez Veiga[1*], Rogério Tadeu Felizi[1], Gislayne Darly Trevisan[1], Daniel de Iracema Gomes Cubero[2], César Eduardo Fernandes[1], Emerson de Oliveira[1]

SUMMARY

OBJECTIVE: The aim of this study was to assess the use of smartphones' messaging apps as a stressor affecting the well-being of gynecologists who use this tool to communicate with patients.

METHODS: A cross-sectional study was conducted with gynecologists who use message applications to communicate with patients. Participants answered the WhatsApp Stress Scale, Oldenburg Burnout Inventory, and the techno-stress questionnaire. The population sample consisted of gynecologists and obstetricians selected by convenience.

RESULTS: Physicians who spent more time using WhatsApp to communicate with patients had higher levels of stress (p=0.010), Burnout (p<0.001), and techno-invasion score (p<0.05).

CONCLUSIONS: A positive association was found between the high frequency of WhatsApp usage for communication with patients and doctor's Burnout and stress, negatively influencing professional's well-being.

KEYWORDS: mobile applications, occupational stress, physician-patient relations, smartphone

INTRODUCTION

We have experienced a technology-driven revolution making effects on our lives. Technology tools take over our daily activities and influence what we consume and how we share experiences with others[1]. Healthcare is not immune to it. Recently, technology is integrated into medical surveillance, diagnosis, treatment, and patient comfort[2]. Therefore, it is not surprising that the 21st century has brought challenges to medical professionals[3].

When computers became available in the 1990s, digital health emerged, followed by telemedicine as soon as the computers could be connected to networks. Technology advanced at an unprecedented pace, while smartphone penetration summoned mobile health[4]. Seemingly, smartphones and communication applications have become an irreplaceable tool in patients' care assistance. Instant messaging services have created a new era in clinical data exchange between patients and clinicians[5,6].

The real-time exchange of interacting technologies enables users to reach doctors immediately, anywhere at any time[7]. WhatsApp Messenger (WhatsApp Inc, Menlo Park, CA, USA), an app emerged in 2009, is part of how doctors and patients communicate in the 21st century, although it had not been specifically developed for medical purposes[8].

WhatsApp is a communication tool that can be downloaded free of cost from the Internet and is available for all mobile platforms. It only requires Internet connection in mobile and allows users to send messages, photos, and videos[9]. Other benefits of the app are improvement of communication, no computer required, time saving, and immediate response[6,8,10].

The following drawbacks have also been reported: increasing workload by staying online 24 h a day, disparity in the sense of urgency, clinical information not being included in medical records, issues of privacy and data protection, and absence of specific legislation[11].

It is usual that the demands placed on people by the changes in modern life and the need to adjust to these changes end up inducing emotional destabilization. Stress emerges as a consequence of persistent efforts to adapt to the existential situation[12]. The association between smartphone use and increased stress was suggested by a previous study[13].

Psychological distress has become a major mental health problem[14]. Depression could result in low productivity, absenteeism, and economic costs, whereas anxiety is frequently accompanied by headache, fatigue, or exhaustion[14]. Additionally, psychological distress among doctors impairs the safety of patients[15].

[1]Centro Universitário Faculdade de Medicina do ABC, Department of Gynecology – Santo André (SP), Brazil.
[2]Centro Universitário Faculdade de Medicina do ABC, Department of Oncology and Hematology – Santo André (SP), Brazil.
*Corresponding author: dramelissaveiga@gmail.com
Conflicts of interest: the authors declare there is no conflicts of interest. Funding: none.
Received on May 05, 2022. Accepted on June 17, 2022.

The goal of the present study was to evaluate the use of messaging apps as a stressor affecting the well-being of gynecologists and obstetricians who use this tool to communicate with patients.

METHODS

We conducted a cross-sectional study between August 2019 and July 2020, approved by the Research Ethics Committee of the ABC Foundation School of Medicine. The population sample consisted of gynecologists and obstetricians selected by convenience. The professionals were personally invited to a regional meeting, and all agreed to participate in the study.

The inclusion criteria were as follows: Brazilian gynecologists and obstetricians, who used WhatsApp to communicate with patients, and agreement to participate in the study according to the informed consent form.

Participants were divided into study groups according to the weekly time of WhatsApp use to communicate with patients: less than 2 h (GI), 2–5 h (GII), and more than 5 h (GIII). The categories were random since there is no consensus on what is excessive use of WhatsApp for the proposed purpose.

Sociodemographic data were collected and the physicians answered three instruments in a self-administered manner: techno-stress questionnaire, WhatsApp Stress Scale (WASS), and Oldenburg Burnout Inventory (OLBI)[16-18].

Participants answered the following questionnaires:

1. Sociodemographic questionnaire.
2. WASS: It is a questionnaire, created and validated by the authors of the present study, to measure how communication applications affect the well-being of gynecologists and obstetricians who use this tool to communicate with patients. The nine items were measured by a 5-point Likert scale, with score averages ranging from 1–5[17].
3. OLBI: It is a standardized questionnaire, validated in Brazilian Portuguese in 2018, consisting of 13 assertions to measure Burnout in two dimensions, namely, emotional exhaustion and disengagement. All dependent variables were measured using a 4-point Likert scale, with score averages ranging from 1–4[18].
4. Techno-stress questionnaire: It is a standardized questionnaire consisting of 11 assertions to measure techno-stress in two dimensions, namely, techno-stress creators and techno-stress inhibitors. We used four domains, i.e., techno-overload, techno-invasion, techno-complexity, and job satisfaction. All dependent variables were measured using a 5-point Likert scale, with score averages ranging from 1–5[16].

The data were tabulated in Microsoft Excel 2003. The IBM-SPSS for Windows software version 20.0 (IBM Corp, Chicago, IL, USA) was used for analysis.

The normality of the data was analyzed using the Kolmogorov-Smirnov test. Analysis of variance (ANOVA) and the Bonferroni test were used to compare continuous variables. The chi-squared test and the likelihood ratio test were used to compare categorical variables.

The scores' questionnaires were analyzed by the mean. The variables worded positively were inverted, thus characterizing that the higher the mean, the higher stress perceived by WASS, and the higher burnout and techno-stress levels.

Statistical tests were two-tailed, with a significance level of 5%.

RESULTS

We included 138 physicians, divided into the three study groups according to the weekly WhatsApp usage time for communication with patients: less than 2 h (GI, n=86), 2–5 h (GII, n=29), and more than 5 h (GIII, n=23).

The mean age of the participants in GI, GII, and GIII was 46.6±13.2, 46.1±12.2, and 41.9±6.8 years, respectively (p=0.249). More than half of the doctors self-identified as female in all groups (p=0.234). All groups had a greater proportion of cohabiting people (p=0.091), persons with at least one child (p=0.633), and persons living in São Paulo city and neighborhood (p=0.548). Most participants in all groups had been working for more than 15 years as a doctor (p=0.599). The professionals who had more office work activity (p=0.019) and who worked more hours a week (p=0.048) communicated more with patients via WhatsApp.

Demographic data are described in Table 1.

Table 2 shows the scores' questionnaires in the groups studied. Doctors who spent more hours communicating with patients via WhatsApp had higher levels of stress perceived by WASS (p=0.010) and emotional exhaustion (Burnout) (p<0.001).

Techno-overload and techno-invasion were related to longer WhatsApp usage time to communicate with patients (p<0.001). Techno-complexity and job satisfaction did not differ between groups. The vast majority of the physicians reported being satisfied with their work (p=0.932). When adjusted for the workload and office work of study participants, the results were similar.

When answering WASS, 74% of the doctors reported frequently answering messages not related to urgent matters, while 78% reported feeling insecure due to the lack of specific regulations related to the use of WhatsApp to communicate with patients. About 82% of professionals believed that this type of

Table 1. Sociodemographic characteristics.

	WhatsApp Group			p-value
	<2 h/week (n=86)	2–5 h/week (n=29)	>5 h/week (n=23)	
Age (years)				
Mean±DP	46.6±13.2	46.1±12.2	41.9±6.8	0.249*
Gender, n (%)				
Female	49 (57)	20 (69)	17 (73.9)	0.234
Male	37 (43)	9 (31)	6 (26.1)	
Marital Status, n (%)				
Single	30 (34.9)	8 (27.6)	9 (39.1)	0.091#
Married	49 (57)	21 (72.4)	14 (60.9)	
Cohabitation	7 (8.1)	0 (0)	0 (0)	
Children, n (%)				
Yes	55 (64)	21 (72.4)	14 (60.9)	0.633
No	31 (36)	8 (27.6)	9 (39.1)	
Residence, n (%)				
São Paulo city and neighborhood	84 (97.7)	28 (96.6)	22 (95.7)	0.548#
Interior of São Paulo	1 (1.2)	0 (0)	1 (4.3)	
Other states	1 (1.2)	1 (3.4)	0 (0)	
Graduate year, n (%)				
1–15 years	29 (33.7)	7 (24.1)	8 (34.8)	0.599
>15 years	58 (66.3)	22 (75.9)	7 (65.2)	
Smoking, n (%)				
Yes	5 (5.8)	1 (3.4)	0 (0)	0.285#
No	81 (94.2)	28 (96.6)	23 (100)	
Alcoholism, n (%)				
Yes	4 (4.7)	3 (10.3)	0 (0)	0.155#
No	82 (95.3)	26 (89.7)	23 (100)	
Physical activity, n (%)				
Yes	49 (57)	15 (51.7)	15 (65.2)	0.618
No	37 (43)	14 (48.3)	8 (34.8)	
Weekly workload, n (%)				
<20 h	2 (2.3)	1 (3.4)	2 (8.7)	0.048#
20–30 h	5 (5.8)	4 (13.8)	0 (0)	
31–40 h	27 (31.4)	8 (27.6)	2 (8.7)	
41–60 h	40 (46.5)	13 (44.8)	11 (47.8)	
>60 h	12 (14)	3 (10.3)	8 (34.8)	
Work-duty activity, n (%)				
Yes	35 (40.7)	11 (37.9)	6 (26.1)	0.438
No	51 (59.3)	18 (62.1)	17 (73.9)	
Office work activity, n (%)				
Yes	74 (86)	28 (96.6)	23 (100)	0.019#
No	12 (14)	1 (3.4)	0 (0)	
Work-surgery activity, n (%)				
Yes	45 (52.3)	20 (69)	16 (69.6)	0.148
No	41 (47.7)	9 (31)	7 (30.4)	
Academic activity, n (%)				
Yes	31 (36)	11 (37.9)	8 (34.8)	0.971
No	55 (64)	18 (62.1)	15 (65.2)	

Test: χ^2; #Likelihood ratio test; *ANOVA.

communication trivializes the medical service, while 73% had already felt annoyed by the lack of remuneration when working through the tool.

Table 3 compares scores that differed between groups. The stress score was higher in GIII than in GI (p=0.008). Emotional exhaustion and techno-overload were higher in GIII than in GI and GII (p<0.05). Techno-invasion was higher in GIII than in GI and GII, and higher in GII than in GI (p<0.05).

DISCUSSION

The key finding of this study was that the high WhatsApp usage for communication with patients can cause doctor's Burnout and stress. Given that the physicians who worked the most hours per week communicated the most with patients through messaging apps, the high rates of stress and Burnout can be attributed, among other factors, to workload. After all, they added working time to an already exhausting routine peculiar to the gynecology setting.

Hours worked per week as a factor independently associated with Burnout is confirmed by the report by Dyrbye for a sample of 7,905 surgeons[19]. Although the WhatsApp usage is due to the perception of numerous advantages reported in clinical practice, increasing the efficiency of doctor-patient communication, it enables online availability 24 h a day, 7 days a week, significantly increasing working hours.

A study conducted in the USA linked long hours worked to sleep disturbances, fatigue, stress, negative mood, and decrements in functioning[20]. In other words, being available professionally for hours at a time can bring undeniable damage to the physician's health.

In our study, techno-invasion and techno-overload were associated with the high WhatsApp usage for communication

Table 3. Bonferroni multiple comparisons.

	Comparison	MD	p-value	95%CI	
				Inferior	Superior
WASS Total score	GI–GII	-0.09	>0.999	-0.53	0.36
	GI–GIII	-0.62	0.008	-1.10	-0.13
	GII–GIII	-0.53	0.083	-1.11	0.05
Burnout Emotional exhaustion	GI–GII	-0.19	0.617	-0.56	0.17
	GI–GIII	-1.12	<0.001	-1.52	-0.72
	GII–GIII	-0.92	<0.001	-1.40	-0.45
Techno-stress Techno-overload	GI–GII	-0.38	0.270	-0.91	0.16
	GI–GIII	-1.26	<0.001	-1.84	-0.68
	GII–GIII	-0.88	0.007	-1.58	-0.19
Techno-stress Techno-invasion	GI–GII	-0.63	0.012	-1.15	-0.11
	GI–GIII	-1.86	<0.001	-2.43	-1.29
	GII–GIII	-1.23	<0.001	-1.91	-0.55

MD: mean difference; CI: confidence interval; WASS: WhatsApp Stress Scale.

Table 2. Questionnaires' descriptions by groups.

	WhatsApp Group			p-value	p¢
	<2 h/week (n=86)	2–5 h/week (n=29)	>5 h/week (n=23)		
WASS Questionnaire					
Mean±DP	3.43±0.92	3.52±0.8	4.05±0.62	0.010*	0.006
Burnout Questionnaire Score emotional exhaustion					
Mean±DP	2.24±0.73	2.43±0.75	3.36±0.52	<0.001*	<0.001
Score disengagement					
Mean±DP	2.13±0.69	2.15±0.71	2.32±0.8	0.536*	0.581
Technological stress questionnaire Techno-overload					
Mean±DP	2.67±1.04	3.05±1.1	3.93±0.85	<0.001*	<0.001
Techno-invasion					
Mean±DP	2.78±1.09	3.41±1.04	4.64±0.39	<0.001*	<0.001
Techno-complexity					
Mean±DP	2.42±0.96	2.64±1.11	2.44±1.14	0.593*	0.849
Job satisfaction					
Mean±DP	4.34±0.7	4.31±0.9	4.39±0.84	0.932*	0.953

Test: χ^2; *ANOVA; ¢Value adjusted for the workload and office work activity.

with patients. Consistent with our results, Waizenegger suggested that techno-overload (constant connectivity) leads to techno-invasion, an important cause of workers' techno-stress[21].

Besides their negative impact on individuals' quality of life, stress and Burnout may also affect the quality of care delivered to patients, which is deeply worrying. A previous study showed that emotional exhaustion was associated with adverse outcomes in patient care and worsening physician-patient relationship[22].

The majority of the participants in our study reported being satisfied with their work. The longer time using WhatsApp to communicate with patients, which was related to higher levels of stress, could negatively influence the professional's satisfaction, a situation not demonstrated. The medical literature described a direct association between stress and Burnout and low job satisfaction[22].

Approximately 73% of the physicians exhibited a concern about electronic communication not being reimbursed. While technology-mediated consultation is a medical act, it is important to define reimbursement strategies to make it financially sustainable. Many physicians in our study reported the feeling that the virtual environment can trivialize the medical service, which has been pointed out earlier as a major disadvantage of the use of WhatsApp in doctor-patient communication[9,11].

As a result of the novelty of this form of physician-patient communication, physicians do not have a lot of experience in dealing with online ethical, legal, and privacy dilemmas. Doctors in the present study reported the concern about online ethical, legal, and privacy dilemmas, which is consistent with a Lebanese study that has shown that 80% of surveys' doctors responders felt virtual communication can result in medico-legal issues[23].

Many issues related to the use of instant messages in doctor-patient communication can influence the quality of life of physicians. The need to adapt to this technology, which became part of clinical practice practically overnight, generates anxiety and stress, which is associated with negative consequences on patient care.

Limitations of the study include a convenience sample and questionnaire distribution being practically limited to the state of São Paulo, which significantly limits the generalizability of the study. Besides, stress and Burnout are multifactorial, and the factors were not fully addressed. Nevertheless, our results provide information that could help in the development of policies and strategies that will result in a better online physician-patient communication and make this form of communication less stressful for physicians.

CONCLUSIONS

The use of messaging apps via a smartphone was a stressor for gynecologists and obstetricians who routinely use this tool to communicate with patients. This results in a serious problem for gynecologists' and obstetricians' quality of life and represents a potential risk to the quality of medical care provided by them.

ACKNOWLEDGMENT

The authors thank all the participants.

AUTHORS' CONTRIBUTION

MGV: Conceptualization, Data curation, Writing – original draft, Writing – review & editing. **RTF:** Conceptualization, Data curation, Writing – original draft, Writing – review & editing. **GDT:** Conceptualization, Data curation, Writing – original draft, Writing – review & editing. **DIGC:** Formal Analysis. **CEF:** Writing – review & editing. **EO:** Formal Analysis.

REFERENCES

1. Powell J, Arvanitis TN. Welcome to the digital health revolution. Digit Health. 2015;1:2055207614561571. https://doi.org/10.1177/2055207614561571
2. Simpkin AL, Dinardo PB, Pine E, Gaufberg E. Reconciling technology and humanistic care: Lessons from the next generation of physicians. Med Teach. 2017;39(4):430-5. https://doi.org/10.1080/0142159X.2017.1270434
3. Mesko B, Győrffy Z. The rise of the empowered physician in the digital health era: viewpoint. J Med Internet Res. 2019;21(3):e12490. https://doi.org/10.2196/12490
4. Győrffy Z, Radó N, Mesko B. Digitally engaged physicians about the digital health transition. PLoS One. 2020;15(9):e0238658. https://doi.org/10.1371/journal.pone.0238658
5. Krynski L, Goldfarb G, Maglio I. Technology-mediated communication with patients: WhatsApp Messenger, e-mail, patient portals. A challenge for pediatricians in the digital era. Arch Argent Pediatr. 2018;116(4):e554-9. https://doi.org/10.5546/aap.2018.eng.e554
6. Petruzzi M, Benedittis M. WhatsApp: a telemedicine platform for facilitating remote oral medicine consultation and improving clinical examinations. Oral Surg Oral Med Oral Pathol Oral Radiol. 2016;121(3):248-54. https://doi.org/10.1016/j.oooo.2015.11.005
7. Yang HL, Lin RX. The impacts of SoLoMo services technostress on anxiety. J Electron Commer Res. 2018;19(2):186-200.
8. Boulos MNK, Giustini DM, Wheeler S. Instagram and WhatsApp in health and healthcare: an overview. Future Internet. 2016;8(3):37. https://doi.org/10.3390/fi8030037

9. Semeniuk GB. Medicina en la era del Whatsapp. Medicina (B Aires). 2019;79(5):407-8. PMID: 31671392
10. Benedictis A, Lettieri E, Masella C, Gastaldi L, Macchini G, Santu C, et al. WhatsApp in hospital? An empirical investigation of individual and organizational determinants to use. PLoS One. 2019;14(1):e0209873. https://doi.org/10.1371/journal.pone.0209873
11. Leão CF, Coelho MES, Siqueira AO, Rosa BAA, Neder PRB. O uso do WhatsApp na relação médico-paciente. Rev Bioét. 2018;26(3):412-9. https://doi.org/10.1590/1983-80422018263261
12. Ballone GJ, Moura EC. Estresse e Trabalho. PsiqWeb. 2008 [cited on Apr 28, 2021]. Available from: http://www.psiqweb.med.br.
13. Thomée S, Härenstam A, Hagberg M. Mobile phone use and stress, sleep disturbances, and symptoms of depression among young adults--a prospective cohort study. BMC Public Health. 2011;11:66. https://doi.org/10.1186/1471-2458-11-66
14. Wang Y, Wang P. Perceived stress and psychological distress among chinese physicians: The mediating role of coping style. Medicine (Baltimore). 2019;98(23):e15950. https://doi.org/10.1097/MD.0000000000015950
15. Hall LH, Johnson J, Watt I, Tsipa A, O'Connor DB. Healthcare Staff Wellbeing, Burnout, and Patient Safety: A Systematic Review. PLoS One. 2016;11(7):e0159015.https://doi.org/10.1371/journal.pone.0159015
16. Ragu-Nathan TS, Tarafdar M, Ragu N, Tu Q. The consequences of technostress for end users in organizations: conceptual development and validation. Inf Syst Res. 2008;19(4):417-33. https://doi.org/10.1287/isre.1070.0165
17. Veiga MG, Fernandes CE, Oliveira E. WhatsApp and gynecologist-patient interaction: development and validation of a questionnaire to assess the stress perceived by the doctor. Rev Bras Ginecol Obstet. 2022;44(5):497-502. https://doi.org/10.1055/s-0042-1744289
18. Schuster MDS, Dias VDV. Oldenburg Burnout Inventory - validation of a new way to measure Burnout in Brazil. Cien Saúde Colet. 2018;23(2):553-62. https://doi.org/10.1590/1413-81232018232.27952015
19. Dyrbye LN, Shanafelt TD, Balch CM, Satele D, Sloan J, Freischlag J. Relationship between work-home conflicts and burnout among American surgeons: a comparison by sex. Arch Surg. 2011;146(2):211-7. https://doi.org/10.1001/archsurg.2010.310
20. Caruso CC. Possible broad impacts of long work hours. Ind Health. 2006;44(4):531-6. https://doi.org/10.2486/indhealth.44.531
21. Waizenegger L, Remus U, Maier R. The social media trap - how knowledge workers learn to deal with constant social connectivity. Proc Annu Hawaii Int Conf Syst Sci. 2016;2016:2115-24. https://doi.org/10.1109/HICSS.2016.267
22. Lo D, Wu F, Chan M, Chu R, Li D. A systematic review of burnout among doctors in China: a cultural perspective. Asia Pac Fam Med. 2018;17:3. https://doi.org/10.1186/s12930-018-0040-3
23. Daniel F, Jabak S, Sasso R, Chamoun Y, Tamim H. Patient-physician communication in the era of mobile phones and social media apps: cross-sectional observational study on lebanese physicians' perceptions and attitudes. JMIR Med Inform. 2018;6(2):e18. https://doi.org/10.2196/medinform.8895

ORIGINAL ARTICLE

https://doi.org/10.1590/1806-9282.20220269

The role of the serum tube agglutination test in the monitoring of human brucellosis: evaluation of post-treatment SAT titers

Betul Copur[1]*, Ozgur Pasa[2]

SUMMARY

OBJECTIVE: Positive results of the serum tube agglutination test that persist after treatment may be interpreted by clinicians as treatment failures. Therefore, our study examined the value of serum tube agglutination test in demonstrating treatment success.

METHODS: In this retrospective study conducted at a single center, the pre- and post-treatment serum tube agglutination test titers of patients diagnosed with brucellosis were compared.

RESULTS: The end-of-treatment serum tube agglutination test titer was negative in 24 (18%) of 139 patients diagnosed with brucellosis. The most common complaints of the patients were fever (78.4%), chills (88.5%), sweating (84.9%), anorexia (79.1%), and arthralgia (63.3%). The rate of positive blood culture before the treatment was 68.3%. The absence of fever (p=0.005) and arthralgia (p=0.024) and the pretreatment serum tube agglutination test titer of <1/160 (p=0.014) were significant markers of serological cure.

CONCLUSION: Although serum tube agglutination test is an effective and very successful test in the diagnosis of brucellosis, our study shows that serum tube agglutination test is not useful in demonstrating the treatment success of human brucellosis in the early post-treatment period.

KEYWORDS: Brucellosis. Bacteremia. Blood culture. Serological follow-up. Agglutination tests.

INTRODUCTION

Brucellosis is the most common zoonotic disease worldwide and occurs mainly in areas where livestock farming is done. Despite low mortality rate, treatment failure and relapse rates are also substantial due to frequent treatment failure and repeated contacts in endemic areas[1-3].

The serum tube agglutination test (SAT) for brucellosis is mostly used for the diagnosis of this disease, and it is not recommended to use this test in treatment monitoring[4-6]. However, our daily practice shows that this test is used in the follow-up of brucellosis patients; a failure to drop titer SAT can often be considered a treatment failure in this patient population and unfortunately leads them to undergo prolonged and excessive treatments. For this reason, this study aimed to investigate the success of SAT in brucellosis monitoring by comparing pre- and post-treatment SAT titers.

METHODS

Study design and patients

Patients aged 16 years and older who were diagnosed with brucellosis and regularly presented to the outpatient clinic Infectious Diseases of Bitlis Tatvan State Hospital every 2–4 weeks between October 1, 2018, and December 31, 2019, were enrolled in this retrospective and single-center study. All patient data were retrieved from our previous study[7]. The study patients were also divided into two groups to compare relevant variables: the end-of-treatment SAT-positive group (those with persistent SAT positivity) and the end-of-treatment SAT-negative group (those with nonpersistent SAT positivity).

Demographic and clinical data

The epidemiological, clinical, and laboratory findings of the patients were retrospectively evaluated. Brucellosis was diagnosed with a SAT titer of ≥1/160 or by isolation of *Brucella* spp. in a blood culture. Clinical improvement was noted in patients who received regular and appropriate treatment for at least 6 weeks and had improved symptoms and signs. A SAT titer of <1/40 at the end of the treatment was accepted as SAT negativity (serological cure), while a titer between 1/40 and 1/160 was considered a low titer. Patients who developed clinical symptoms within 6 months of the treatment and had at least a twofold increase in SAT titers or growth of *Brucella* spp. in blood culture were considered relapses.

[1]Haseki Training and Research Hospital, Department of Infectious Diseases and Clinical Microbiology – Istanbul, Turkey.
[2]Bitlis Tatvan State Hospital, Department of Clinical Microbiology – Bitlis, Turkey.
*Corresponding author: betul_sadic@hotmail.com
Conflicts of interest: the authors declare there is no conflicts of interest. Funding: none.
Received on May 06, 2022. Accepted on May 23, 2022.

Statistical analysis

The SPSS 15.0 program for Windows was used for statistical analysis. Descriptive statistics were given as numbers and percentages for categorical variables, and median and interquartile range for numerical variables. Comparisons of numerical variables between two independent groups were performed using the Mann-Whitney U test because the condition of normal distribution was not met. Rates in groups were compared using the chi-square test. Risk factors were analyzed using the logistic regression analysis, considering variables with a $p<0.250$. The alpha significance level was set at $p<0.05$.

RESULTS

In total, 139 patients diagnosed with brucellosis were included in the study. While 24 (18%) patients had negative end-of-treatment SAT titers, 115 (82%) had positive end-of-treatment SAT titers. Of the patients, 67 (48.2%) were male, 72 (51.8%) were female, and their mean age was 34 years (IQR 23–46) (Table 1).

In all, 29.6% of patients with persistent end-of-treatment SAT positivity and 25% of patients whose SAT became negative at the end of treatment were evaluated as having complicated brucellosis (p=0.653). The most common complaints of the patients were fever, chills, sweating, anorexia, and arthralgia. While 78% of the patients complained of fever, 52% had fever at admission. The proportion of patients with fever in the history was significantly higher (82.6 vs. 58.3%, p=0.09) in the end-of-treatment SAT-positive group (those with persistent SAT positivity) than that in the end-of-treatment SAT-negative group (those with nonpersistent SAT positivity). This difference was not observed in patients with fever at admission (51.3 vs. 54.2%, p=0.799) (Table 2).

Patients with persistent end-of-treatment SAT positivity had a significantly higher proportion of those with a pretreatment SAT titer of >1/160 (91.3 vs. 75%, p=0.034). Sixteen patients with a SAT titer of <1/160 (which is considered a low titer) were diagnosed with brucellosis after the growth of *Brucella* spp. in blood culture. In all, 2 of the 16 patients had a negative (corresponding to a SAT titer of <1/40) pretreatment SAT. Relapse occurred in five patients within 6 months of treatment. Only one of these patients was diagnosed with relapse after the SAT titer increased twofold, while three patients were diagnosed with relapse after isolation of

Table 1. Demographic and epidemiological characteristics of patients with brucellosis.

Characteristics	All patients, n (%)	End-of-treatment SAT-positive group, n (%)	End-of-treatment SAT-negative group, n (%)	p
Number of patients	139	115	24	
Gender				
Male	67 (48.2)	52 (45.2)	15 (62.5)	0.123
Female	72 (51.8)	63 (54.8)	9 (37.5)	
Age	34 (23–46)	34 (23–45)	40.5 (27.5–48.75)	0.301
Profession				
Livestock farming	98 (70.5)	78 (67.8)	20 (83.3)	0.130
Homemaker	16 (11.5)	15 (13.0)	1 (4.2)	0.306
Student	4 (2.9)	3 (2.6)	1 (4.2)	0.536
Other	21 (15.1)	19 (16.5)	2 (8.3)	0.530
Residence address				
Bay	72 (51.8)	59 (51.3)	13 (54.2)	0.799
District	61 (43.9)	50 (43.5)	11 (45.8)	0.833
City Center	6 (4.3)	6 (5.2)	0 (0.0)	0.530
Possible transmission route of the disease				
Consumption of unpasteurized milk and milk products	90 (64.7)	72 (62.6)	18 (75.0)	0.248
Contact with sick animals and their secretions	67 (48.2)	57 (49.6)	10 (41.7)	0.481
Family history of brucellosis	43 (30.9)	34 (29.6)	9 (37.5)	0.444
Relapse	17 (12.2)	14 (12.2)	3 (12.5)	1.000
Unknown	14 (10.1)	12 (10.4)	2 (8.3)	1.000

Brucella spp. in blood culture, although SAT titers were not significant for diagnosis.

In multiple regression analysis, pretreatment SAT <160 [OR: 4.739, 95%CI 0.061–0.727, p=0.014], absence of fever [OR: 4.484, 95%CI 0.079–0.633, p=0.005], and absence of arthralgia [OR: 3.215, 95%CI 0.112–0.860, p=0.024] were found to be the predictors of post-treatment serologic cure (Table 3).

DISCUSSION

Our study found that the end-of-treatment SAT titers became negative in only 18% of patients with brucellosis who were treated at the correct time and dose and whose clinical and laboratory results improved.

Brucella antibodies can be detected in serum for a long time after appropriate treatment[1]. In a study of 92 patients, it was

Table 2. Clinical characteristics of patients with brucellosis.

Characteristics	All patients, n (%)	End-of-treatment SAT-positive group, n (%)	End-of-treatment SAT-negative group, n (%)	p
Clinical form				
Acute	104 (74.8)	87 (75.7)	17 (70.8)	0.621
Subacute	35 (25.2)	28 (24.3)	7 (29.2)	
Complicated patient				
Sacroiliitis	12 (8.6)	10 (8.7)	2 (8.3)	1.000
Spondylodiscitis	14 (10.1)	12 (10.4)	2 (8.3)	1.000
Peripheral arthritis	3 (2.2)	3 (2.6)	0 (0.0)	1.000
Orchitis	2 (1.5)	1 (0.9)	1 (4.2)	0.321
Hepatitis	4 (2.9)	4 (3.5)	0 (0.0)	1.000
Other	5 (3.6)	4 (3.5)	1 (4.2)	1.000
Noncomplicated patient	99 (71.2)	81 (70.4)	18 (75.0)	0.653
Relapsing patient	17 (12.2)	14 (12.2)	3 (12.5)	1.000
Symptoms and signs/laboratory				
Fever (in the history)	109 (78.4)	95 (82.6)	14 (58.3)	0.009
Fever (at admission)	72 (51.8)	59 (51.3)	13 (54.2)	0.799
Chills	123 (88.5)	103 (89.6)	20 (83.3)	0.479
Sweating	118 (84.9)	101 (87.8)	17 (70.8)	0.055
Anorexia	110 (79.1)	91 (79.1)	19 (79.2)	0.997
Nausea	51 (36.7)	39 (33.9)	12 (50.0)	0.137
Weight loss	15 (10.8)	13 (11.3)	2 (8.3)	1.000
Arthralgia	88 (63.3)	76 (66.1)	12 (50.0)	0.137
Myalgia	86 (61.9)	69 (60.0)	17 (70.8)	0.320
Headache	49 (35.3)	41 (35.7)	8 (33.3)	0.829
Backache	54 (38.8)	46 (40.0)	8 (33.3)	0.542
Splenomegaly	49 (35.3)	43 (37.4)	6 (25.0)	0.248
Hepatomegaly	36 (25.9)	33 (28.7)	3 (12.5)	0.099
Lymphadenomegaly	10 (7.2)	8 (7.0)	2 (8.3)	0.683
Anemia (Hgb g/dl) (<12 for females, <14 for males)	53 (38.1)	44 (38.3)	9 (37.5)	0.944
Leukopenia (<4000/mm^3)	10 (7.2)	9 (7.8)	1 (4.2)	1.000
Thrombocytopenia (<150,000/mm^3)	12 (8.6)	11 (9.6)	1 (4.2)	0.691
Positive blood culture	95 (68.3)	81 (70.4)	14 (58.3)	0.246
Prognosis				
Clinical improvement	134 (96.4)	110 (95.7)	24 (100)	0.587

Bold value indicates statistical significance at the p<0.05 level.

Table 3. Factors determining post-treatment SAT negativity in patients with brucellosis.

	p	OR	95%CI	
Gender (ref: male) Female	0.082	2.392	0.156	1.118
Absence of fever (in the history)	0.005	4.484	0.079	0.633
Absence of arthralgia	0.024	3.215	0.112	0.860
Pretreatment SAT titer <1/160	0.014	4.739	0.061	0.727

Bold values indicate statistical significance at the p<0.05 level.

reported that SAT titers were still positive in 48% of patients 1.5 years after the completion of treatment[8]. In another study comparing pre- and post-treatment SAT titers, it was found that SAT positivity persisted 80% after treatment and the 2 ME (mercaptoethanol) agglutination test became negative in all patients[9]. Similarly, the end-of-treatment SAT positivity rate was 82% in our study. In a study in which the SAT titers of 175 patients with brucellosis who showed clinical improvement were followed for 2 years, serological cure was 24% at 1 year and 87% at 2 years[10]. In a similar study conducted in patients with acute brucellosis in Saudi Arabia, where brucellosis is endemic, the SAT cure rate in the 1st month after treatment was reported to be 8.3%, and in the same study, male gender, advanced age, and use of fewer than three antibiotics during treatment were associated with post-treatment SAT positivity in the univariate analysis. At the same time, no significant marker of serological cure was found in the multiple analysis[11]. According to a report from another endemic region of our country, the post-treatment serological cure was 29.3%[12]. However, in our study, the post-treatment serological cure was 18%, and when multiple analyses were performed, a pretreatment SAT titer of <1/160 (OR: 4.739), absence of fever (OR: 4.484), and absence of arthralgia (OR: 3.215) were found to be important predictors for serological cure (Table 3).

In a study in which the SAT titers of 35 patients diagnosed with and recovered from brucellosis were followed for 2 years, it was shown that this test became negative to varying degrees and with low frequency in persistent and relapsing patients, whereas it became negative more rapidly and to a greater extent in patients with acute brucellosis. The same study concluded that the SAT is not suitable for monitoring chronic patients and predicting relapses[6]. In our study, the proportion of patients with acute disease and relapse was similar in the end-of-treatment SAT-positive and SAT-negative groups (75.7 and 70.8%, p=0.621; 12.2 and 12.5%, p=1, respectively) (Table 2). Our study also measured SAT titers only in the 1st month after treatment, and SAT titers decreased in 59% of patients and remained the same in 23%. Of our five relapsing patients, only one was diagnosed with relapse after SAT titers increased two-fold, while three were diagnosed with relapse after isolation of *Brucella* spp. in blood culture, although SAT titers were not significant for diagnosis. Our data support studies showing that SAT is not very successful in detecting relapse.

When comparing Brucella isolation rates before treatment, no statistical difference was found between patients with the end-of-treatment SAT-positive and SAT-negative (70.4 vs. 58.3%, p=0.246). Since bacteremia can occur periodically in brucellosis, blood culture is not always useful to demonstrate treatment success and clinical improvement[13]. In contrast, culture tests are not useful in monitoring brucellosis because of the high risk of contamination via the laboratory[14]. In our study, 16 patients with a SAT titer of <1/160 were diagnosed with brucellosis based on the isolation of *Brucella* spp. in blood culture. A blood culture may be a suitable diagnostic tool to diagnose early acute brucellosis when serological tests are not yet positive or to diagnose relapse when serological tests are inadequate and unreliable[9,15,16].

Coactivation of the humoral and cellular immune systems is one of the defense mechanisms developed by the host against *Brucella* bacteria. Cellular immunity plays the main role in healing. Although the presence of specific antibodies is important in diagnosing the disease, their success in monitoring the disease is limited. After successful treatment, IgM-type antibodies may be positive in low titers for months or years[1]. The long-term presence of *Brucella* antibodies makes it difficult to distinguish from relapse or previous infection. In this case, high IgG avidity is helpful to rule out active infection[1,17].

Although enzyme immunoassay (EIA) is not superior to other serological tests in the diagnosis of brucellosis, it is the most sensitive serological test in disease surveillance[18,19]. A study investigating the value of 2-ME and *Brucella* EIA in treatment monitoring revealed that IgM (EIA) is safer in the diagnosis and treatment monitoring of acute brucellosis, preventing 45.6% of unnecessary treatments[20]. In their study, Tumturk et al. demonstrated a significant difference between pre- and post-treatment IgM titers in patients with brucellosis and reported that there was no such difference between pre- and post-treatment IgG levels, especially in chronic patients. Based on these data, they concluded that the combined use of IgG and IgM tests in the diagnosis and monitoring of brucellosis would provide more accurate results[21].

When brucellosis is not treated, chronic infections and relapses may occur, which are undesirable complications of brucellosis. The evaluation of serological tests in conjunction

with clinical characteristics may be helpful to assess the success of treatment. EIA, 2-ME, Brucellacapt, and Coombs tests are now available for serological monitoring. Tests other than the EIA are relatively inexpensive and can be easily performed at any center. Rational serological surveillance with clinical data can prevent unnecessary antibiotic treatment and make a positive contribution to patient and environmental health.

Considering the data in the literature and in our study, it has been elucidated that SAT is not suitable to monitor brucellosis and to indicate the success of brucellosis treatment, apart from its high success in diagnosing the disease. However, clinicians may have to use this test for treatment follow-up. In this case, the interpretation of SAT by experienced physicians and/or combined use with other antibody tests may prevent prolonged treatments and increased treatment costs. Therefore, there is a need for tests that can be used to monitor the disease and are easy to interpret so that persistent SAT titer positivity can result in unnecessary and prolonged treatment, but there is still a need for comprehensive studies on this topic.

ACKNOWLEDGMENTS

All procedures performed in this study involving human participants were in accordance with the ethical standards of the National Research Committee and with the ethical standards of the Declaration of Helsinki. This study was approved by the Ethics Committee of Haseki Training and Research Hospital (approval number: 2021-67, date: 14/07/2021). Written informed consent was waived, given the retrospective nature of this study.

AUTHORS' CONTRIBUTIONS

BC: Conceptualization, Data curation, Formal Analysis, Methodology, Software, Supervision, Validation, Visualization, Writing – original draft, Writing – review & editing. **OP**: Conceptualization, Data curation, Visualization.

REFERENCES

1. Gul HC, Erdem H. Brucellosis (*Brucella* species) In: Mandell GI, Benett JE, Dolin R (eds). Principles and practice of infectious diseases. Philadelphia, PA: Churchill Livingstone; 2015. p. 2573-758.
2. Colmenero JD, Reguera JM, Martos F, Sánchez-De-Mora D, Delgado M, Causse M, et al. Complications associated with *Brucella melitensis* infection: a study of 530 cases. Medicine (Baltimore). 1996;75(4):195-211. https://doi.org/10.1097/00005792-199607000-00003
3. Aygen B, Doganay M, Sumerkan B, Yildiz O, Kayabas U. Clinical manifestations, complications and treatment of brucellosis: a retrospective evaluation of 480 patients. Med Malad Infect. 2002;32(9):485-93. https://doi.org/10.1016/S0399-077X(02)00403-1
4. Gazapo E, Gonzalez Lahoz J, Subiza JL, Baquero M, Gil J, de la Concha EG. Changes in IgM and IgG antibody concentrations in brucellosis over time: importance for diagnosis and follow-up. J Infect Dis. 1989;159(2):219-25. https://doi.org/10.1093/infdis/159.2.219
5. Pellicer T, Ariza J, Foz A. Specific antibodies detected during relapse of human brucellosis. J Infect Dis. 1988;157(5):918-24. https://doi.org/10.1093/infdis/157.5.918
6. Baldi PC, Miguel SE, Fossati CA, Wallach JC. Serological follow-up of human brucellosis by measuring IgG antibodies to lipopolysaccharide and cytoplasmic proteins of *Brucella* species. Clin Infect Dis. 1996;22(3):446-55. https://doi.org/10.1093/clinids/22.3.446
7. Copur B, Sayili U. Laboratory and clinical predictors of focal involvement and bacteremia in brucellosis. Eur J Clin Microbiol Infect Dis. 2022;41(5):793-801. https://doi.org/10.1007/s10096-022-04436-1
8. Buchanan TM, Faber LC. 2-mercaptoethanol *Brucella* agglutination test: usefulness for predicting recovery from brucellosis. J Clin Microbiol. 1980;11(6):691-3. https://doi.org/10.1128/jcm.11.6.691-693.1980
9. Elfaki MG, Al-Hokail AA, Nakeeb SM, Al-Rabiah FA. Evaluation of culture, tube agglutination, and PCR methods for the diagnosis of brucellosis in humans. Med Sci Monit. 2005;11(11):MT69-74. PMID: 16258407
10. Roushan MR, Amiri MJ, Laly A, Mostafazadeh A, Bijani A. Follow-up standard agglutination and 2-mercaptoethanol tests in 175 clinically cured cases of human brucellosis. Int J Infect Dis. 2010;14(3):e250-3. https://doi.org/10.1016/j.ijid.2009.05.008
11. Almuneef M, Memish ZA. Persistence of *Brucella* antibodies after successful treatment of acute brucellosis in an area of endemicity. J Clin Microbiol. 2002;40(6):2313. https://doi.org/10.1128/JCM.40.6.2313.2002
12. Benli A. Brusellosis. In: Aydın M, Kutlu SS. (eds). XXI. Turkish clinical microbiology and infectious diseases congress. Istanbul: Turkish Society of Clinical Microbiology and Infectious Diseases; 2021.
13. Pappas G, Akritidis N, Bosilkovski M, Tsianos E. Brucellosis. N Engl J Med. 2005;352(22):2325-36. https://doi.org/10.1056/NEJMra050570
14. Mesureur J, Arend S, Cellière B, Courault P, Cotte-Pattat PJ, Totty H. A MALDI-TOF MS database with broad genus coverage for species-level identification of *Brucella*. PLoS Negl Trop Dis. 2018;12(10):e0006874. https://doi.org/10.1371/journal.pntd.0006874
15. Memish Z, Mah MW, Al Mahmoud S, Al Shaalan M, Khan MY. *Brucella* bacteraemia: clinical and laboratory observations in 160 patients. J Infect. 2000;40(1):59-63. https://doi.org/10.1053/jinf.1999.0586
16. Kadanali A, Ozden K, Altoparlak U, Erturk A, Parlak M. Bacteremic and nonbacteremic brucellosis: clinical and laboratory observations. Infection. 2009;37(1):67-9. https://doi.org/10.1007/s15010-008-7353-3
17. Kutlu SS, Celikbaş A, Ergönül O, Kutlu M, Aksaray S, Güvener E, et al. The value of the immunoglobulin G avidity test for the serologic diagnosis of brucellosis. Mikrobiyol Bul. 2003;37(4):261-7. PMID: 14748263

18. Lucero NE, Foglia L, Ayala SM, Gall D, Nielsen K. Competitive enzyme immunoassay for diagnosis of human Brucellosis. J Clin Microbiol. 1999;37(10):3245-8. https://doi.org/10.1128/JCM.37.10.3245-3248.1999

19. Camacho-Martínez JC, Rios-Lugo MJ, Gaytán-Hernández D, Hernández-Mendoza H. Comparison of a Brucella enzyme immunoassay and the standard agglutination with 2-mercaptoethanol test in the diagnosis and monitoring of brucellosis in mexican patients. Clin Lab. 2020;66(9). https://doi.org/10.7754/Clin.Lab.2020.190932

20. Kuyumcu ÇA, Erol S, Adaleti R, Şenbayrak S, Deniz S, Barkay O. Comparison of coombs gel test with ELISA and standard tube agglutination tests used in serological diagnosis of brucellosis. Infect Dis Clin Microbiol. 2020;2(1):1-7. https://doi.org/10.36519/idcm.2019.0024

21. Tumturk A, Yetkin MA, Tülek N, Dilek Kilic. Serum agglutination test and "Enzyme-linked immunosorbent assay" method in the diagnosis and follow-up of brucellosis. Klimik Derg. 2004;17(2):107-12. https://doi.org/10.36519/idcm.2019.0024

ORIGINAL ARTICLE

https://doi.org/10.1590/1806-9282.20220295

Systemic immune-inflammation index as a novel predictor of atrial fibrillation after off-pump coronary artery bypass grafting

Dursun Topal[1*], Ufuk Turan Kursat Korkmaz[2], Yusuf Velioglu[3], Ahmet Yuksel[3], Ibrahim Donmez[4], Erhan Renan Uçaroğlu[2], Seyit Ali Kayis[5]

SUMMARY

OBJECTIVE: This study aims to examine the predictive role of systemic immune-inflammation index on postoperative new-onset atrial fibrillation in patients undergoing off-pump coronary artery bypass grafting.

METHODS: A total of 722 patients undergoing elective off-pump coronary artery bypass grafting between January 2017 and September 2021 were included in this study and divided into two groups as the atrial fibrillation group (n=172) and the non-atrial fibrillation group (n=550). Both groups were compared in terms of patients' baseline clinical features, operative and postoperative variables, and preoperative hematological indices derived from the complete blood count analysis. Multivariate logistic regression and receiver-operating characteristic curve analyses were performed to detect the independent predictors of postoperative new-onset atrial fibrillation.

RESULTS: The median age and length of hospital stay in the atrial fibrillation group were significantly higher than those in the non-atrial fibrillation group. The median values of white blood cell, platelet, neutrophil, neutrophil/lymphocyte ratio, platelet/lymphocyte ratio, and systemic immune-inflammation in the atrial fibrillation group were significantly greater than in those in the non- atrial fibrillation group. Logistic regression analysis demonstrated that age, platelet, platelet/lymphocyte ratio, and systemic immune-inflammation were independent predictors of postoperative new-onset atrial fibrillation. receiver-operating characteristic curve analysis revealed that systemic immune-inflammation of $706.7\times10^3/mm^3$ constituted cut-off value to predict the occurrence of new-onset atrial fibrillation with 86.6% sensitivity and 29.3% specificity.

CONCLUSION: Our study revealed for the first time that systemic immune-inflammation predicted new-onset atrial fibrillation after off-pump coronary artery bypass grafting.

KEYWORDS: Atrial fibrillation. Off pump coronary artery bypass.

INTRODUCTION

Atrial fibrillation (AF) is the most frequent dysrhythmia after coronary artery bypass grafting (CABG) and its incidence has been reported as 10–40% in the literature[1]. New-onset AF following CABG has been demonstrated to be associated with serious morbidity, mortality, and increased financial burden[2]. To reduce this increased morbidity, mortality, and financial burden, it is important to determine the patients with a higher risk of postoperative AF and thereby to take necessary precautions so that AF does not occur. Therefore, simply available, inexpensive, and reliable biomarkers that can be utilized in daily clinical practice are required for these purposes.

For the pathogenesis of new-onset AF after CABG, many factors such as surgical trauma, intraoperative cardiopulmonary bypass usage and cardioplegia administration, perioperative discontinuation or inappropriate use of beta-blocker agents, hypoxia, and electrolyte imbalance are held responsible. Nevertheless, less information is available about the electro-pathophysiological molecular mechanisms and factors leading to postoperative AF. In contrast, the inflammatory process is also known to be one of the contributing pathophysiological factors in AF occurrence[3,4]. Various inflammatory biomarkers such as C-reactive protein, interleukins, and tumor necrosis factor-α have been extensively studied in relation to AF. In addition to these markers, hematological indices obtained from complete blood count (CBC) test such as white blood cell (WBC)[5], red cell distribution width (RDW)[6], mean platelet volume (MPV)[6], neutrophil/lymphocyte ratio (NLR)[7], and platelet/lymphocyte ratio (PLR)[8] have been investigated as potential prognostic and predictive biomarkers for postoperative new-onset AF.

[1]Bursa City Hospital, Department of Cardiology – Bursa, Turkey.
[2]Bolu Abant Izzet Baysal University, Faculty of Medicine, Department of Cardiovascular Surgery – Bolu, Turkey.
[3]Bursa City Hospital, Department of Cardiovascular Surgery – Bursa, Turkey.
[4]Bolu Abant Izzet Baysal University, Faculty of Medicine, Department of Cardiology – Bolu, Turkey.
[5]Bolu Abant Izzet Baysal University, Faculty of Medicine, Department of Biostatistics – Bolu, Turkey.
*Corresponding author: drdursuntopal@hotmail.com
Conflicts of interest: the authors declare there is no conflicts of interest. Funding: none.
Received on May 31, 2022. Accepted on July 01, 2022.

Systemic immune-inflammation index (SII) is a novel biomarker that develops based on platelet count and NLR (SII=platelets count×NLR) and demonstrates patients' inflammatory and immune statuses simultaneously. It was shown that high SII levels were related to poor outcomes and the index was an important prognostic marker in various types of cancers[9]. SII was also reported to independently predict the major adverse cardiovascular events such as nonfatal myocardial infarction (MI), nonfatal stroke, heart failure, and cardiac death in patients with coronary artery disease (CAD) undergoing percutaneous coronary intervention[10]. Moreover, a recent study demonstrated that high SII levels were associated with poor outcomes after elective off-pump CABG[11]. In contrast, to the best of our knowledge, a relationship between SII and new-onset AF in patients undergoing off-pump CABG has never been examined. Thus, we designed this study to examine whether a potential relationship between SII and new-onset AF was present in patients undergoing elective isolated off-pump CABG. Additionally, we also investigated other possible predictive factors and perioperative outcomes of the new-onset AF after off-pump CABG.

METHODS

Study population and design

The study was started once approval was obtained from the local ethics committee. This was a retrospective observational cohort study and conducted on patients undergoing elective isolated off-pump CABG at a tertiary referral center in Turkey between January 2017 and September 2021. The study population consisted of a total of 722 patients, and patients were divided into two groups, namely, AF group (n=172) and non-AF group (n=550), according to the occurrence of new-onset AF during the postoperative period. Patients' preoperative baseline clinical characteristics, comorbid conditions, laboratory parameters obtained from the CBC analysis, intraoperative data, postoperative outcomes, and complications were screened through the computerized medical database of the hospital, recorded, and compared between the groups. Thus, the predictive risk factors and perioperative results of new-onset AF after off-pump CABG were determined. Patients with a history of previous AF or other cardiac dysrhythmias, those undergoing emergency, reoperative or on-pump CABG, and concomitant cardiac operation such as mitral valve surgery were excluded from the study.

In approximately past 7 years, we preferred and routinely performed the ''off-pump technique" for patients undergoing CABG to avoid the detrimental effects of cardiopulmonary bypass. All patients undergoing off-pump CABG were informed about the operation and perioperative process, and their verbal and written consents were obtained before the operation. They were operated via a standard median sternotomy under general anesthesia. Internal thoracic artery and vena saphena magna were used as primary bypass grafts in most of the patients.

Postoperative monitoring

During the postoperative first 48 h in ICU, electrocardiogram (ECG), invasive central venous and arterial pressures, and oxygen saturation of the patients were continuously monitored, and arterial blood gas analyses were performed regularly every 2–4 h. Cardiac rhythms of patients were assessed by obtaining standard 12-lead ECGs every day for the remaining days until discharge. In addition, heart rate and rhythm were assessed by palpation of the radial pulse at least once in every 4 h. An additional 12-lead ECG was obtained and analyzed in case of tachycardia, palpitation, or a suspicion of an irregular cardiac rhythm. New-onset AF was diagnosed with the existence of an irregular RR interval and an absence of P wave on the ECG.

Laboratory analysis

Blood samples were taken from a peripheral vein after a 6–8-h fasting period. The samples were placed into sterile tubes containing a standard amount of anticoagulant and were quickly delivered to the laboratory for the analysis. To determine preoperative values of the parameters of the CBC test, the samples were studied in an automatic CBC analysis device (Beckman Coulter Inc., CA, USA). The studied and derived CBC parameters for this study were hemoglobin (HGB), hematocrit (HCT), mean corpuscular volume (MCV), platelet (PLT), neutrophil (NEU), lymphocyte (LYM), platelet distribution width (PDW), plateletcrit (PCT), WBC, RDW, MPV, NLR, PLR, and SII. The SII was calculated using the formula "platelet count × neutrophil/lymphocyte ratio."

Statistical analysis

The Shapiro-Wilk test was used to evaluate the normality of variables. Continuous variables were presented as median (min–max) values, while categorical variables were expressed as numbers (percentages). Continuous variables were analyzed using the Mann-Whitney U-test, while categorical variables were analyzed using the chi-square test. Multiple explanatory variable logistic regression analysis was performed to determine the risk factors/covariates for AF. Receiver-operating characteristic (ROC) curve analysis was performed to determine the cut-off values of selected variables, via logistic regression, for

AF from area under the curve (AUC). The ROC curve analysis was performed using the "Optimal Cutpoints" library of R software[12]. The R software was used to perform the statistical analyses (R Core Team, 2021)[13]. A p-value <0.05 was regarded as statistically significant for all analyses.

RESULTS

Patients with new-onset AF were significantly older than those without AF, and the median ages were 69 (38–85) and 62 (35–87) years for the AF group and the non-AF group, respectively (p=0.001). There were no significant differences with regard to other baseline clinical characteristics and comorbidities between the groups. When the laboratory parameters were compared between the groups, it was detected that the median values of WBC, PLT, NEU, NLR, PLR, and SII in the AF group were significantly greater than those in the non-AF group (Table 1).

When operative and postoperative data were considered, we found that the median length of hospital stay in the AF group was significantly longer than that in the non-AF group (6 [5–24] days for the AF group vs. 5 [4–39] days for the non-AF group; p=0.001). In terms of other operative and postoperative variables, the groups were similar and no significant differences were detected (Table 2).

Following the determination of the potentially significant risk factors, a multivariate logistic regression analysis was performed to assess the relationship between the occurrence of new-onset AF and independent predictors by adjusting for significant variables. According to multivariate logistic regression analysis, age, PLT, PLR, and SII were detected to be independent predictors of new-onset AF.

The ROC curve analysis demonstrated that age of 66 years constituted cut-off value for predicting the occurrence of new-onset AF with 57.5% sensitivity and 64.7% specificity, PLT of $177\times10^3/mm^3$ constituted cut-off value for predicting the occurrence of new-onset AF with 88.9% sensitivity and 21.1% specificity, PLR of 14.52 constituted cut-off value for predicting the occurrence of new-onset AF with 61.0% sensitivity and 51.1% specificity, and SII of $706.7\times10^3/mm^3$ constituted cut-off value for predicting the occurrence of new-onset AF with 86.6% sensitivity and 29.3% specificity (Figure 1).

Table 1. Preoperative clinical characteristics and laboratory parameters.

	Non-AF group (n=550)	AF group (n=172)	p-value
Age (year)	62 (35–87)	69 (38–85)	0.001
Gender (male) (%)	351 (63.8)	112 (65.1)	0.568
Weight (kg)	77 (50–130)	77 (55–122)	0.253
Height (cm)	170 (145–190)	168 (145–190)	0.170
BMI (kg/m^2)	27.2 (18.5–44.1)	27.0 (18.4–39.4)	0.658
Obesity (%)	134 (24.4)	36 (20.9)	0.410
LMCA disease (%)	100 (18.2)	27 (15.7)	0.527
LVEF level	55 (25–70)	50 (25–70)	0.201
LA diameter (cm)	3.7 (2.5–6.5)	3.9 (2.7–6.3)	0.185
Beta blocker usage (%)	223 (40.5)	68 (39.5)	0.883
Hypertension (%)	356 (64.7)	105 (61.0)	0.432
Diabetes mellitus (%)	208 (37.8)	73 (42.4)	0.319
Hyperlipidemia (%)	215 (39.1)	67 (39.0)	1.000
Myocardial infarction	195 (35.5)	66 (38.4)	0.546
Chronic renal dysfunction (%)	43 (7.8)	9 (5.2)	0.399
Chronic liver disease (%)	2 (0.4)	0 (0.0)	1.000
Peripheral arterial disease (%)	50 (9.1)	20 (11.6)	0.404
COPD (%)	47 (8.5)	18 (10.5)	0.585
Previous PCI (%)	68 (12.4)	28 (16.3)	0.234
Previous CVE (%)	43 (7.8)	11 (6.4)	0.651
Smoking (%)	155 (28.2)	43 (25.0)	0.362
HGB (g/dL)	13.5 (8.3–19.2)	13.3 (8.4–19.0)	0.329

Continue...

Table 1. Continuation.

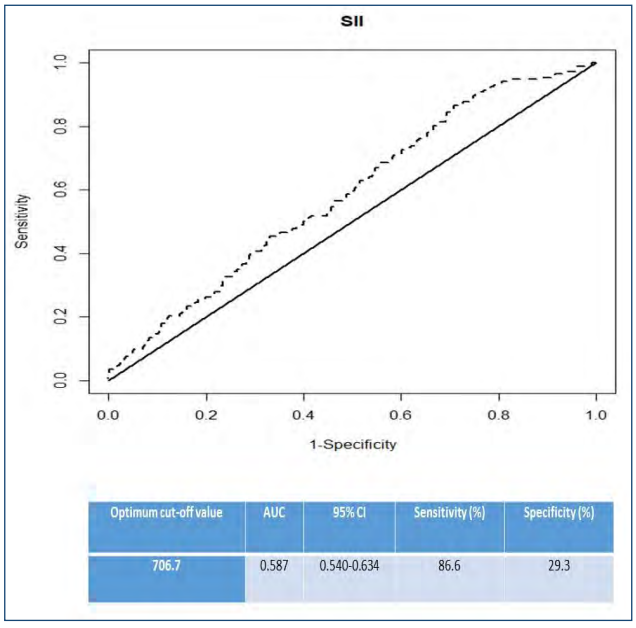
	Non-AF group (n=550)	AF group (n=172)	p-value
HCT (%)	39 (24.8–57.6)	40 (24.0–57.0)	0.212
MCV (fL)	87.5 (63.2–105.0)	87.7 (65.9–103.3)	0.147
RDW (%)	16 (11.0–34.0)	16 (13.0–24.2)	0.598
WBC (u/mm^3)	8 (3.0–23.0)	9 (4.0–23.0)	0.049
PLT (10^3/mm^3)	232 (61–729)	247 (97–787)	0.016
NEU (%)	69.9 (23.5–96.2)	72.7 (28.8–94.2)	0.001
LYM (%)	17 (4.4–50.5)	14.6 (5.0–43.4)	0.128
MPV (fL)	8 (2.0–16.0)	8 (5.8–17.0)	0.875
RDW (%)	17.5 (13.3–22.4)	17.5 (14.8–22.4)	0.598
PCT (%)	0.17 (0.04–1.05)	0.17 (0.04–0.92)	0.581
NLR	4.04 (0.86–16.02)	4.68 (1.45–17.66)	0.011
PLR	14.35 (2.72–67.60)	16.61 (3.06–65.66)	0.006
SII (10^3/mm^3)	991.4 (175.0–4895.4)	1150.1 (199.2–5594.3)	0.001

AF: atrial fibrillation; BMI: body mass index; LMCA: left main coronary artery; LVEF: left ventricular ejection fraction; LA: left atrium; COPD: chronic obstructive pulmonary disease; PCI: percutaneous coronary intervention; CVE: cerebrovascular event; HGB: hemoglobin; HCT: hematocrit; MCV: mean corpuscular volume; RDW: red cell distribution width; PCT: plateletcrit; NLR: neutrophil-to-lymphocyte ratio; PLR: platelet-to-lymphocyte ratio; SII: systemic immune-inflammation index. Data were expressed as median (minimum-maximum) for continuous variables or number (%) for categorical variables. Continuous variables were compared using independent samples t-test or Wilcoxon rank sum test. Categorical variables were reported as frequency (percent) and compared using Pearson's χ^2 test. Bold values indicate statistical significance at the p<0.05 level.

Table 2. Intraoperative and postoperative variables.

	Non-AF group (n=550)	AF group (n=172)	p-value
LITA usage (%)	516 (94.0)	162 (94.2)	0.841
Complete revascularization (%)	519 (94.4)	156 (90.7)	0.128
Number of distal bypass	3 (1–7)	4 (1–6)	0.499
Extubation time (h)	6 (2–30)	6 (2–19)	0.204
Length of ICU stay (h)	24 (24–360)	30 (24–288)	0.113
Length of hospital stay (day)	5 (4–39)	6 (5–24)	0.001
Inotrope requirement (%)	103 (18.7)	29 (16.9)	0.660
IABP requirement (%)	25 (4.5)	12 (7.0)	0.287
Low cardiac output syndrome (%)	25 (4.5)	12 (7.0)	0.287
Myocardial infarction (%)	18 (3.3)	6 (3.5)	1.000
Cerebrovascular event (%)	17 (3.1)	6 (3.5)	0.999
Reintubation (%)	20 (3.6)	6 (3.5)	1.000
Pneumonia (%)	19 (3.5)	8 (4.7)	0.623
Mediastinitis (%)	19 (3.5)	7 (4.1)	0.493
Reexploration for bleeding (%)	23 (4.2)	7 (4.1)	1.000
ARD requiring hemodialysis (%)	15 (2.7)	4 (2.3)	0.989
Gastrointestinal bleeding (%)	5 (0.9)	2 (1.2)	1.000
In-hospital mortality (%)	12 (2.2)	2 (1.2)	0.597

AF: atrial fibrillation; LITA: left internal thoracic artery; ICU: intensive care unit; IABP: intraaortic balloon pump; ARD: acute renal dysfunction. Data were expressed as median (minimum-maximum) for continuous variables or number (%) for categorical variables. Continuous variables were compared using independent samples t-test or Wilcoxon rank sum test. Categorical variables were reported as frequency (percent) and compared using Pearson's χ^2 test. Bold value indicates statistical significance at the p<0.05 level.



Optimum cut-off value	AUC	95% CI	Sensitivity (%)	Specificity (%)
706.7	0.587	0.540-0.634	86.6	29.3

Figure 1. Receiver-operating characteristic curve for systemic immune-inflammation index.

DISCUSSION

Our study revealed that patients in the AF group were significantly older and had a longer length of hospital stay compared with those in the non-AF group. Although among hematological indices, WBC, PLT, NEU, NLR, PLR, and SII levels in the AF group were significantly greater than those in the non-AF group, according to multivariate analysis, only PLT, PLR, and SII were gained significantly and considered the associated predictive indices for postoperative new-onset AF. In our opinion, the most intriguing finding of the study was that SII independently predicts new-onset AF after off-pump CABG for the first time in the existing literature.

Determining the predictive risk factors of new-onset AF following the cardiac surgery is critical because it allows for the development of preventive measures and necessary prompt management. The use of several medications, such as β-blockers, statins, and steroids, for prophylaxis against postoperative AF should be considered in the preoperative period. In contrast, although numerous potential risk factors for postoperative new-onset AF have been identified in different studies, "advanced age" is the most known predictive variable that has been identified practically in every study found in the literature[1-4]. Our study confirmed that advanced age was a substantial and independent risk factor for postoperative new-onset AF as previously reported in the literature.

Studies investigating hematological indices obtained from a simple CBC test for prediction of new-onset AF after cardiac surgery have increased recently, and these hematological indices have become the focus of attention on this topic. The CBC test is inexpensive, easily and quickly accessible in many centers, and includes many different reliable indices. Among the indices, WBC, RDW, PLT, and MPV as well as NLR and PLR are the most studied and identified predictive variables for new-onset AF[14]. Although various indices derived from the CBC test have been reported to predict new-onset AF after CABG in different studies, the results are often inconclusive and inconsistent with each other. In contrast, a recent systematic review and meta-analysis including a total of 6,098 patients from 22 studies that fit the eligibility criteria showed that preoperative PLT, MPV, WBC, NLR, and RDW were associated predictive hematological indices with new-onset AF after cardiac surgery[15]. In our study, we detected PLT as well as PLR as predictive hematological indices for new-onset AF following off-pump CABG.

SII is a novel hematological marker that is observed using the CBC test by bringing together three inflammatory peripheral cell counts (platelet, neutrophil, and lymphocyte), which reflects patients' inflammatory and immune statuses simultaneously. SII has been widely studied in patients with cancer and it emerged as a significant hematological prognostic indicator in many types of cancer[9]. SII has also been examined in many different cardiovascular diseases, such as CAD[10], severe calcific aortic stenosis[16], infective endocarditis[17], and pulmonary embolism[18]. Additionally, in a large-scale cohort study on 13,929 middle-aged and older Chinese adults who were free of cardiovascular disease and cancer, the relationship of SII with incident cardiovascular diseases including stroke and CAD was examined, and a high SII level was detected to be significantly associated with the cardiovascular diseases[19]. Moreover, Bağcı et al.[20] recently investigated the predictive capacity of SII for the detection of new-onset AF in patients with ST-elevation MI and showed that SII predicted new-onset AF following ST-elevation MI. In contrast, the predictive role of SII on postoperative outcomes in patients undergoing cardiac surgery has also been recently studied. Yoon et al.[21] assessed the prognostic implications of preoperative SII on 213 patients undergoing isolated tricuspid valve surgery and demonstrated that high SII levels were independently associated with the major early-term perioperative complications. Dey et al.[11] conducted a retrospective single-center risk-prediction study on 1,007 patients undergoing elective off-pump CABG, and revealed that the SII cut-off value of $878.06\times10^3/mm^3$ predicted poor outcomes, such as major adverse cardiovascular events, renal failure, sepsis, and death, with 97.6% sensitivity and 91% specificity. In this study, we revealed that the SII cut-off value of $706.7\times10^3/mm^3$ predicted postoperative new-onset AF with 86.6% sensitivity and 29.3% specificity.

Our study had several limitations. The major limitations of our study were its single-centered design and retrospective nature. Another important limitation was the lack of a correlation analysis with other inflammatory markers such as C-reactive protein and interleukins. Additionally, heart rhythm monitoring could not be performed on a continuous basis following an ICU stay. Although in the following days, after ICU heart rhythm was routinely monitored with standard ECGs at least twice a day and an additional ECG was obtained in all cases when any rhythm abnormality was suspected, there was a possibility of unnoticed short-time and transient attacks of asymptomatic AF.

CONCLUSION

Our study demonstrated that age, PLT, PLR and SII were independent predictive risk factors of new-onset AF following off-pump CABG. Among these aforementioned factors, SII was detected to predict postoperative new-onset AF for the first time in the literature, and to the best of our knowledge, our study is the first clinical research to examine the predictive role of SII on new-onset AF in patients undergoing off-pump CABG. Nonetheless, further well-designed studies with larger patient participation are needed to support the results of our study and obtain more evident scientific information.

AUTHORS' CONTRIBUTIONS

DT: Data curation, Formal Analysis, Writing – original draft, Writing – review & editing. **UTKK:** Conceptualization, Data curation, Formal Analysis, Writing – original draft, Writing – review & editing. **YV:** Conceptualization, Data curation, Formal Analysis, Writing – review & editing. **AY:** Conceptualization, Data curation, Formal Analysis, Writing – original draft. **ID:** Conceptualization, Data curation, Formal Analysis, Writing – review & editing. **ERU:** Data curation, Writing – review & editing. **SAK:** Formal Analysis, Writing – review & editing.

REFERENCES

1. Velioglu Y, Yuksel A. Predictors of Postoperative Atrial Fibrillation after Beating-Heart Coronary Artery Bypass Surgery: Is Cardiopulmonary Bypass a Risk Factor? Acta Cardiol Sin. 2019;35(5):468-75. https://doi.org/10.6515/ACS.201909_35(5).20190325A
2. LaPar DJ, Speir AM, Crosby IK, Fonner E Jr, Brown M, Rich JB, et al. Postoperative atrial fibrillation significantly increases mortality, hospital readmission, and hospital costs. Ann Thorac Surg. 2014;98(2):527-33;discussion533. https://doi.org/10.1016/j.athoracsur.2014.03.039
3. Rezaei Y, Peighambari MM, Naghshbandi S, Samiei N, Ghavidel AA, Dehghani MR, et al. Postoperative atrial fibrillation following cardiac surgery: from pathogenesis to potential therapies. Am J Cardiovasc Drugs. 2020;20(1):19-49. https://doi.org/10.1007/s40256-019-00365-1
4. Korkmaz UTKK, Ucaroglu ERU. Aortic knob width as a novel predictor of postoperative atrial fibrillation following off-pump coronary artery bypass grafting. Med-Science. 2021;10(4):1145-50. https://doi.org/10.5455/medscience.2021.03.097
5. Jacob KA, Buijsrogge MP, Frencken JF, Ten Berg MJ, Suyker WJ, van Dijk D, et al. White blood cell count and new-onset atrial fibrillation after cardiac surgery. Int J Cardiol. 2017;228:971-6. https://doi.org/10.1016/j.ijcard.2016.11.038
6. Ozsin KK, Sanri US, Toktas F, Yavuz S. Relationship between red cell distribution width and mean platelet volume with new onset atrial fibrillation afteroff-pump coronary artery bypass grafting. Bratisl Lek Listy. 2018;119(6):335-40. https://doi.org/10.4149/BLL_2018_063
7. Liu Z, Nguyen Khuong J, Borg Caruana C, Jackson SM, Campbell R, Ramson DM, et al. The Prognostic Value of Elevated Perioperative Neutrophil-Lymphocyte Ratio in Predicting Postoperative Atrial Fibrillation After Cardiac Surgery: A Systematic Review and Meta-Analysis. Heart Lung Circ. 2020;29(7):1015-24. https://doi.org/10.1016/j.hlc.2019.11.021
8. Gungor H, Babu AS, Zencir C, Akpek M, Selvi M, Erkan MH, et al. Association of preoperative platelet-to-lymphocyte ratio with atrial fibrillation after coronary artery bypass graft surgery. Med Princ Pract. 2017;26(2):164-8. https://doi.org/10.1159/000453614
9. Yang R, Chang Q, Meng X, Gao N, Wang W. Prognostic value of Systemic immune-inflammation index in cancer: a meta-analysis. J Cancer. 2018;9(18):3295-302. https://doi.org/10.7150/jca.25691
10. Yang YL, Wu CH, Hsu PF, Chen SC, Huang SS, Chan WL, et al. Systemic immune-inflammation index (SII) predicted clinical outcome in patients with coronary artery disease. Eur J Clin Invest. 2020;50(5):e13230. https://doi.org/10.1111/eci.13230
11. Dey S, Kashav R, Kohli JK, Magoon R, ItiShri, Walian A, et al. Systemic immune-inflammation index predicts poor outcome after elective off-pump CABG: a retrospective, single-center study. J Cardiothorac Vasc Anesth. 2021;35(8):2397-404. https://doi.org/10.1053/j.jvca.2020.09.092
12. López-Ratón M, Rodríguez-Álvarez MX, Cadarso-Suárez C, Sampedro FG. Optimalcutpoints: An R package for selecting optimal cutpoints in diagnostic tests. J Stat Soft. 2014;61(8):1-36. https://doi.org/10.18637/jss.v061.i08
13. R Core Team. R: A language and environment for statistical computing. R Foundation for Statistical Computing, Vienna, Austria. 2021. Available from: https://www.R-project.org/
14. Weymann A, Ali-Hasan-Al-Saegh S, Sabashnikov A, Popov AF, Mirhosseini SJ, Liu T, et al. Prediction of new-onset and recurrent atrial fibrillation by complete blood count tests: a comprehensive systematic review with meta-analysis. Med Sci Monit Basic Res. 2017;23:179-222. https://doi.org/10.12659/msmbr.903320
15. Weymann A, Ali-Hasan-Al-Saegh S, Popov AF, Sabashnikov A, Mirhosseini SJ, Liu T, et al. Haematological indices as predictors of

atrial fibrillation following isolated coronary artery bypass grafting, valvular surgery, or combined procedures: a systematic review with meta-analysis. Kardiol Pol. 2018;76(1):107-18. https://doi.org/10.5603/KP.a2017.0179

16. Erdoğan M, Öztürk S, Kardeşler B, Yiğitbaşı M, Kasapkara HA, Baştuğ S, et al. The relationship between calcific severe aortic stenosis and systemic immune-inflammation index. Echocardiography. 2021;38(5):737-44. https://doi.org/10.1111/echo.15044
17. Agus HZ, Kahraman S, Arslan C, Yildirim C, Erturk M, Kalkan AK, et al. Systemic immune-inflammation index predicts mortality in infective endocarditis. J Saudi Heart Assoc. 2020;32(1):58-64. https://doi.org/10.37616/2212-5043.1010
18. Gok M, Kurtul A. A novel marker for predicting severity of acute pulmonary embolism: systemic immune-inflammation index. Scand Cardiovasc J. 2021;55(2):91-6. https://doi.org/10.1080/14017431.2020.1846774
19. Xu M, Chen R, Liu L, Liu X, Hou J, Liao J, et al. Systemic immune-inflammation index and incident cardiovascular diseases among middle-aged and elderly Chinese adults: The Dongfeng-Tongji cohort study. Atherosclerosis. 2021;323:20-9. https://doi.org/10.1016/j.atherosclerosis.2021.02.012
20. Bağcı A, Aksoy F. Systemic immune-inflammation index predicts new-onset atrial fibrillation after ST elevation myocardial infarction. Biomark Med. 2021;15(10):731-9. https://doi.org/10.2217/bmm-2020-0838
21. Yoon J, Jung J, Ahn Y, Oh J. Systemic immune-inflammation index predicted short-term outcomes in patients undergoing isolated tricuspid valve surgery. J Clin Med. 2021;10(18):4147. https://doi.org/10.3390/jcm10184147

ORIGINAL ARTICLE

https://doi.org/10.1590/1806-9282.20220298

Predictors of pain catastrophizing in women with systemic lupus erythematosus

Gizem Irem Kinikli[1*], Gamze Arin Bal[1], Emine Gozde Aydemir-Guloksuz[2], Gulay Kinikli[2]

SUMMARY

OBJECTIVE: The aim of this study was to identify predictive factors associated with pain catastrophizing in women with systemic lupus erythematosus (SLE).

METHODS: A total of 104 volunteered women with a diagnosis of systemic lupus erythematosus participated in the study. Pain Catastrophizing Scale, Body Awareness Questionnaire, Tampa Scale of Kinesiophobia, and Beck Depression Inventory were used to assess patients. Correlations between pain catastrophizing (dependent variable) and independent variables (age, body mass index, disease activity, organ damage, depression, kinesiophobia, and body awareness) were analyzed with Pearson's rho correlation analysis. The multiple stepwise linear regression models with R^2 were used to compare across the models and explain the total variance. The significance level of a p-value was considered significant if $p \leq 0.05$.

RESULTS: There were no correlations between Pain Catastrophizing Scale and age, Beck Depression Inventory, disease activity, and organ damage ($p>0.05$). Pain Catastrophizing Scale was correlated with Tampa Scale of Kinesiophobia ($r=0.585$; $p<0.001$), Beck Depression Inventory ($r=0.511$; $p<0.001$), and Body Awareness Questionnaire ($r=0.277$; $p<0.005$). The regression analysis showed that the predictor factors of pain catastrophizing in women with systemic lupus erythematosus were TSK (B 0.411; $p<0.001$), Beck Depression Inventory (B 0.363; $p<0.001$), Body Awareness Questionnaire (B 0.273; $p<0.001$), and body mass index (B -0.169; $p=0.02$) (Nagelkerke $R^2=0.52$).

CONCLUSIONS: As a result, the most related factors on pain catastrophizing were kinesiophobia, depression, body awareness, and body mass index in women with systemic lupus erythematosus. We suggest assessing these parameters as predictive of pain catastrophizing throughout systemic lupus erythematosus management.

KEYWORDS: Catastrophization. Pain. Systemic lupus erythematosus.

INTRODUCTION

Systemic lupus erythematosus (SLE) is a chronic, autoimmune disease with a broad spectrum of clinical symptoms affecting almost all organ systems[1]. Pain, musculoskeletal symptoms, fatigue, depression, and cognitive deficits are common, in addition to skin-related and systemic manifestations[2]. These findings can be aggravated by a disease or found independently linked to the physical and psychological restraints[3,4].

One of the first and most common symptoms reported by SLE patients is pain, frequently caused by musculoskeletal conditions. Also, it is shown that the physiopathology of pain impacts patients as well as inflammation of joints[5]. There is a link between cognitive, affective, and behavioral factors and pain catastrophizing which stimulates avoidance, fear, and depression[6].

Pain catastrophizing is magnifying pain sensations, inability to deal with pain, and feeling helpless and has been proven to develop a chronic cycle ending in central sensitization[7]. Pain catastrophizing strongly correlates with depression, coping skills, physical functioning, and quality of life in rheumatic diseases, particularly in SLE[6]. Whichever the pain results, patients with SLE are likely to develop maladaptive coping skills, perception, body awareness, and fear of movement.

Understanding the relationship between pain catastrophizing and related factors may help identify the main rehabilitation targets in SLE patients. This study aimed to identify factors predicting pain catastrophizing in women with SLE. We hypothesized that kinesiophobia, depression level, body awareness, and body mass index (BMI) predict pain catastrophizing in women with SLE.

METHODS

This cross-sectional study was conducted between 2018 and 2019 at Ankara University, Faculty of Medicine, Department of Rheumatology. The Ethical Institution of the Ankara University

[1]Hacettepe University, Faculty of Physical Therapy and Rehabilitation, Department of Musculoskeletal Rehabilitation – Ankara, Turkey.
[2]Ankara University, Faculty of Medicine, Department of Rheumatology – Ankara, Turkey.
*Corresponding author: cguvendik@hotmail.com
Conflicts of interest: the authors declare there is no conflicts of interest. Funding: none.
Received on June 26, 2022. Accepted on June 28, 2022.

approved the study protocol with the number 06-301-17. All assessments were made if patients agreed to participate in the study when they came for their routine controls, and all the participants were provided with verbal and written informed consent according to the Declaration of Helsinki. Individuals who met the American College of Rheumatology 1997 criteria for diagnosis of SLE[8] and volunteered to participate were included in the study. Exclusion criteria were difficulties reading and understanding Turkish and having a psychological disorder.

A rheumatologist performed a physical examination and assessed disease-specific manifestations, disease activity, and disease-related organ damage. Disease activity and organ damage were evaluated with the Revised Systemic Lupus Activity Measure (SLAM-R)[9] and Systemic Lupus International Collaborating Clinics/American College of Rheumatology Damage Index (SLICC/ACR-DI)[10], respectively. The SLAM-R estimates a degree of severity for the last month, and the score range is 0–86, where a score ≥7 is considered a flare[9]. The SLICC/ACR-DI is divided into nine organ systems with scores ranging from 0 to 47, and SLICC/ACR-DI ≥1 was considered to have organ damage[10].

Patient-reported outcome measurements

Pain Catastrophizing Scale

Turkish PCS was used to measure how people catastrophize in response to pain. This scale is a 5-Likert scale with 13 questions and evaluates the feelings and thoughts of a person when they are experiencing pain[11].

Body Awareness Questionnaire

The BAQ is a tool with psychometric properties that reflect the concept of body awareness (such as self-reported predictions about the body, disease, and sleep cycle). It is a Likert-type questionnaire consisting of 18 items and 4 subgroups. A high survey score means that the body awareness level is high[12].

Tampa Scale for Kinesiophobia

The TSK is a 17-question 4-point Likert scale that measures fear of movement/re-injury. The total score ranges between 17 and 68 points, and a score equal to 37 or higher means an individual has kinesiophobia[13].

Beck Depression Inventory

BDI was used to measure characteristics, attitudes, and symptoms of depression. It is a valid and reliable questionnaire having four cutoff scores: 0–12 for minimal, 13–18 for mild, 19–28 for moderate, and 29–63 for severe depression in the Turkish population[14].

Statistical analyses

SPSS version 23 (IBM Corp., Armonk, NY, USA) was used for statistical analysis. Correlations between pain catastrophizing (dependent variable) and independent variables (age, BMI, disease activity, organ damage, body awareness, kinesiophobia, and depression) were analyzed with Pearson's rho correlation analysis; a value of 1.0 was interpreted as perfect, 0.9–0.7 as strong, 0.6–0.4 moderate, 0.3–0.1 weak, and 0 as zero. The multiple stepwise linear regression models with R^2 were used to compare across the models and explain the total variance. The significance level of a p-value was considered significant if $p \leq 0.05$.

RESULTS

This study included 104 women with SLE. The mean age of the patients was 49.49±7.19 years, and the mean BMI was 27.17±4.01 kg/m². The disease activity level measured by SLAM-R was 5.39±3.68, and the disease damage index measured by SLICC/ACR-DI was 0.58±0.87. There were no correlations between PCS (22.12±12.09) and age, BMI, SLAM-R, and SLICC/ACR-DI ($p>0.05$) (Table 1). PCS was correlated with BAQ (88.94±19.85) ($p<0.005$), TSK (42.94±7.76), and BDI (15.63±11.18) ($p<0.001$) (Table 1).

A multiple stepwise linear regression analysis was built to check for variables independently affecting PCS. The independent variables (BMI, SLAM-R, SLICC/ACR-DI, BAQ, TSK, and BDI) were entered into the stepwise regression model. The regression analysis showed that the predictor factors of pain catastrophizing in women with SLE were TSK (B 0.411; $p<0.001$), BDI (B 0.363; $p<0.001$), BAQ (B 0.273; $p<0.001$), and BMI (B -0.169; $p=0.02$) (Nagelkerke $R^2=0.52$) (Table 2).

Table 1. Bivariate correlations between pain catastrophizing scale and disease-related factors.

n=104	r	p
Age (years)	0.141	0.155
BMI (kg/m²)	-0.084	0.399
SLAM-R (0–86)	0.105	0.293
SLICC-DI (0–47)	0.153	0.123
BAQ (0–126)	0.277	0.005*
TSK (17–68)	0.585	<0.001*
BDI (0–63)	0.511	<0.001*

*p<0.001. BMI: Body mass index; SLAM-R: Revised Systemic Lupus Activity Measure; SLICC/ACR-DI: Lupus International Collaborating Clinics/American College of Rheumatology Damage Index; BAQ: Body Awareness Questionnaire; TSK: Tampa Scale for Kinesiophobia; BDI: Beck Depression Inventory.

Table 2. The regression analysis showing the predictor factors of pain catastrophizing in women with systemic lupus erythematosus.

Model		Unstandardized coefficients		Standardized coefficients	t	*p
		B	Standard error	Beta		
Independent variables	Tampa Scale of Kinesiophobia	0.642	0.125	0.411	5.130	<0.001
	Beck Depression Scale	0.392	0.086	0.363	4.573	<0.001
	Body Awareness Questionnaire	0.168	0.045	0.273	3.745	<0.001
	Body mass index	-0.543	0.229	-0.169	-2.368	0.020

Dependent variable: Pain Catastrophizing Scale; *p<0.001; R2=0.518

DISCUSSION

Our study investigated predictive factors of pain catastrophizing in women with SLE. Pain catastrophizing was correlated with body awareness, kinesiophobia, and depression. As a result, in regression analyses, body awareness, kinesiophobia, depression, and BMI were significant predictors of pain catastrophizing in women with SLE. In the literature, body awareness and kinesiophobia are not currently reported as predictive factors of pain catastrophizing in individuals with SLE. Therefore, this study's results also highlight these predictors in the SLE population regarding pain catastrophizing.

Pain catastrophizing is a factor that contains psychological and physical parameters. Although there is no agreement on what pain catastrophizing is, the main components are defined as rumination, magnification, and helplessness, and its understanding expands beyond these[15]. Since it is known that pain catastrophizing is related to pain intensity and disability, predicting factors that affect pain catastrophizing is a topic that is still compelling and intriguing. Since a human being is considered far from only being a biological creature, psychological and social parameters affect humans, varying from person to person. Our study shows that fear of movement, depressive mood, awareness of your body and symptoms, and BMI are considered predictors of catastrophizing. These findings emphasize the importance of considering pain catastrophizing and being careful to not missing possible predictors of pain catastrophizing during treatment.

The relationship between age, disease activity, organ damage, kinesiophobia, depression levels, BMI, and pain catastrophizing of women was investigated in this study. There was no significant correlation with age, disease activity, and organ damage, but others were significantly correlated with pain catastrophizing. Similarly, Somers et al. investigated the relationship between pain coping cognitions, pain catastrophizing and physical symptoms, and psychological distress in SLE patients. These authors found that self-efficacy and catastrophizing correlated with pain, stiffness, fatigue, and positive and negative mood[16]. Our findings support these results as these psychological parameters engage each other.

Body awareness comprises physical conditions, cognitions, and body experiences with the psychosocial background of oneself. Similarly, in this study, body awareness predicted pain catastrophizing in women with SLE. Body awareness is the general description of embodied identity, which is related to two categories: "living in the body" and "living concerning others and society[17]." Therefore, our results are more predictable than having negative beliefs about the body, and negative thoughts and experiences with pain would deteriorate catastrophizing.

It is shown that kinesiophobia and depression significantly affect patients with SLE[18]. In our study, it was found that pain catastrophizing was associated with both kinesiophobia and depression. Most importantly, kinesiophobia was the most crucial variable predicting pain catastrophizing, which makes sense considering these relationships. One reason for this result might be that 85.4% of enrolled patients had kinesiophobia. Since pain causes fear of movement and depression in rheumatic diseases, patients are more likely to develop more catastrophizing beliefs and behaviors with the chronic nature of the disease[7].

In addition to all these psychosocial factors, the only physical finding was BMI as a predictor of pain catastrophizing in this study. Previous studies showed that obesity is related to disease activity and other outcomes in SLE patients[19,20]. In our study, BMI was not related to disease activity but was a predictor of pain catastrophizing. BMI was a predictor because 80.8% of our patients had a BMI of 25 or above. Besides, there is a lack of studies investigating the relationship between BMI and pain catastrophizing in the SLE population.

The main limitation of this study is that the population consisted only of women. Since SLE is a disease primarily seen

in women, the results are not surprising but cannot be generalized to the whole SLE population. In addition, it is well known that women have more tendency to have pain catastrophizing than men[21]. It is also known that genetic factors and hormone levels affect the symptoms of the disease[22]. Therefore, the lack of medical record information about the hormonal status of our patients is another limitation. We suggest examining the effects of hormonal and menopausal conditions on pain catastrophizing for further studies.

CONCLUSIONS

We recommend healthcare professionals working with women with SLE consider predictors in managing the disease. Thus, identifying disease-related parameters effective for pain catastrophizing, developing coping strategies with them, and reducing chronic pain in SLE patients can increase their quality of life. Further studies are needed to support our results, including gender and hormonal status.

Clinical Impact

- Kinesiophobia, depression, body awareness, and BMI are significant predictors of pain catastrophizing in women with SLE.
- Health professionals working with the SLE population should consider the abovementioned factors in the treatment process.

AUTHORS' CONTRIBUTION

GIK: Conceptualization, Formal Analysis, Writing – original draft. **GAB:** Formal Analysis, Writing – original draft. **EG:** Aydemir-Guloksuz Data curation, Writing – original draft. **GK:** Data curation.

REFERENCES

1. Dörner T, Furie R. Novel paradigms in systemic lupus erythematosus. Lancet. 2019;393(10188):2344-58. https://doi.org/10.1016/S0140-6736(19)30546-X
2. Leuchten N, Milke B, Winkler-Rohlfing B, Daikh D, Dörner T, Johnson SR, et al. Early symptoms of systemic lupus erythematosus (SLE) recalled by 339 SLE patients. Lupus. 2018;27(9):1431-6. https://doi.org/10.1177/0961203318776093
3. Shi Y, Li M, Liu L, Wang Z, Wang Y, Zhao J, et al. Relationship between disease activity, organ damage and health-related quality of life in patients with systemic lupus erythematosus: A systemic review and meta-analysis. Autoimmun Rev. 2021;20(1):102691. https://doi.org/10.1016/j.autrev.2020.102691
4. Falasinnu T, Drenkard C, Bao G, Mackey S, Lim SS. The problem of pain in systemic lupus erythematosus: an explication of the role of biopsychosocial mechanisms. J Rheumatol. 2021;48(8):1279-89. https://doi.org/10.3899/jrheum.200595
5. Nichilatti LP, Fernandes JM, Marques CP. Physiopathology of pain in systemic erythematosus lupus. Lupus. 2020;29(7):721-6. https://doi.org/10.1177/0961203320919872
6. Shim E-J, Hahm B-J, Go DJ, Lee KM, Noh HL, Park SH, et al. Modeling quality of life in patients with rheumatic diseases: the role of pain catastrophizing, fear-avoidance beliefs, physical disability, and depression. Disabil Rehabil. 2018;40(13):1509-16. https://doi.org/10.1080/09638288.2017.1300691
7. Martinez-Calderon J, Jensen MP, Morales-Asencio JM, Luque-Suarez A. Pain Catastrophizing and function in individuals with chronic musculoskeletal pain: a systematic review and meta-analysis. Clin J Pain. 2019;35(3):279-93. https://doi.org/10.1097/AJP.0000000000000676
8. Hochberg MC. Updating the American College of Rheumatology revised criteria for the classification of systemic lupus erythematosus. Arthritis Rheum. 1997;40(9):1725. https://doi.org/10.1002/art.1780400928
9. Bae S, Koh H, Chang D, Kim M, Park J, Kim S. Reliability and validity of systemic lupus activity measure-revised (SLAM-R) for measuring clinical disease activity in systemic lupus erythematosus. Lupus. 2001;10(6):405-9.https://doi.org/10.1191/096120301678646146
10. Gladman DD, Goldsmith CH, Urowitz MB, Bacon P, Fortin P, Ginzler E, et al. The Systemic Lupus International Collaborating Clinics/American College of Rheumatology (SLICC/ACR) Damage Index for Systemic Lupus Erythematosus International Comparison. J Rheumatol. 2000;27(2):373-6. PMID: 10685799
11. Süren M, Okan I, Gökbakan AM, Kaya Z, Erkorkmaz Ü, Arıcı S, et al. Factors associated with the pain catastrophizing scale and validation in a sample of the Turkish population. Turk J Med Sci. 2014;44(1):104-8. https://doi.org/10.3906/sag-1206-67
12. Mehling WE, Gopisetty V, Daubenmier J, Price CJ, Hecht FM, Stewart A. Body awareness: construct and self-report measures. PLoS One. 2009;4(5):e5614. https://doi.org/10.1371/journal.pone.0005614
13. Yilmaz ÖT, Yakut Y, Uygur F, Uluğ N. Tampa Kinezyofobi Ölçeği'nin Türkçe versiyonu ve test-tekrar test güvenirliği. Fizyoter Rehabil. 2011;22(1):44-9.
14. Kapci EG, Uslu R, Turkcapar H, Karaoglan A. Beck Depression Inventory II: evaluation of the psychometric properties and cut-off points in a Turkish adult population. Depress Anxiety. 2008;25(10):E104-10. https://doi.org/10.1002/da.20371
15. Petrini L, Arendt-Nielsen L. Understanding Pain Catastrophizing: Putting Pieces Together. Front Psychol. 2020;11:603420. https://doi.org/10.3389/fpsyg.2020.603420
16. Somers TJ, Kurakula PC, Criscione-Schreiber L, Keefe FJ, Clowse ME. Self-efficacy and pain catastrophizing in systemic lupus erythematosus: relationship to pain, stiffness, fatigue, and psychological distress. Arthritis Care Res (Hoboken). 2012;64(9):1334-40. https://doi.org/10.1002/acr.21686
17. Gyllensten AL, Skär L, Miller M, Gard G. Embodied identity--a deeper understanding of body awareness. Physiother Theory Pract. 2010;26(7):439-46.https://doi.org/10.3109/09593980903422956
18. Yentür SB, Karatay S, Oskay D, Tufan A, Küçük H, Haznedaroğlu Ş. Kinesiophobia and related factors in systemic lupus erythematosus patients. Turk J Med Sci. 2019;49(5):1324-31. https://doi.org/10.3906/sag-1804-152

19. Teh P, Zakhary B, Sandhu VK. The impact of obesity on SLE disease activity: findings from the Southern California Lupus Registry (SCOLR). Clin Rheumatol. 2019;38(2):597-600. https://doi.org/10.1007/s10067-018-4336-3

20. Patterson SL, Schmajuk G, Jafri K, Yazdany J, Katz P. Obesity is Independently Associated With Worse Patient-Reported Outcomes in Women with Systemic Lupus Erythematosus. Arthritis Care Res (Hoboken). 2019;71(1):126-33. https://doi.org/10.1002/acr.23576

21. Etherton J, Lawson M, Graham R. Individual and gender differences in subjective and objective indices of pain: gender, fear of pain, pain catastrophizing and cardiovascular reactivity. Appl Psychophysiol Biofeedback. 2014;39(2):89-97. https://doi.org/10.1007/s10484-014-9245-x

22. Soares-Júnior J, Sorpreso IE, Curado JN, Ferreira Filho ES, Simões RS, Bonfa E, et al. Hormone therapy effect on menopausal systemic lupus erythematosus patients: a systematic review. Climacteric. 2022:1-7. https://doi.org/10.1080/13697137.2022.2050205

ORIGINAL ARTICLE

https://doi.org/10.1590/1806-9282.20220325

What is the effect of tumor diameter, lymph node metastases, and SUVmax value on prognosis in limited-stage small cell lung cancer?

Filiz Çimen[1*], Melike Aloglu[1], Sevim Düzgün[1], Ayşegül Şentürk[1], Şükran Atikcan[1], Özlem Özmen[2]

SUMMARY

OBJECTIVE: This study was designed to investigate the link between survival and prognostic factors such as tumor size, lymph node metastasis, and metabolic activity detected on positron emission tomography/computed tomography in patients with limited-stage small cell lung carcinoma.

METHODS: Patients who were admitted to our hospital with pathological diagnosis of limited-stage small cell lung cancer between January 2015 and December 2019 and were older than 18 years were retrospectively screened.

RESULTS: A total of 77 patients, including 10 females and 67 males, were included in the study. While there were 39 patients over 60 years of age, 38 patients were under 60.

The ratios of male patients, N stage, multiple lymph nodes, distant metastasis, brain metastasis, and prophylactic cranial irradiation in the deceased patients' group were significantly (p=0.008, p=0.000, p=0.000, p=0.000, p=0.013, p=0.000, respectively) higher than those in the living patients' group. In the univariate model, we observed that gender, smoking, T stage, N stage, multiple lymph nodes, distant metastasis, brain metastasis, liver metastasis, sequential chemotherapy, sequential radiotherapy, concurrent chemoradiotherapy, and prophylactic cranial irradiation had significant effect (p=0.049, p=0.021, p=0.022, p=0.000, p=0.000, p=0.000 p=0.003, p=0.037, p=0.029, p=0.049, p=0.000, respectively) on survival time. In the multivariate model, smoking, N stage, liver metastasis, and prophylactic cranial irradiation demonstrated significant independent effect (p=0.010, p=0.003, p=0.004, p=0.000, respectively) on survival time.

CONCLUSION: Our findings provide useful information for better patient management, especially in terms of negative factors on the continuation of survival during and after the treatment of limited-stage small cell lung carcinoma patients.

KEYWORDS: Lung cancer. Small cell lung cancer. Lymph node metastases. PET-CT. Prognosis.

INTRODUCTION

Accounting for approximately 15% of lung cancers, small cell lung cancer (SCLC) is a high-grade neuroendocrine tumor characterized by rapid growth and early metastatic spread[1]. While SCLC incidence has decreased recently, SCLC patients have a poor prognosis and a 5-year survival rate is only about 6%[2].

The majority (around 70%) of SCLC patients are diagnosed with extensive-stage small cell lung cancer (ES-SCLC). Only 30% of SCLC patients are diagnosed with limited-stage small cell lung cancer (LS-SCLC); however, their prognosis does still not look optimistic with a median survival time of 15–20 months[3]. As per the conventional VALG staging, LS-SCLC is a disease that is restricted to one hemithorax and can be safely encompassed within a single radiation portal[4].

^{18}F-fluorodeoxyglucose positron emission tomography (FDG-PET) is a valuable imaging method employed in staging SCLC[5]. PET can detect additional areas of disease that could not be detected by conventional computed tomography (CT). Furthermore, PET may be useful in predicting prognosis. Many studies confirmed the prognostic significance of metabolic parameters measured by FDG-PET in SCLC[6-8]. These parameters reflect the maximum standardized uptake value (SUV_{max}), disease activity, and tumor burden.

Recently, more studies have been conducted to investigate the prognosis-related risk factors to improve survival of SCLC patients. A variety of clinical factors, such as the patient's age, gender, performance status, and clinical stage, may affect the prognosis of SCLC patients[9]. Tumor size and lymph node (LN) metastasis were found to be a prognostic

[1]Ankara University, Faculty of Health Sciences, Ataturk Chest Diseases and Thoracic Surgery Training and Research Hospital, Chest Disease Department – Ankara, Turkish.

[2]Ankara University, Faculty of Health Sciences, Ataturk Chest Diseases and Thoracic Surgery Training and Research Hospital, Nuclear Medicine Department – Ankara, Turkish.

*Corresponding author: fhcimen@yahoo.com

Conflicts of interest: the authors declare there is no conflicts of interest. Funding: none.

Received on April 01, 2022. Accepted on June 17, 2022.

factor of cancer in NSCLC[10,11]. These findings thus suggested that tumor size and LN metastasis may also be prognostic factors of SCLC.

The standard treatment recommended for LS-SCLC in the current NCCN guidelines is concurrent chemoradiotherapy (CRT)[12]; prophylactic cranial irradiation (PCI) is planned for LS-SCLC patients who respond well to induction therapy. While the effectiveness of first-line therapy is as high as 80%, recurrence is observed within 6 months of completion of initial therapy in most patients[13].

There are not comprehensive studies as to which PET parameters demonstrate better prognostic performance in LS-SCLC. We, therefore, aimed to examine prognostic roles of SUV_{max} parameters. This study is designed to investigate the link between survival and prognostic factors such as tumor size, LN metastasis, and metabolic activity detected on PET-CT in patients with LS-SCLC.

METHODS

We retrospectively screened patients who were admitted to Health Sciences University Ataturk Chest Diseases and Thoracic Surgery Training and Research Hospital with pathological diagnosis of LS-SCLC between January 2015 and December 2019 and were older than 18 years. Demographic characteristics, LN metastasis, tumor size, and metabolic activity uptake in PET, in addition to clinicopathological, therapeutic, and prognostic data, were systematically extracted from medical records and analyzed.

In this cohort, 77 LS-SCLC cases were identified. Clinical stage of the disease was determined by results obtained from CT, PET scans, and magnetic resonance imaging. PCI was also evaluated.

Since it is a retrospective record review, Informed Consent Form is not needed and there are no costs to the budget.

Statistical analysis

In the descriptive statistics of the data, mean, standard deviation, median, minimum–maximum, frequency, and ratio values were used. The Kolmogorov-Smirnov test was used to measure the distribution of variables. The Mann-Whitney U-test was used to analyze the quantitative independent data, while the chi-square test was used to analyze the qualitative independent data, and Fisher's exact test was employed when the chi-square test conditions were not met. Cox regression (univariate-multivariate) and the Kaplan-Meier method were used for survival analysis. SPSS version 27.0 program was used in the analyses.

RESULTS

A total of 77 patients, including 10 females and 67 males, were included in the study. While there were 39 patients over 60 years of age, 38 patients were under 60. Patients' data are summarized in Table 1.

Age, smoking rate, diagnosis method, tumor localization distribution, T stage distribution, mass diameter, local recurrence rate, and PET SUV_{max} value did not differ significantly ($p>0.05$) between the groups of the deceased and living patients. The ratio of male patients in the deceased patients' group was significantly ($p=0.008$) higher than in the living patients' group. The ratio of N stage in the deceased patients' group was significantly ($p=0.000$) higher than in the living patients' group. The ratio of multiple LNs in the deceased patients' group was significantly ($p=0.000$) higher than in the living patients' group (Table 2).

The ratios of distant metastasis in the deceased patients' group were significantly ($p=0.000$) higher than in the living patients' group. The rate of brain metastases with distant metastases in the deceased patient group was found to be significantly higher ($p=0.013$) compared to the living patients' group.

The ratios of bone, liver, adrenal, and contralateral lung metastases in the deceased and living patients' groups did not show significant difference ($p>0.05$) (Table 2).

The ratios of chemotherapy, radiotherapy (RT), and concurrent CRT in the deceased and living patients' groups did not show significant difference ($p>0.05$). The ratio of PCI in the deceased patients' group was significantly ($p=0.000$) higher than in the living patients' group (Table 2).

Key features and univariate analysis

In the univariate model, age, diagnostic method, localization, mass diameter, local recurrence, bone metastasis, adrenal metastasis, contralateral lung metastasis, PET SUV_{max}, and sequential RT were not observed to have a significant ($p>0.05$) effect on survival time. In the univariate model, we observed that gender, smoking, T stage, N stage, multiple LNs, distant metastasis, brain metastasis, liver metastasis, chemotherapy, RT, concurrent CRT, and PCI had significant effect ($p=0.049$, $p=0.021$, $p=0.022$, $p=0.000$, $p=0.000$, $p=0.000$, $p=0.003$, $p=0.037$, $p=0.029$, $p=0.0049$, $p=0.000$, respectively) on survival time (Table 3).

Multivariate analysis

In the multivariate model, smoking, N stage, liver metastasis, and PCI demonstrated significant independent effect ($p=0.010$, $p=0.003$, $p=0.004$, $p=0.000$, respectively) on survival time (Table 3).

Table 1. Patients' data.

		Min–Max	Median	Mean ± SD/n (%)
Age	≤60			38 ± 49.4
	>60			39 ± 50.6
Sex	Female			10 ± 13.0
	Male			67 ± 87.0
Smoking	No			17 ± 22.1
	Yes			60 ± 77.9
Diagnostic method	FOB			46 ± 59.7
	FNA			14 ± 18.2
	Mediastinoscopy			4 ± 5.2
	EBUS			13 ± 16.9
Localization	Right up			14 ± 18.2
	Right mid.			23 ± 29.9
	Right b.			4 ± 5.2
	Left up			33 ± 42.9
	Left b.			2 ± 2.6
T stage	I			18 ± 23.4
	II			49 ± 63.6
	III			10 ± 13.0
N stage	I			31 ± 40.3
	II			46 ± 59.7
Lymph node	Single			31 ± 40.3
	Multiple			46 ± 59.7
Tumor diameter		1 – 7	5	4.5 ± 1.5
Tumor diameter (cm)	≤4			32 ± 41.6
	>4			45 ± 58.4
Local recurrence	(–)			56 ± 72.7
	(+)			21 ± 27.3
Distance metastasis	No			41 ± 53.2
	Yes			36 ± 46.8
Brain				15 ± 19.5
Bone				12 ± 15.6
Liver				8 ± 10.4
Adrenal				3 ± 3.9
Contr. lung				4 ± 5.2
Chemotherapy	No			38 ± 49.4
	Yes			39 ± 50.6
Radiotherapy	No			45 ± 58.4
	Yes			32 ± 41.6
Concurrent CRT	No			40 ± 51.9
	Yes			37 ± 48.1
PCI	No			14 ± 18.2
	Yes			63 ± 81.8
Mortality	No			32 ± 41.6
	Yes			45 ± 58.4
Following time (month)		5 – 72	29	31.3 ± 16.3

FOB: Fiber optic bronchoscopy; FNA: Fine-Needle Aspiration; EBUS: Endobronchial ultrasound; T stage: Tumour stage; N stage: Node stage; Contr. Lung: Contralateral lung; CRT: Chemoradiotherapy; PCI: Prophylactic cranial irradiation.

Table 2. Comparison of living and deceased patients' data.

		Living		Deceased		p	
		Mean ± sd/n (%)	Median	Mean ± sd/n (%)	Median		
Age	≤60	16 ± 50.0		22 ± 48.9		0.923	X^2
	>60	16 ± 50.0		23 ± 51.1			
Sex	Female	8 ± 25.0		2 ± 4.4		0.008	X^2
	Male	24 ± 75.0		43 ± 95.6			
Smoking	No	11 ± 34.4		6 ± 13.3		0.028	X^2
	Yes	21 ± 65.6		39 ± 86.7			
Diagnostic method	FOB	19 ± 59.4		27 ± 60.0		0.856	X^2
	FNA	7 ± 21.9		7 ± 15.6		0.682	X^2
	Med. copy	0 ± 0.0		4 ± 8.9		0.225	X^2
	EBUS	6 ± 18.8		7 ± 15.6		0.952	X^2
Localization	Right up	6 ± 18.8		8 ± 17.8		0.913	X^2
	Right mid.	8 ± 25.0		15 ± 33.3		0.549	X^2
	Right b.	1 ± 3.1		3 ± 6.7		0.634	X^2
	Left up	17 ± 53.1		16 ± 35.6		0.222	X^2
	Left b.	0 ± 0.0		2 ± 4.4		0.505	X^2
PET $SU_{Vma}x$		15.0 ± 8.6	13.9	13.2 ± 6.4	11.2	0.213	m
T stage	I	8 ± 25.0		10 ± 22.2		0.093	X^2
	II	23 ± 71.9		26 ± 57.8			
	III	1 ± 3.1		9 ± 20.0			
N stage	I	21 ± 65.6		10 ± 22.2		0.000	X^2
	II	11 ± 34.4		35 ± 77.8			
Lymph node	Single	21 ± 65.6		10 ± 22.2		0.000	X^2
	Multiple	11 ± 34.4		35 ± 77.8			
Tumor diameter		4.4 ± 1.6	5.0	4.6 ± 1.5	5.0	0.575	m
Tumor diameter (cm)	≤4	15 ± 46.9		17 ± 37.8		0.425	X^2
	>4	17 ± 53.1		28 ± 62.2			
Local recurrence	No	25 ± 78.1		31 ± 68.9		0.370	X^2
	Yes	7 ± 21.9		14 ± 31.1			
Distance metastasis	No	27 ± 84.4		14 ± 31.1		0.000	X^2
	Yes	5 ± 15.6		31 ± 68.9			
Brain		2 ± 6.3		13 ± 28.9		0.013	X^2
Bone		3 ± 9.4		9 ± 20.0		0.205	X^2
Liver		1 ± 3.1		7 ± 15.6		0.078	X^2
Adrenal		0 ± 0.0		3 ± 6.7		0.136	X^2
Contr. lung		0 ± 0.0		4 ± 8.9		0.137	X^2
Chemotherapy	No	19 ± 59.4		19 ± 42.2		0.138	X^2
	Yes	13 ± 40.6		26 ± 57.8			
Radiotherapy	No	19 ± 59.4		26 ± 57.8		0.889	X^2
	Yes	13 ± 40.6		19 ± 42.2			
Concurrent CRT	No	14 ± 43.8		26 ± 57.8		0.225	X^2
	Yes	18 ± 56.3		19 ± 42.2			
PCI	No	0 ± 0.0		14 ± 31.1		0.000	X^2
	Yes	32 ± 100.0		31 ± 68.9			

[m]Mann-Whitney U-test. [X²] χ^2 test. FOB: Fiber optic bronchoscopy; FNA: Fine-Needle Aspiration; EBUS: Endobronchial ultrasound; Med: Median; PET SUV: Positron emission tomography standardised uptake value; T stage: Tumour stage; N stage: Node stage; CRT: Chemoradiotherapy; PCI: Prophylactic cranial irradiation. χ^2: Significant p-value ≤0.05 according to paired χ^2 test. Bold and italics indicate significant values: p<0.05.

Table 3. Comparison of univariate and multivariate model.

	Univariate model			Multivariate model		
	HR	95%CI	p	HR	95%CI	p
Age	1.34	0.74 – 2.42	0.331			
Sex	4.16	1.00 – 17.28	0.049			
Smoking	2.80	1.17 – 6.71	0.021	3.30	1.33 – 8.21	0.010
Diagnostic method	1.05	0.81 – 1.36	0.712			
Localization	1.05	0.83 – 1.34	0.667			
PET SUV_{max}	0.97	0.93 – 1.02	0.229			
T stage	2.01	1.11 – 3.65	0.022			
N stage	4.69	2.26 – 9.74	0.000	3.24	1.48 – 7.10	0.003
Lymph node multiple	4.69	2.26 – 9.74	0.000			
Tumor diameter		0.91 – 1.36	0.282			
Local recurrence	1.27	0.67 – 2.41	0.459			
Distant metastasis	3.56	1.88 – 6.77	0.000			
Brain	2.85	1.44 – 5.65	0.003			
Bone	1.17	0.56 – 2.44	0.676			
Liver	2.37	1.05 – 5.34	0.037	3.515	1.501 – 8.232	0.004
Adrenal	1.54	0.47 – 5.03	0.473			
Contr. lung	1.47	0.52 – 4.12	0.466			
Chemotherapy	1.95	1.07 – 3.54	0.029			
Radiotherapy	1.15	0.64 – 2.09	0.642			
Concurrent CRT	0.55	0.30 – 1.00	0.049			
PCI	0.11	0.06 – 0.23	0.000	0.13	0.06 – 0.28	0.000

Cox regression (forward likelihood ratio); HR: Hazard ratio; PET SUV: Positron emission tomography standardized uptake value; T stage: Tumour stage; N stage: Node stage; Contr. Lung: Contralateral lung; CRT: Chemoradiotherapy; PCI: Prophylactic cranial irradiation. Bold and italics indicate significant values: p<0.05.

DISCUSSION

SCLC accounts for approximately 15% of all lung cancers and demonstrates a quite aggressive clinical course with a maximum of around 25% of 5-year survival rate even in limited-stage disease (LS-SCLC)[14]. Factors affecting survival in LS-SCLC, therefore, have often been studied. Male gender, old age, African American race, involvement of main bronchus, and poor performance status were reported as poor prognostic factors in LS-SCLC[15,16], while young age, smoking cessation, concurrent CRT, platinum-based chemotherapy, surgical treatment, pulmonary RT procedure, receiving >50 Gy of RT, and PCI were determined to increase survival[17-19]. In our study, gender and concurrent CRT were effective on survival in the univariate analysis while they were not found to be independent prognostic factors in the multivariate analysis. However, we determined that smoking history was an effective factor independently predictive of survival.

N stage is another factor whose relationship with SCLC survival has been examined. Salem et al. reported that the patients without mediastinal LN involvement showed better survival rates in their CRT study in stages 1–2 SCLC patients[20]. Guan and Zhang also found in their study involving 88 LS-SCLC patients that the presence of lymphadenopathy at mediastinal levels 2 and 3 before chemotherapy was associated with SCLC recurrence[21]. In a study in China, tumor size and LN metastasis were determined to be independent prognostic factors in stage 3A SCLC, and tumor size ≤4 cm and single LN metastasis were found to be associated with longer survival[22]. In our study, similar to the literature data, N stage was found to be an independent factor effective on survival in LS-SCLC.

Another independent factor found to be effective on LS-SCLC survival in this study was PCI. Although a study in the literature reports that PCI has no effect on the development time of brain metastasis and overall survival (OS) in SCLC patients

who underwent N0 M0 surgical resection[23], it has been concluded that PCI significantly increased survival in both extensive- and limited-stage diseases[24], extensive-stage elderly patient (≥70 years) group[25], SCLC patients in complete remission[26], LS-SCLC patients who underwent definitive surgery[27], and LS-SCLC patients who underwent definitive CRT[28].

Pre-CRT PET/CTs were analyzed in 120 individuals with LS-SCLC. On univariate analysis, SUV_{max}, SUV_{mean}, metabolic tumor volume (MTV), and total lesion glycolysis (TLG) of the primary tumor were not associated with OS, local-regional failure (LRF), or disease-free survival (DFS). On univariate analysis, MTV was substantially associated with DFS (p=0.024), but not on multivariate analysis. In LS-SCLC, pretreatment PET-CT scans and advanced metric measures had no independent prognostic significance[29]. Also in our study, we did not observe a significant difference in PET-CT SUV_{max} values.

Our study is designed to investigate the link between survival and prognostic factors such as tumor size, LN metastasis, and metabolic activity detected on PET-CT in LS-SCLC patients.

In the univariate model, we observed that gender, smoking, T stage, N stage, multiple LNs, distant metastasis, brain metastasis, liver metastasis, sequential chemotherapy, sequential RT, concurrent CRT, and PCI had significant effect on survival time. In the multivariate model, smoking, N stage, liver metastasis, and PCI demonstrated significant independent effect on survival time.

Our findings will provide useful information for especially the management of LS-SCLC patients.

CONCLUSION

Chemoradiotherapy can be used to treat LS-SCLC, and improvements in radiotherapy have greatly increased overall survival. According to the findings of our study and previous research, concurrent CRT is the cornerstone of care for LS-SCLC. In addition, PCI improves OS and DFS and reduces the incidence of cranial metastases. The N stage, smoking, and gender all have a significant impact on survival.

AUTHORS' CONTRIBUTION

FÇ: Conceptualization, Data curation, Writing – original draft. **MA:** Data curation, Writing – original draft. **SD:** Data curation. **AŞ:** Data curation. **ŞA:** Conceptualization. **ÖÖ:** Formal Analysis.

REFERENCES

1. Kalemkerian GP, Akerley W, Bogner P, Borghaei H, Chow LQ, Downey RJ, et al. Small cell lung cancer. J Natl Compr Canc Netw. 2013;11(1):78-98. https://doi.org/10.6004/jnccn.2013.0011
2. Cancer Research UK [Internet]. Survival. 2017 [cited on Jun 15, 2020]. Available from: https://www.cancerresearchuk.org/about-cancer/lung-cancer/survival
3. Rudin CM, Giaccone G, Ismaila N. Treatment of Small-Cell Lung Cancer: American Society of Clinical Oncology Endorsement of the American College of Chest Physicians Guideline. J Oncol Pract. 2016;12(1):83-6. https://doi.org/10.1200/JOP.2015.008201
4. Micke P, Faldum A, Metz T, Beeh KM, Bittinger F, Hengstler JG, et al. Staging small cell lung cancer: Veterans Administration Lung Study Group versus International Association for the Study of Lung Cancer--what limits limited disease? Lung Cancer. 2002;37(3):271-6. https://doi.org/10.1016/s0169-5002(02)00072-7
5. Kamel EM, Zwahlen D, Wyss MT, Stumpe KD, von Schulthess GK, Steinert HC. Whole-body (18)F-FDG PET improves the management of patients with small cell lung cancer. J Nucl Med. 2003;44(12):1911-7. PMID: 14660716
6. Lee YJ, Cho A, Cho BC, Yun M, Kim SK, Chang J, et al. High tumor metabolic activity as measured by fluorodeoxyglucose positron emission tomography is associated with poor prognosis in limited and extensive stage small-cell lung cancer. Clin Cancer Res. 2009;15(7):2426-32. https://doi.org/10.1158/1078-0432.CCR-08-2258
7. Kwon SH, Hyun SH, Yoon JK, An YS, Oh YT, Choi JH, et al. The highest metabolic activity on FDG PET is associated with overall survival in limited-stage small-cell lung cancer. Medicine (Baltimore). 2016;95(5):e2772. https://doi.org/10.1097/MD.0000000000002772
8. Chang H, Lee SJ, Lim J, Lee JS, Kim YJ, Lee WW. Prognostic significance of metabolic parameters measured by 18F-FDG PET/CT in limited-stage small-cell lung carcinoma. J Cancer Res Clin Oncol. 2019;145(5):1361-7. https://doi.org/10.1007/s00432-019-02848-9
9. Foster NR, Mandrekar SJ, Schild SE, Nelson GD. Age, gender, performance status and stage outperformed stage alone in predicting overall survival (OS) in patients with small cell lung cancer: a pooled analysis of 1,623 patients from the North Central Cancer Treatment Group. J Clin Oncol. 2007;25(18_suppl):7723. https://doi.org/10.1200/jco.2007.25.18_suppl.7723
10. Zhang J, Gold KA, Lin HY, Swisher SG, Xing Y, Lee JJ, et al. Relationship between tumor size and survival in non-small-cell lung cancer (NSCLC): an analysis of the surveillance, epidemiology, and end results (SEER) registry. J Thorac Oncol. 2015;10(4):682-90. https://doi.org/10.1097/JTO.0000000000000456
11. Deng XF, Jiang L, Liu QX, Zhou D, Hou B, Cui K, et al. Lymph node micrometastases are associated with disease recurrence and poor survival for early-stage non-small cell lung cancer patients: a meta-analysis. J Cardiothorac Surg. 2016;11:28. https://doi.org/10.1186/s13019-016-0427-x
12. Zhuoqun W. Analysis of prognostic factors in 92 patients with small cell lung [D]. Dalian: Dalian Medical University; 2017.
13. Zarogoulidis K, Ziogas E, Papagiannis A, Charitopoulos K, Dimitriadis K, Economides D, et al. Interferon alpha-2a and combined chemotherapy as first line treatment in SCLC patients:

a randomized trial. Lung Cancer. 1996;15(2):197-205. https://doi.org/10.1016/0169-5002(95)00583-8

14. Amini A, Byers LA, Welsh JW, Komaki RU. Progress in the management of limited-stage small cell lung cancer. Cancer. 2014;120(6):790-8. https://doi.org/10.1002/cncr.28505
15. Foster NR, Mandrekar SJ, Schild SE, Nelson GD, Rowland Junior KM, Deming RL, et al. Prognostic factors differ by tumor stage for small cell lung cancer: a pooled analysis of North Central Cancer Treatment Group trials. Cancer. 2009;115(12):2721-31. https://doi.org/10.1002/cncr.24314
16. Lally BE, Geiger AM, Urbanic JJ, Butler JM, Wentworth S, Perry MC, et al. Trends in the outcomes for patients with limited stage small cell lung cancer: An analysis of the Surveillance, Epidemiology, and End Results database. Lung Cancer. 2009;64(2):226-31. https://doi.org/10.1016/j.lungcan.2008.08.010
17. Chen J, Jiang R, Garces YI, Jatoi A, Stoddard SM, Sun Z, et al. Prognostic factors for limited-stage small cell lung cancer: a study of 284 patients. Lung Cancer. 2010;67(2):221-6. https://doi.org/10.1016/j.lungcan.2009.04.006
18. Aynaci Ö, Canyilmaz E, Serdar L, Kandaz M, Bahat ZM, Yoney A. Survival and prognostic factors in limited stage small cell lung cancer: A retrospective study from northeast Turkey. J Cancer Res Ther. 2016;12(1):238-43. https://doi.org/10.4103/0973-1482.151446
19. Xie D, Marks R, Zhang M, Jiang G, Jatoi A, Garces YI, et al. Nomograms Predict Overall Survival for Patients with Small-Cell Lung Cancer Incorporating Pretreatment Peripheral Blood Markers. J Thorac Oncol. 2015;10(8):1213-20. https://doi.org/10.1097/JTO.0000000000000585
20. Salem A, Mistry H, Hatton M, Locke I, Monnet I, Blackhall F, et al. Association of chemoradiotherapy with outcomes among patients with stage I to II vs stage III small cell lung cancer: secondary analysis of a randomized clinical trial. JAMA Oncol. 2019;5(3):e185335. https://doi.org/10.1001/jamaoncol.2018.5335
21. Guan Y, Zhang X. Determination of Risk Factors Related to Supraclavicular Recurrence for Limited-Stage Small Cell Lung Cancer (SCLC) Patients. Med Sci Monit. 2019;25:4968-73. https://doi.org/10.12659/MSM.916279
22. Wang L, Dou X, Liu T, Lu W, Ma Y, Yang Y. Tumor size and lymph node metastasis are prognostic markers of small cell lung cancer in a Chinese population. Medicine (Baltimore). 2018;97(31):e11712. https://doi.org/10.1097/MD.0000000000011712
23. Lou Y, Zhong R, Xu J, Qiao R, Teng J, Zhang Y, et al. Does surgically resected small-cell lung cancer without lymph node involvement benefit from prophylactic cranial irradiation? Thorac Cancer. 2020;11(5):1239-44. https://doi.org/10.1111/1759-7714.13381
24. Schild SE, Foster NR, Meyers JP, Ross HJ, Stella PJ, Garces YI, et al. Prophylactic cranial irradiation in small-cell lung cancer: findings from a North Central Cancer Treatment Group Pooled Analysis. Ann Oncol. 2012;23(11):2919-24. https://doi.org/10.1093/annonc/mds123
25. Rule WG, Foster NR, Meyers JP, Ashman JB, Vora SA, Kozelsky TF, et al. Prophylactic cranial irradiation in elderly patients with small cell lung cancer: findings from a North Central Cancer Treatment Group pooled analysis. J Geriatr Oncol. 2015;6(2):119-26. https://doi.org/10.1016/j.jgo.2014.11.002
26. Aupérin A, Arriagada R, Pignon JP, Le Péchoux C, Gregor A, Stephens RJ, et al. Prophylactic cranial irradiation for patients with small-cell lung cancer in complete remission. Prophylactic Cranial Irradiation Overview Collaborative Group. N Engl J Med. 1999;341(7):476-84. https://doi.org/10.1056/NEJM199908123410703
27. Chen MY, Hu X, Xu YJ, Chen M. The impact of prophylactic cranial irradiation for post-operative patients with limited stage small cell lung cancer. Medicine (Baltimore). 2018;97(44):e13029. https://doi.org/10.1097/MD.0000000000013029
28. Farooqi AS, Holliday EB, Allen PK, Wei X, Cox JD, Komaki R. Prophylactic cranial irradiation after definitive chemoradiotherapy for limited-stage small cell lung cancer: Do all patients benefit? Radiother Oncol. 2017;122(2):307-12. https://doi.org/10.1016/j.radonc.2016.11.012
29. Ong LT, Dunphy M, Foster A, Woo KM, Zhang Z, Perez CA, et al. Prognostic value of preradiotherapy (18)F-FDG PET/CT volumetrics in limited-stage small-cell lung cancer. Clin Lung Cancer. 2016;17(3):184-8. https://doi.org/10.1016/j.cllc.2015.07.004

ORIGINAL ARTICLE

https://doi.org/10.1590/1806-9282.20220333

Assessment of dynamic thiol-disulfide homeostasis in patients with lipoid proteinosis (Urbach-Wiethe syndrome)

Seyhan Taskin[1*], Hakim Celik[1], Abdullah Taskin[2], Mustafa Aksoy[3], Isa An[4], Yavuz Yesilova[5]

SUMMARY

OBJECTIVE: Lipoid proteinosis is a rare autosomal recessive genetic dermatological disease that occurs due to the accumulation of hyaline material in the skin and mucous membranes. This study aimed to investigate whether dynamic thiol-disulfide homeostasis is a new marker of oxidative stress in patients suffering from lipoid proteinosis.

METHODS: The study group involved 17 patients with lipoid proteinosis and 17 healthy controls with same gender and age. Native thiol, total thiol, disulfide levels, and thiol-disulfide indexes were measured with the fully automated spectrophotometric method described by Erel and Neselioglu, and the results of the two groups were statistically analyzed.

RESULTS: Serum total thiol and native thiol levels were significantly lower in lipoid proteinosis group compared to the control group (p=0.020 and p=0.014, respectively). The disulfide levels were found to be higher in lipoid proteinosis group, but there was no significant difference between two groups.

CONCLUSIONS: Impaired dynamic thiol-disulfide homeostasis was observed in lipoid proteinosis patients, suggesting that thiol-disulfide homeostasis may have a role in the pathogenesis of this disease.

KEYWORDS: Lipoid proteinosis. Mucous membrane. Oxidative stress. Thiol. Disulfides.

INTRODUCTION

Lipoid proteinosis, also known as Urbach-Wiethe syndrome, is an infrequent genetically inherited disease, characterized by the accumulation of amorphous hyaline substance in various parts of the body, including the skin and mucous membranes[1]. In the first year of life, it usually presents with hoarseness, which occurs as a result of the accumulation of hyaline-like substances in the vocal cords[2]. In addition, it causes typical symptoms such as oral erosions, thickened eyelid papules, skin lesions, and sublingual frenulum in the following years[3]. This disease is a multisystem disease that includes not only dermatological symptoms but also neurological and psychiatric symptoms[4].

It has been reported that the mutated extracellular matrix protein 1 (*ECM1*) gene plays a role in the pathogenesis of lipoid proteinosis disease[5]. The *ECM1* gene mediates a critical role in several biological activities, such as angiogenesis, cell adhesion, and cell differentiation. It also contributes to the preservation of the structural integrity and functions of the skin[6]. Mutations in this gene cause ECM1 protein not to be produced or loss of function in the produced proteins[5]. Non-functional ECM1 protein causes pathological changes in homeostatic balance. This results in the formation of clinical manifestations typical of lipoid proteinosis disease[7]. Although it is stated that lipoid proteinosis occurs due to genetic reasons, information about the pathophysiology of this disease is quite limited.

Besides genetic and environmental factors, deterioration in oxidant-antioxidant balance has been demonstrated to have an significant role in the onset and progression of several diseases[8,9]. This process, which is reported as oxidative stress, can be assessed using several biochemical factors[10]. Thiol-disulfide homeostasis is a novel and important systemic marker of oxidative stress[11]. Thiols can easily react with free radicals due to their structure, disulfide bonds are formed as a result of this oxidation reaction. These reactions are reversible and reducible. Thus, the dynamic conversion between thiols and disulfide bonds helps maintain the intracellular redox environment[12]. Thiol-disulfide homeostasis has a crucial function in many biological activities, such as oxidative stress, programmed cell death, cellular signal transduction, antioxidant defense, and enzymatic activities[13,14]. In

[1]Harran University, Faculty of Medicine, Department of Physiology – Sanliurfa, Turkey.
[2]Harran University, Faculty of Health Sciences, Department of Nutrition and Dietetics – Sanliurfa, Turkey.
[3]Harran University, Faculty of Medicine, Department of Dermatology – Sanliurfa, Turkey.
[4]Sanlıurfa Training and Research Hospital, Department of Dermatology – Sanlıurfa, Turkey.
[5]Lokman Hekim University, Faculty of Medicine, Department of Dermatology – Ankara, Turkey.
*Corresponding author: seyhan_taskin@yahoo.com
Conflicts of interest: the authors declare there is no conflicts of interest. Funding: none.
Received on May 23, 2022. Accepted on June 17, 2022.

this study, we aimed to investigate whether dynamic thiol-disulfide hemostasis acts as a new marker of oxidative stress in lipoid proteinosis patients.

METHODS

This study included 17 patients who were diagnosed with lipoid proteinosis as a result of clinical and histopathological examinations and 17 gender- and age-matched healthy control. Patient and healthy control who had a history of alcohol consumption / smoking; had an infectious disease, acute or chronic systemic diseases; and took drug or vitamin were excluded from this study. The study was approved by the Clinical Research Ethics Committee of the Harran University (approval number: 21/22/11). It was conducted as per the Declaration of Helsinki and Good Clinical Practice guidelines. The informed consent form was obtained from all participants or their parents.

Blood specimen from the volunteers (lipoid proteinosis patients and healthy controls) were collected following at least 8 h of fasting into biochemical tubes and centrifuged at 1500*g* for 10 min, and then the separated serum specimens were stored in the freezer at -86°C until to analyze thiol-disulfide homeostasis. Serum thiol-disulfide homeostasis parameters were evaluated using the methods described by Erel and Neselioglu[11]. Total thiol and native thiol levels were measured directly. Then, disulfide levels were obtained by calculating the half of difference between the total and native thiol content. The oxidized thiol ratio (disulfide/total thiol), reduced thiol ratio (native thiol/total thiol), and thiol oxidation-reduction (disulfide/native thiol) ratios were also computed. At the end of these measurements and calculations, six parameters were obtained. Native thiol, total thiol, and disulfide levels were represented as µmol/L.

Statistical analyses

SPSS program version 25.0 (SPSS Inc., Chicago, IL, USA) was used for statistical analyses. Pearson's chi-square analytic method was used to compare categorical variables. Data obtained from this study were investigated using Shapiro-Wilk or Kolmogorov-Smirnov test to determine whether or not they are normally distributed. The Student's t-test was used to compare continuous variables with a normal distribution, whereas the Mann-Whitney U-test was applied to comparisons of non-normally distributed variables. Values are expressed as mean±standard deviation for normally variables and median (Q1–Q3) for non-normally variables. A p-value<0.05 was considered statistically significant.

RESULTS

There were no statistically significant differences between lipoid proteinosis patients and control group in terms of age [17.0 (14–20.5) vs. 18.0 (10.5–21.5), p=0.704], gender distribution [F/M (%); 9/8 (52.9/47.1) vs. 12/5 (70.6/29.4), p=0.290], and body mass index (BMI) (22.25±1.56 kg/m^2 vs. 21.50±1.63 kg/m^2, p=0.186). Characteristics of the study groups are represented in Table 1.

The native thiol and total thiol levels were significantly lower in lipoid proteinosis patients compared to the control group (216.58±37.43 µmol/L vs. 251.89±41.83 µmol/L and 324.56±30.05 µmol/L vs. 356.41±44.10 µmol/L; p=0.014 and p=0.020) (Table 2, Figure 1). However, the mean serum level of dynamic disulfide was insignificantly increased in the lipoid proteinosis patients [51.58 (36.04–71.19) µmol/L] compared to the control group [50.23 (44.73–62.45) µmol/L, p=0.931]. Moreover, oxidized thiol, which indicates oxidation, was higher in lipoid proteinosis patients compared to the control group, while the antioxidant indicator, reduced thiol, was found to

Table 1. Characteristics of the study groups.

	Lipoid proteinosis (n=17)	Control (n=17)	p-value[a]
Age (years)	17.0 (14-20.5)	18.0 (10.5-21.5)	0.704[b]
Gender (F/M), n (%)	9/8 (52.9/47.1)	12/5 (70.6/29.4)	0.290
BMI (kg/m^2)	22.25±1.56	21.50±1.63	0.186[c]

[a]Data are expressed as median (Q1–Q3), numbers (%), and mean±standard deviation where appropriate. [b]Obtained from Mann-Whitney U-test. [c]Obtained from independent-samples t-test.

Table 2. Thiol-disulfide levels and ratios of the lipoid proteinosis patients and control group.

	Lipoid proteinosis (n=17)	Control (n=17)	p-value[a]
Native thiol (µmol/L)	216.58±37.43	251.89±41.83	**0.014[b]**
Total thiol (µmol/L)	324.56±30.05	356.41±44.10	**0.020[b]**
Disulfide (µmol/L)	51.58 (36.04–71.19)	50.23 (44.73–62.45)	0.931[c]
Oxidized thiol (%)	8.24±3.04	7.36±1.58	0.301[b]
Reduced thiol (%)	33.51±6.09	35.27±3.16	0.299[b]
Thiol oxidation-reduction (%)	11.85 (7.45–16.27)	9.74 (8.29–13.31)	0.524[c]

Bold values indicate statistically significant at p<0.05. [a]Data are expressed as mean±standard deviation and median (Q1–Q3) where appropriate. [b]Obtained from independent-samples t-test. [c]Obtained from Mann-Whitney U-test.

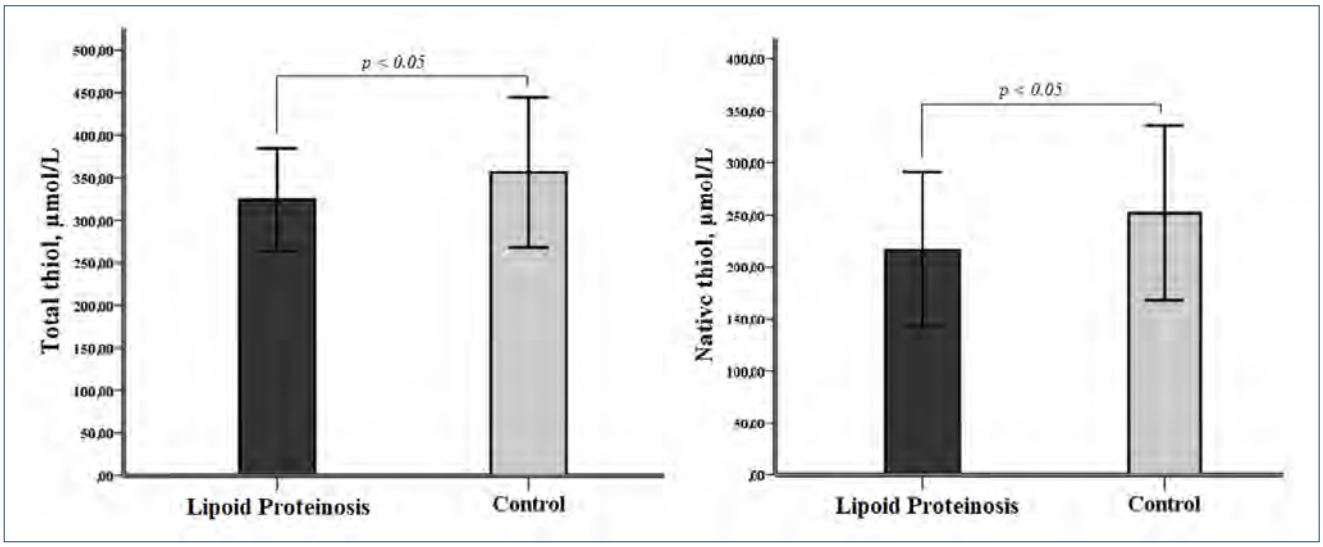


Figure 1. Total thiol and native thiol levels of lipoid proteinosis patients and control group.

be lower, but these changes were not statistically significant. Thiol oxidation-reduction ratio was higher in lipoid proteinosis patients than in the control group, but it was not statistically significant (Table 2).

DISCUSSION

Lipoid proteinosis is a very rare disease worldwide. It is autosomal recessive genodermatosis that occurs due to the accumulation of hyaline-like material in the skin and mucous membranes due to mutations in ECM1[5]. Although the mutated gene causing lipoid proteinosis has been identified, the exact mechanism underlying this inherited disorder is still unknown. It is known that oxidative stress is effective in the pathophysiology of many diseases[15]. To the best of our knowledge, there is no study evaluating the oxidative stress from the perspective of thiol-disulfide homeostasis in patients with lipoid proteinosis. Our results show that thiol-disulfide homeostasis shifts toward the oxidative side in lipoid proteinosis patients.

The shift of changes in the cellular redox state toward the oxidation direction is defined as oxidative stress. And this condition is an important risk factor for the development of various pathologies in the structure and function of many organs[15]. Dynamic thiol-disulfide homeostasis is frequently preferred as a new and important marker of oxidative stress[11]. This technique can be used as a reliable, practical technique to evaluate oxidative stress[16].

There are studies reporting that dermatological diseases cause changes in thiol-disulfide homeostasis. Sener et al. reported that disulfide levels were increased in patients with rosacea[17]. Akdag et al., in a study with chronic urticaria patients, found that native thiol and total thiol levels significantly decreased[18]. Another study revealed higher levels of native thiol and total thiol and lower levels of disulfide in atopic dermatitis[8]. Kilic et al., in a study with psoriasis patients, found that plasma disulfide levels significantly decreased and native thiol levels increased[19]. It has been reported that oxidative stress has a role in the pathophysiology of these dermatological diseases, whose clinical features, laboratory findings, and treatments are different from each other.

While there are studies on the role of inflammatory parameters, genetic tests, histopathological examinations, and radiological findings in the pathophysiology of lipoid proteinosis disease, there is only one study reporting its relationship with oxidative stress[10,20-23]. Total oxidant status, lipid hydroperoxide, and advanced oxidation protein products are important oxidant parameters. Celik et al. stated that these oxidant parameters increased in the lipoid proteinosis group compared to the control group. In the same study, it was stated that antioxidant parameters (total antioxidant status and ferric-reducing antioxidant power) decreased and oxidant antioxidant balance is impaired in patients with lipoid proteinosis[10].

Almost all of the physiological and biochemical reactions take place in a sensitive redox homeostasis. Thiol-disulfide level has a critical importance in providing and maintaining this homeostasis [11,24]. In our research, it was found that the total thiol and native thiol levels were decreased and disulfide levels were increased in the lipoid proteinosis patients when compared to the control group. Thiols, which act as free radical scavengers, are primarily consumed as antioxidants in case of oxidative stress[25].

Therefore, the decrease in the total thiol pool paves the way for an increase in oxidative stress. Thiol-disulfide balance in patients with lipoid proteinosis was found to be impaired and shifted to disulfide direction. These data indicate the presence of oxidative stress. Increased disulfide formation may cause structural and functional disorders at the cellular level. Thiol-disulfide balance is likely to have a role in etiopathogenesis of lipoid proteinosis.

CONCLUSIONS

This is the first study to examine the relationship between lipoid proteinosis and oxidative stress from the perspective of a new measurement method, thiol-disulfide homeostasis. Our results show that thiol-disulfide homeostasis shifts toward the oxidative side in lipoid proteinosis patients. This study may contribute to the understanding of the etiopathogenesis of lipoid proteinosis. Further research studies with larger numbers of patients are needed to define the role of thiol-disulfide homeostasis in the process of lipoid proteinosis.

Limitation

The limitations of this study include the small number of patients. However, it should be considered that this disease is a very rare dermatological disease worldwide.

AUTHORS' CONTRIBUTIONS

ST: Conceptualization, Data curation, Formal Analysis, Writing – original draft, Writing – review & editing. **HC:** Conceptualization, Formal Analysis, Writing – review & editing. **AT:** Formal Analysis, Writing – review & editing. **MA:** Conceptualization, Data curation, Formal Analysis, Writing – review & editing. **IA:** Conceptualization, Data curation, Formal Analysis, Writing – review & editing. **YY:** Data curation, Formal Analysis, Writing – review & editing.

REFERENCES

1. Urbach E, Wiethe C. Lipoidosis cutis et mucosae. Virchows Arch Path Anat. 1929;273:285-319. https://doi.org/10.1007/BF02158983
2. Yükkaldiran A, Aksoy M, Yeşilova Y, Demir M, Iynen I, An İ, et al. The frequency of laryngeal involvement in lipoid proteinosis patients. Ann Med Res. 2019;4:1. https://doi.org/10.5455/annalsmedres.2019.01.059
3. Xu W, Wang L, Zhang L, Han D, Zhang L. Otolaryngological manifestations and genetic characteristics of lipoid proteinosis. Ann Otol Rhinol Laryngol. 2010;119(11):767-71. PMID: 21140637
4. Teive HA, Pereira ER, Zavala JA, Lange MC, Paola L, Raskin S, et al. Generalized dystonia and striatal calcifications with lipoid proteinosis. Neurology. 2004;63(11):2168-9. https://doi.org/10.1212/01.wnl.0000145602.64073.c2
5. Hamada T, McLean WH, Ramsay M, Ashton GH, Nanda A, Jenkins T, et al. Lipoid proteinosis maps to 1q21 and is caused by mutations in the extracellular matrix protein 1 gene (ECM1). Hum Mol Genet. 2002;11(7):833-40. https://doi.org/10.1093/hmg/11.7.833
6. Sercu S, Zhang M, Oyama N, Hansen U, Ghalbzouri AE, Jun G, et al. Interaction of extracellular matrix protein 1 with extracellular matrix components: ECM1 is a basement membrane protein of the skin. J Invest Dermatol. 2008;128(6):1397-408. https://doi.org/10.1038/sj.jid.5701231
7. An İ, Aksoy M, Ozturk M, Ayhan E. Lipoid proteinosis. Mucosa. 2021;4(2):30-40. https://doi.org/10.33204/mucosa.936953
8. Karacan G, Ercan N, Bostanci I, Alisik M, Erel O. A novel oxidative stress marker of atopic dermatitis in infants: thiol-disulfide balance. Arch Dermatol Res. 2020;312(10):697-703. https://doi.org/10.1007/s00403-020-02054-5
9. Yilmaz CN, Gemcioglu E, Baser S, Erten S, Erel O. Thiol/disulfide homeostasis impaired in patients with primary Sjögren's syndrome. J Med Biochem. 2021;40(3):270-6. https://doi.org/10.5937/jomb0-27281
10. Celik H, Aksoy M, An I, Koyuncu I. The investigation of oxidative stress parameters in patients with lipoid proteinosis. J Harran Univ Med Fac. 2019;16(1):1-7.
11. Erel O, Neselioglu S. A novel and automated assay for thiol/disulphide homeostasis. Clin Biochem. 2014;47(18):326-32. https://doi.org/10.1016/j.clinbiochem.2014.09.026
12. Jones DP, Liang Y. Measuring the poise of thiol/disulfide couples in vivo. Free Radic Biol Med. 2009;47(10):1329-38. https://doi.org/10.1016/j.freeradbiomed.2009.08.021
13. Circu ML, Aw TY. Reactive oxygen species, cellular redox systems, and apoptosis. Free Radic Biol Med. 2010;48(6):749-62. https://doi.org/10.1016/j.freeradbiomed.2009.12.022
14. Biswas S, Chida AS, Rahman I. Redox modifications of protein-thiols: emerging roles in cell signaling. Biochem Pharmacol. 2006;71(5):551-64. https://doi.org/10.1016/j.bcp.2005.10.044
15. Pizzino G, Irrera N, Cucinotta M, Pallio G, Mannino F, Arcoraci V, et al. Oxidative stress: harms and benefits for human health. Oxid Med Cell Longev. 2017;2017:8416763. https://doi.org/10.1155/2017/8416763
16. Erel Ö, Erdoğan S. Thiol-disulfide homeostasis: an integrated approach with biochemical and clinical aspects. Turk J Med Sci. 2020;50(SI-2):1728-38. https://doi.org/10.3906/sag-2003-64
17. Sener S, Akbas A, Kilinc F, Baran P, Erel O, Aktas A. Thiol/disulfide homeostasis as a marker of oxidative stress in rosacea: a controlled spectrophotometric study. Cutan Ocul Toxicol. 2019;38(1):55-8. https://doi.org/10.1080/15569527.2018.1517124
18. Akdag S, Ozmen S, Ercan N, Bostanci I, Neselioglu S. Assessment of thiol/disulphide homoeostasis and ischaemia-modified albumin and their relationship with disease severity in children with chronic urticaria. Cutan Ocul Toxicol. 2020;39(3):269-73. https://doi.org/10.1080/15569527.2020.1790589
19. Kilic A, Yorulmaz A, Erdogan S, Cakmak SK, Guney E, Sen O, et al. An evaluation of thiol/disulphide homeostasis in patients with psoriasis. Postepy Dermatol Alergol. 2017;34(5):464-7. https://doi.org/10.5114/ada.2017.71113

20. Aksoy M, An I. Evaluation of inflammatory parameters in lipoid proteinosis patients. Dermatol Ther. 2020;33(6):e14495. https://doi.org/10.1111/dth.14495

21. An İ, Güldür ME, Aksoy M, Yeşilova Y, Ozturk M. Histopathological findings in patients with lipoid proteinosis. Turk Dermatoloji Derg. 2019;13(3):99-102. https://doi.org/10.4103/TJD.TJD_8_19

22. Hamada T, Wessagowit V, South AP, Ashton GH, Chan I, Oyama N, et al. Extracellular matrix protein 1 gene (ECM1) mutations in lipoid proteinosis and genotype-phenotype correlation. J Invest Dermatol. 2003;120(3):345-50. https://doi.org/10.1046/j.1523-1747.2003.12073.x

23. Loos E, Kerkhofs L, Laureyns G. Lipoid proteinosis: a rare cause of hoarseness. J Voice. 2019;33(2):155-8. https://doi.org/10.1016/j.jvoice.2017.05.024

24. Dröge W. Free radicals in the physiological control of cell function. Physiol Rev. 2002;82(1):47-95. https://doi.org/10.1152/physrev.00018.2001

25. Prakash M, Shetty MS, Tilak P, Anwar N. Total thiols: biomedical importance and their alteration in various disorders. Online J Health Allied Scs. 2009;8(2):1-9.

ORIGINAL ARTICLE

https://doi.org/10.1590/1806-9282.20220367

Body image and sexual function in women with polycystic ovary syndrome: a case-control study

Yılda Arzu Aba[1*], Bulat Aytek Şik[2]

SUMMARY

OBJECTIVES: The study aimed to determine the impact of polycystic ovary syndrome on women's body image and sexual function.

METHODS: In this case-control study, 97 women with polycystic ovary syndrome and 95 healthy women were interviewed in a hospital using the Personal Information Form, Body Image Scale, and Female Sexual Function Index.

RESULTS: The total score of body image of women in the polycystic ovary syndrome group was found to be 132.11±19.44 and it was 133.35±21 in the control group; there was no statistically significant difference between them (p>0.05). In this study, 74.23% of the women with polycystic ovary syndrome (+) experienced sexual dysfunction. Sex drive, arousal, lubrication, orgasm, and averages of pain subscales and female sexual function index total score were found to be significantly lower in the polycystic ovary syndrome group than in the control group (p<0.05).

CONCLUSION: The findings suggest a difference between women with polycystic ovary syndrome and healthy women in terms of sexual function, while body image was similar in both groups. Our data suggest that the polycystic ovary syndrome has a negative effect on the sexuality.

KEYWORDS: polycystic ovary syndrome; body image; sexual dysfunction; Turkish women.

INTRODUCTION

Polycystic ovary syndrome (PCOS) is an endocrine disorder that affects women's lives negatively, with short- and long-term risks, usually beginning in the peripubertal period. Its frequency is reported as 6–21% among women of reproductive age and approximately 15% in the Turkish population[1,2]. Typical clinical symptoms include oligomenorrhea or amenorrhea, hirsutisms, acne, seborrhea, hair loss, infertility, and obesity, although these are not found to the same degree and frequency in each patient. Although PCOS is a disease characterized by metabolic and cosmetic problems, it is currently evident that the disease causes psychological and reproductive/sexual problems[3,4]. The diagnosis of PCOS is difficult as well as challenging in similar cases. Therefore, the recommendation of criteria diagnosis and exclusion of other affection are necessary[5].

Body image is a concept that covers an individual's health status, physical appearance and skills, and attitudes and perceptions related to their sexuality, forming the physical nature of the self[6]. In many societies, characteristics such as youth and beauty can be considered the most important individual characteristics. Factors such as the individual's age, sex, personality structure, the value given to the changing body part, and whether the change is visible can influence the response to the change in the body[7]. In this respect, it is obvious that the physical and psychological changes observed in women with PCOS may affect their body image. In the literature, it is stated that changes in body appearance in women with PCOS negatively affected body image compared with healthy women[8,9].

It has been reported that changes in a woman's external appearance negatively affect their behavioral orientation and interpersonal relationships[10]. In Erbil's study on women of reproductive age, it was found that positive body image also positively affected sexual functions[11]. It has been reported that the impact of PCOS on sexual functions was related to the effect of menstrual irregularity, acne, hirsutism, alopecia, and androgen-dependent obesity on the female identity of the patient. In addition, long-term health risks, infertility, and changes in the physical appearance and body are considered to induce sexual dysfunction by causing psychological stress[12]. The possible negative effects of PCOS on sexual life are generally associated with menstrual irregularity and other clinical findings. These women feel more depressed and less feminine because they think their feminine image is being affected. Sexual function, physical, socioemotional, and intellectual aspects depend on integration[13]. In the study by Silva et al., it was stated that this syndrome in women with PCOS did not affect the initiation of sexuality, forms of expressing sexuality, intimate communication with their partners, and sexual

[1]Bandırma Onyedi Eylül University, Faculty of Health Sciences, Department of Nursing – Balıkesir, Turkey.
[2]Sisli Kolan International Hospital, Department of Reproductive Endocrinology and Infertility – Istanbul, Turkey.
*Corresponding author: yildaarzum@hotmail.com

Conflicts of interest: the authors declare there is no conflicts of interest. Funding: none.
Received on May 06, 2022. Accepted on May 16, 2022.

satisfaction. It seems that the literature is not solid on the sexuality of women with PCOS[14].

As a result, there are insufficient data to understand the relationship between body image and sexual functions in PCOS. The aim of this case-control study was to evaluate the body image and sexual function of women with PCOS using healthy women as the control group.

METHODS

Design

This was a case-control study performed on 192 women [97 with PCOS (study group), 95 healthy volunteers (control group)], who were admitted to the Şişli Kolan Hospital Reproductive Health and Family Planning Center in Istanbul between January 2019 and June 2019.

Sample

The minimum sample size was calculated using the Power Analysis and Sample Size 11 (PASS) statistical software (NCSS LLC, Kaysville, Utah, USA). The sample size was calculated according to the frequency of an event when the population size was unknown. There was only one study investigating the prevalence of sexual dysfunction in Turkish women with PCOS, which found that 57% of women with PCOS experienced sexual dysfunction[15]. Accordingly, the sample size was calculated as alpha=0.05, beta=0.20 and 1–b=0.80, p=0.5, basic risk=0.20, and the sample number for each group was determined as at least 92.

The inclusion criteria in this study were determined according to the aims of this study and a literature review.

The PCOS group: Patients who were diagnosed as having PCOS according to the Rotterdam criteria (oligoanovulation, clinical, and/or biochemical hyperandrogenism findings, polycystic ovaries shown on ultrasonography, and other etiological causes ruled out)[16], who agreed to participate in the study, were ≥18 years old, ≤40 years old (as they are more likely to experience premenopausal and perimenopausal changes, and their sexual function decreases with age), were married or had regular sexual partners, were sexually active, and were literate were included in this group.

The control group: Women who came for regular health checks (pap smear and pelvic exam), who agreed to participate in the study, were 18–40 years old, were married or had regular sexual partners, were sexually active, and were literate were included in this group.

Data collection tools

The data were obtained using the Sociodemographic Data Form, Body Image Scale, and Female Sexual Function Index (FSFI).

Sociodemographic Data Form: The data form prepared by the researchers contained questions about identifying the characteristics of women, their body mass index (BMI), menstrual characteristics, and symptoms such as hirsutism and acne. In the study, hirsutism and acne findings were subjectively evaluated as "yes" or "no" according to the patients' statements.

Body Image Scale (BIS): The answers to 40 items are evaluated and measured to determine the person's satisfaction with the function of different body parts. The lowest score on the scale is 40 and the highest is 200. Higher scores mean that body image is evaluated positively[17].

Female Sexual Function Index (FSFI): This index is a Likert-type index consisting of 19 items that assess women's sexual dysfunction in the last 4 weeks. A maximum of 36 and a minimum of 2 points are taken from the index. The presence of sexual dysfunction is accepted in women receiving a total FSFI score of 26.55 or below[18].

Application

The women who agreed to the interview and gave their written consent were directed to a private room where they completed the questionnaire. The Sociodemographic Data Form was completed through face-to-face interviews. The body image scale and FSFI were completed by the participants themselves in order to make them feel comfortable. Surveys were conducted after anthropometric measurements (height and weight) and BMI calculations were made.

Ethic approval

The study protocol was designed in compliance with the principles of the Declaration of Helsinki. Prior to data collection, necessary approvals and permissions were obtained from the Bandırma Onyedi Eylül University Non-Invasive Research Ethics Committee (Decision Date and No.: 05.12.2018, 2018-12.03) and the General Director of the Şişli Kolan Hospital, respectively. In addition, the verbal and written informed consent of women included in the study was obtained after they were informed of the purpose and method of the research.

Analysis of data

In this study, statistical analysis was performed using the NCSS (Number Cruncher Statistical System) 2007 Statistical Software (Utah, USA) package program. In addition to descriptive statistical methods (mean and standard deviation), the independent t-test was used for comparison of binary groups of variables showing normal distribution, and the chi-square test was used for comparison of qualitative data. Logistic regression was used to estimate odds ratios (ORs) and 95% confidence intervals

(CIs) of the factors that affected sexual function. The internal consistency of the BIS and FSFI was assessed using Cronbach's alpha coefficient. The significance level was accepted as p<0.05.

RESULTS

The average age of patients with PCOS was 28.23±4.56 years. Of the patients, 65.98% were secondary school graduates, 77.32% had a job, 58.76% had moderate-income status, 44.33% were married, 39.18% used cigarettes, and 17.53% used alcohol. The average age of the women in the control group was 29.33±5.61 years. There was no statistically significant difference between the study and control groups in terms of sociodemographic variables (p>0.05) (Table 1).

Table 2 shows the total score averages of the BIS, FSFI, and their subdimensions in the PCOS and control groups. The total score averages of the FSFI and subdimensions in women with PCOS and control group were compared. The total score average of the FSFI and sexual drive, arousal, lubrication, orgasm, and pain subdimensions in women with PCOS was significantly lower than in the control group (p<0.05) (Table 2).

Table 1. Demographic and clinical characteristics of patients with Polycystic ovary syndrome and control groups.

Demographic and clinical characteristics		PCOS group n=97		Control group n=95		Test
Age		Mean±SD		Mean±SD		t: 6.92 p=0.085*
		28.23±4.56		29.33±5.61		
BMI		25.08±4.3		22.34±3.74		t: 2.98 **p=0.003***
		n (%)		n (%)		
Level of education	Elementary	18	18.55	15	15.79	χ^2: 1.36 p=0.054+
	Secondary	64	65.98	47	49.47	
	University	15	15.46	33	34.74	
Employment status	Employed	75	77.32	84	88.42	χ^2: 0.55 p=0.162+
	Unemployed	22	22.68	11	11.58	
Income level	Poor	5	5.15	18	18.95	χ^2: 1.83 p=0.040+
	Moderate	57	58.76	56	58.95	
	Good	35	36.08	21	22.11	
Marital status	Married	43	44.33	56	58.95	χ^2: 1.22 p=0.092+
	Single	54	55.67	39	41.05	
Cigarette smoking	Yes	38	39.18	28	29.47	χ^2: 2.00 p=0.157+
	No	59	60.82	67	70.53	
Alcohol consumption	Yes	17	17.53	14	14.73	χ^2: 1.22 0.269+
	No	80	82.47	81	85.26	
Menstrual irregularity	Yes	50	51.55	18	18.95	χ^2: 22.29 **p=0.001+**
	No	47	48.45	77	81.05	
Acne	Yes	28	28.87	21	22.11	χ^2: 1.15 p=0.283+
	No	69	71.13	74	77.89	
Hirsutism	Yes	29	29.90	12	12.63	χ^2: 8.51 **p=0.004+**
	No	68	70.10	83	87.37	
Belly fat	Yes	40	41.24	21	22.11	χ^2: 9.26 **p=0.002+**
	No	57	58.76	74	77.89	
Hair loss	Yes	18	18.56	27	28.42	χ^2: 2.60 p=0.107+
	No	79	81.44	68	71.58	
Oily skin	Yes	24	24.74	15	15.79	χ^2: 2.37 p=0.123+
	No	73	75.26	80	84.21	

*Independent t-test and χ^2 test. PCOS: Polycystic ovary syndrome; BMI: Body mass index; Mean±SD: mean and standard deviation. Bold values indicate statistical significance at the p<0.05 level.

Table 2. Comparison of mean total body image scale and female sexual function index scores between the Polycystic ovary syndrome and control groups.

Body Image Scale and Female Sexual Function Index	PCOS group n=97 Mean±SD	Control group n=95 Mean±SD	t-test	p-value*
Total Score Body Image Scale	132.11±19.44	133.35±21	-0.42	0.670
Total Score FSFI	16.65±5.93	18.89±6.53	3.26	**0.001**
Desire	3.41±1.15	3.85±1.13	3.65	**0.009**
Arousal	2.53±1.21	3.19±1.16	3.30	**0.002**
Lubrication	2.36±0.95	3.5±0.69	-3.11	**0.001**
Orgasm	2.49±0.67	3.51±0.66	-4.16	**0.003**
Satisfaction	2.37±1.07	2.43±1.14	-0.39	0.299
Pain	3.31±1.37	4.97±1.17	3.31	**0.001**

*Independent t-test. PCOS: Polycystic ovary syndrome; Mean±SD: mean and standard deviation. Bold values indicate statistical significance at the p<0.05 level.

In the study, it was determined that 74.23% of the women in the PCOS group and 44.21% of the women in the control group experienced sexual dysfunction, and the difference was statistically significant (p<0.05).

There was a positive correlation at weak and very weak levels between the body image of women and the total score averages of the subdimensions of desire, arousal, and sexual satisfaction in the FSFI in the PCOS group (r=0.380, p=0.001; r=0.234, p=0.026; r=0.257, p=0.016). A logistic regression analysis was completed using the variables that were significant according to the estimated relative risk calculation. In this study, irregular menstruation (AOR: 2.99; 95%CI 0.60–14.98; p=0.018) and the presence of hirsutism (AOR 2.43; 95%CI 0.01–4.58; p=0.011) were identified as risk factors affecting sexual function (Table 3).

Table 3. Factors affecting sexual function in the Polycystic ovary syndrome group according to the logistic regression model.

(n=97)	β	SE	AOR (95%CI)	p-value*
Age				
<30	0.04	0.09	1.04 (0.88–1.22)	0.683
>30			Ref	
BMI				
< 24.9	-0.15	0.12	0.86 (0.68–1.09)	0.216
≥ 25.0			Ref	
Irregular menstruation				
Yes	1.09	0.82	2.99 (0.60–14.98)	**0.018**
No			Ref	
Acne				
Yes	0.30	0.96	1.35 (0.21–2.92)	0.999
No			Ref	
Hirsutism				
Yes	1.50	0.94	2.43 (0.01–4.58)	**0.011**
No			Ref	
Alopecia				
Yes	1.37	0.57	0.34 (0.23–1.99)	0.590
No			Ref	
Belly Fat				
Yes	0.43	0.79	0.95 (0.20–2.61)	0.892
No			Ref	

SE: standard error; AOR: adjusted odds ratio; 95%CI: confidence interval; BMI: Body mass index. *p-values derived from Wald test for each variable overall. Bold values indicate statistical significance at the p<0.05 level.

DISCUSSION

This study was conducted to determine the relationship between body image and sexual function in healthy women diagnosed as having PCOS. Current studies have shown conflicting results, indicating that PCOS is either "ineffective" or "moderately effective" on sexual function. Studies related to body image and sexual function are very limited[10,19,20] and have never been discussed earlier in the Turkish population.

The sexual function of women is provided by the balanced interaction of many factors. Endocrine disorders and disturbances in emotional and social areas can cause sexual dysfunction. Hyperandrogenic dermopathy and the feeling of being unattractive due to being overweight can cause low self-esteem and problems in sexual relations with partners. Studies have shown that body image levels are similar in healthy women and women with PCOS[7,21,22]. In contrast to these studies, Himelein and Thatcher compared the body image of women with PCOS and infertile women and found that the body image level of women with PCOS was lower than that of infertile women[23]. It is inevitable that the health problems caused by PCOS in the short and long term will affect women psychosocially as well as physically. Body image, especially in the early reproductive period, is an effective factor in the acceptance of young people in society. Health professionals should address this issue

in detail because the problems associated with the disease can cause more serious social problems, especially in this age group.

In our study, it was determined that 74.23% of women in the PCOS group and 44.21% of healthy women experienced sexual dysfunction. Similar to our study, Murgel et al. and Pastoor et al. concluded that sexual function and feelings of sexual attractiveness were significantly affected in women with PCOS in their meta-analyses[13,24]. In one of the most extensive (n=30,000) studies on the prevalence of female sexual problems conducted in the United States, 43% of women reported having some degree of sexual dysfunction[25]. Although these findings show that sexual dysfunction is an existing problem in women, the presence of PCOS alone appears to be an important factor affecting sexual function. It is thought that personal knowledge and thoughts are important in the formation of differences in incidence rates of sexual dysfunction along with social factors.

Clinical factors such as high BMI, acne, lubrication, hair loss, and hirsutism in patients with PCOS can affect an individual's perception of sexual attractiveness[8]. In our study, hirsutism and irregular menstruation were findings about which women with PCOS complained constantly, and they were the most important factors affecting sexual function. Anger et al. found that there was a negative correlation between high BMI and sexual function in women with PCOS[26]. Women's sexual dysfunction is affected by biological, psychological, medical, and many other factors, so it is expected that there would be differences in the results of the studies.

Body image is the strongest predictor of appearance-related distraction during sexual intercourse in men and women. Anxious behavior during sexual intercourse, conscious focus on body image, and avoidance of certain positions are behaviors that damage sexual function. In our study, a positive weak relationship between body image and sexual function was determined. As the body dissatisfaction of women in the PCOS group increased, their negativity about sexual function also increased. In addition to these findings, it was found that menstrual irregularity and hirsutism, which are clinical findings in women with PCOS, affect sexual function. In their research, La Rocque and Cioe observed that women who reported negative body image were more likely to avoid sexual intercourse than those who reported positive body image[27]. Hoyt and Kogan reported that people who did not enjoy their sex life were less satisfied with their body appearance than those who had sexual satisfaction[28]. In their study, van den Brink et al. observed a significant relationship between body image and sexual satisfaction[29]. However, their study emphasized that a positive body image was equally important for both women and men in shaping positive sexual experiences. Recent studies show that PCOS symptoms such as changes in body weight, acne, and hirsutism negatively affect body image and sexual health[10]. The findings reported in our study support the results in the literature.

Strengths and limitations of the study

One of the key strengths of this study is that this is the first study to evaluate body image and sexual function in women with PCOS in the Turkish population. In addition, the comparison of the data obtained with the PCOS group with the healthy control group is another strength of this study.

This research has certain limitations. One of these limitations pertains to the omission of biochemical assays (plasma concentration of estradiol, testosterone, and androstenedione) in the analysis. One of the most important factors affecting body image in women with PCOS is hirsutism. An important limitation is that the Ferriman-Gallwey score was not used in the determination of hirsutism in this study. In addition, another limitation of this study is related to the nature of cross-sectional studies as having statistically significant associations between sexual dysfunction and body image is not sufficient to prove the existence of a causal relationship.

In recent years, there has been a growing interest in the impact of PCOS on women's health-related quality of life. Currently, due to the lack of definitive treatment for PCOS, the management of the disease aims at alleviating symptoms, preventing long-term complications, and improving quality of life. Health professionals working with adolescents, and women in particular, need to be informed about the signs and symptoms of PCOS, the bio-psycho-social effects on women, diagnosis and treatment methods, and management of the disease.

CONCLUSION

In our study, it was determined that the body image level of women with PCOS was above average and that three out of every four women experienced sexual dysfunction. The presence of irregular menstruation in women with PCOS was found to increase the risk of sexual dysfunction by 2.99 times and the presence of hirsutism by 2.43 times. A satisfying sex life is as important for healthy women as it is for women with PCOS. Our findings suggest that sexual function should be part of the clinical evaluation of every woman with PCOS.

AUTHORS' CONTRIBUTIONS

YAA: Conceptualization, Supervision, Writing – original draft, Writing – review & editing. **BAS:** Data curation, Supervision, Writing – original draft, Writing – review & editing.

REFERENCES

1. Kite C, Lahart IM, Afzal I, Broom DR, Randeva H, Kyrou H, et al. Exercise, or exercise and diet for the management of polycystic ovary syndrome: a systematic review and meta-analysis. Syst Rev. 2019;8(1):51. https://doi.org/10.1186/s13643-019-0962-3
2. Öztürk A, Kucur SK, Seven A, Deveci E, Özencan H, Yilmaz O, et al. Temperament and character differences of patients with polycystic ovary syndrome. J Gynecol Obstet Hum Reprod. 2019;48(4):255-9. https://doi.org/10.1016/j.jogoh.2019.01.006
3. Gholinezhad M, Gholsorkhtabaramiri M, Esmaeilzadeh S, Ghanbarpour A. (2018). Insulin resistance and adverse metabolic profile in overweight/obese and normal weight of young women with polycystic ovary syndrome. Casp J Intern Med. 2018:(9),260-7. https://doi.org/10.22088/cjim.9.3.260
4. Hemati T, Moghadami-Tabrizi N, Davari-Tanha F, Salmanian B, Javadian P. High plasma homocysteine and insulin resistance in patients with polycystic ovarian syndrome. Iran J Reprod Med. 2011;9(3):223-8. PMID: 26396568
5. Soares Júnior JM, Baracat MC, Maciel GA, Baracat EC. Polycystic ovary syndrome: controversies and challenges. Rev Assoc Med Bras (1992). 2015:61(6):485-7. https://doi.org/10.1590/1806-9282.61.06.485
6. Hamurcu P, Öner C, Telatar B, Yeşilda . The impact of obesity on self-esteem and body image. Türk Aile Hek Derg. 2015;19(3):122-8. https://doi.org/10.15511/tahd.15.02122
7. Nazik H, Özdemir F, Nazik E, Arslan S. The body image and self-esteem of women with polycystic ovary syndrome. Ankara Sağlık Bilimleri Dergisi. 2014 [cited on Fev. 2, 2020];3(1-3):1-12. Available from: https://dergipark.org.tr/tr/download/article-file/509720
8. Alur-Gupta S, Chemerinski A, Liu C, Lipson J, Allison K, Sammel M, Dokras A. Body image distress increased in women with PCOS and mediates depression and anxiety. Fertil Steril. 2019:112(5):930-8. https://doi.org/10.1016/j.fertnstert.2019.06.018
9. Bazarganipour F, Ziaei S, Montazeri A, Foroozanfard F, Kazemnejad A, Faghihzadeh S. Body image satisfaction and self-esteem status among the patients with polycystic ovary syndrome. Iran J Reprod Med. 2013;11(10):829-36. PMID: 24639704
10. Kogure GS, Ribeiro VB, Lopes IP, Furtado CLM, Kodato S, Silva Sá MF, et al. Body image and its relationships with sexual functioning, anxiety, and depression in women with polycystic ovary syndrome. J Affect Disord. 2019;15(253):385-93. https://doi.org/10.1016/j.jad.2019.05.006
11. Erbil N. The relationships between sexual function, body image, and body mass index among women. Sex Disabil. 2013;31:63-70. https://doi.org/10.1007/s11195-012-9258-4
12. Rowland DL, McNabney SM, Mann AR. Sexual function, obesity, and weight loss in men and women. Sex Med Rev. 2017;5(3):323-38. https://doi.org/10.1016/j.sxmr.2017.03.006
13. Murgel ACF, Simões RS, Maciel GAR, Soares JM-Jr, Baracat EC. Sexual dysfunction in women with polycystic ovary syndrome: systematic review and meta-analysis. J Sex Med. 2019;16(4):542-50. https://doi.org/10.1016/j.jsxm.2019.01.313
14. Silva JSP, Fonseca AM, Bagnoli VR, Cavalcanti AL, Soares Júnior JM, Baracat EC. Sexuality in women with polycystic ovary syndrome: a pilot study. Einstein (São Paulo). 2010:8(4):397-403. https://doi.org/10.1590/S1679-45082010AO1836
15. Yıldız A, Dogan O. Sexual dysfunction in women with polycystic ovary syndrome. Kocaeli Med J. 2017[cited on Nov. 10, 2019];6(2):17-23. Available from: https://jag.journalagent.com/kocaelitip/pdfs/KTD-18189-RESEARCH_ARTICLE-YILDIZ.pdf
16. Rotterdam ESHRE/ASRM-Sponsored PCOS consensus workshop group. Revised 2003 consensus on diagnostic criteria and long-term health risks related to polycystic ovary syndrome (PCOS). Hum Reprod. 2004;19(1):41-7. https://doi.org/10.1093/humrep/deh098
17. Hovardaoglu S. Body Image Scale. Psychiatry, Psychology, Psychopharmacology Journal. 1993;1(1):26.
18. Aygin D, Eti-Aslan F. The Turkish adaptation of the female sexual function index. Turkey Clinics J Med Sci. 2005;25(3):393-9.
19. Kowalczyk R, Skrzypulec-Plinta V, Nowosielski K, Lew-Starowicz Z. Sexuality in women with polycystic ovary syndrome. Ginekol Pol. 2015;86(2):100-6. https://doi.org/10.17772/gp/1995
20. Castelo-Branco C, Naumova I. Quality of life and sexual function in women with polycystic ovary syndrome: a comprehensive review. Gynecol Endocrinol. 2020;36(2):96-103. https://doi.org/10.1080/09513590.2019.1670788
21. Morotti E, Persico N, Battaglia B, Fabbri R, Meriggiola MC, Venturoli S, et al. Body imaging and sexual behavior in lean women with polycystic ovary syndrome. J Sex Med. 2013:10(11):2752-60. https://doi.org/10.1111/jsm.12284
22. Beyazıt F, Şahin B, Ertekin H, Gencer M. The effect of hirsutismus and body mass index on body image and anxiety in patients with polycystic ovarian syndrome. J Clin Obstet Gynecol. 2017;27(3):130-7. https://doi.org/10.5336/gynobstet.2017-56085
23. Himelein MJ, Thatcher SS. Depression and body image among women with polycystic ovary syndrome. J Health Psychol. 2006;11:613-25. https://doi.org/10.1177/1359105306065021
24. Pastoor H, Timman R, Klerk CD, Bramer WM, Laan ETM, Laven JSE. Sexual function in women with polycystic ovary syndrome: A systematic review and meta-analysis. Reprod Biomed Online. 2018;37(6):750-60. https://doi.org/10.1016/i.rbmo.2018.09.010
25. Johannes CB, Clayton AH, Odom DM, Rosen RC, Russo PA, Shifren JL, et al. Distressing sexual problems in United States women revisited: prevalence after accounting for depression. J Clin Psychiatry. 2009;70(12):1698-706. https://doi.org/10.4088/JCP.09m05390gry
26. Anger JT, Brown AJ, Amundsen CL. Sexual dysfunction in women with polycystic ovary syndrome: the effects of testosterone, obesity, and depression. J Pelvic Med Surg. 2007;13(3):119-24. https://doi.org/10.1097/SPV.0b013e318062225e
27. La Rocque CL, Cioe J. An evaluation of the relationship between body image and sexual avoidance. J Sex Res. 2011;48(4):397-408. https://doi.org/10.1080/00224499.2010.499522
28. Hoyt WD, Kogan LR. Satisfaction with body image and peer relationships for males and females in a college environment. Sex Roles. 2001;45:199-215. https://doi.org/10.1023/a:1013501827550
29. Van den Brink F, Vollmann M, Sternheim LC, Berkhout LJ, Zomerdijk RA, Woertman L. Negative body attitudes and sexual dissatisfaction in men: the mediating role of body self-consciousness during physical intimacy. Arch Sex Behav. 2018;47:693-701. https://doi.org/10.1007/s10508-017-1016-3

ORIGINAL ARTICLE

https://doi.org/10.1590/1806-9282.20220368

Protocol of care for foreign-body ingestion in children: a qualitative study

Dario Silva da Silva Júnior[1], Jandrei Rogério Markus[2], Aline Barbosa Lopes[3], Lucas da Silva Sousa[4], Erika da Silva Maciel[1], Ladislau Ribeiro do Nascimento[1], Luiz Sinésio Silva-Neto[1], Aldair Martins Barasuol[1], André Pontes-Silva[5,6*], Fernando Rodrigues Peixoto Quaresma[1]

SUMMARY

OBJECTIVE: This study aimed to suggest a care protocol for foreign-body ingestion, address the clinical aspects, and identify the ingested object, severity, and professional conduct.

METHODS: This is a qualitative study. We used books and original articles published in national and international journals (BIREME, SCIELO, LILACS, and MEDLINE/PubMed) in Portuguese, Spanish, and English.

RESULTS: The ingestion of a radiolucent object should be evaluated radiographically and with endoscopy for cases with symptoms of impaction and radiolucent objects. Coins are the most commonly involved foreign bodies. In asymptomatic patients, it often requires only a conservative form of management. Ingestion of batteries, magnets, and sharp objects carries a high risk of serious clinical complications and should have an endoscopic or surgical approach. In view of this, each pediatric emergency service, based on these recommendations, has the possibility to develop an individual protocol to identify and remove the ingested foreign body.

CONCLUSIONS: Protocol of care for foreign-body ingestion in children depends on the object ingested, time of ingestion, symptoms, and local epidemiological context. This study provides some suggestions for decision-making in the conduct of health professionals.

KEYWORDS: Pediatrics. Accidents, home. Emergency medical services. Public health.

INTRODUCTION

Foreign-body ingestion is a common complaint in children's emergency medical services. It usually has an accidental etiology; however, it can be intentional and deliberate. The first description of accidental foreign-body ingestion occurred in 1692, when the 4-year-old Crown Prince of Brandenburg, Frederick the Great, swallowed a shoe buckle. The types of foreign bodies are very varied. In the United States, coins are the most accidentally ingested objects, while in China and other Eastern countries, fish bones and bones of animals served as food are the most common foreign bodies in emergencies[1].

Although foreign-body ingestion is common in emergency medical services, there are no care protocols for this clinical scenario. This study aimed to suggest a care protocol for foreign-body ingestion, address the clinical aspects, and identify the ingested object, severity, and professional conduct.

METHODS

This is a qualitative study performed in accordance with the Standards for Reporting Qualitative Research (SRQR). We searched in books and scientific articles that analyzed foreign-body ingestion in pediatrics. As inclusion criteria, full original articles were used, published in the period from 2000 to 2019 (Portuguese, Spanish, and English). As exclusion criteria, incomplete articles were considered, which did not cover the specific theme and were duplicated in the databases.

We retrieved the articles through the following databases: BIREME, SCIELO, LILACS, and MEDLINE/PubMed. We used the descriptors: "corpos estranhos," "acidentes domésticos," "pediatria" (in Portuguese); "cuerpo extraño," "acidentes domésticos," "pediatria" (in Spanish); and "foreign bodies," "Accidents, Home," "pediatrics" (in English).

[1]Universidade Federal do Tocantins, Postgraduate Program in Science and Health Teaching – Palmas (TO), Brazil.
[2]Universidade Federal do Tocantins, Department of Pediatrics – Palmas (TO), Brazil.
[3]Universidade de São Paulo, Faculty of Medicine – São Paulo (SP), Brazil.
[4]Universidade Federal do Tocantins, School of Medicine – Palmas (TO), Brazil.
[5]Universidade Federal de São Carlos, Postgraduate Program in Physiotherapy – São Carlos (SP), Brazil.
[6]Universidade Federal do Maranhão, Postgraduate Program in Adult Health – São Luís (MA), Brazil.
*Corresponding author: contato.andrepsilva@gmail.com
Conflicts of interest: the authors declare there is no conflicts of interest. Funding: none.
Received on June 02, 2022. Accepted on June 12, 2022.

RESULTS

Most cases of foreign-body ingestion in pediatrics occur unintentionally. About 98% of cases occur unintentionally[2]. North American data show that more than 110,000 foreign bodies were ingested in the United States in 2011, with more than 85% occurring in the pediatric population[3]. This condition is widely associated with infants and young children, with a peak between the ages of 6 months and 3 years[4]. Other studies conducted outside the United States have also confirmed the peak incidence of foreign-body ingestion in children between the ages of 6 months and 6 years, with an equal distribution between boys and girls[5].

In a retrospective study between the years 2010 and 2013, including children under 14 years old, in a pediatric urgency and emergency hospital in Spain, it was found that of the 226,666 consultations, 1608 were for suspected foreign-body ingestion and 970 cases of ingestion mainly of fish bones or coins, among children aged 4.7 years and with slight male predominance (53.9%)[6].

In Brazil, according to data from DATASUS, between January 2010 and December 2019, there were 33,408 hospitalizations for the treatment of "penetration effects of foreign-body ingestion in a natural orifice" in children aged under 9 years, with a predominance of the middle-aged (1–4 years) group. However, there is no way to discriminate, from the data provided by the system, the type of foreign body, as well as the anatomical location of diagnosis, which makes some public policy difficult due to a lack of epidemiological diagnosis (Figure 1).

DISCUSSION

In Brazil, Inmetro tests regulate and inspect the quality of products, among which are children's toys, produced in the country or imported in terms of quality, durability, indication of age group, and risk of accidents. With this protective purpose, the Brazilian Society of Pediatrics created in 1998 the national campaign to prevent accidents and against violence in childhood and adolescence, covering guidance to health professionals through scientific documents.

Most ingested objects pass through the gastrointestinal tract without causing injury; however, they can be lodged in any part of the gastrointestinal tract, which can cause mucosal damage, obstruction, and even perforations. Of inadvertently ingested objects, 10–20% require endoscopic removal, with less than 1% requiring open surgical intervention[7].

The incidence of impaction of foreign bodies varies from 2–15%. The most common regions of these impactions are the cricopharyngeal area, the middle third of the esophagus, lower esophageal sphincter, pylorus, and ileocecal valve. Children may be particularly vulnerable to foreign bodies retained in the esophagus due to their small diameter compared to adolescents and adults[8].

Some anatomical and functional conditions of the esophagus and gastrointestinal tract predispose to greater retention of the ingested object, such as strictures, rings, esophageal dysmotility, achalasia, dysphagia, history of esophageal atresia, tracheoesophageal fistula, or previous gastrointestinal tract surgery[3].

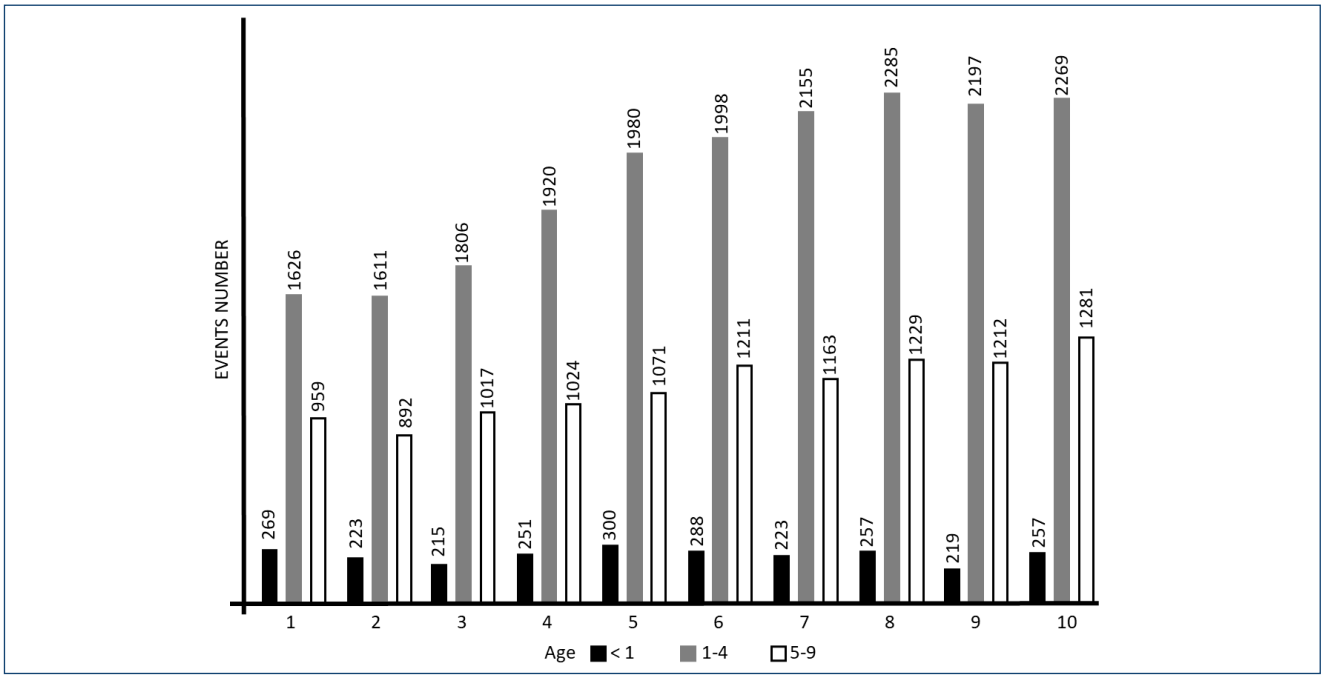


Figure 1. Age group as a function of years.

In particular, batteries, magnets, caustic liquids, and sharp objects pose a significant risk for complications and should have an emergent assessment and, if possible, early removal[3,7]. It is essential to rule out the possibility of ingesting batteries, as their electrical charge can react with saliva, increasing the risk of perforation and requiring emergency removal[7,9]. Severe damage can occur in less than 2 h after esophageal battery impaction[9,10].

Clinical characteristics after foreign-body ingestion

A variety of signs and symptoms have been widely reported in children following ingestion or aspiration of a foreign body; approximately half of the children who ingest foreign bodies remain asymptomatic[6]. When symptoms are present, they are often nonspecific and are based on the type of foreign body, location of the obstruction, the size of the object, and the duration of impaction, promoting more significant symptomatology when they injure or impact the esophagus; older children or adults may complain of odynophagia and sore throat. Babies may experience vomiting, drooling, or cough[11].

There may be symptoms such as fever, recurrent pneumonia due to bronchoaspiration, and even stunting if the object is impacted for a prolonged period in the esophagus[12]. A recent case, described by Mancone et al.[13], reports a clinical condition of a 3-year-old child with dysphagia for 1 year, associated only with hypersalivation and progressive weight loss. The patient was evaluated by several pediatricians, who attributed the signs and symptoms to a clinical condition of severe reflux, leading to repeated attempts at antacid therapy, without clinical improvement. With a radiography, the diagnosis of chronic esophageal impaction was made after unwitnessed foreign-body ingestion.

Akingbola et al.[14] reported an unprecedented case of movement disorder and lethargy in a 10-month-old infant after foreign-body ingestion (medium-sized rock gravel). The authors concluded that foreign-body ingestion in children may mimic intussusception or occult central nervous system disease. Therefore, a hypothesis of foreign-body ingestion in a child with an acute onset of movement disorder and lethargy is necessary.

Diagnosis

Physical examination is normal in most children with foreign-body ingestion (airway and breathing should be evaluated initially)[6]; abnormal findings may include neck swelling or crepitus, suggesting possible esophageal perforation[5], and inspiratory or expiratory stridor, suggesting the possibility of obstruction.

The symptoms of obstruction, erosion, or perforation in the stomach or intestine are abdominal pain, nausea, vomiting, fever, hematochezia, or melena, and it is possible to observe pneumoperitoneum radiographic images, inadequate gas distribution, and distention of loops with liquid level[15]. The diagnosis of foreign-body ingestion is based on three important elements: eyewitness reports obtained from anamnesis, radiographs, and endoscopic findings. Radiographs must be obtained to locate and characterize foreign-body ingestion[7,16] .

However, many sharp objects are not visible on an x-ray, so endoscopy can be performed in view of the patient's complaint and symptoms, even if the x-ray is negative[3]. Digestive endoscopy is considered a diagnostic and therapeutic technique[6]. Ultrasonography is an accurate modality in the detection of radiolucent foreign body. Emergency physicians can be trained to provide a degree of accuracy comparable to more experienced sonographers[17].

Nation and Jiang[18] propose an emergency foreign-body removal protocol that uses a portable metal detector as a screening tool in order to shorten the waiting time for the operating room or hospital discharge, in addition to minimizing exposure to radiation in children, avoiding repeated x-rays.

The batteries appear on radiography as a peripheral double density in the anteroposterior view or as a slanted edge in a lateral view. Ingested magnets must be evaluated with several radiographic views because if two magnets are ingested together, which is particularly dangerous, they can give the false impression of just one magnet in a single view[19].

Management of the foreign body in the pharynx or esophagus

Objects in the oropharynx can often be removed under direct laryngoscopy. Therefore, an asymptomatic child with an esophageal coin, having no underlying abnormalities of the esophagus and trachea, can be observed for 8–24 h with a repeat radiograph[20]. The incidence of esophageal perforation by an impacted foreign body is 2–15%. Foreign bodies in the hypopharynx are not easily removed. There can be disastrous consequences of this impaction when large enough to obstruct the esophagus, larynx, or lower respiratory tract, causing vomiting, suffocation, or death[11].

In the same way, sharp objects such as chicken bones, fish bones, pins, razor blades, needles, and toothpicks, among others, present a greater risk of perforation of the gastrointestinal tract. These deserve special care[3,20] and must be removed within 2 h if patients are symptomatic[4].

Management of foreign bodies in the stomach

Most of the foreign objects in the stomach or duodenum pass through the gastrointestinal tract uneventfully. Considering the risk

of complications, they should be removed endoscopically, if possible. Due to the evolution and increased awareness of the usefulness of upper digestive endoscopy in children, endoscopic removal of foreign-body ingestion can be considered an option, in addition to the traditional method of waiting for spontaneous passage[3].

The NASPGHAN Endoscopy Committee recommends removing the battery or magnets from the gastric cavity within 2 h in symptomatic children, regardless of the size of the foreign body. Regarding swallowed coins, expectant treatment can be performed or removed within 24 h if they cause gastric symptoms[4]. Table 1 describes some recommendations from the NASPGHAN Endoscopy Committee.

The experiment carried out by Anfang et al.[21] suggests that, between the ingestion of the battery and the specialized evaluation by the physician, honey or Carafate should be given to the patient, as they have the potential to reduce the severity of injuries if the battery is retained in the esophagus. Honey is a weak acid, with a sweet and viscous taste found in most homes. It provides additional protection acting as a physical barrier, given its high consistency; however, it should not be used in children aged under 1 year. Carafate suspension is a weak acid, approved by the Food and Drug Administration for the treatment of duodenal ulcers, but not available in the Brazilian market.

Management of foreign body in the intestine

Most foreign bodies in the small intestine pass spontaneously without complications. Therefore, caregivers should be advised to check for foreign-body ingestion in children's stools. If the object is not eliminated within a week, it is necessary to obtain an x-ray to identify the precise location of the swallowed foreign body[22]. However, a less liberal approach would be to follow the object with serial radiographs and, if it does not move distally within 24 h, consider intervention for removal[23].

If a single magnet has been ingested, it can be followed up conservatively, followed by serial radiographs[24]. A laxative solution, such as PEG 3350 (polyethylene glycol), can be used to help intestinal transit and magnet exit[3,19]. Ingestion of multiple magnets is very dangerous because they can attract each other through the intestinal walls, leading to pressure necrosis, intestinal ulceration and perforation, and fistula formation[24].

If the magnets were past the stomach and the patient is asymptomatic (no sign of obstruction or perforation), the magnets should be removed by enteroscopy or colonoscopy[24]. Symptomatic cases with vomiting, severe abdominal pain, intestinal bleeding, or fever should be evaluated by the pediatric surgery team[3,19].

The protocol of care for foreign-body ingestion in children, based on a literature scan, is available and can be downloaded at link (https://drive.google.com/file/d/1osGdaXY5HwzySxNKA2RMGLBLZTeNWyk9/view).

CONCLUSIONS

Protocol of care for foreign-body ingestion in children depends on the object ingested, time of ingestion, symptoms, and local epidemiological context. This study provides some suggestions for decision-making in the conduct of health professionals.

Table 1. Endoscopic intervention after foreign-body ingestion.

Object	Localization	Symptomatology	Removal
Currency	*Esophagus*	Yes No	Immediate Mediate
	Stomach	Yes No	Mediate Elective
Battery	Esophagus	Independent	Immediate
	Stomach	Yes No	Immediate Mediate
Magnet	Esophagus	Yes No	Immediate Mediate
	Stomach	Yes No	Immediate Mediate
Pointed foreign body	Esophagus	Independent	Immediate
	Stomach	Yes No	Immediate Mediate
Large foreign body	Esophagus	Independent	Mediate
	Stomach	Independent	Mediate

Immediate <2 h; Mediate <24 h; Elective >24 h; Large foreign body >2 cm.

ACKNOWLEDGMENTS

To the Programa de Pós-Graduação em Ensino em Ciências e Saúde (PPGECS), and Pró-Reitoria de Pós-Graduação (PROPESQ) at the Universidade Federal do Tocantins.

AUTHORS' CONTRIBUTIONS

DSSJ: Conceptualization, Data curation, Formal Analysis, Funding acquisition, Investigation, Methodology, Project administration, Resources, Supervision, Validation, Visualization, Writing – original draft, Writing – review & editing. **JRM:** Conceptualization, Data curation, Formal Analysis, Funding acquisition, Investigation, Methodology, Project administration, Resources, Supervision, Validation, Visualization, Writing – original draft, Writing – review & editing. **ABL:** Conceptualization, Data curation, Formal Analysis, Funding acquisition, Investigation, Methodology, Project administration, Resources, Supervision, Validation, Visualization, Writing – original draft, Writing – review & editing. **LSS:** Conceptualization, Data curation, Formal Analysis, Funding acquisition, Investigation, Methodology, Project administration, Resources, Supervision, Validation, Visualization, Writing – original draft, Writing – review & editing. **ESM:** Conceptualization, Data curation, Formal Analysis, Funding acquisition, Investigation, Methodology, Project administration, Resources, Supervision, Validation, Visualization, Writing – original draft, Writing – review & editing. **LRN:** Conceptualization, Data curation, Formal Analysis, Funding acquisition, Investigation, Methodology, Project administration, Resources, Supervision, Validation, Visualization, Writing – original draft, Writing – review & editing. **LSSN:** Conceptualization, Data curation, Formal Analysis, Funding acquisition, Investigation, Methodology, Project administration, Resources, Supervision, Validation, Visualization, Writing – original draft, Writing – review & editing. **AMB:** Conceptualization, Data curation, Formal Analysis, Funding acquisition, Investigation, Methodology, Project administration, Resources, Supervision, Validation, Visualization, Writing – original draft, Writing – review & editing. **AP-S:** Conceptualization, Data curation, Formal Analysis, Funding acquisition, Investigation, Methodology, Project administration, Resources, Supervision, Validation, Visualization, Writing – original draft, Writing – review & editing. **FRPQ:** Conceptualization, Data curation, Formal Analysis, Funding acquisition, Investigation, Methodology, Project administration, Resources, Supervision, Validation, Visualization, Writing – original draft, Writing – review & editing.

REFERENCES

1. Zhang S, Cui Y, Gong X, Gu F, Chen M, Zhong B. Endoscopic management of foreign bodies in the upper gastrointestinal tract in South China: a retrospective study of 561 cases. Dig Dis Sci. 2010;55(5):1305-12. https://doi.org/10.1007/s10620-009-0900-7
2. Kay M, Wyllie R. Pediatric foreign bodies and their management. Curr Gastroenterol Rep. 2005;7(3):212-8. https://doi.org/10.1007/s11894-005-0037-6
3. Wright CC, Closson FT. Updates in pediatric gastrointestinal foreign bodies. Pediatr Clin North Am. 2013;60(5):1221-39. https://doi.org/10.1016/j.pcl.2013.06.007
4. Kramer RE, Lerner DG, Lin T, Manfredi M, Shah M, Stephen TC, et al. Management of ingested foreign bodies in children: a clinical report of the NASPGHAN Endoscopy Committee. J Pediatr Gastroenterol Nutr. 2015;60(4):562-74. https://doi.org/10.1097/MPG.0000000000000729
5. Bharathi M, Satish K, Vikram V, Kiruthiga M. A study on radio opaque foreign body in digestive tract of children. Front Pediatr. 2018;4(2):352-5. https://doi.org/10.18203/issn.2454-5929.ijohns20180503
6. Lobeiras A, Zugazabeitia A, Uribarri N, Mintegi S. Consultas relacionadas con la ingesta de un cuerpo extraño en Urgencias [Emergency department consultations due to foreign body ingestion]. An Pediatr (Barc). 2017;86(4):182-7. https://doi.org/10.1016/j.anpedi.2015.11.014
7. Kim FS, Scott AR, Ramakrishna J. Case 2: Dysphagia to Solid Foods in a 17-month-old Boy. Pediatr Rev. 2017;38(10):488-9. https://doi.org/10.1542/pir.2016-0232
8. McNeill MB, Sperry SL, Crockett SD, Miller CB, Shaheen NJ, Dellon ES. Epidemiology and management of oesophageal coin impaction in children. Dig Liver Dis. 2012;44(6):482-6. https://doi.org/10.1016/j.dld.2012.01.001
9. Jatana KR, Rhoades K, Milkovich S, Jacobs IN. Basic mechanism of button battery ingestion injuries and novel mitigation strategies after diagnosis and removal. Laryngoscope. 2017;127(6):1276-82. https://doi.org/10.1002/lary.26362
10. Litovitz T, Whitaker N, Clark L, White NC, Marsolek M. Emerging battery-ingestion hazard: clinical implications. Pediatrics. 2010;125(6):1168-77. https://doi.org/10.1542/peds.2009-3037
11. Chen G, Luo Y, Pan H, Teng Y, Liang Z, Li L. Uncommon foreign body in the hypopharynx: A case report. Medicine (Baltimore). 2018;97(26):e11242. https://doi.org/10.1097/MD.0000000000011242
12. Yatuhara CR, Carvalho VEL. Pronto-socorro "corpo estranho em trato gastrointestinal." In: Schvartsman C, Reis AG, Farhat SCL, editors. Pronto-socorro. 3rd ed. São Paulo: Manole Editora; 2018.
13. Mancone S, Tummala N, Pranikoff T, Plonk DP. Case 4: Chronic Dysphagia and Weight Loss in a 3-year-old Boy. Pediatr Rev. 2019;40(4):202-4. https://doi.org/10.1542/pir.2017-0335
14. Akingbola O, Singh D, Blecker U. Movement Disorder Associated With Foreign Body Ingestion. Pediatrics. 2017;139(4):e20161967. https://doi.org/10.1542/peds.2016-1967
15. Uyemura MC. Foreign body ingestion in children. Am Fam Physician. 2005;72(2):287-91. PMID: 16050452
16. Green SS. Ingested and Aspirated Foreign Bodies. Pediatr Rev. 2015 Oct;36(10):430-6;quiz437. https://doi.org/10.1542/pir.36-10-430

17. Orlinsky M, Knittel P, Feit T, Chan L, Mandavia D. The comparative accuracy of radiolucent foreign body detection using ultrasonography. Am J Emerg Med. 2000;18(4):401-3. https://doi.org/10.1053/ajem.2000.7315

18. Nation J, Jiang W. The utility of a handheld metal detector in detection and localization of pediatric metallic foreign body ingestion. Int J Pediatr Otorhinolaryngol. 2017;92:1-6. https://doi.org/10.1016/j.ijporl.2016.10.035

19. Hussain SZ, Bousvaros A, Gilger M, Mamula P, Gupta S, Kramer R, et al. Management of ingested magnets in children. J Pediatr Gastroenterol Nutr. 2012;55(3):239-42. https://doi.org/10.1097/MPG.0b013e3182687be0

20. Kim SH, Kwon OY, Park KN, Hwang UJ. Leg lateral reach test: The reliability and correlation with thoraco-lumbo-pelvic rotation range. J Sci Med Sport. 2017;20(1):2-5. https://doi.org/10.1016/j.jsams.2016.04.006

21. Anfang RR, Jatana KR, Linn RL, Rhoades K, Fry J, Jacobs IN. pH-neutralizing esophageal irrigations as a novel mitigation strategy for button battery injury. Laryngoscope. 2019;129(1):49-57. https://doi.org/10.1002/lary.27312

22. Chung JH, Kim JS, Song YT. Small bowel complication caused by magnetic foreign body ingestion of children: two case reports. J Pediatr Surg. 2003;38(10):1548-50. https://doi.org/10.1016/s0022-3468(03)00514-1

23. Louie MC, Bradin S. Foreign body ingestion and aspiration. Pediatr Rev. 2009;30(8):295-301,quiz301. https://doi.org/10.1542/pir.30-8-295

24. Lee JH. Foreign body ingestion in children. Clin Endosc. 2018;51(2):129-36. https://doi.org/10.5946/ce.2018.039

ORIGINAL ARTICLE

https://doi.org/10.1590/1806-9282.20220375

Evaluation of the promoter methylation status of hypoxia factor 3A and interleukin-6 genes and expression levels of mir-130b and mir-146b in childhood obesity

Esra Tekcan[1*], Nurten Kara[1], Hasan Murat Aydın[2], Ümmet Abur[3], Mohsen Abbaszadeh[3]

SUMMARY

OBJECTIVE: Obesity, which causes many serious diseases, is increasing exponentially in childhood across the world. Epigenetic changes, as well as genetics, play an important role in the process of adipogenesis. Therefore, we aimed to examine the expression levels of obesity-related MicroRNA-130b and MicroRNA-146b and the methylation status of hypoxia factor 3A and interleukin-6 genes associated with obesity in children.

METHODS: This study was performed with 98 individuals (49 obese children and 49 controls) whose DNA was isolated from peripheral blood. Gene promoter methylations were analyzed by methylation-specific Polymerase chain reaction. In addition, expression levels of MicroRNAs were determined by quantitative real-time Polymerase chain reaction in 30 children (15 obese children and 15 controls).

RESULTS: Methylation status of interleukin-6 gene was 93.9% in obese children (n=46/49) and 100% (n=49/49) in control group (p>0.05). There was no methylation for hypoxia factor 3A gene (p>0.05). As a result of the study, there was no statistically significant difference in terms of methylation status for hypoxia factor 3A and interleukin-6 genes in the obese group compared to the control group. However, we found that expression levels of MicroRNA-130b (p<0.01) and MicroRNA-146b (p<0.001) were higher in the obese group.

CONCLUSIONS: Results support that MicroRNA-130b and MicroRNA-146b are potential biomarkers for the prevention and early diagnosis of obesity. This is the first study on childhood obesity in the Middle Black Sea region of Turkey. We believe that the results obtained by expanding the studies in our country and neighboring countries will be more decisive.

KEYWORDS: DNA methylation. Epigenomics. MicroRNA. Obesity.

INTRODUCTION

Obesity is defined as abnormal or excessive fat accumulation that may impair health and cause morbidity and finally mortality by affecting many organs[1]. It is also an increasingly growing problem in childhood worldwide and it is a serious nutritional disorder that may lead to serious health problems in future if no measures are taken in early stage[2]. In 2016, approximately 40 million children under the age of 5, as well as 340 million children between the ages of 5 and 19 years, were affected by overweight or obesity[3]. According to COSI-TUR (Childhood Obesity Surveillance Initiative), the rate of overweight was 14.6% and that of obesity was 9.9% in primary school second-grade children in Turkey in 2016[4]. This rapid increase in obesity is not only due to genetic factors but also due to environmental factors that cause epigenetic effects[5].

Hypoxia occurs due to the decrease in the amount of blood entering adipocytes with the growth of adipose tissue in obese subjects. Methylation of *hypoxia factor 3A* (*HIF3A*) gene is related to body mass index (BMI) and adiposity. It was also reported that obesity is associated with a low degree of chronic inflammation and increased interleukin-6 (IL-6) levels[5,6]. It is known that miRNAs play an important role in adipose tissue differentiation, proliferation, and lipid and glucose metabolism[7]. Identifying obesity-associated miRNAs that cause inadequate or overexpression of proteins in cells may be a therapeutic target for future treatment by using anti-miRNA oligonucleotides targeting these miRNAs. There are several other miRNAs associated with obesity; however, due to limited cost, we compared the expression levels of only two miRNAs in this study.

The tissue-specific epigenetic is subject to stunning changes during childhood development. A study has reported a correlation between methylation in adipose tissue and peripheral blood in adults, but it has not proved whether this holds true for children[7]. Therefore, we aimed to observe the methylation

[1]Ondokuz Mayis University, Faculty of Medicine, Department of Medical Biology – Samsun, Turkey.
[2]Ondokuz Mayis University, Faculty of Medicine, Department of Pediatric Endocrinology – Samsun, Turkey.
[3]Ondokuz Mayis University, Faculty of Medicine, Department of Medical Genetics – Samsun, Turkey.
*Corresponding author: esrabkr@hotmail.com

Conflicts of interest: the authors declare there is no conflicts of interest. Funding: Scientific Research Project Office of Ondokuz Mayıs University, Turkey (project no: PYO.TIP.1904.18.003).
Received on May 26, 2022. Accepted on June 24, 2022.

status of *HIF3A and IL-6* genes and expression levels of miR-130b and miR-146b, which are thought to be associated with childhood obesity from peripheral blood.

As methylation is more tissue specific, it was necessary to use adipose tissue for most genes. In this study, blood sample was used in order to look for the methylation of obesity-related genes whose expression can be observed in the blood. Our study individuals involved adolescent in the Central Black Sea region and present previously unexplored data. It aims to support the data presented in previous studies in different populations. This is the first study to epigenetically examined *HIF3A and IL-6* genes among Turkish obese children.

METHODS

Participants and peripheral blood collection

This study was carried out among children aged 6–12 years who were diagnosed with obesity (BMI>95th) before puberty period and who visited Ondokuz Mayıs University Faculty of Medicine Pediatric Endocrinology from the Middle Black Sea region of Turkey. A total of 98 children (49 obese children and 49 healthy controls) were selected to examine methylation status. The sample size was determined by statistical power analysis. To evaluate obese and control DNA methylations, 20 obese patients and 20 controls were selected, with 97% power to detect d=0.122 difference (with a maximum deviation of 0.11) at the 95% confidence interval. For miRNA expression analysis, a total RNA of 30 (15 obese subjects and 15 controls) samples were isolated from the whole peripheral blood samples of 98 volunteers. Again, 12 obese patients and 12 controls were calculated for 96% power to detect d=0.138 difference (with a maximum deviation of 0.15) at the 94% confidence interval to evaluate obese and control miRNA expression. This study was approved by Ethics Committee of the OMÜ KAEK (registration number 2016/301). In this study, chronic disease, chronic drug use, and endocrine, metabolic, or genetic short status were determined as exclusion criteria.

DNA isolation and bisulfite conversion and methylation-specific polymerase chain reaction

DNA was isolated from peripheral blood samples using Pure Link® Genomic DNA Mini Kit (Invitrogen, USA). EpiJET Bisulfite Conversion Kit (Thermo Fisher Scientific, Lithuania) was used for bisulfite modification of DNA. Specific primers for methylation-specific PCR analysis were designed with the "MethPrimer" database (Table 1). DreamTaq™ Hot Start DNA polymerase was used (Thermo Fisher Scientific). A 25-µl total volume of PCR reaction conditions was as follows:

For *IL-6*: initial denaturation was at 97°C for 5 min, followed by 40 cycles of 96°C for 45 s, 56°C for 45 s, and 72°C for 60 s. The final extension was at 72°C for 7 min.

For *HIF3A*: initial denaturation was at 98°C for 10 min, followed by 40 cycles of 97°C for 45 s, 60°C for 45 s, and 72°C for 70 s. The final extension was at 72°C for 7 min.

Agarose gel electrophoresis

A 2% of micropore (Prona, Nu micropor) agarose gel was prepared to display the MSP product. A 50-bp DNA marker (Thermo Fisher Scientific, Lithuania) was used as the marker and gel and viewed using UV transilluminator.

RNA extraction and quantitative real-time polymerase chain reaction

Total RNA was isolated from whole peripheral blood samples using Quick-RNA™ Whole Blood kit (Zymo Research, USA). Total RNA was reverse transcribed to cDNA using Ipsogen® RT Kit 33, V1 kit (QIAGEN, Germany). The reaction mixture was 15 µl. Incubation conditions were as follows: 16°C for 30

Table 1. MSP sequences, hybridization temperatures, and expected amplicon sizes.

Primer name	Base sequence 5′-3′	Base number	Temp. (°C)	Amplicon size (bp)
IL-6 MSP-F	ATAGGTAAGATATTAGGTGAATCGA	25	56	166
IL-6 MSP-R	TTTCTAAAACTATTATAAAAATAAAACGTA	30	53	166
IL-6 USP-F	ATAGGTAAGATATTAGGTGAATTGA	25	55	166
IL-6 USP-R	TTTCTAAAACTATTATAAAAATAAAACATA	30	52	166
HIF-3A MSP-F	TAGGTTTGGCGTGGTATAGTTAATC	25	60	259
HIF-3A MSP-R	CCCGAAACGTTCTTAACTCG	20	57	259
HIF-3A USP-F	TTTAGGTTTGGTGTGGTATAGTTAATTG	28	59	262
HIF-3A USP-R	CCCCAAAACATTCTTAACTCAC	22	57	262

HIF-3A: hypoxia factor 3A; MSP: methylation-specific primer; USP: unmethylated-specific primer; F: forward; R: reverse; IL-6: interleukin-6. Primers designed with the "MethPrimer" database http://www.urogene.org/cgi-bin/methprimer/methprimer.cgi.

min, 42°C for 30 min, and 85°C for 5 min (Thermal Cycler GeneAmp PCR System 9700, Applied Biosystems, USA). For miR-146b and miR-130b qRT-PCR analysis, Taqman™ MicroRNA Assay (Applied Biosystems) and Premix Ex Taq™ master mix (Perfect Real Time, Takara, Japan) were used. RNA was normalized using the *ABL* housekeeping gene (İpsogen, BCR-ABL1 Mbcr IS-MMR) in each sample[8]. Using standards with a known number of molecules, one can establish a standard curve and determine the amount of target present in the test sample. To ensure accurate standard curves, we use four standard dilutions for *ABL*. The kit also includes an IS-MMR calibrator allowing conversion of results to the international scale. For *ABL* gene, raw CT values obtained from plasmid standard dilutions are plotted according to the log copy number. We compare the *ABL* gene with known copy number in the kit with our miRNAs whose copy number is unknown, and we obtain information about the copy number. We compare our *ABL*-normalized obese and control miRNAs with each other. As a result, with CT values, we obtained information about copy numbers increase or decrease of obese individuals compared to controls.

Rotor-gene Q 5 PLEX HRM (Germany, USA) device used for qRT-PCR. The miR-130b microRNA sequence is ACUCUUUCCCUGUUGCACUAC, while miR-146b microRNA sequence is UGAGAACUGAAUUCCAUAGGCUG (http://www.mirbase.org). The relative abundance of each miRNA transcript in each sample was determined using the comparative $2^{-\Delta\Delta Ct}$ method and an endogenous housekeeping control gene. Cycle threshold (CT) values of participants (obese and control) and increase or decrease ratio of expression levels in miR-146b-5p/*ABL* and miR-130b/*ABL* were calculated according to the Livak's formula[9]:

$$\Delta CT = CT_{\text{target gene}} - CT_{\text{reference gene}}$$
$$\Delta\Delta CT = \Delta CT_{\text{obese}} - \Delta CT_{\text{control}}$$

Statistical analysis

The relationship between parameters was evaluated using Fisher's exact test using OpenEpi version 3.01 (last updated: May 6, 2013). SPSS software was used for data analyzing (version 22.0, SPSS Inc., Chicago, IL, USA). The statistical significance of miRNA expression was analyzed by the Student's t-test, considering statistically significant at $p<0.05$.

RESULTS

Hypoxia factor 3A and interleukin-6 promoter methylation analysis results

The mean age of 49 obese groups (22 females, 27 males) whose methylation profile was analyzed was 10.0±1.9 years, and the mean age of 49 healthy controls (29 females, 20 males) was 9.2±2.0 years. *HIF3A* gene methylation was not detected in either group. *IL-6* gene methylation was detected in 93.9% (46/49, $p>0.05$) of the obese group and 100% (49/49, $p>0.05$) of the control group. According to results of the tests, there was no statistical significance between the patient and control groups in terms of the promoter methylation profile of *HIF-3A* and *IL-6* genes ($p>0.05$, Table 2).

MicroRNA-146b and microRNA-130b quantitative real-time-polymerase chain reaction analysis results

The expression of obese miR-146b according to the control group was increased in 14 of 15 children, with an average 25.5±17.3-fold ($p<0.001$). Similarly, the expression of miR-130b increased in 14 of 15 obese children, with an average 8.5±5.3-fold ($p<0.01$).

The qRT-PCR analysis results of the expression levels of miR-146b and miR-130b in obese and control groups were given in Table 3 and Figure 1.

DISCUSSION

One of the most studied mechanisms as an epigenetic determinant of childhood obesity is DNA methylation[2]. In many studies, there was evidence showing that the *HIF3A* gene is associated with anthropometric parameters in childhood[2]. Previous studies have reported that methylation of the *HIF3A*

Table 2. Distribution of hypoxia factor 3A and interleukin-6 genes promoter methylation profiles in the obese and control groups (obese n=49, control n=49).

Gene	Group	Number (n)	Methylated (%)	Unmethylated (%)	p-value
HIF3A	Obese	49	0	49 (100)	>0.05*
HIF3A	Control	49	0	49(100)	
IL-6	Obese	49	46 (93.9)	3 (6.1)	>0.05*
IL-6	Control	49	49 (100)	0	

HIF-3A: hypoxia factor 3A; IL-6: interleukin-6. *Statistically significant.

gene is associated with BMI and adiposity[6,10]. In our study, we observed that there was no significant difference in methylation status of *HIF3A* genes in the obese group compared to the control group (p<0.01). The temporal sequence between epigenetic changes and the onset of childhood obesity is uncertain because epigenetics may be altered by a wide range of stimuli, including metabolic changes associated with obesity itself. Most of the studies included in the review use a cross-sectional design that makes it impossible to decipher the temporal order of events. Some DNA methylation studies have used longitudinal designs or statistical techniques such as Mendelian randomization to resolve this relationship[2]. In the ALSPAC (avon longitudinal study of parents and children) cohort, childhood BMI was associated with methylation at *HIF3A* gene in adolescence, but childhood methylation was not robustly associated with BMI in adolescence, and based on Mendelian randomization, *HIF3A* methylation did not play a causal role on BMI[2]. The children participating in our study were in pre-adolescent, so we may not have observed *HIF3A* gene methylation in our study.

Cytokines production causes an increase in white adipose tissue in obesity subjects[5]. In our study, there was no significant difference in methylation status of *IL-6* gene in the obese group compared to the control group (p<0.01), similar to results obtained by Zhang et al.[11]. Na et al.[12] reported that *IL-6* methylation can be used as a molecular biomarker for the assessment of obesity risk, finding which is in contrast to our results. The mechanism that can explain the increased IL-6 levels in obese can be attributed to the ability of fat tissue to produce and secrete IL-6[13]. In our study, DNA methylation may not reflect the actual methylation profile since DNA methylation was analyzed from peripheral blood, not directly from the affected adipose tissue. miRNAs, which are considered to be epigenetically important in regulating the expression of genes, play an active role in insulin secretion, cholesterol biosynthesis, fat metabolism, and adipogenesis.

In our study, miRNA profiles were examined in 30 children (15 obese and 15 control) whose proficiency was supported by power analysis due to project budget limitations. However, circulating mir-130b and mir-146b expression levels were found to be high in obese children, although the number of samples studied was limited. Mansego et al.[14] in 24 children (12 obese children and 12 controls) and Quyang et al.[15] in a total of 12 children (6 obese children and 6 controls) reported that the miRNA profiles were associated with early childhood obesity from peripheral blood.

Previous study showed that miR-130b expression in abdominal subcutaneous adipose tissue and plasma was low in obese. Lacomino and Siani[16] concluded that the level of miR-130b in the blood was found to be higher in obese children, as in our study (p<0.01). Wang et al.[17] determined miR-130b as a potential biomarker for overweight, hypertriglyceridemia, and metabolic syndrome. TGF-β signaling pathway is significant in the arrangement of energy homeostasis and studies suggest that miR-130b secreted from adipose tissues mediate the metabolic regulatory effect of TGF-β and TGF-β can stimulate miR-130b secretion from adipocytes[17]. This explains the 8.5±5.3-fold increase in miR-130b expression in the obese group in our study. Prtas-Puig et al.[18] proved that circulating miRNAs were unregulated in prepubescent obese children,

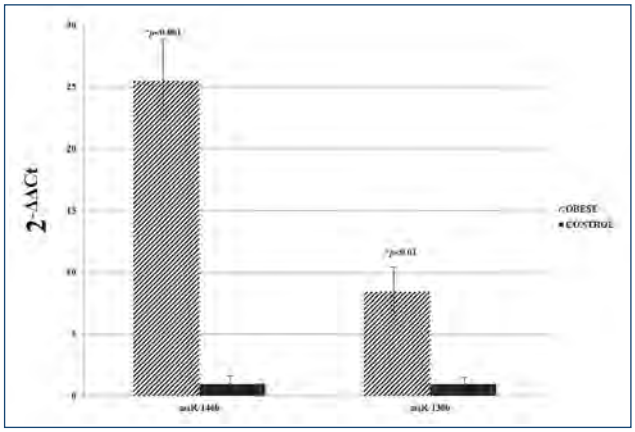


Figure 1. Graphical representation of $2^{-\Delta\Delta Ct}$ averages for the obese and control groups.

Table 3. Expression levels of MicroRNA-130b and MicroRNA-146b in the obese and control groups.

		CT	*ABL* CT	ΔCT (Avg. *miR* CT– Avg. *ABL* CT)	ΔΔCT (Avg. ΔCT obese– Avg. ΔCT control)	Normalized miR Amount relative to control $2^{-\Delta\Delta Ct}$	p-value
MicroRNA-130b	Obese	26.5	20.6	5.8	-3.1	8.5*	0.008556 (*p<0.01)
	Control	31.4	22.4	8.9	0	1	
MicroRNA-146b	Obese	20.9	19.1	1.7	-4.6	25.5*	0.000001 (*p<0.001)
	Control	25.5	19.0	6.4	0	1	

CT: cycle threshold; ABL: abelson tyrosine-protein kinase. *Statistically significant.

which is similar to our results. Therefore, early detection of abnormal miRNA profile will be useful in the early diagnosis of obesity.

In addition, miR-146b expressed during adipogenic differentiation and its level increased in overweight, obese, and high fat diet mice[19]. The fact that the miR-146b expression level of obese individuals was 25.5±17.3-fold increase higher than the control group in our study supports this situation ($p<0.001$). Overexpression of *Kruppel-like factor 7 (KLF7)* inhibits expression of some adipogenic transcription factor genes and suppresses adipogenesis[19]. The inhibitory effects of miR-146b on *KLF7* expression and experimentally demonstrated that *KLF7* is the direct target of miR-146b[19]. Therefore, increased mir-146b expression in obesity supports adipogenesis indirectly. Sharma et al.[20] confirmed that the expression of miR-146a and miR-146b significantly correlated with BMI in adipose tissues. Studies indicate that miR-146b can make significant contributions to obesity formation in children[21]. Also, obese mice who were administered anti-miR-146b for 3 days to destroy miR-146b have shown losing weight[6]. These results indicate that miR-146b may be a potential target for the treatment of obesity.

CONCLUSION

The role of epigenetic pathways in the prevention and treatment of increasingly common obesity is one of the current research areas. More studies are needed in both larger and different populations to support the results.

ACKNOWLEDGMENT

This study was supported by Scientific Research Project Office of Ondokuz Mayıs University, Turkey (project no: PYO. TIP.1904.18.003).

AUTHORS' CONTRIBUTION

ET: Conceptualization, Data curation, Formal analysis, Investigation, Methodology, Resources, Software, Validation, Writing – original draft. **NK:** Conceptualization, Investigation, Funding acquisition, Methodology, Supervision, Project administration. **HMA:** Funding acquisition, Resources, Software, Supervision, Visualization. **ÜA:** Data curation, Funding acquisition, Software, Validation. **MA:** Data curation, Funding acquisition, Formal analysis, Resources, Software.

REFERENCES

1. Gallardo-Escribano C, Buonaiuto V, Ruiz-Moreno MI, Vargas-Candela A, Vilches-Perez A, Benitez-Porres J, et al. Epigenetic approach in obesity: DNA methylation in a prepubertal population which underwent a lifestyle modification. Clin Epigenetics. 2020;12(1):144. https://doi.org/10.1186/s13148-020-00935-0
2. Alfano R, Robinson O, Handakas E, Nawrot TS, Vineis P, Plusquin M. Perspectives and challenges of epigenetic determinants of childhood obesity: A systematic review. Obes Rev. 2022;23(Suppl 1):e13389. https://doi.org/10.1111/obr.13389
3. Apperley LJ, Blackburn J, Erlandson-Parry K, Gait L, Laing P, Senniappan S. Childhood obesity: A review of current and future management options. Clin Endocrinol (Oxf). 2022 Mar;96(3):288-301. https://doi.org/10.1111/cen.14625
4. Yılmazbaş P, Gökçay G. Childhood obesity and its prevention. J Child 2018;18(3):103-12. 10.5222/j.child.2018.59389
5. Cerdó T, García-Santos JA, Bermúdez MG, Campoy C. The role of probiotics and prebiotics in the prevention and treatment of obesity. Nutrients. 2019;11(3):635. https://doi.org/10.3390/nu11030635
6. Wang S, Song J, Yang Y, Zhang Y, Wang H, Ma J. HIF3A DNA methylation is associated with childhood obesity and ALT. PLoS One. 2015;10(12):e0145944.https://doi.org/10.1371/journal.pone.0145944
7. McGregor RA, Choi MS. microRNAs in the regulation of adipogenesis and obesity. Curr Mol Med. 2011;11(4):304-16. https://doi.org/10.2174/156652411795677990
8. Tuncer SB, Akdeniz D, Celik B, Kilic S, Sukruoglu O, Avsar M, et al. The expression levels of miRNA-15a and miRNA-16-1 in circulating tumor cells of patients with diffuse large B-cell lymphoma. Mol Biol Rep. 2019;46(1):975-80. https://doi.org/10.1007/s11033-018-4554-4
9. Livak KJ, Schmittgen TD. Analysis of relative gene expression data using real-time quantitative PCR and the 2(-Delta Delta C(T)) Method. Methods. 2001;25(4):402-8. https://doi.org/10.1006/meth.2001.1262
10. Lee S, Kim HJ, Han S, Jeon JP, Park SI, Yu HY, et al. Positive correlation of cg16672562 methylation with obesity-related traits in childhood obesity, and its independence with underlying HIF3A (hypoxia-inducible factor 3a) genetic background. Oncotarget. 2017;8(40):67473-81. https://doi.org/10.18632/oncotarget.18707
11. Zhang JF, Fu WM, He ML, Wang H, Wang WM, Yu SC, et al. MiR-637 maintains the balance between adipocytes and osteoblasts by directly targeting Osterix. Mol Biol Cell. 2011;22(21):3955-61. https://doi.org/10.1091/mbc.E11-04-0356
12. Na YK, Hong HS, Lee WK, Kim YH, Kim DS. Increased methylation of interleukin 6 gene is associated with obesity in Korean women. Mol Cells. 2015;38(5):452-6. https://doi.org/10.14348/molcells.2015.0005
13. Wisse BE. The inflammatory syndrome: the role of adipose tissue cytokines in metabolic disorders linked to obesity. J Am Soc Nephrol. 2004;15(11):2792-800. https://doi.org/10.1097/01.ASN.0000141966.69934.21

14. Mansego ML, Garcia-Lacarte M, Milagro FI, Marti A, Martinez JA; GENOI members. DNA methylation of miRNA coding sequences putatively associated with childhood obesity. Pediatr Obes. 2017;12(1):19-27. https://doi.org/10.1111/ijpo.12101

15. Ouyang S, Tang R, Liu Z, Ma F, Li Y, Wu J. Characterization and predicted role of microRNA expression profiles associated with early childhood obesity. Mol Med Rep. 2017;16(4):3799-806. https://doi.org/10.3892/mmr.2017.7118

16. Iacomino G, Siani A. Role of microRNAs in obesity and obesity-related diseases. Genes Nutr. 2017;12:23. https://doi.org/10.1186/s12263-017-0577-z

17. Wang YC, Li Y, Wang XY, Zhang D, Zhang H, Wu Q, et al. Circulating miR-130b mediates metabolic crosstalk between fat and muscle in overweight/obesity. Diabetologia. 2013;56(10):2275-85. https://doi.org/10.1007/s00125-013-2996-8

18. Prats-Puig A, Ortega FJ, Mercader JM, Moreno-Navarrete JM, Moreno M, Bonet N, et al. Changes in circulating microRNAs are associated with childhood obesity. J Clin Endocrinol Metab. 2013;98(10):E1655-60. https://doi.org/10.1210/jc.2013-1496

19. Cheng Z, Zheng L, Almeida FA. Epigenetic reprogramming in metabolic disorders: nutritional factors and beyond. J Nutr Biochem. 2018;54:1-10. https://doi.org/10.1016/j.jnutbio.2017.10.004

20. Sharma NK, Varma V, Ma L, Hasstedt SJ, Das SK. Obesity associated modulation of miRNA and Co-regulated target transcripts in human adipose tissue of non-diabetic subjects. Microrna. 2015;4(3):194-204. https://doi.org/10.2174/2211536604666151103121817

21. Ahn J, Lee H, Jung CH, Jeon TI, Ha TY. MicroRNA-146b promotes adipogenesis by suppressing the SIRT1-FOXO1 cascade. EMBO Mol Med. 2013;5(10):1602-12. https://doi.org/10.1002/emmm.201302647

ORIGINAL ARTICLE

https://doi.org/10.1590/1806-9282.20220405

Whole-Exome Sequencing (WES) results of 50 patients with chronic kidney diseases: a perspective of Alport syndrome

Cüneyd Yavaş[1,2,3*], Cemal Ün[2], Evrim Çelebi[3], Alper Gezdirici[3], Mustafa Doğan[3], Ezgi Gökpinar İli[3], Tunay Doğan[3], Nehir Özdemir Özgentürk[4]

SUMMARY

OBJECTIVE: Chronic kidney disease (CKD) remains one of the major common health problems, and the number of people affected by the disease is progressively increasing in Turkey and worldwide. This study aimed to investigate molecular defects in Alport syndrome (AS) and other genes in patients with clinically suspected CKD using whole-exome sequencing (WES).

METHODS: Patients with clinical suspicion of CKD were included in the study. Molecular genetic analyses were performed on genomic DNA by using WES.

RESULTS: A total of 15 with 5 different pathogenic or likely pathogenic variants were identified in CKD patients, with a diagnostic rate of 30%. Eight variants of uncertain significance were also detected. In this study, 10 variants were described for the first time. As a result, we detected variants associated with CKD in our study population and found AS as the most common CKD after other related kidney diseases.

CONCLUSIONS: Our results suggest that in heterogeneous diseases such as CKD, WES analysis enables accurate identification of underlying molecular defects promptly. Although CKD accounts for 10–14% of all renal dysfunction, molecular genetic diagnosis is necessary for optimal long-term treatment, prognosis, and effective genetic counseling.

KEYWORDS: Chronic kidney disease. Alport syndrome. Variant. Whole-exome sequencing.

INTRODUCTION

Chronic kidney disease (CKD) is a major public health problem, with increasing incidence and prevalence[1] and affecting more than 10% of people worldwide[2]. CKD is associated with disease enclosing many disorders such as metabolic and end-stage renal failure and is a leading cause of death[3], showing one of the highest increases in mortality for 10 years[4]. However, it is generally not recognized by people and specialists[5]. Moreover, clinical trials in nephrology are still insufficient for diagnosis, which has limited therapeutic options to alter disease progression and high costs for the health system[6].

The description of hereditary (genetic) risk factors for CKD can enable early detection and increase our understanding of the pathogenesis of the disease. Genetic factors include both Mendelian (monogenic) and polygenic risk. Recent clinical sequencing studies have detected diagnostic variants in 10–25% of patients of various CKD populations, suggesting a high burden of Mendelian disorders among patients with nephropathy[7].

Alport syndrome (AS) is the most common CKD after other related kidney diseases[8]. Recent and comprehensive studies have reported that most patients with CKD have variants in AS-related genes[9]. AS is a well-defined genetic disorder characterized by kidney failure, hematuria, hearing impairment, and vision abnormalities[10] and it is one of the hereditary causes of nephropathies and can genetically be transmitted from one generation to the next as a recessive dominant or X-linked[8] because of variants in the *COL4A3, COL4A4*, and *COL4A5* genes, which encode, respectively, α3, α4, and α5 chains of collagen type IV that consist of glomerular basement membrane in the kidney[10]. With the development of technologies such as massively parallel sequencing, it is possible to treat complex diseases that are difficult to diagnose more cheaply and precisely[9]. Our study aimed to detect variant in AS genes in CKD and contribute new variants to the literature.

[1]Yildiz Technical University, Graduate School of Natural and Applied Sciences, Department of Molecular Biology and Genetics – Istanbul, Turkey.
[2]Ege University, Faculty of Science, Department of Biology Molecular Biology Section – Bornova (İzmir), Turkey.
[3]Başaksehir Çam and Sakura City Hospital, Department of Medical Genetics – Istanbul, Turkey.
[4]Yildiz Technical University, Faculty of Arts and Sciences, Department of Molecular Biology and Genetics – Istanbul, Turkey.
*Corresponding author: cuneydyavas@gmail.com
Conflicts of interest: the authors declare there is no conflicts of interest. Funding: none.
Received on March 17, 2022. Accepted on June 12, 2022.

METHODS

A total of 50 unrelated patients with a clinical CKD were included in the study after obtaining informed consent from the patients and their parents for medical examination and genomic analysis. The procedures adhered to the Declaration of Helsinki, and the Ethics Committee approved the relevant studies of the Basaksehir Cam and Sakura City Hospital (E-96317027-000-8273 2021.03.02/KAEK). All the patients met the generally accepted clinical diagnostic criteria for abnormalities of kidney structure or function present more than 3 months.

Genomic DNA was extracted from peripheral blood, and whole-exome sequencing (WES) was performed by capturing the coding regions and splice sites of target genes (101 genes) via the Twist Human Comprehensive Exome kit panel. After library enrichment and quality control, the samples were sequenced on the BGI platform (Shenzhen, China) with 100-bp paired-end reads at an average sequencing depth of ×100. Annotation of detected variants was performed using www.genomize.com.tr (version 6.14.4), interval, Franklin, VarSome, ClinVar, OMIM, and Pubmed. Variants with a frequency higher than 0.1% were filtered out. dbNSFP (contains MetaLR, MetaSVM, MetaRNN, REVEL, SIFT, PolyPhen-2, LRT, Mutation Taster 4.2 versions) was used to predict variants' pathogenicity (deleteriousness). Detected variants were classified as "pathogenic," "likely pathogenic (LP)," or "variants of uncertain significance (VUS)" according to the international guidelines of the ACMG. These variants are listed in Tables 1 and 2.

RESULTS

When 23 of 50 patients who underwent WES due to CKD were evaluated together, it was seen that 15 (65%) patients were older than 17 years and 8 (35%) were younger than 17 years (Tables 1 and 2). Of the 23 detected variants, 10 are novel types. Variants in the genes *COL4A3* (c.4153+1del, c.4123C>T, c.4222A>G, c.1061C>T), *PKD1* (c.6260_6263dup, c.7401del, c.4168C>T), *PKD2* (c.872T>C), *LMX1B* (c.237G>T), and *PLCE1* (c.5410_5411del) were described for the first time in this report (Tables 1 and 2). The genes with variants in 23 patients were *COL4A3*, *COL4A4*, *COL4A5*, *COQ8B*, *FN1*, *LMX1B*, *MEFV*, *PKD1*, *PKD2*, *PLCE1,* and *SLC34A1*. Variants were found in *PKD1* in 7 of 23 patients, in *COL4A3* in 5, in *COL4A4* in 1, and in *COL4A5* in 2 patients.

Within the scope of the study, the WES results of 50 patients diagnosed with CKD were evaluated. Pathogenic/LP variants were detected in 15 (30%) of 50 patients following ACMG criteria (Figure 1). Of these 15 patients, 4 (27%) had pathogenic/LP variants in genes other than AS genes (*COL4A3*, *COL4A4,* or *COL4A5*). Variants in genes associated with AS were detected in 8 (35%) of 23 patients (Table 2).

Variants in the AS-related genes *COL4A3*, *COL4A4*, and *COL4A5* were found in 8 (35%) of 23 CKD patients who underwent WES (Table 2). Variants were detected in the *COL4A3* gene in five of these eight patients, in the *COL4A4* gene in one, and in the *COL4A5* gene in two patients. One of

Table 1. Characteristics of detected variations.

P	G	Age	Gene	Variant	Variant type	Zygosity	ACMG classification	Patient frequency	Novelty
P1	F	37	*PKD2*	c.872T>C (p.Leu291Pro)	Missense mutation	Het	LP	N/A	**Novel**
P2	M	6	*LMX1B*	c.237G>T (p.Glu79Asp)	Missense mutation	Het	P	N/A	**Novel**
P4	F	9	*MEFV*	c.2080A>G (p.Met694Val) c.442G>C (p.Glu148Gln)	Missense mutation Missense mutation	Het Het	P B	*f* = 0.000282 *f* = 0.0711	rs61752717 rs3743930
P5	M	2	*FN1*	c.4151T>C (p.Ile1384Thr)	Missense mutation	Het	V	*f* = 0.0000159	rs768047478
P8	M	0	*PLCE1*	c.5410_5411del (p.Phe1804LeufsTer15)	Small deletion (frame shift)	Homo	P	N/A	**Novel**
P9	M	11	*COQ8B*	c.1027C>T (p.Arg343Trp)	Missense mutation	Homo	LP	*f* = 0.000004	rs398122981
P10	F	51	*PKD1*	c.7666C>T (p.Gln2556Ter)	Nonsense mutation	Het	P	N/A	rs1567184366
P12	M	38	*PKD1*	c.8302G>A (p.Val2768Met)	Missense mutation	Het	P	*f* = 0.0000081	rs1456510041
P13	F	6	*PKD1*	c.2308C>T (p.Arg770Trp)	Missense mutation	Het	V	*f* = 0.0000147	rs771288493
P15	M	29	*PKD1*	c.6260_6263dup (p.Arg2089ProfsTer20)	Small insertion (frame shift)	Het	P	N/A	**Novel**
P17	F	58	*SLC34A1*	c.1325C>T (p.Pro442Leu)	Missense mutation	Het	V	*f* = 0.0000159	rs760010857
P18	F	21	*PKD1*	c.7401del (p.Asn2468ThrfsTer152)	Small deletion (frame shift)	Het	P	N/A	**Novel**
P19	F	32	*PKD1*	c.4168C>T (p.Gln1390Ter)	Nonsense mutation	Het	P	N/A	**Novel**
P23	M	9	*CD2AP*	c.902A>T (p.Lys301Met)	Missense mutation	Het	P	*f* = 0.000191	rs141778404
P24	M	57	*PKD1*	c.3877G>A (p.Val1293Ile)	Missense mutation	Het	V	*f* = 0.0000168	rs774353552

P: patient; G: gender; F: female; M: male; N/A: not available. The genes, variant types, zygosities, pathogenicity, frequency, and database numbers of the detected variations were determined according to the ACMG guideline. Six variations were detected, which were novels.

Table 2. Clinical characteristics of the patients and detected Alport syndrome genes.

P	G	Age	Clinical or pathological diagnosis before WES-based analysis	Spot urine protein/ creatinine ratio (0–150 mg/g)	Serum albumin (35–52 g/L)	Serum creatinine (0.5–0.9 mg/dL)	Serum globulin (26–46 g/L)	Alport gene	Variant	Variant type	Zygosity	ACMG classification	Patient frequency	Novelty
P3	F	7	SRNS	190↑	25↓	0.51	17↓	*COL4A3*	c.3829G>A (p.Gly1277Ser)	Missense mutation	Het	P	*f* = 0.000377	rs190598500
P7	F	17	Pancytopenia, bleeding diathesis, NS	178↑	34↓	0.43↓	23↓	*COL4A3*	c.4421T>C (p.Leu1474Pro)	Missense mutation	Het	P	*f* = 0.0027	rs200302125
P11	F	9	SRNS, FSGS	4137↑	34↓	0.68↑	22↓	*COL4A3*	c.4153+1del	Splicing deletion	Homo	LP	N/A	**Novel**
P14	F	0	NS	130	26↓	1.48↑	15↓	*COL4A3*	c.4123C>T (p.Pro1375Ser)	Missense mutation	Het	LP	N/A	**Novel**
P22	F	10	NS	151↑	46	0.38↓	21↓	*COL4A3*	c.3182G>A (p.Gly1061Asp)	Missense mutation	Het	VUS	*f* = 0.000197	rs202078295
P20	M	2	FSGS, NS	38157↑	23↓	0.19↓	20↓	*COL4A4*	c.665C>T (p.Pro222Leu)	Missense mutation	Het	VUS	*f* = 0.000122	rs773533313
P6	F	5	SRNS	8812↑	38	0.18↓	21↓	*COL4A5*	c.4222A>G (p.Thr1408Ala)	Missense mutation	Het	VUS	N/A	**Novel**
P21	F	6	NS	7664↑	25↓	0.38↓	19↓	*COL4A5*	c.1061C>T (p.Thr354Ile)	Missense mutation	Het	VUS	N/A	**Novel**

P: patient; G: gender; WES: Whole-Exome Sequencing; F: female; M: male; N/A: not available; SRNS: steroid-resistant nephrotic syndrome; NS: nephrotic syndrome; FSGS: focal segmental glomerulosclerosis. The genotype-phenotype correlation of the patients carrying the AS genes in which the variations were detected the most was calculated, and the damaging effects were examined according to the laboratory findings.

the novel variants detected in the *COL4A3* gene of two patients was homozygous and the other heterozygous, and both were not previously reported in the literature. These two novel variants were classified as LP according to the ACMG. Both heterozygous novel variants in the *COL4A5* genes of two patients were not previously reported in the literature. These variants were classified as VUS, according to the ACMG. Heterozygous variant in the *COL4A4* gene was detected in only one patient. The protein/creatinine ratio in the spot urine of patients with variants in the *COL4A4* and *COL4A5* genes was significantly higher than in patients with variants in the *COL4A3* gene.

Variants were found in genes other than the AS-related genes in 15 (65%) of 23 patients who underwent WES due to CKD and were found to have the variants (Table 1).

DISCUSSION

Frequently, it is clinically challenging to distinguish CKD type. In general, CKD diagnosis can be made based on morphological, pathological, and genetic examination after complaints such as persistent alterations in kidney structure or function, filtration disorders, proteinuria, and hematuria[11]. The prevalence of all stages of CKD in studies varies between 7 and 12% in different regions of the world. Therefore, multiple patients with this monogenic form of CKD genetic testing emerge as an important tool in determining the cause of CKD, especially in children and young adults[12]. To date, 101 genes thought to be responsible for the CKD phenotype have been identified in the HPO database. Some gene groups responsible for the CKD phenotype stand out in the studies. Studies have shown that patients diagnosed with CKD have pathogenic variants, mostly in AS and polycystic disease (PD) genes[13]. The prominent gene groups in our study are genes related to AS and PD. Because of this, we focused on patients with detected variants in AS genes. In this study, the rate of patients diagnosed with AS gene was 35%. Furthermore, the frequency of disease-causing variants in CKD is likely to differ between different ethnic groups depending on age, gender, and the molecular analysis methods used for diagnosis[14]. Many CKD-associated genes have yet to be identified, and it is believed that unidentified CKD genes may play a role in populations with low detection rates[15].

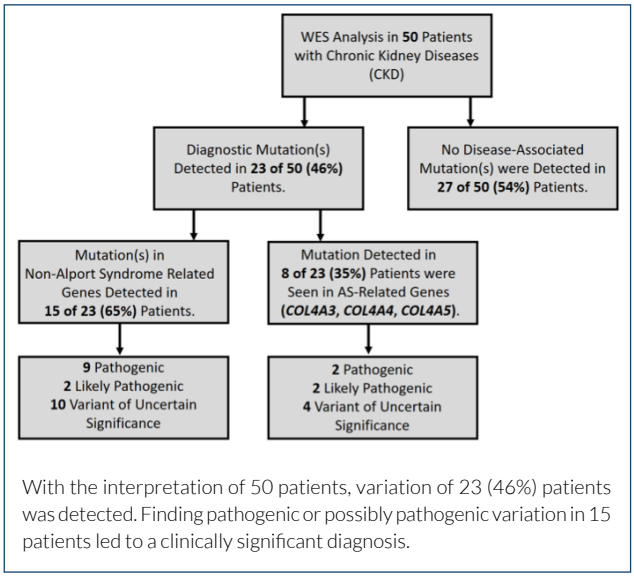


Figure 1. Flowchart of the Whole-Exome Sequencing analysis.

According to the U.S. Renal Data System (USRDS, https://www.usrds.org/), approximately 0.2% of adults and 3% of children with end-stage renal disease (ESRD) in the United States are diagnosed with AS. In this study, AS genes were found to be higher in patients with CKD and variant, with a rate of 35%. Also extensive studies, significant findings were observed at the rate of 24% as a diagnostic value[9], but this rate was higher than the literature in our study (30% rate). In our study, dominant inheritance was more common than recessive and X-linked inheritance.

WES studies make it possible to identify new genes and detect significant variants from defined genes by rapidly and simultaneously examining genes related to monogenic CKD; the number of patients diagnosed with monogenic CKD can be expected to increase rapidly. In this study, we identified a possible pathogenic/pathogenic (i.e., high-risk) CKD-associated variant in 30% of our patients and provided a comprehensive description of these patients' clinical and variational characteristics. A total of 15 variants in 23 patients were of the high-risk type, 5 (33.3%) patients had *PKD1* variant, 4 (26.6%) had AS genes variant, and other genes (40.1%) had variant. For physicians, the most current challenge in the molecular genetic diagnosis of CKD is the evaluation of VUS, which perhaps represents a barrier to clinical interpretation. As a result, disaggregation analysis studies on family members will be particularly useful and, in some cases, even vital. In addition, extensive in silico analyses of the structural and functional impact on the protein product may be useful for some. We believe that our cases will contribute to developing the scientific literature on CKD. Clinically, there is no difference between patients with renal impairment (patients with VUS or no variant) and patients with confirmed CKD (i.e., patients with a probable pathogenic/pathogenic variant). However, among carriers of the AS gene variant, individuals with recessive inheritance and the COL4A5 variant had a higher protein/creatinine ratio (Table 2).

This study showed that for most patients, genetic diagnoses could be made clinically for patients. In this study, we manifest that our results highlight the potential of genetic findings to change the diagnostic value of consultation. For example, eight patients with the most detected variants of *COL4A3*, *COL4A4,* or *COL4A5* did not have clinical diagnoses of classically associated with AS. Although these patients do not have eye and ear nose and throat findings, due to the detection of variants, patients with clinical nephropathy variant are diagnosed and treated according to the variant type[16]. In addition, it was determined how effective the variants detected in AS-related genes were in the clinic shown in Table 2. Consistent with recent studies, we identified autosomal and X-linked forms of AS among patients with a clinical diagnosis of kidney disease, supporting the variable phenotypic expression of variants in type IV collagen genes[9,17].

To make a clinical diagnosis in nephrology, the need to "revise the disease ontology based on molecular classifiers" has been emphasized in some publications[18]. Our findings support the diagnostic utility of exome sequencing among the different clinical categories of kidney disease, the most detecting variant in AS-related genes. Therefore, looking at AS genes first in nephropathy patients in low-budget laboratories is recommended. It also highlights the potential of genetic testing to guide treatments for diseases accurately.

Large databases of controls, such as ExAC and gnomAD[19], are of great value for interpreting detected variants and deciding clinical relevance based on their frequency in the population. New variant annotation algorithms that take into account genomic context to assess variant intolerance can facilitate variant classification in patients independent of previous clinical reports[20] and help standardize disease association interpretation. Therefore, many initiatives are currently examining the clinical relevance of genes and variants for diagnosing diseases (e.g., ClinGen (www.clinicalgenome.org) and will provide further evidence of the usefulness of genetic testing in various clinical settings[21]. When the novel variants detected in our study are analyzed according to population frequencies, and in silico analysis, it predicts that protein function may be impaired.

CONCLUSIONS

Large-scale genetic studies are needed to understand the genetic aspects of CKD in Turkey and other populations. Observational studies of CKD often reveal seemingly conflicting relationships between traditional risk factors and outcomes, making it difficult to predict outcomes in studies of CKD patients with normal kidney function. However, many completed CKD studies are limited by tentative results of uncertain clinical relevance or narrow eligibility criteria that limit external validity, and the implementation of proven treatments remains a challenge. Therefore, the nephrology community should capitalize on the recent interest in new approaches to experimental design, such as practical clinical trials[22]. Therefore, genetic approaches are important for treatment and diagnosis. Our study has shown that the most common CKD subtype is AS.

AUTHORS' CONTRIBUTIONS

CY: Conceptualization, Data curation, Formal analysis, Methodology, Writing – original draft, Writing – review & editing. **CÜ:** Data curation, Formal analysis. **EÇ:** Conceptualization, Data curation, Formal analysis, Methodology, Writing – original draft. **AG:** Data curation, Formal analysis. **MD:** Data curation, Formal analysis. **EGİ:** Data curation, Formal analysis. **TD:** Conceptualization, Data curation, Formal analysis, Methodology, Writing – original draft. **NÖÖ:** Data curation, Formal analysis.

REFERENCES

1. Eckardt KU, Coresh J, Devuyst O, Johnson RJ, Köttgen A, Levey AS, et al. Evolving importance of kidney disease: from subspecialty to global health burden. Lancet. 2013;382(9887):158-69. https://doi.org/10.1016/S0140-6736(13)60439-0
2. Levin A, Tonelli M, Bonventre J, Coresh J, Donner JA, Fogo AB, et al. Global kidney health 2017 and beyond: a roadmap for closing gaps in care, research, and policy. Lancet. 2017;390(10105):1888-917. https://doi.org/10.1016/S0140-6736(17)30788-2
3. Naghavi M, Abajobir AA, Abbafati C, Abbas KM, Abd-Allah F, Abera SF, et al. Global, regional, and national age-sex specific mortality for 264 causes of death, 1980–2016: a systematic analysis for the Global Burden of Disease Study 2016. Lancet. 2017;390(10100):1151-210. https://doi.org/10.1016/S0140-6736(17)32152-9
4. Jha V, Garcia-Garcia G, Iseki K, Li Z, Naicker S, Plattner B, et al. Chronic kidney disease: global dimension and perspectives. Lancet. 2013;382(9888):260-72. https://doi.org/10.1016/S0140-6736(13)60687-X
5. Chen TK, Knicely DH, Grams ME. Chronic kidney disease diagnosis and management: a review. JAMA. 2019;322(13):1294-304. https://doi.org/10.1001/jama.2019.14745
6. Wuttke M, Li Y, Li M, Sieber KB, Feitosa MF, Gorski M, et al. A catalog of genetic loci associated with kidney function from analyses of a million individuals. Nat Genet. 2019;51(6):957-72. https://doi.org/10.1038/s41588-019-0407-x
7. Carlassara L, Zanoni F, Gharavi AG. Familial aggregation of CKD: gene or environment? Am J Kidney Dis. 2021;77(6):861-2. https://doi.org/10.1053/j.ajkd.2020.12.010

8. Torra R, Furlano M. New therapeutic options for Alport syndrome. Nephrol Dial Transplant. 2019;34(8):1272-9. https://doi.org/10.1093/ndt/gfz131
9. Lata S, Marasa M, Li Y, Fasel DA, Groopman E, Jobanputra V, et al. Whole-exome sequencing in adults with chronic kidney disease: a pilot study. Ann Intern Med. 2018;168(2):100-9. https://doi.org/10.7326/M17-1319
10. Kruegel J, Rubel D, Gross O. Alport syndrome--insights from basic and clinical research. Nat Rev Nephrol. 2013;9(3):170-8. https://doi.org/10.1038/nrneph.2012.259
11. Wang WJ, Cai GY, Chen XM. Cellular senescence, senescence-associated secretory phenotype, and chronic kidney disease. Oncotarget. 2017;8(38):64520-33. https://doi.org/10.18632/oncotarget.17327
12. Romagnani P, Remuzzi G, Glassock R, Levin A, Jager KJ, Tonelli M, et al. Chronic kidney disease. Nat Rev Dis Primers. 2017;3:17088. https://doi.org/10.1038/nrdp.2017.88
13. Vivante A, Hildebrandt F. Exploring the genetic basis of early-onset chronic kidney disease. Nat Rev Nephrol. 2016;12(3):133-46. https://doi.org/10.1038/nrneph.2015.205
14. Groopman EE, Marasa M, Cameron-Christie S, Petrovski S, Aggarwal VS, Milo-Rasouly H, et al. Diagnostic utility of exome sequencing for kidney disease. N Engl J Med. 2019;380(2):142-51. https://doi.org/10.1056/NEJMoa1806891
15. Hildebrandt F. Genetic kidney diseases. Lancet. 2010;375(9722):1287-95. https://doi.org/10.1016/S0140-6736(10)60236-X
16. Canetta PAA, Radhakrishnan J. The evidence-based approach to adult-onset idiopathic nephrotic syndrome. Front Pediatr. 2015;3:78. https://doi.org/10.3389/fped.2015.00078
17. Riedhammer KM, Braunisch MC, Gunthner R, Wagner M, Hemmer C, Strom TM, et al. Exome sequencing and identification of phenocopies in patients with clinically presumed hereditary nephropathies. Am J Kidney Dis. 2020;76(4):460-70. https://doi.org/10.1053/j.ajkd.2019.12.008
18. Inrig JK, Califf RM, Tasneem A, Vegunta RK, Molina C, Stanifer JW, et al. The landscape of clinical trials in nephrology: a systematic review of Clinicaltrials.gov. Am J Kidney Dis. 2014;63(5):771-80. https://doi.org/10.1053/j.ajkd.2013.10.043
19. Lek M, Karczewski KJ, Minikel EV, Samocha KE, Banks E, Fennell T, et al. Analysis of protein-coding genetic variation in 60,706 humans. Nature. 2016;536(7616):285-91. https://doi.org/10.1038/nature19057
20. Petrovski S, Wang Q, Heinzen EL, Allen AS, Goldstein DB. Genic intolerance to functional variation and the interpretation of personal genomes. PLoS Genet. 2013;9(8):e1003709. https://doi.org/10.1371/journal.pgen.1003709
21. Vassy JL, Christensen KD, Schonman EF, Blout CL, Robinson JO, Krier JB, et al. The impact of whole-genome sequencing on the primary care and outcomes of healthy adult patients: a pilot randomized trial. Ann Intern Med. 2017;167(3):159-69. https://doi.org/10.7326/M17-0188
22. Boer IH, Kovesdy CP, Navaneethan SD, Peralta CA, Tuot DS, Vazquez MA, et al. Pragmatic clinical trials in CKD: opportunities and challenges. J Am Soc Nephrol. 2016;27(10):2948-54. https://doi.org/10.1681/ASN.2015111264

ORIGINAL ARTICLE

https://doi.org/10.1590/1806-9282.20220406

Comparison of the autonomic nervous system dysfunction between different chronic spine disorders: neck pain versus low back pain

André Pontes-Silva[1*], Daniela Bassi-Dibai[2], Cid André Fidelis-de-Paula-Gomes[3], Cesário da Silva Souza[4], Flavio de Oliveira Pires[5], Cristiano Teixeira Mostarda[1], Almir Vieira Dibai-Filho[1]

SUMMARY

OBJECTIVE: This study aims to compare heart rate variability (HRV) between patients with chronic neck pain and patients with chronic low back pain and to correlate the chronic pain variables with heart rate variability indices.

METHODS: This is a cross-sectional study. We divided the sample into two groups: neck pain (n=30) and low back pain (n=30). We used the Numeric Pain Rating Scale, Neck Disability Index, Roland-Morris Disability Questionnaire, Pain-Related Catastrophizing Thoughts Scale, Tampa Scale of Kinesiophobia, and Pain Self-Efficacy Questionnaire. For heart rate variability analysis, we used the following indices: mean RR, standard deviation of all RR intervals, mean heart rate, root mean square differences of successive RR intervals, triangular index, triangular interpolation of the interval histogram, low-frequency band in arbitrary units and in absolute values, high-frequency band in arbitrary units and in absolute values, standard deviation of the instantaneous beat-to-beat variability (standard deviation 1), long-term standard deviation of continuous RR intervals (standard deviation 2), and Stress Index. We used Student's t-test for comparisons and Spearman's coefficient for correlations.

RESULTS: We observe insignificant values in the differences between the groups. Disability and self-efficacy were correlated with heart rate variability only in patients with chronic neck pain, whereas catastrophizing and kinesiophobia showed greater correlations with heart rate variability in patients with chronic low back pain.

CONCLUSIONS: Autonomic dysfunction of individuals with chronic neck pain, when compared to patients with chronic low back pain, does present insignificant differences.

KEYWORDS: Musculoskeletal disorders. Neurology. Parasympathetic nervous system. Sympathetic nervous system.

INTRODUCTION

Autonomic nervous system is responsible for managing, in part, the heart rate; thus, due to neurological actions to preserve the organism's homeostatic balance, the sympathetic and parasympathetic components generate variations in the intervals between heartbeats (from moment to moment), called RR intervals[1], obtained by electrocardiograph or cardiofrequency meters[2]. Heart rate variability (HRV), a method that uses indices derived from RR intervals, is used to study the sympathetic and parasympathetic interaction of the autonomic nervous system in situations of health, disease, and human performance[3].

Clinically, HRV (divided into time and frequency domains) is used to monitor the autonomic nervous system's regulation on organism (when a patient is in pain, sympathetic activity increases, whereas when a patient is relaxed, the parasympathetic system takes control). A drop in the time-domain parameter indicates an increase in the sympathetic activity (or a decrease in the parasympathetic activity). A high frequency and the standard deviation of all RR intervals, in the frequency domain, represent a state of excitement of the parasympathetic system, whereas a low frequency, and low-frequency/high-frequency ratio, represents a state of inhibition of the parasympathetic system, or a state of excitement of the sympathetic system. As such, several mathematical models (HRV indices) are calculated in an attempt to describe the activities of the autonomic nervous system[4].

[1]Universidade Federal do Maranhão, Postgraduate Program in Adult Health – São Luís (MA), Brazil.
[2]Universidade Ceuma, Postgraduate Program in Programs Management and Health Services – São Luís (MA), Brazil.
[3]Universidade Nove de Julho, Postgraduate Programa in Rehabilitation Sciences – São Paulo (SP), Brazil.
[4]Centro Universitário Tiradentes, Department of Physical Therapy – Maceió (AL), Brazil.
[5]Universidade Federal do Maranhão, Department of Physical Education – São Luís (MA), Brazil.
*Corresponding author: contato.andrepsilva@gmail.com
Conflicts of interest: the authors declare there is no conflicts of interest. Funding: This work was partially supported by Coordenação de Aperfeiçoamento de Pessoal de Nível Superior (CAPES), finance code 001.
Received on April 27, 2022. Accepted on April 30, 2022.

Autonomic dysfunction is a situation in which there is an autonomic imbalance between sympathetic and parasympathetic activities (sympathovagal balance), and the scientific literature shows some clinical conditions that have autonomic dysfunction, which are identifiable by HRV indices, such as temporomandibular disorder[5], fibromyalgia[6], diabetic neuropathy[7], neurofibromatosis[8], cancer[9], brain death[10], chronic pain[1], COVID-19[11], neurological dysfunction[12], coronary artery disease[13], ventricular arrhythmia, and sudden cardiac death[14].

Regarding scientific literature about chronic pain in the spine, studies have shown that both chronic neck pain (CNP)[1,15] and chronic low back pain (LBP)[1,16] (when compared to healthy controls) are correlated with autonomic dysfunction (identified by HRV indices)[15–17]. We know that HRV indices are correlated with pain intensity, disability, and catastrophizing in individuals with CNP[15]; besides, there is evidence in the literature suggesting that patients with LBP have lower parasympathetic activation and consequently sympathetic predominance[16].

However, the autonomic dysfunction in CNP, compared to LBP, has not been investigated, and this creates a gap in studies of the nervous system focusing on chronic pain of the spine. As such, the aim of this study was to compare the HRV of patients with CNP and patients with LBP and to correlate the chronic pain variables with HRV indices.

METHODS

Study design

This is a cross-sectional study. Participants included in the study validated their participation by signing the informed consent form. All procedures were approved by the Ethics Committee on Research of the Universidade Federal do Maranhão (opinion number 3.408.949).

Participants

The recruitment of participants took place after the research was disseminated verbally, as well as using posters, pamphlets, social networks, and messaging applications from January 2020 to September 2020. We carried the collection of variables out in a reserved, bright room, without external noise, and air-conditioned at 23°C, located in a physiotherapy clinic (Buriticupu, MA, Brazil).

We calculated the sample size using the software G*Power (version 3.1.9.7, Universität Düsseldorf, Germany), considering an effect size of 0.80 when comparing two independent groups (t-test, two-tailed), according to a previous study[18]. We performed the calculation with an alpha error of 5% and a statistical power of 80%. Thus, the number of required sample was estimated as 26 participants per group.

This study is composed of two groups: CNP (n=30) and LBP (n=30). The inclusion criteria for both the groups were as follows: age between 18 and 59 years, both sexes, sedentary or irregularly active, and with a report of pain for more than 90 days. In addition, as a diagnostic criterion for neck pain, we considered a score on the Numeric Pain Rating Scale (NPRS) ≥3[19,20] and on the Neck Disability Index (NDI) ≥5 points[21,22], and for low back pain, we considered a score on NPRS score ≥3[19,20] and on the Roland Morris Disability Questionnaire (RMDQ) ≥5 points[23,24].

The exclusion criteria considered in this study were as follows: presence of specific chronic pain, with pain attributable to a specific and identifiable cause, such as history of spinal surgery and/or vertebral fractures, spondylosis, and spondylolisthesis, presence of radiculopathy and/or herniated disk confirmed by imaging and neurological impairment by physical examination (presence of altered sensitivity, reflex, and/or muscle strength); physical therapy treatment history for spine pain in the last 90 days or medicated (analgesics and/or anti-inflammatory) in the last 7 days; medical diagnosis of cancer, rheumatological, neurological, psychiatric, cardiovascular, or metabolic diseases; and report of other concomitant acute or chronic pain[25].

Pain measurement

In addition to the NPRS[20], NDI[22], and RMDQ[24], we applied the following instruments: Pain-Related Catastrophizing Thoughts Scale (PCTS)[26], Tampa Scale of Kinesiophobia (TSK)[27], Pain Self-Efficacy Questionnaire (PSEQ)[28], and International Physical Activity Questionnaire (IPAQ)[29].

NPRS is a scale used to quantify the pain intensity using a sequence of 11 numbers, in which 0 represents "no pain" and 10 "the worst pain imaginable." The pain intensity was assessed at rest and after active spinal movements. This scale is validated for Portuguese[20].

NDI is a questionnaire adapted and validated for the Brazilian population[22], capable of measuring disability in individuals with neck pain. It consists of 10 items with 6 response possibilities, ranging from 0–5. The total score varies from 0 to 50 points; the higher the value, the greater the disability[15,22].

RMDQ is a questionnaire adapted and validated for the Brazilian population, capable of measuring disability in individuals with low back pain. It consists of 24 items that describe situations experienced by people with low back pain, with

scores ranging from 0–24 points. Thus, the higher the score, the greater the disability[24].

PCTS consists of nine items arranged on a Likert scale, which varies in numerical measure from 0–5, associated with the words "almost never" and "almost always." The total score is obtained by adding the total score and dividing by the number of items answered. The final score ranges from 0–5 points; the higher the score, the greater the occurrence of catastrophizing thoughts, according to the version adapted for the Brazilian population[26].

TSK is a validated scale for the Brazilian population capable of assessing kinesiophobia. It is a self-administered instrument and consists of 17 items. For each item, there are four options with their respective values in ascending order: totally disagree (equal to 1 point), partially disagree (2 points), partially agree (3 points), and totally agree (4 points). It is necessary to invert the scores of items 4, 8, 12, and 16 to calculate the final score, which ranges from 17 to 68. The higher the score, the greater the kinesiophobia[27].

PSEQ is a self-administered instrument capable of evaluating and expressing, in numbers, the patient's confidence in manifesting themselves in the situations presented in the 10 items (taking pain into account). For each item, there are six options with their respective values in ascending order, representing self-efficacy from 0 "not confident" to 6 "totally confident." The final score (0–60) is obtained by adding the values. The higher the score, the greater the self-efficacy in pain conditions[28].

IPAQ indirectly measures the level of physical activity of individuals and has validation for the Brazilian population. The instrument has four questions (with two options each) that investigate the physical effort performed at work and the activities of daily living, including walking to get from place to place, regular or not recreational activities, sports, moderate, and vigorous physical exercises. After analyzing the questionnaire and following the instructions, it is possible to classify individuals into sedentary, irregularly active, active, and very active[29].

Heart rate variability measurement

We measured HRV using a Polar V800 cardiofrequency meter (Polar Electro OY, Kempele, Finland) and a sensor attached to the rib cage (sternum region) to capture the heart rate; this instrument is already used in research in this scenario[14,15]. Before collection, all individuals were instructed to avoid eating chocolate, avoid drinking coffee, and avoid using thermogenic and energy drinks; during the procedure, they were instructed not to speak or sleep.

Before obtaining the RR intervals from moment to moment, each individual remained at rest for 10 min in the supine position. Then, we made two HRV records: 10 min in the supine and 10 min in the standing positions. In addition, we observed each participant's respiratory rate (described as breaths per minute); to maintain the individual rhythm of the breathing cycle, the participants were unaware that the researcher observed and recorded each inspiration/expiration.

Heart rate variability analysis

With the aid of a microcomputer, we transferred the files to the Kubios HRV analysis software, version 2 beta (Matlab, Kuopio, Finland), and analyzed them using a series of 256 sequential RR intervals, from which was chosen, using qualitative visual inspection, the section with the highest signal stability and normal distribution. The series of RR intervals was observed at the frequency of 5 Hertz (Hz), and the data were filtered to remove variations below 0.04 Hz and above 1.0 Hz; only segments >90% of purely sinus beats were included in the final analysis. Therefore, a quantitative analysis of the variability of RR intervals was performed using linear and nonlinear methods in the domains of time and frequency.

Heart rate variability indices

We used the indices with the largest scientific contingent[15,30-33]. Linear indices were as follows: RR intervals mean (mean RR) expressed in milliseconds (ms); standard deviation of all RR intervals (STD-RR) between two consecutive normal heartbeats, in ms; heart rate mean (mean HR) expressed in beats per minute (bpm); root mean square differences of successive RR intervals (rMSSD) in ms; triangular index (RR Tri) in ms; triangular interpolation of the interval histogram (TINN) in ms; low-frequency band in arbitrary units (LF) between 0.03 and 0.14 Hz and in absolute values (power LF) in ms^2; and high-frequency band in arbitrary units (HF) above 0.15 Hz and in absolute values (power HF) in ms^2. Nonlinear indices were as follows: standard deviation of the instantaneous beat-to-beat variability (SD1); long-term standard deviation of continuous RR intervals (SD2); and stress index.

Statistical analysis

We compared the categorical variables through Fisher's exact and/or chi-squared tests. For comparisons between quantitative variables, we used Student's t-test for unpaired and normally distributed samples, with analysis performed using histograms and Shapiro-Wilk's test. In the correlations between the variables, we used the Spearman's correlation coefficient (rho). The interpretation of the coefficients was based on the following classification: from 0.26 to 0.49, weak; from 0.50–0.69, moderate; from 0.70–0.89, strong; and from 0.90–1.00,

very strong[34]. We used the SPSS software (version 17, Chicago, Illinois, USA) for data processing.

Comparisons of HRV indices between groups were expressed as mean, standard deviation (SD), mean difference (MD), confidence interval of difference (95%CI), and effect size calculated using Cohen's d, with the categorization based on the values established by Cohen[35]: less than 0.2 (small effect), about 0.5 (moderate effect), and greater than 0.8 (large effect). Due to the multiple comparisons between the groups, we used the Bonferroni's correction[36], with level of significance set at 0.003 (i.e., 0.05/number of comparisons performed), and the effect size >0.8. For the correlations, the level of significance was set at 0.05.

RESULTS

A total of 105 individuals were recruited for this study. There was a sample loss of 45 participants for the following reasons: presence of systemic disease (n=19), specific pain (n=14), atypical HRV signals (n=8), and withdrawal during collection (n=4). Thus, the final sample (n=60) composed of 30 participants in the CNP group and 30 participants in the LBP group; in both groups, most of the sample was women (CNP=86.7%; LBP=80%, p>0.05) and physically inactive (CNP=86.7%; LBP=80%, p>0.05).

Table 1 describes the characteristics of the study participants, with a significant difference (p≤0.003) observed only in the disability (on percentage). Table 2 describes the comparisons of HRV indices between the CNP and LBP groups; we observe insignificant values in the differences between the groups (p>0.003) and in the effect size (d<0.80). Then, we observe significant values of correlation (p<0.05) between HRV indices and other study variables (Table 3).

DISCUSSION

In comparison of HRV indices, we observe insignificant values in the differences between the groups and effect size. Regarding the disabilities generated by pain in the spine, we observed that LBP is 14.65% more disabling than CNP; however, the incapacity generated by CNP generates greater autonomic dysfunction, as shown by the highest correlations with HRV indices.

Regarding the HRV indices correlated with different chronic pain conditions in the spine, the literature presents several studies that corroborate some of our findings when indicating dysregulation of the parasympathetic nervous system[1,15,17], since this was confirmed both in patients with CNP and LBP in this study.

Table 1. Characteristics of the study participants: chronic neck pain (n=30) and chronic low back pain (n=30).

	Mean (SD)	95%CI	p-value
Age (years)			
CNP	31.5 (8.4)	28.34–34.66	0.692
LBP	30.6 (7.7)	27.78–33.55	
Body mass (kg)			
CNP	66.8 (11.1)	62.69–70.10	0.838
LBP	66.1 (15.9)	60.15–72.08	
Stature (m)			
CNP	162.0 (0.1)	1.60–1.64	0.781
LBP	163.0 (0.1)	1.59–1.66	
Body mass index (kg/m^2)			
CNP	25.4 (3.9)	23.10–26.93	0.563
LBP	24.8 (4.6)	23.10–26.54	
Waist (cm)			
CNP	78.6 (8.7)	75.40–81.90	0.655
LBP	79.8 (12.2)	75.30–84.47	
Chronicity of pain (months)			
CNP	63.0 (45.6)	45.94–80.06	0.425
LBP	54.0 (40.9)	38.70–69.30	
Pain at rest (NPRS, 0–10)			
CNP	6.5 (1.9)	5.85–7.28	0.837
LBP	6.6 (1.8)	5.98–7.36	
Pain after movements (NPRS, 0–10)			
CNP	7.0 (2.2)	6.22–7.92	0.863
LBP	6.9 (2.2)	6.14–7.79	
Catastrophizing (PCTS, 0–5)			
CNP	2.5 (1.2)	2.10–3.06	0.545
LBP	2.3 (1.1)	1.98–2.80	
Kinesiophobia (TSK, 17–68)			
CNP	42.8 (6.7)	40.28–45.32	0.738
LBP	43.4 (7.7)	40.52–46.34	
Self-Efficacy (PSEQ, 0–60)			
CNP	40.5 (12.6)	35.81–45.26	0.919
LBP	40.8 (12.6)	36.16–45.57	
Disability (score)			
CNP [NDI, 0–50]	14.1 (6.4)	11.73–16.54	N/A
LBP [RMDQ, 0–24]	10.3 (5.3)	8.30–12.30	
Converted disability (0–100%)			
CNP	28.2 (12.8)	23.46–33.07	0.002*
LBP	42.9 (22.2)	34.60–51.23	

CNP: chronic neck pain; LBP: low back pain; SD: standard deviation; CI: confidence interval; NPRS: numeric pain rating scale; PCTS: pain-related catastrophizing thoughts scale; TSK: tampa scale of kinesiophobia; PSEQ: pain self-efficacy questionnaire; NDI: neck disability index; RMDQ: Roland-Morris disability questionnaire; N/A: not applicable.
*Significant difference (t-test; p-value≤0.003).

Table 2. Comparison of the heart rate variability indices between groups: chronic neck pain (n=30) and chronic low back pain (n=30).

	In supine						In standing					
	Group	Mean	SD	MD	95%CI	d	Group	Mean	SD	MD	95%CI	d
HRV (linear)												
Mean RR (ms)	CNP	803.31	111.11	-15.18	-69.64–39.28	0.144	CNP	638.53	115.30	-61.06	-117.35– -4.78	0.561
	LBP	818.49	99.32				LBP	699.59	102.10			
STD-RR (ms)	CNP	29.15	12.33	-4.18	-11.01–2.65	0.316	CNP	27.51	15.97	-1.75	-9.73–6.25	0.113
	LBP	33.32	14.03				LBP	29.26	14.93			
Mean HR (bpm)	CNP	75.93	9.51	1.55	-3.29–6.40	-0.116	CNP	96.58	15.33	9.19	2.13–16.24	-0.672
	LBP	74.38	9.23				LBP	87.40	11.74			
rMSSD (ms)	CNP	28.82	15.83	-7.91	-16.75–0.94	0.462	CNP	21.39	20.63	-1.93	-12.06–8.20	0.098
	LBP	36.73	18.30				LBP	23.31	18.50			
RR Tri	CNP	7.47	2.58	-1.15	-2.60–0.29	0.410	CNP	6.84	3.16	-1.35	-3.10–0.39	0.403
	LBP	8.62	3.01				LBP	8.20	3.58			
TINN (ms)	CNP	148.83	68.30	-20.37	-56.87–16.14	0.288	CNP	138.60	88.95	-2.80	-43.71–38.11	0.035
	LBP	169.20	72.88				LBP	141.40	67.96			
LF (nu)	CNP	50.99	19.12	8.40	-1.06–17.86	-0.459	CNP	66.98	21.75	2.53	-7.99–13.06	-0.124
	LBP	42.59	17.45				LBP	64.45	18.86			
HF (nu)	CNP	48.92	19.07	-8.37	-17.81–1.07	0.458	CNP	32.95	21.66	-2.58	-13.07–7.92	0.127
	LBP	57.29	17.43				LBP	35.53	18.84			
LF/HF (ratio)	CNP	1.72	2.36	0.77	-0.14–1.67	-0.440	CNP	4.36	5.68	1.04	-1.39–3.47	-0.221
	LBP	0.95	0.74				LBP	3.32	3.46			
Power LF (ms^2)	CNP	376.79	335.76	-111.25	-323.41–100.92	0.271	CNP	451.54	648.06	-89.52	-389.12–210.07	0.154
	LBP	488.04	473.59				LBP	541.06	502.06			
Power HF (ms^2)	CNP	394.96	416.70	-213.25	-449.57–23.06	0.466	CNP	243.38	404.59	-102.18	-386.77–182.41	0.186
	LBP	608.21	494.44				LBP	345.56	665.37			
HRV (nonlinear)												
SD1 (ms)	CNP	20.41	11.21	-5.60	-11.86–0.66	0.462	CNP	15.15	14.62	-1.37	-8.54–5.81	0.098
	LBP	26.01	12.96				LBP	16.51	13.11			
SD2 (ms)	CNP	35.43	14.42	-3.22	-11.27–4.83	0.207	CNP	34.88	19.15	-2.67	-12.14–6.81	0.146
	LBP	38.65	16.65				LBP	37.55	17.47			
SD2/SD1 (ratio)	CNP	1.95	0.70	0.35	0.03–0.66	-0.575	CNP	3.20	1.45	0.59	-0.02, 1.21	-0.493
	LBP	1.60	0.50				LBP	2.61	0.87			
Stress Index	CNP	22.39	38.12	7.83	-6.26–21.93	-0.287	CNP	19.57	7.94	1.32	-2.49–5.13	-0.179
	LBP	14.56	5.82				LBP	18.25	6.75			
Respiratory rate (bpm)												
	CNP	17.59	3.68	-0.09	-2.06–1.88	0.024	CNP	14.04	3.34	-0.82	-2.49–0.85	0.253
	LBP	17.68	3.95				LBP	14.86	3.13			

SD: standard deviation; MD: mean difference; CI: confidence interval; Cd: Cohen's d; HRV: heart rate variability; Mean RR: RR intervals mean; STD-RR: standard deviation of all RR intervals between two consecutive normal heartbeats; Mean HR: heart rate mean; BPM: beats or breaths per minute; rMSSD: root mean square differences of successive RR intervals; RR Tri: triangular index; TINN: triangular interpolation of the interval histogram; LF: low-frequency band in arbitrary units and in absolute values; HF: high-frequency band in arbitrary units and in absolute values; SD1: standard deviation of the instantaneous beat-to-beat variability; SD2: long-term standard deviation of continuous RR intervals.
Insignificant difference (independent t-test, $p>0.003$); insignificant effect size (Cohen's $d<0.8$).

Table 3. Correlations between heart rate variability indices and other study variables: chronic neck pain (n=30) and chronic low back pain (n=30).

	Chronic neck pain (n=30)							Chronic low back pain (n=30)						
	CPM	NPRSa	NPRSb	PCTS	TSK	PSEQ	NDI	CPM	NPRSa	NPRSb	PCTS	TSK	PSEQ	RMDQ
HRV supine (linear)														
Mean RR (ms)	0.184	-0.026	-0.226	-0.085	-0.112	0.144	0.069	-0.033	-0.024	-0.337	**-0.397***	-0.264	0.121	-0.210
STD-RR (ms)	-0.063	-0.248	-0.242	-0.140	-0.050	**0.571***	**-0.444***	-0.224	0.038	-0.308	**-0.414***	-0.180	0.216	-0.123
Mean HR (bpm)	-0.186	0.022	0.224	0.088	0.116	-0.142	-0.069	0.033	0.024	0.337	**0.397***	0.264	-0.121	0.210
rMSSD (ms)	-0.093	-0.211	-0.130	-0.211	-0.181	**0.504***	**-0.466***	-0.117	-0.048	**-0.362***	**-0.516***	-0.246	0.286	-0.199
RR Tri	-0.114	-0.361	**-0.386***	0.042	-0.049	**0.462***	**-0.376***	-0.161	-0.094	**-0.472***	**-0.475***	-0.215	0.193	-0.245
TINN (ms)	-0.107	-0.239	-0.226	-0.162	-0.059	**0.548***	**-0.448***	-0.196	0.040	-0.244	**-0.422***	-0.210	0.249	-0.112
LF (nu)	0.099	0.117	0.053	0.189	**0.427***	**-0.409***	0.336	-0.184	0.219	0.052	0.339	0.018	-0.322	0.092
HF (nu)	-0.099	-0.117	-0.053	-0.189	**-0.427***	**0.409***	-0.336	0.179	-0.217	-0.050	-0.349	-0.025	0.323	-0.091
LF/HF (ratio)	0.095	0.120	0.051	0.188	**0.425***	**-0.410***	0.330	-0.179	0.217	0.050	0.349	0.025	-0.323	0.091
Power LF (ms^2)	-0.104	-0.165	-0.281	0.139	0.233	0.125	-0.084	-0.305	0.118	-0.244	-0.234	-0.145	-0.087	-0.071
Power HF (ms^2)	-0.228	-0.251	-0.349	-0.057	-0.203	**0.493***	**-0.442***	-0.115	-0.109	**-0.426***	**-0.518***	-0.170	0.229	-0.216
HRV supine (nonlinear)														
SD1 (ms)	-0.093	-0.211	-0.130	-0.211	-0.181	**0.504***	**-0.466***	-0.117	-0.048	**-0.362***	**-0.516***	-0.246	0.286	-0.199
SD2 (ms)	-0.095	-0.251	-0.348	-0.102	-0.007	**0.531***	**-0.432***	-0.281	0.052	-0.261	-0.354	-0.149	0.107	-0.084
SD2/SD1 (ratio)	0.146	-0.011	-0.157	0.086	0.270	-0.223	0.263	-0.200	0.053	0.096	0.267	0.145	-0.307	0.145
Stress Index	-0.038	0.291	0.310	0.091	-0.012	**-0.549***	**0.381***	0.174	-0.059	0.302	0.443*	0.222	-0.224	0.157
HRV standing (linear)														
Mean RR (ms)	-0.049	0.125	-0.334	0.043	-0.072	0.074	-0.136	-0.088	-0.040	-0.112	**-0.451***	**-0.389***	-0.074	-0.090
STD-RR (ms)	**-0.448***	-0.002	-0.236	-0.090	-0.225	0.196	**-0.408***	**-0.397***	-0.042	-0.178	-0.224	-0.164	-0.102	0.083
Mean HR (bpm)	0.049	-0.125	0.334	-0.043	0.072	-0.074	0.136	0.088	0.040	0.112	**0.451***	**0.389***	0.074	0.090
rMSSD (ms)	**-0.432***	0.121	-0266	0.021	-0.211	0.126	-0.215	-0.269	-0.104	-0.218	**-0.453***	**-0.373***	-0.074	-0.012
RR Tri	-0.277	0.007	-0.270	-0.069	-0.074	0.112	**-0.414***	-0.278	0.028	-0.142	-0.270	-0.240	-0.142	0.085
TINN (ms)	**-0.484***	0.039	-0.169	-0.041	-0.179	0.079	-0.309	**-0.424***	-0.042	-0.181	-0.197	-0.175	-0.093	0.135
LF (nu)	**0.393***	-0.118	0.074	-0.205	0.128	-0.019	0.041	0.051	0.099	0.059	0.336	0.326	0.016	0.042
HF (nu)	**-0.393***	0.118	-0.074	0.205	-0.128	0.019	-0.041	-0.051	-0.099	-0.059	-0.336	-0.326	-0.016	-0.042
LF/HF (ratio)	**0.393***	-0.118	0.074	-0.205	0.128	-0.019	0.041	0.051	0.099	0.059	0.336	0.326	0.016	0.042
Power LF (ms^2)	-0.087	-0.135	-0.324	-0.212	-0.106	0.298	**-0.447***	-0.321	0.032	-0.078	0.074	-0.027	-0.170	0.111
Power HF (ms^2)	**-0.444***	0.093	-0.264	0.037	-0.213	0.232	-0.343	-0.268	0.015	0.013	-0.244	**-0.416***	-0.079	0.112
HRV standing (nonlinear)														
SD1 (ms)	**-0.432***	0.121	-0.266	0.021	-0.211	0.126	-0.215	-0.269	-0.104	-0.218	**-0.453***	**-0.373***	-0.074	-0.012
SD2 (ms)	**-0.403***	-0.038	-0.267	-0.055	-0.110	0.175	**-0.427***	**-0.424***	-0.020	-0.175	-0.158	-0.127	-0.132	0.113
SD2/SD1 (ratio)	0.340	-0.168	0.138	-0.148	0.081	0.020	-0.088	-0.031	0.008	0.037	**0.440***	0.350	0.003	0.001
Stress Index	**0.435***	-0.034	0.262	0.082	0.289	-0.183	**0.368***	**0.367***	0.076	0.229	0.309	0.214	0.092	-0.078

CPM: chronicity of pain in months; NPRSa: Numeric Pain Rating Scale at rest; NPRSb: Numeric Pain Rating Scale after movements; PCTS: Pain-Related Catastrophizing Thoughts Scale; TSK: Tampa Scale of kinesiophobia; PSEQ: Pain Self-Efficacy Questionnaire; NDI: Neck Disability Index; RMDQ: Rolan-Morris Disability Questionnaire; HRV: heart rate variability; Mean RR: RR intervals mean; STD-RR: standard deviation of all RR intervals between two consecutive normal heartbeats; Mean HR: heart rate mean; rMSSD: root mean square differences of successive RR intervals; RR Tri: triangular index; TINN: triangular interpolation of the interval histogram; LF: low-frequency band in arbitrary units and in absolute values; HF: high-frequency band in arbitrary units and in absolute values; SD1: standard deviation of the instantaneous beat-to-beat variability; SD2: long-term standard deviation of continuous RR intervals.

*Significant correlation (Spearman's correlation coefficient, $p<0.05$).

When using the heart as an object of investigation of the sympathetic and parasympathetic activities of the nervous system, this study concentrated the collections for the analysis of the physiological parameters in a specific organ that has greater proximity to the cervical region and the parasympathetic system. Thus, even if the CNP is less disabling than the LBP, it is possible to understand the fact that we found greater correlations with HRV indices in the CNP, since parasympathetic actions are more accurate and harmonic in the cervical-brain stem-heart complex, while sympathetic actions, located anatomically close to the lumbar region, are imprecise, less related to parasympathetic ramifications, and more systemic from a physiological point of view[15-17].

Since HRV has significant correlations with a wide range of psychosocial factors in which irregular emotional responses are associated with autonomic dysregulation and reduced HRV, when considering that LBP is more disabling than CNP and that HRV is considered an autonomic marker of emotional regulation capacity[37], it is possible to understand the fact that catastrophizing pain in patients with LBP is more correlated with linear and nonlinear HRV indices than in patients with CNP, because the more disabling the spinal pain, the more catastrophic thoughts and fear exist.

This study has limitations. The menstrual cycle was not a controlled variable, we recorded the RR intervals using a cardiofrequency meter, and the majority of the sample was women. Thus, we emphasize the need for further studies to reproduce this research using other devices for recording RR intervals, such as, electrocardiogram, H10 Polar[38], Bluetooth sensor (wireless)[39], and Elite HRV (smartphone app)[40]; in addition, we suggest studies to compare samples containing the same amounts of both sexes in the groups.

CONCLUSIONS

The autonomic dysfunction of individuals with CNP, when compared to patients with LBP, does present insignificant differences. Both groups showed correlations between pain measures and HRV; however, disability and self-efficacy were correlated with HRV only in patients with CNP, while catastrophizing and kinesiophobia showed greater correlations with HRV in patients with LBP.

Ethical approval: Research involving human subjects complied with all relevant national regulations, institutional policies (Resolutions 196/1996 and 466/2012), and is in accordance with the tenets of the Helsinki Declaration (as amended in 2013), and has been approved by the equivalent research ethical committee (protocol number: 3.408.949).

ACKNOWLEDGMENTS

I dedicate this publication to my beloved mother, Maria de Fátima Pontes Silva (Dona Pretinha), and grandmother, Maria Luiza de Oliveira Pontes (Dona Luiza, *in memoriam*), you kindly gave me (and give me) the strength to walk in the life's road; to my great friend Fabíola Almeida, who kindly gave me access to the clinic to evaluate the study participants; and to my good friend/brother/professor Almir Vieira Dibai Filho, who kindly trusted me. I love you all.

AUTHORS' CONTRIBUTIONS

APS: Conceptualization, Data curation, Formal Analysis, Writing – original draft. **DBD:** Conceptualization, Formal Analysis. **CAFPG:** Conceptualization. **CSS:** Formal Analysis, Writing – original draft. **FOP:** Formal Analysis, Writing – original draft. **CTM:** Conceptualization, Formal Analysis. **AVDF:** Conceptualization, Formal Analysis.

REFERENCES

1. Tracy LM, Ioannou L, Baker KS, Gibson SJ, Georgiou-Karistianis N, Giummarra MJ. Meta-analytic evidence for decreased heart rate variability in chronic pain implicating parasympathetic nervous system dysregulation. Pain. 2016;157(1):7-29. https://doi.org/10.1097/j.pain.0000000000000360
2. Goudman L, Brouns R, Linderoth B, Moens M. Effects of Spinal Cord Stimulation on Heart Rate Variability in Patients With Failed Back Surgery Syndrome: Comparison Between a 2-lead ECG and a Wearable Device. Neuromodulation. Published online 2019:1-17. https://doi.org/10.1111/ner.13091
3. Sripanidkulchai B, Promthep K, Tuntiyasawasdikul S, Tabboon P, Areemit R. Extract enhances physical fitness and modulates parameters of heart rate variability in adolescent student-athletes: a randomized, double-blind, placebo-controlled clinical study supplementation of Kaempferia parviflora extract enhances physical fitness. J Diet Suppl. 2020;0(0):1-18. https://doi.org/10.1080/19390211.2020.1852356
4. Hsu CC, Chen SR, Lee PH, Lin PC. The effect of music listening on pain, heart rate variability, and range of motion in older adults after total knee replacement. Clin Nurs Res. 2019;28(5):529-47. https://doi.org/10.1177/1054773817749108
5. Chinthakanan S, Laosuwan K, Boonyawong P, Kumfu S, Chattipakorn N, Chattipakorn SC. Reduced heart rate variability and increased saliva cortisol in patients with TMD. Arch Oral Biol. 2018;90:125-9. https://doi.org/10.1016/j.archoralbio.2018.03.011
6. Meeus M, Goubert D, De Backer F, Struyf F, Hermans L, Coppieters I, et al. Heart rate variability in patients with fibromyalgia and patients with chronic fatigue syndrome: a systematic review. Semin Arthritis Rheum. 2013;43(2):279-87. https://doi.org/10.1016/j.semarthrit.2013.03.004

7. Christensen MMB, Hommel EE, Jørgensen ME, Fleischer J, Hansen CS. Glycemic variability and diabetic neuropathy in young adults with type 1 diabetes. Front Endocrinol (Lausanne). 2020;11:644. https://doi.org/10.3389/fendo.2020.00644
8. Allen TM, Struemph KL, Toledo-Tamula MA, Wolters PL, Baldwin A, Widemann B,. The relationship between heart rate variability, psychological flexibility, and pain in neurofibromatosis type 1. Pain Pract. 2018;18(8):969-78. https://doi.org/10.1111/papr.12695
9. Palma S, Keilani M, Hasenoehrl T, Crevenna R. Impact of supportive therapy modalities on heart rate variability in cancer patients–a systematic review. ***Disabil Rehabil***. 2020;42(1):36-43. https://doi.org/10.1080/09638288.2018.1514664
10. Schwerdtfeger AR, Schwarz G, Pfurtscheller K, Thayer JF, Jarczok MN, Pfurtscheller G. Heart rate variability (HRV): From brain death to resonance breathing at 6 breaths per minute. Clin Neurophysiol. 2020;131(3):676-93. https://doi.org/10.1016/j.clinph.2019.11.013
11. Rangon C-M, Krantic S, Moyse E, Fougère B. The vagal autonomic pathway of COVID-19 at the crossroad of Alzheimer's disease and aging: a review of knowledge. J Alzheimer's Dis Reports. 2020;4(1):537-51. https://doi.org/10.3233/adr-200273
12. Chiera M, Cerritelli F, Casini A, Barsotti N, Boschiero D, Cavigioli F, et al. Heart rate variability in the perinatal period: a critical and conceptual review. Front Neurosci. 2020;14:1-23. https://doi.org/10.3389/fnins.2020.561186
13. Ishikawa M. Clinical potential of pupillary light reflex and heart rate variability parameters as biomarkers for assessing pain relief effects on autonomic function: A prospective longitudinal study. Biomed Phys Eng Express. 2020;6(5):55003. https://doi.org/10.1088/2057-1976/aba132
14. Godoy M, Takakura I, Correa P. The relevance of nonlinear dynamic analysis (Chaos Theory) to predict morbidity and mortality in patients undergoing surgical myocardial revascularization. Arq Ciênc Saúde. 2005;12(4):167-71.
15. Santos-de-Araújo AD, Dibai-Filho AV, Santos SN, Alcântara EV, Souza CS, Gomes CAFP, et al. Correlation Between chronic neck pain and heart rate variability indices at rest: a cross-sectional study. J Manipulative Physiol Ther. 2019;42(4):219-26. https://doi.org/10.1016/j.jmpt.2018.11.010
16. Bandeira PM, Reis FJJ, Sequeira VCC, Chaves ACS, Fernandes O, Arruda-Sanchez T. Heart rate variability in patients with low back pain: a systematic review. Scand J Pain. 2021;21(3):426-33. https://doi.org/10.1515/sjpain-2021-0006
17. Telles S, Sharma SK, Gupta RK, Bhardwaj AK, Balkrishna A. Heart rate variability in chronic low back pain patients randomized to yoga or standard care. BMC Complement Altern Med. 2016;16(1):1-7. https://doi.org/10.1186/s12906-016-1271-1
18. Altug F, Kavlak E, Kurtca MP, Ünal A, Cavlak U. Comparison of pain intensity, emotional status and disability level in patients with chronic neck and low back pain. J Back Musculoskelet Rehabil. 2015;28(3):505-8. https://doi.org/10.3233/BMR-140548
19. Ostelo RWJG, Deyo RA, Stratford P, Waddell G, Croft P, Von Korff M, Bouter LM, De Vet HC. Interpreting change scores for pain and functional status in low back pain: Towards international consensus regarding minimal important change. Spine (Phila Pa 1976). 2008;33(1):90-4. https://doi.org/10.1097/BRS.0b013e31815e3a10
20. Ferreira-Valente MA, Pais-Ribeiro JL, Jensen MP. Validity of four pain intensity rating scales. ***Pain***. 2011;152(10):2399-404. https://doi.org/10.1016/j.pain.2011.07.005
21. Dibai-Filho AV, Oliveira AK, Girasol CE, Dias FRC, Jesus Guirro RR. Additional effect of static ultrasound and diadynamic currents on myofascial trigger points in a manual therapy program for patients with chronic neck pain: a randomized clinical trial. Am J Phys Med Rehabil. 2017;96(4):243-52. https://doi.org/10.1097/PHM.0000000000000595
22. Cook C, Richardson JK, Braga L, Menezes A, Soler X, Kume P, et al. Cross-cultural adaptation and validation of the Brazilian Portuguese version of the neck disability index and neck pain and disability scale. Spine (Phila Pa 1976). 2006;31(14):1621-7. https://doi.org/10.1097/01.brs.0000221989.53069.16
23. Oliveira RF, Costa LOP, Nascimento LP, Rissato LL. Directed vertebral manipulation is not better than generic vertebral manipulation in patients with chronic low back pain: a randomised trial. J Physiother. 2020;66(3):174-9. https://doi.org/10.1016/j.jphys.2020.06.007
24. Costa LOP, Maher CG, Latimer J, Ferreira PH, Pozzi GC, Ribeiro RN. Psychometric characteristics of the Brazilian-Portuguese versions of the functional rating index and the roland morris disability questionnaire. Spine (Phila Pa 1976). 2007;32(17):1902-7. https://doi.org/10.1097/BRS.0b013e31811eab33
25. Pontes-Silva A, Avila MA, Araujo AS, Penha TFC, Takahasi HY, Bassi-Dibai D, et al. Assessment of the reliability of the leg lateral reach test to measure thoraco-lumbo-pelvic rotation in individuals with chronic low back pain. J Manipulative Physiol Ther. 2021;44(7):566-72. https://doi.org/10.1016/j.jmpt.2021.12.001
26. Sardá-Junior J, Nicholas MK, Pereira IA, Pimenta CAM, Asghari A, Cruz RMC. Validation of the pain-related catastrophizing thoughts scale. Bangladesh J Med Sci. 2008;34(1):1-17. https://doi.org/10.5935/0104-7795.20080001
27. Siqueira FB, Teixeira-Salmela LF, Magalhães LDC. Analysis of the psychometric properties of the Brazilian version of the Tampa scale for Kinesiophobia. 2007;15(1):19-24. https://doi.org/10.1590/S1413-78522007000100004
28. Nicholas MK. The pain self-efficacy questionnaire: taking pain into account. Eur J Pain. 2007;11(2):153-163. https://doi.org/10.1016/j.ejpain.2005.12.008
29. Matsudo SM, Araújo T, Matsudo V, Andrade D, Oliveira LC, Braggion G. International physical activity questionnarie (IPAQ): study of validity and reliability in Brazil. Rev Bras Ativ Fis Saúde. 2001[cited on Apr 27, 2022];6(2):6-18. Available from: https://rbafs.org.br/RBAFS/article/view/931/1222
30. Task Force of the European Society of Cardiology the North American Society of Pacing E. Heart rate variability: standards of measurement, physiological interpretation, and clinical use. Circulation. 1996;93(6):1043-65. https://doi.org/10.1111/j.1540-8167.2006.00501.x
31. Pincus SM. Approximate entropy as a measure of system complexity. Proc Natl Acad Sci U S A. 1991;88(6):2297-301. https://doi.org/10.1073/pnas.88.6.2297
32. Piskorski J, Guzik P. Geometry of the Poincaré plot of RR intervals and its asymmetry in healthy adults. Physiol Meas. 2007;28(3):287-300. https://doi.org/10.1088/0967-3334/28/3/005
33. Sztajzel J. Heart rate variability: A noninvasive electrocardiographic method to measure the autonomic nervous system. Swiss Med Wkly. 2004;134(35-36):514-22. https://doi.org/2004/35/smw-10321
34. Dibai-Filho AV, Packer AC, Costa ACS, Rodrigues-Bigaton D. The chronicity of myogenous temporomandibular disorder changes the skin temperature over the anterior temporalis muscle. J Bodyw Mov Ther. 2014;18(3):430-4. https://doi.org/10.1016/j.jbmt.2013.11.001
35. Cohen J. Statistical power analysis for the behavioral sciences. Academic Press; 1977.
36. Curtin F, Schulz P. Multiple correlations and Bonferroni's correction. Biol Psychiatry. 1998;44(8):775-7. https://doi.org/10.1016/S0006-3223(98)00043-2

37. Macatee RJ, Albanese BJ, Schmidt NB, Cougle JR. The moderating influence of heart rate variability on stressor- elicited change in pupillary and attentional indices of emotional processing: an eye-tracking study. Physiol Behav. 2017;176(3):139-48. https://doi.org/10.1016/j.biopsycho.2016.11.013

38. Pereira RA, Alves JLB, Silva JHC, Costa MS, Silva AS. Validity of a smartphone application and chest strap for recording RR intervals at rest in Athletes. Int J Sports Physiol Perform. 2020;15(6):896-9. https://doi.org/10.1123/ijspp.2019-0406

39. Correia B, Dias N, Costa P, Pêgo JM. Validation of a wireless bluetooth photoplethysmography sensor used on the earlobe for monitoring heart rate variability features during a stress-inducing mental task in healthy individuals. Sensors (Switzerland). 2020;20(14):1-19. https://doi.org/10.3390/s20143905

40. Perrotta AS, Jeklin AT, Hives BA, Meanwell LE, Warburton DER. Validity of the elite hrv smartphone application for examining heart rate variability in a field-based setting. J Strength Cond Res. 2017;31(8):2296-302. https://doi.org/10.1519/JSC.0000000000001841

ORIGINAL ARTICLE

https://doi.org/10.1590/1806-9282.20220410

Prognostic value of the TyG index for in-hospital mortality in nondiabetic COVID-19 patients with myocardial injury

Halil İbrahim Biter[1], Muhsin Kalyoncuoğlu[1], Aydın Rodi Tosu[1], Sinem Çakal[1], Ziya Apaydın[1], Ayça Gümüşdağ[1], Tufan Çınar[2*], Ferhat Eyüpkoca[3], Erdal Belen[1], Mehmet Mustafa Can[1]

SUMMARY

OBJECTIVE: The purpose of this study was to explore the efficacy of the triglyceride glucose (TyG) index on in-hospital mortality in nondiabetic coronavirus disease 2019 (COVID-19) patients with myocardial injury.

METHODS: This was a retrospective study, which included 218 nondiabetic COVID-19 patients who had myocardial injury. The TyG index was derived using the following equation: log [serum triglycerides (mg/dL) ×fasting blood glucose (mg/dL)/2].

RESULTS: Overall, 49 (22.4%) patients died during hospitalization. Patients who did not survive had a higher TyG index than survivors. In multivariate Cox regression analysis, it was found that the TyG index was independently associated with in-hospital death. A TyG index cutoff value greater than 4.97 was predicted in-hospital death in nondiabetic COVID-19 patients with myocardial damage, with 82% sensitivity and 66% specificity. A pairwise evaluation of receiver operating characteristic (ROC) curves demonstrated that the TyG index (AUC: 0.786) had higher discriminatory performance than both triglyceride (AUC: 0.738) and fasting blood glucose (AUC: 0.660) in predicting in-hospital mortality among these patients.

CONCLUSIONS: The TyG index might be used to identify high-risk nondiabetic COVID-19 patients with myocardial damage.

KEYWORDS: Triglyceride. COVID-19. Myocardial. Damage.

INTRODUCTION

Coronavirus disease 2019 (COVID-19) caused by the severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) has been a global pandemic since December 2019[1]. Although the lungs are its primary target, it can damage other organs and systems as well. Targeting the cardiovascular system is critical since the overall prognosis is poor, particularly in individuals with underlying cardiovascular disorders (CVD)[1]. Remarkably, severe COVID-19 individuals have higher risk of heart failure and thrombotic complications[1].

Insulin resistance (IR) is one of the most significant CVD risk factor[2]. In addition, IR is thought to be an independent risk factor for poor cardiovascular outcomes in diabetic individuals[3]. In addition, numerous cross-sectional and prospective studies have provided clinical evidence that IR is associated with elevated cardiovascular risk in nondiabetic individuals that is independent from other risk factors[4]. Although IR may be assessed directly using a hyperinsulinemic euglycemic glucose clamp or an insulin suppression test, these procedures are difficult, expensive, and complicated. The recently developed triglyceride glucose (TyG) index, on the other hand, is an easily measurable indicator with good sensitivity and specificity in predicting the IR and its accompanying metabolic abnormalities. Recently, it has been proposed that the TyG index as a surrogate marker of IR is an independent risk predictor for adverse cardiovascular events in nondiabetic patients who are diagnosed with acute coronary syndrome undergoing percutaneous coronary intervention[5]. To the best of our knowledge, no data exist in the literature assessing the TyG index's prognostic value for in-hospital mortality in nondiabetic COVID-19 patients with myocardial damage. As a result, the focus of this research was to explore the prognostic accuracy of the TyG index for in-hospital mortality in nondiabetic COVID-19 subjects with myocardial injury.

METHODS

We evaluated the clinical notes of 350 consecutive individuals with a definite diagnosis of COVID-19 and myocardial damage in this retrospective, observational research. Patients who were

[1]Health Sciences University, Sultangazi Haseki Training and Research Hospital, Department of Cardiology – Istanbul, Turkey.
[2]Health Sciences University, Sultan Abdülhamid Han Training and Research Hospital, Department of Cardiology – Istanbul, Turkey.
[3]Doctor Nafiz Korez Sincan State Hospital – Ankara, Turkey.
*Corresponding author: drtufancinar@gmail.com
Conflicts of interest: the authors declare there is no conflicts of interest. Funding: none.
Received on June 29, 2022. Accepted on July 02, 2022.

under the age of 18 (n=2), had diabetes (n=87), were pregnant (n=5), died at admission (n=7), were transported to another hospital (n=18), or had incomplete baseline data (n=13) were eliminated from the research.

The hospital electronic database was used to gather patients' baseline clinical and demographic properties such as body mass index (BMI), hypertension, diabetes mellitus (DM), current smoking status, coronary artery disease (CAD), chronic heart failure (CHF), chronic renal failure (CRF), cerebrovascular accident (CVA), cancer, and chronic obstructive pulmonary disease (COPD). A skilled team of physicians independently evaluated all data. Our study procedure followed the principles of the Helsinki Declaration, and it was approved by the Local Ethics Commission (decision number: 46-2022).

A positive SARS-CoV-2 laboratory report was interpreted as a positive finding on a real-time reverse-transcriptase polymerase chain reaction test of nasal or pharyngeal swab materials. According to the Fourth Universal Definition of Myocardial Infarction, myocardial damage was confirmed when the blood level of cardiac troponin surged over the 99th percentile upper reference threshold. The normal range of cardiac troponin in our institution was 0–14 pg/mL.

All fasting venous blood samples, including fasting blood glucose (FBG) and triglycerides, were obtained following admission. The TyG index was derived using the following equation: log [serum triglycerides (mg/dL) × FBG (mg/dL)/2]. The major goal of this study was to examine the COVID-19-related in-hospital mortality over the follow-up period. To acquire mortality data, the national death notification system and hospital records were analyzed.

Statistical analysis

Frequencies and percentages are used to represent categorical variables. The chi-square test was used to compare categorical data between groups. Continuous variables having a normal distribution were reported as mean (standard deviation [SD]), whereas those with a non-normal distribution were expressed as median (interquartile ranges [IQR]). The Kolmogorov-Smirnov test was used to determine the normality of variable distributions. The Student's t-test or Mann-Whitney U test was used to evaluate continuous variables between groups depending on distribution normality. Univariable and multivariable Cox regression analyses (enter technique) were used to determine the independent risk variables for in-hospital mortality. To identify the independent predictors of in-hospital death, parameters with a $p<0.05$ in univariable analysis were included in the multivariate Cox regression analysis. All findings provided as hazard ratio (HR) and 95% confidence interval (CI). The TyG score and its variables (triglyceride and FBG) were not included in the same multivariable Cox regression analysis models to avoid model overfitting. Triglyceride and FBG levels were assessed using a different multivariate analytic model (model 1) that did not contain the TyG index. The receiver operating characteristics (ROC) curve analysis was performed to assess the sensitivity and specificity of the TyG index, as well as its cutoff value in predicting in-hospital mortality. The area under the curve (AUC) was calculated to assess the diagnostic accuracy and discriminatory capability of TyG, triglyceride, and FBG levels. Using Youden's index, the best cutoff value was derived from the point of maximum sensitivity and specificity. A pairwise evaluation of ROC curves was also conducted to examine the discriminatory performance of TyG, triglyceride, and FBG. The Kaplan-Meier and long-rank tests were used to evaluate survival for the low and high TyG groups. The statistical significance level was set at $p=0.05$. For all statistical analyses, the Statistical Package for the Social Sciences version 24.0 software program (IBM Corp., Armonk, NY, USA) was used. The models' ROC curves were compared using the MEDCALC program (Software bvba version 13, Ostend, Belgium).

RESULTS

This research consisted of 218 nondiabetic individuals with a median age of 62 (57–74) years who had COVID-19 and had experienced myocardial damage. During hospitalization, 22.4 % of the patients (n=49) died. The participants in the research were categorized into two groups: those who died (nonsurvivor group) and those who did not (survivor group). Patients who died were older and overweight and had a greater prevalence of CAD, CHF, CRF, COPD, and malignancies than those who lived. In regard to laboratory measurements, nonsurvivors had greater triglyceride, FBG, TyG index, uric acid, C-reactive protein (CRP), and D-dimer levels; but they had lower estimated glomerular filtration rate, albumin, and lymphocyte levels. In terms of admission cardiac troponin levels, there was no difference between the two groups. Table 1 shows the study cohort's detailed demographic, clinical, and laboratory data.

In multivariable models 1 and 2, age, CHF, malignancy, uric acid, and TyG index (HR: 3.704 (95%CI 1.997–6.869, $p<0.001$) were predictors of in-hospital death (Table 2). Remarkably, both triglyceride and FBG were not independently associated with in-hospital mortality. When the discriminating power of the triglyceride, FBG, and TyG indexes were compared, it was discovered that the TyG index outperformed both triglyceride and FBG (Figure 1). An ROC curve analysis revealed that a TyG index value greater than 4.92 was an independent predictor

Table 1. Demographic, clinical, in-hospital outcomes and laboratory parameters of the study cohort.

	Survivors (n=169)	Non-survivors (n=49)	p-value
Male gender, n (%)	110 (65.1)	32 (65.3)	0.978
Age, year	60 [51-73]	71 [61-82]	<0.001
BMI, kg/m^2	25.9±2.6	27.1±2.9	0.005
Risk factors, n (%)			
CAD	31 (18.3)	19 (38.8)	0.003
CHF	20 (11.8)	14 (28.6)	0.004
Hypertension	66 (39.1)	23 (46.9)	0.323
CRF	28 (16.6)	15 (30.6)	0.030
Current smoking	49 (29)	14 (28.6)	0.954
COPD	31 (18.3)	17 (34.7)	0.015
Cancer	15 (8.9)	10 (20.4)	0.026
CVA	10 (5.9)	3 (6.1)	0.957
ACEI/ARB use history	49 (29)	14 (28.6)	0.954
In-hospital outcomes			
Needing ICU, n (%)	16 (9.5)	25 (51)	<0.001
Invasive mechanical ventilation, n (%)	6 (3.6)	21 (42.9)	<0.001
ARDS, n (%)	15(8.9)	18 (36.7)	<0.001
MOF, n (%)	3 (1.8)	7 (14.3)	<0.001
Acute kidney injury, n (%)	4 (2.4)	6 (12.2)	0.004
Fatal ventricular arrhythmia	1 (0.6)	5 (10.2)	<0.001
High grade AV block	2 (1.2)	0 (0)	0.444
Hospitalization period, days	7 [5-13]	13 [9-16]	<0.001
Laboratory findings			
Blood glucose, mg/dL	118 [93.5-153]	151 [107.5-223]	<0.001
Triglyceride, mg/dL	144 [103-200]	216 [165-344]	<0.001
TyG	4.86 [4.66-5.10]	5.25 [5.0-5.52]	<0.001
Uric acid, mg/dL	5.6±2.3	7.2±3.2	<0.001
eGFR, mL/min/1.73m^2	82 [63-100]	69 [42-83]	0.014
WBC, 10^3/uL	7.8 [5.1-10.1]	9.2 [6.5-13.5]	<0.001
Neutrophil, 10^3/uL	5.9 [3.6-8.2]	7.3 [5.2-12.4]	<0.001
Lymphocyte, 10^3/uL	1.0 [0.7-1.3]	0.7 [0.5-1.0]	<0.001
Hemoglobin, g/L	12.3±2.1	11.7±2.6	0.085
Platelet, 10^3/uL	211 [159-281]	219 [171-333]	0.537
D-Dimer, µg FEU/mL	0.7 [0.3-1.5]	1.5 [0.8-2.4]	<0.001
Ferritin, ng/mL	414 [158-757]	429 [138-1009]	0.364
CRP, mg/L	74 [32-155]	138 [64-243]	<0.001
Albumin, g/L	33.6±5.2	30.4±4.7	<0.001
Hs-Troponin I, pg/mL	45.8 [28 -91]	46.4 [24-118]	0.329

Continuous variables are presented as median (interquartile range) or mean (SD), Nominal variables presented as frequency (%). BMI: body mass index; CAD: coronary artery disease; CHF: congestive heart failure; CRF: chronic heart failure; COPD: chronic obstructive lung disease; CVA: cerebrovascular accident; ACEI/ARB: angiotensinogen converting enzyme/angiotensinogen receptor blockers; ICU: intensive care unit; ARDS: acute respiratory distress syndrome; MOF: multi organ failure; AV: atrioventricular; TyG: triglyceride glucose; eGFR: estimated glomerular filtration; WBC: white blood cell; CRP: C-reactive protein.

of in-hospital death with 89% specificity and 56% sensitivity in nondiabetic COVID-19 patients with myocardial damage. According to the Kaplan-Meier curves, individuals with a TyG index had a considerably increased risk of in-hospital death.

DISCUSSION

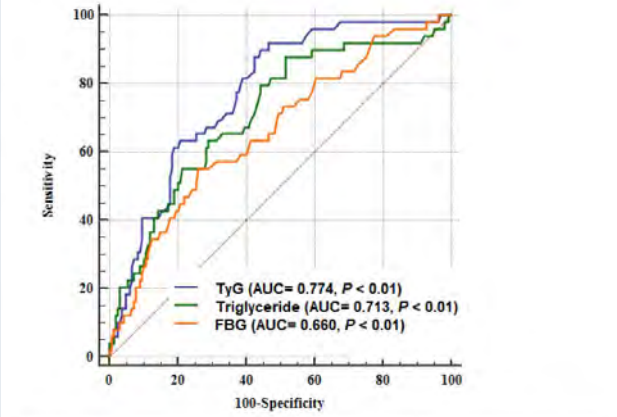
The following are the main results of this study:

1. In hospitalized nondiabetic COVID-19 patients with myocardial injury, the TyG index was independently related with in-hospital mortality;
2. TyG index was a better predictor than both triglyceride and FBG; and
3. Patients with TyG index greater than 4.92 were at high risk for in-hospital mortality in nondiabetic COVID-19 patients having myocardial injury.

The most common clinical manifestation of COVID-19 infection is lung involvement, although it can also cause cardiac complications, leading to poor prognosis[6]. Several recent investigations have found that the presence of CVD, in particular, is a risk factor in the progression of COVID-19 disease[1]. The presence of CHF was linked to in-hospital mortality in the current research. Although CAD was not determined to be a predictor, it was more prevalent in nonsurvivors. In keeping with earlier findings, nonsurvivors had higher rates of CRF, COPD, and cancer than survivors[7]. As a result, people with comorbidities such as CVD are not only more likely to become infected, but they are also more likely to develop more severe and fatal infections.

One of the primary causes of mortality from COVID-19 is myocardial damage[8]. According to several retrospective investigations, the incidence of cardiac myocyte damage in COVID-19 individuals ranges between 5 and 28%[9]. Cardiac troponin levels are strong indicators of worse outcomes in COVID-19 patients, in which may have a predictive role in optimizing risk categorization in such individuals[10,11]. Furthermore, elevated blood glucose levels upon admission and throughout hospitalization are linked to severe COVID-19 infection[12]. Although the cause of altered glucose and lipid metabolism in COVID-19 patients is unknown, the possible cause of high blood glucose during SARS-CoV-2 infection is connected to new-onset IR instead of insulin insufficiency. Further, it has been shown that IR may persist even after the virus has been eradicated[13].

Hyperinsulinemia may contribute to greater SARS-CoV-2 viremia in individuals with IR and diabetes because insulin enhances membrane transcription of angiotensin-converting enzyme 2 (ACE 2) in



Variables	Difference between areas	95%CI	z statistic	p
TyG vs Triglyceride	0.061	0.002 ?0.121	2.012	0.044
TyG vs FBG	0.114	0.040 ?0.187	3.037	0.002
FBG vs Triglyceride	0.052	-0,065 ?0.170	0.871	0.384

Figure 1. Diagnostic accuracy and discriminatory performance of triglyceride glucose, triglyceride, and blood glucose for detecting the in-hospital mortality using area under curve values.

Table 2. Independent risk factors that were found to be independently associated with in-hospital mortality according to univariate and multivariate models*.

	Univariate HR (95%CI)	p-value	Multivariate-1 HR (95%CI)	p-value	Multivariate-2 HR (95%CI)	p-value
Age	1.042 (1.017-1.067)	0.001	1.032 (1.006-1.058)	0.016	1.030 (1.005-1.055)	0.017
CAD	1.952 (1.088-3.502)	0.025	1.157 (0.594-2.253)	0.669	1.146 (0.541-2.023)	0.894
CHF	3.890 (2.029-7.461)	<0.001	2.216 (1.002-4.902)	0.049	2.274 (1.041-5.056)	0.039
Cancer	2.269 (1.126-4.570)	0.022	2.295 (1.048-5.022)	0.038	2.407 (1.146-5.056)	0.020
Uric acid	1.177 (1.076-1.288)	<0.001	1.139 (1.031-1.259)	0.011	1.130 (1.025-1.246)	0.014
Glucose	1.004 (1.002-1.007)	0.001	1.003 (1.000-1.006)	0.058	-	-
TG	1.001 (1.000-1.003)	0.008	1.001 (1.000-1.003)	0.054	-	-
TyG	3.711 (2.174-6.336)	<0.001	-	-	3.704 (1.997-6.869)	<0.001

*The variables with a p-value of less than 0.05 in the univariate analysis were incorporated into the multivariate cox regression analysis by using Enter method. HR: hazard ratio; CI: confidence interval; CAD: coronary artery disease; CHF: congestive heart failure; TG: triglyceride; TyG: triglyceride glucose.

the pneumocyte, which acts as a SARS receptor. Hyperinsulinemia and hyperglycemia can promote clotting, hence raising inflammation and the risk of thrombosis. Hyperinsulinemia raises plasminogen activator type 1 levels, which promotes thrombosis by blocking fibrinolysis, whereas hyperglycemia raises blood coagulation and the generation of pro-inflammatory cytokines, such as TNF-alpha and IL-6[14]. The mentioned factors may help explain the link between IR and unfavorable cardiovascular events in COVID-19 disease.

Even though IR may be determined directly using a hyperinsulinemic euglycemic glucose clamp or an insulin suppression test, these procedures are complex and costly in medical practice. Given the difficulties of directly assessing insulin action and the lack of a standardized insulin test, the TyG index may be related to CVD as a proxy of IR. The TyG index has been connected to CVD risk factors such as hypertension and metabolic syndrome. Some studies found that the TyG index was correlated to CVD in high-risk individuals, such as those with DM or CRF[15,16]. An elevated TyG index was also demonstrated to be a valuable alternative instrument for evaluating cardiovascular risk in nondiabetic individuals at the preclinical condition[17]. While some researchers have examined the relationships between the TyG index, IR, and CVD in the non-COVID-19 population. To the best of our knowledge, this is the first study to focus at the TyG index's prognostic value in nondiabetic COVID-19 patients with myocardial damage. The likely explanation behind the TyG index relation with worse cardiovascular outcome in COVID-19 has not yet been explained; however, we believe the following hypotheses may be relevant. First, the TyG index can indicate IR, which has been linked to endothelial dysfunction, oxidative stress, and inflammatory reaction. Second, the TyG index is related to IR, which can generate an instability in glucose metabolism, resulting in persistent hyperglycemia, as well as modify lipid metabolism, suggesting that such metabolic abnormalities may lead to cardiovascular damage. Finally, the TyG index is related to arterial stiffness as measured by pulse pressure and brachial-ankle pulse wave velocity, all of which are key risk factors for adverse cardiovascular outcomes[18].

Limitations

Our study may, however, have major limitations. First, our study was a retrospective assessment of a limited database that based on single-center experience. Second, we only examined the baseline TYG index upon admission, and the alterations revealed by serial measurements may have an incremental prognostic value. Third, we did not collect data about plasma insulin levels, HbA1c, Homeostatic Model Assessment-IR, and brain natriuretic peptide. More multicenter prospective investigations including more participants are required to assess the TyG index's predictive accuracy in detecting poor cardiovascular outcome in the nondiabetic COVID-19 cohort.

CONCLUSIONS

We believe that TyG could be part of cardiovascular evaluation to identify nondiabetic COVID-19 patients with myocardial injury who are at high risk of having worse prognosis.

AUTHORS' CONTRIBUTIONS

HIB: Conceptualization, Data curation, Funding acquisition, Investigation, Methodology, Project administration, Resources, Writing – original draft, Writing – review & editing. **MK:** Conceptualization, Formal analysis, Investigation, Methodology, Software, Writing – original draft, Writing – review & editing. **ART:** Conceptualization, Investigation, Software, Writing – original draft, Writing – review & editing. **SÇ:** Funding acquisition, Writing – review & editing. **ZA:** Data curation, Funding acquisition, Writing – review & editing. **AG:** Data curation, Funding acquisition, Writing – review & editing. **TÇ:** Project administration, Resources, Visualization, Writing – original draft, Writing – review & editing. **FE:** Validation, Visualization, Writing – original draft, Writing – review & editing. **EB:** Project administration, Resources, Supervision, Validation, Writing – review & editing. **MMC:** Project administration, Resources, Supervision, Validation, Writing – review & editing.

REFERENCES

1. Larcher R, Besnard N, Akouz A, Rabier E, Teule L, Vandercamere T, et al. Admission high-sensitive cardiac troponin T level increase is independently associated with higher mortality in critically ill patients with COVID-19: a multicenter study. J Clin Med. 2021;10(8):1656. https://doi.org/10.3390/jcm10081656
2. Barzegar N, Tohidi M, Hasheminia M, Azizi F, Hadaegh F. The impact of triglyceride-glucose index on incident cardiovascular events during 16 years of follow-up: Tehran Lipid and Glucose Study. Cardiovasc Diabetol. 2020;19(1):155. https://doi.org/10.1186/s12933-020-01121-5
3. Jeppesen J, Hansen TW, Rasmussen S, Ibsen H, Torp-Pedersen C, Madsbad S. Insulin resistance, the metabolic syndrome, and risk of incident cardiovascular disease: a population-based study. J Am Coll Cardiol. 2007;49(21):2112-9. https://doi.org/10.1016/j.jacc.2007.01.088
4. Adeva-Andany MM, Martínez-Rodríguez J, González-Lucán M, Fernández-Fernández C, Castro-Quintela E. Insulin resistance is a cardiovascular risk factor in humans. Diabetes Metab Syndr. 2019;13(2):1449-55. https://doi.org/10.1016/j.dsx.2019.02.023

5. Zhao Q, Zhang TY, Cheng YJ, Ma Y, Xu YK, Yang JQ, et al. Triglyceride-glucose index as a surrogate marker of insulin resistance for predicting cardiovascular outcomes in nondiabetic patients with non-st-segment elevation acute coronary syndrome undergoing percutaneous coronary intervention. J Atheroscler Thromb. 2021;28(11):1175-94. https://doi.org/10.5551/jat.59840
6. Wang D, Hu B, Hu C, Zhu F, Liu X, Zhang J, et al. Clinical characteristics of 138 hospitalized patients with 2019 novel coronavirus-infected pneumonia in Wuhan, China. JAMA. 2020;323(11):1061-9. https://doi.org/10.1001/jama.2020.1585
7. Huang C, Wang Y, Li X, Ren L, Zhao J, Hu Y, et al. Clinical features of patients infected with 2019 novel coronavirus in Wuhan, China. Lancet. 2020;395(10223):497-506. https://doi.org/10.1016/S0140-6736(20)30183-5
8. Deng Q, Hu B, Zhang Y, Wang H, Zhou X, Hu W, et al. Suspected myocardial injury in patients with COVID-19: evidence from front-line clinical observation in Wuhan, China. Int J Cardiol. 2020;311:116-21. https://doi.org/10.1016/j.ijcard.2020.03.087
9. El Rhalete A, Rhazi I, Bensaid A, Zaid I, Bkiyer H, Ismaili N, et al. Cardiovascular injuries during COVID-19 infection: a PROCESS-compliant case series from the Eastern Morocco. Ann Med Surg (Lond). 2021;65:102309. https://doi.org/10.1016/j.amsu.2021.102309
10. Tanboğa IH, Canpolat U, Çetin EHÖ, Kundi H, Turan S, Celik O, et al. The prognostic role of cardiac troponin in hospitalized COVID-19 patients. Atherosclerosis. 2021;325:83-8. https://doi.org/10.1016/j.atherosclerosis.2021.04.006
11. Qin JJ, Cheng X, Zhou F, Lei F, Akolkar G, Cai J, et al. Redefining cardiac biomarkers in predicting mortality of inpatients with COVID-19. Hypertension. 2020;76(4):1104-12. https://doi.org/10.1161/HYPERTENSIONAHA.120.15528
12. Cheng MP, Cau A, Lee TC, Brodie D, Slutsky A, Marshall J, et al. Acute cardiac injury in coronavirus disease 2019 and other viral infections-a systematic review and meta-analysis. Crit Care Med. 2021;49(9):1558-66. https://doi.org/10.1097/CCM.0000000000005026
13. Habets MAW, Sturkenboom HN, Tio RA, Belfroid E, Hoogervorst-Schilp J, Siebelink HJ, et al. How often and to what extent do admitted COVID-19 patients have signs of cardiac injury? Neth Heart J. 2021;29(Suppl 1):5-12. https://doi.org/10.1007/s12471-021-01571-w
14. Dweck MR, Bularga A, Hahn RT, Bing R, Lee KK, Chapman AR, et al. Global evaluation of echocardiography in patients with COVID-19. Eur Heart J Cardiovasc Imaging. 2020;21(9):949-58. https://doi.org/10.1093/ehjci/jeaa178
15. Guo W, Zhu W, Wu J, Li X, Lu J, Qin P, et al. Triglyceride glucose index is associated with arterial stiffness and 10-year cardiovascular disease risk in a Chinese population. Front Cardiovasc Med. 2021;8:585776. https://doi.org/10.3389/fcvm.2021.585776
16. Toro-Huamanchumo CJ, Urrunaga-Pastor D, Guarnizo-Poma M, Lazaro-Alcantara H, Paico-Palacios S, Pantoja-Torres B, et al. Triglycerides and glucose index as an insulin resistance marker in a sample of healthy adults. Diabetes Metab Syndr. 2019;13(1):272-7. https://doi.org/10.1016/j.dsx.2018.09.010
17. Ali J, Khan FR, Ullah R, Hassan Z, Khattak S, Lakhta G, et al. Cardiac troponin I levels in hospitalized COVID-19 patients as a predictor of severity and outcome: a retrospective cohort study. Cureus. 2021;13(3):e14061. https://doi.org/10.7759/cureus.14061
18. Li L, Hill J, Spratt JC, Jin Z. Myocardial injury in severe COVID-19: identification and management. Resuscitation. 2021;160:16-7. https://doi.org/10.1016/j.resuscitation.2020.11.040

ORIGINAL ARTICLE

https://doi.org/10.1590/1806-9282.20220421

Evaluation of the quality of life of patients with premature ejaculation (lifelong and acquired)

Bahadır Ermeç[1], Uğur Yucetas[2], Haydar Güler[3], Mehmet Gokhan Culha[1*], Mustafa Kadıhasanoğlu[3]

SUMMARY

OBJECTIVE: The aim of this study was to evaluate the quality of life of patients with lifelong and acquired premature ejaculation and to examine its relationship with depression and anxiety.

METHODS: Between February 2017 and January 2018, a total of 175 patients with premature ejaculation and 132 control men who applied to the urology department of the training and research hospital with the complaint of Premature Ejaculation were included. Patients were divided into three groups according to International Society for Sexual Medicine (ISSM) criteria as follows: Group 1, lifelong premature ejaculation; Group 2, acquired premature ejaculation, and Group 3, control group without premature ejaculation. A detailed medical history of patients was obtained and physical examinations were performed. Intravaginal ejaculation latency time (IELT) was recorded and patients were administered International Erectile Function Index-5 (IIEF-5), Premature Ejaculation Diagnostic Tool (PEDT), Sexual Health Inventory for Men (SHIM), Beck Depression Inventory (BDI), State-Trait Anxiety Inventory (STAI)-1 and STAI-2, and Short Form-36 (SF-36).

RESULTS: The mean mental component score (MCS) of the SF-36 was 51.65±6.57 in the lifelong premature ejaculation group, 49.33±8.65 in the acquired premature ejaculation group, and 61.12±11.09 in the control group ($p<0.0001$). The mean physical component score (PCS) was 50.99±7.43 in the lifelong premature ejaculation group, 48.32±11.58 in the acquired premature ejaculation group, and 55.17±8.10 in the control group ($p<0.0001$). Quality of life of premature ejaculation patients as assessed by SF-36 was lower in the subscales of physical functioning, general health perception, vitality, and role limitations due to emotional functioning, compared to the control group.

CONCLUSIONS: Lifelong and acquired premature ejaculation patients deteriorate their quality of life: the deterioration in these patients' quality of life also negatively affects their depression and anxiety states.

KEYWORDS: Premature ejaculation. Ejaculation. Quality of life. Latency time.

INTRODUCTION

Premature ejaculation (PE) is a common sexual disorder in men and approximately one in three men suffer from PE, of which underlying mechanisms have not yet been fully well understood[1]. Based on the 2014 definition of the International Society for Sexual Medicine (ISSM), PE is stated as the inability to control or delay ejaculation, resulting in dissatisfaction or distress for the patient. It is classified as lifelong or acquired PE. Lifelong PE is defined as ejaculation that always or almost always occurs prior to or within 1 min of vaginal penetration from the first sexual experience, while acquired PE is a clinically significant and disturbing decline in the ejaculation time, often up to 3 min[2].

In the literature, psychological negative effects occur in men with PE and in their female partners, including anxiety, depression, and distress. Psychosocial or interpersonal distress caused by PE can affect the quality of life (QoL) of men and their partner relationships, self-respect, and self-confidence. This situation can create an obstacle for men who is not in a relationship in establishing new relationships[3,4].

In recent years, as the awareness of individuals on sexual attitudes has increased, more attention is paid to the impact on the QoL for patients and sexual partners with PE. Both patients and their partners complain of decreased sexual self-respect, self-esteem, and QoL[5].

[1]University of Health Sciences, Prof. Dr. Cemil Tascioglu City Hospital, Department of Urology – Istanbul, Turkey.
[2]Istanbul Training and Research Hospital, Department of Urology – Istanbul, Turkey.
[3]Kanuni Sultan Suleyman Training and Research Hospital, Department of Urology – Istanbul, Turkey.
*Corresponding author: gokhan_culha64@hotmail.com
Conflicts of interest: the authors declare there is no conflicts of interest. Funding: none.
Received on July 03, 2022. Accepted on July 04, 2022.

Although there are studies investigating the relationship between PE and QoL in the literature, there is no clear consensus. The aim of this study was to evaluate the QoL of patients with lifelong and acquired PE and to examine its relationship with depression and anxiety.

METHODS

Ethical compliance

The study was approved by the Istanbul Training and Research Hospital Ethics Committee. Written informed consent of each patient was obtained.

Study design and study population

This prospective study was conducted with male patients suffering from PE who applied to the urology clinic of a training and research hospital between February 2017 and January 2018 and patients presenting for reasons other than PE. Patients who applied with the complaint of PE and sexually active male patients who applied to the urology outpatient clinic with the complaint of PE were included in the study. Inclusion criteria were being a male over the age of 18, having regular sexual intercourse within the past 6 months, and being volunteer to participate in the study. Patients with erectile dysfunction (ED), receiving medical treatment for PE, taking neuropsychiatric drugs such as SSRIs and tranquilizers within the past 6 months, and having undergone pelvic surgery were excluded from the study. A total of 12 patients refused to participate in the study. Also, 25 patients were excluded from the study for various reasons: 10 patients use SSRIs, 8 patients had concomitant ED, and 7 patients undergone pelvic surgery.

The patients were divided into three groups according to the ISSM PE criteria as follows: (patients with IELT <1 min and lifelong complaints lifelong PE, IELT <3 min and patients with PE later on acquired PE): Group 1, lifelong PE, n=62; Group 2, acquired PE, n=113; and Group 3, control group without PE, n=132. A detailed medical history of the patients was obtained and physical examinations were performed. Intravaginal ejaculation latency time (IELT) of the patients was recorded and the patients were administered the International Erectile Function Index-5 (IIEF-5), Premature Ejaculation Diagnostic Tool (PEDT), Sexual Health Inventory for Men (SHIM), the Beck Depression Inventory (BDI), the State-Trait Anxiety Inventory (STAI)-1 and STAI-2, and Short Form-36 (SF-36) surveys. The information of the participants was filled in by face-to-face interview with the urologist.

Assessment tools and outcome measures

The PEDT is a five-item tool to evaluate frequency, control, minimal stimulation, distress, and interpersonal difficulties. PEDT consists of five questions. The total score ranges from 2 to 22. A total score ≤9 excludes a diagnosis of PE[6]. The Turkish validity and reliability studies of the PEDT were carried out by Şerefoglu et al.[7].

The IIEF-5 is used to assess ED status. The IIEF-5 questionnaire includes questions 1–5 of the IIEF, which consists of 15 questions, in total[8]. Each question was evaluated with a percentage Likert scale. The total score to be obtained from the questionnaire is between 5 and 25. Linguistic validation was done by Turunç et al.[9]. An IIEF-5 score lower than 21 is considered ED. The SHIM questionnaire consists of five questions. The scores between 18 and 25, 14 and 17, and 10 and 13 are considered normal, mild, and moderate ED, respectively, while a score of ≤9 is considered severe ED according to the total score obtained from the survey[9].

Participants' IELTs were recorded as estimated.

The BDI is a 21-question multiple-choice tool used to measure the severity of depression. Depression levels according to the total score obtained from the scale are expressed[10,11]. The score to be taken from each question varies between 0 and 3. The total score obtained from the scale varies between 0 and 63. A score above 9 is indicated as depression, while 10–16 points as mild, 17–29 as moderate, and 30–63 points as severe depression. Linguistic validation was made by Hisli Sahin[12].

The STAI-1 and STAI-2 consist of 20 items. The total score ranges from 20 to 80. A high score indicates a high level of anxiety[13]. The linguistic validity was performed by Öner and Le Compte in 1983[14]. It is a Likert-type scale that measures state and trait anxiety levels separately with 20 questions. High scores indicate high anxiety levels, and low scores indicate low anxiety levels. There are two types of statements in Trait Anxiety Inventories. Direct statements express negative emotions, and reversed statements express positive emotions. The reversed statements in the State Anxiety Inventory are items 1, 2, 5, 8, 10, 11, 15, 16, 19, and 20. The reversed statements in the Trait Anxiety Inventory constitute items 21, 26, 27, 30, 33, 36, and 39. After the total weights of the direct and reversed statements are found separately, the total weight score of the reverse statements is subtracted from the total weight score obtained for the direct statements. A predetermined and unchanging value is added to this number. This constant value is 50 for the State Anxiety Inventory and 35 for the Trait Anxiety Inventory. The most recent value is the individual's anxiety score. The State Anxiety Inventory (State Anxiety Scale) is a very sensitive tool for evaluating abruptly changing emotional reactions. The Trait

Anxiety Inventory (SDS), which consists of 20 items in the second part of the inventory, aims to measure the continuity of the anxiety that the person generally tends to experience. Score ranges from 20 (low anxiety) to 80 (high anxiety).

As of 1990, 149 items were identified in previous studies including more than 22,000 individuals. The SF-20, a 20-item form, was first prepared using a factor analysis. However, the SF-36 form was developed by increasing the number of items to 36 items to increase the number of psychometric characteristics included and enhance the scope[15]. We used SF-36 for QoL of the participants. SF-36 is a test consisting of 36 items filled by the patient himself to obtain information about the health status of the person. SF-36 provides the opportunity to evaluate the health status of the person with eight subparameters. These subparameters are Physical function, Body pain, Limitation due to physical problems, Emotional well-being, Social function, Energy/Fatigue, General health perception, Mental health. The higher the score, the higher the QoL. With the mental and physical collection of these eight subdimensions, mental component score and physical component score emerge. Linguistic validation of the SF-36 was done by Kocyigit et al.[16].

Statistical analysis

Statistical analysis was performed using the SPSS version 25.0 software (IBM Corp., Armonk, NY, USA). Descriptive data were expressed in mean±standard deviation (SD), median (min-max) or, number and frequency, where applicable. The distribution of the variables was assessed using the Kolmogorov-Smirnov test. One-way analysis of variance (ANOVA) and Kruskal-Wallis tests were used to evaluate between groups and a post-hoc analysis was performed using the Tukey's and Mann-Whitney U honestly significant difference tests. A $p<0.05$ was considered statistically significant.

RESULTS

A total of 307 patients were included in the study. The mean age of the patients was 34.44 years (SD: 16.67) (min–max: 21–55), and the mean body mass index was 27.1 kg/m^2 (SD: 12.6) (min-max: 19.6–32.7). There was a statistically significant difference among the groups in terms of age ($p=0.004$), PEDT ($p<0.0001$), IELT ($p<0.0001$), IIEF-5 ($p<0.0001$), BDI ($p<0.0001$), STAI-1 ($p=0.01$), and STAI-2 ($p<0.0006$) scores (Table 1).

The QoL was assessed using the SF-36. The mean mental component score (MCS) of the SF-36 was 51.65 (SD: 6.57) in the lifelong PE group, 49.33 (SD: 8.65) in the acquired PE group, and 61.12 (SD: 11.09) in the control group ($p<0.0001$). The mean physical component score (PCS) was 50.99 (SD: 7.43) in the lifelong PE group, 48.32 (SD: 11.58) in the acquired PE group, and 55.17 (SD: 8.10) in the control group ($p<0.0001$) (Table 2). The QoL of the patients with PE was lower in the subscales of physical functioning, general health perception, vitality, and role limitations due to emotional functioning, compared to the control group (Table 3).

DISCUSSION

In this comparison, we assessed the QoL of patients with lifelong and acquired PE. The results demonstrated that the anxiety scores of the lifelong PE patients were higher than those in the control group and the acquired PE group. In addition, patients with acquired PE had lower erection functions compared to other groups. Also, a significant decrease was observed in the QoL scores of the patients with PE compared to the control group. The QoL in the subscales of physical functioning, general health perception, and role limitations due to emotional

Table 1. Characteristics of the population and results of the questionnaires applied to patients with premature ejaculation and control group.

	Lifelong PE (n=62)	Acquired PE (n=113)	Control (n=132)	p
Age (years)	35.1±6.2	35.8±4.8	33.1±5.6	0.004
BMI (kg/m^2)	25.8±3.4	27.6±3.6	26.6±3.6	0.4
Sexual intercourse frequency (per week)	2.2±1.1	2.1±1.1	2.5±1	0.0001
PEDT	19 (10)	19 (9)	8 (6)	0.0001
IELT (s)	52 (65)	61 (50)	300 (360)	0.0001
IIEF-5	22.4±7	18.1±7.2	26.2±6	0.0001
SHIM	17.8±5.8	13.6±5.2	21.1±4.1	0.0001
BDI	8 (8)	11 (13)	5.2 (8.7)	0.0001
STAI-1	45.1±7.1	43.1±8.2	40.2±6.3	0.01
STAI-2	46±7	42.8±7.2	42.7±7.8	0.0006

ANOVA and Kruskal-Wallis test were used. PE: premature ejaculation; BMI: body mass index; PEDT: premature ejaculation diagnostic tool; IELT: intravaginal ejaculation latency time; IIEF-5: international index of erectile function-5; SHIM: sexual health inventory for men; BDI: Back Depression Inventory; STAI: State Trait Anxiety Inventory.

Table 2. QoL assessment of the premature ejaculation patients and control group.

	Acquired PE	Lifelong PE	Control	p
SF-36, MCS (mean)	49.33±8.65	51.65±6.57	61.12±11.09	0.0001
SF-36, PCS (mean)	48.32±11.58	50.99±7.43	55.17±8.10	0.0001

ANOVA test and post-hoc Tukey's test were used. PE: premature ejaculation; MCS: mean mental component score; PCS: physical component score.

Table 3. Comparison of premature ejaculation patients and control group.

	Acquired PE	Lifelong PE	Control	p
Physical function	83.3±13.8	88.2±17.1	89.9±16.2	0.001
Role limitations due to physical functions	79.3±28.3	80.9±29.6	81.9±31.3	0.35
Pain	20 (25)	20 (56)	18 (4)	0.37
General perception of health	64.4±19.1	64.7±18.1	70.6±19.3	0.04
Energy/vitality	54.2±191.	52.5±21.7	60.3±20.4	0.046 ANOVA
Social function	81.2±21.1	83.1±21.9	85.5±17.3	0.28
Role limitations due to emotional problems	69.7±34.6	78.4±32	78.8±30.4	0.04
Mental health	58.3±17	65.9±17.7	65.8±19.1	0.46 ANOVA

Kruskal-Wallis, one-way ANOVA, post-hoc Tukey's, and Mann-Whitney U tests were used. PE: premature ejaculation.

functioning decreased significantly in the lifelong PE group, compared to the acquired PE group.

In our study, the most important adverse effect of sexual dysfunctions was impaired QoL in the PE patients. In a 2002 study, about half of the patients participating in the study had symptoms of PE, and 65% of the patients were not sexually satisfied[17]. The patients with PE reported an increase in various negative effects, including decreased self-esteem, mental preoccupation, psychological distress, interpersonal difficulties, and intense feelings of shame/guilt, anxiety/tension, and fear of failure[18].

The effects of PE on the QoL are not only affected to patients, but they also pose a problem to their partners. Psychological distress, decreased sexual satisfaction, and interpersonal difficulty are among the effects experienced by partners of PE patients. In a study, it was shown that both patients and their spouses experienced almost equal distress, triggering other problems in their relationship[19].

Comorbid conditions such as ED, prostate infection or inflammation, and hormonal imbalance have been thought to play a role in the etiology of PE, particularly of acquired PE[20]. The level of depression and anxiety increase in acquired PE patients, thereby resulting in an increased severity of depression and anxiety with performance anxiety[21]. In the present study, the IIEF scores were lower (p<00001) and the BDI (p<0.0001) and the STAI-1 (p=0.01) and STAI-2 (p<0.0006) scores were higher in the acquired PE group. These results are consistent with the literature[21].

There have been previous studies evaluating the QoL in PE. McCabe[3] evaluated the relation between intimacy and the QoL and sexual dysfunction based on the responses to 36 items using the Personal Assessment of Intimacy in Relationships (PAIRS) test. A validated QoL scale was also used. The authors suggested that the QoL of men with sexually dysfunction was lower. In another study, Rowland et al.[22] examined a total of 207 male patients and their female partners and found that the QoL of both patients and their partners was low. In a recent prevalence study conducted in Egypt, the frequency of PE was 26.7% and PE had a negative effect on QoL in both patients and their partner[23]. In this study, it was also reported that the QoL scores were lower in young patients. In our study, we divided the patients in to two groups as lifelong PE group and acquired PE group and compared them with the control group without PE. The findings of the study stated that the QoL in the lifelong and acquired PE groups was lower than that the control group and that the QoL of the acquired PE patients was lower than the lifelong PE patients. This finding can be attributed to the higher tendency of the patients with acquired PE to anxiety and depression.

Nonetheless, there are some limitations to this study. First, we made the evaluation of IELT of the patients based on an estimation without using an objective measurement tool. Another limitation is that the QoL of female partners was unable to be

evaluated. Finally, the other forms of PE, i.e., natural variable and subjective PE, were not included in the study.

CONCLUSIONS

PE is a condition that impairs the QoL of individuals. Both lifelong PE and acquired PE complaints decrease the QoL of patients. However, the impairment in the QoL is more pronounced in patients with acquired PE. Further, larger studies are needed to confirm these findings and to draw a firm conclusion regarding the effect of PE on QoL.

AUTHORS' CONTRIBUTIONS

BE: Conceptualization, Data curation, Formal analysis, Methodology, Software, Supervision, Writing – original draft, Writing – review & editing. **MK:** Conceptualization, Data curation, Formal analysis, Methodology, Software, Supervision, Writing – original draft, Writing rireview & editing. **UY:** Conceptualization, Data curation, Formal analysis, Supervision. **HG:** Data curation, Methodology, Writing – review & editing. **MGC:** Formal analysis, Software, Writing – original draft,

REFERENCES

1. Rosen RC. Prevalence and risk factors of sexual dysfunction in men and women. Curr Psychiatry Rep. 2000;2(3):189-95. https://doi.org/10.1007/s11920-996-0006-2
2. Serefoglu EC, McMahon CG, Waldinger MD, Althof SE, Shindel A, Adaikan G, et al. An evidence-based unified definition of lifelong and acquired premature ejaculation: report of the second international society for sexual medicine ad hoc committee for the definition of premature ejaculation. Sex Med. 2014;2(2):41-59. https://doi.org/10.1002/sm2.27
3. McCabe MP. Intimacy and quality of life among sexually dysfunctional men and women. J Sex Marital Ther. 1997;23(4):276-90. https://doi.org/10.1080/00926239708403932
4. Symonds T, Roblin D, Hart K, Althof S. How does premature ejaculation impact a man s life? J Sex Marital Ther. 2003;29(5):361-70. https://doi.org/10.1080/00926230390224738
5. Rosen RC, Althof S. Impact of premature ejaculation: the psychological, quality of life, and sexual relationship consequences. J Sex Med. 2008;5(6):1296-307. https://doi.org/10.1111/j.1743-6109.2008.00825.x
6. Symonds T, Perelman MA, Althof S, Giuliano F, Martin M, May K, et al. Development and validation of a premature ejaculation diagnostic tool. Eur Urol. 2007;52(2):565-73. https://doi.org/10.1016/j.eururo.2007.01.028
7. Serefoglu EC, Yaman O, Cayan S, Asci R, Orhan I, Usta MF, et al. Prevalence of the complaint of ejaculating prematurely and the four premature ejaculation syndromes: results from the Turkish Society of Andrology Sexual Health Survey. J Sex Med. 2011;8(2):540-8. https://doi.org/10.1111/j.1743-6109.2010.02095.x
8. Rosen RC, Riley A, Wagner G, Osterloh IH, Kirkpatrick J, Mishra A. The international index of erectile function (IIEF): a multidimensional scale for assessment of erectile dysfunction. Urology. 1997;49(6):822-30. https://doi.org/10.1016/s0090-4295(97)00238-0
9. Turunç T, Deveci S, Güvel S, Peşkircioğlu L. The assessment of Turkish validation with 5 question version of International Index of Erectile Function (IIEF-5). Turk Üroloji Dergisi. 2007;33(1):45-9.
10. Beck AT, Steer RA. Internal consistencies of the original and revised Beck Depression Inventory. J Clin Psychol. 1984;40(6):1365-7. https://doi.org/10.1002/1097-4679(198411)40:6<1365::aid-jclp2270400615>3.0.co;2-d
11. Hisli Sahin N. Use of the Beck Depression Inventory with Turkish University Students: reliability, validity and factor analysis. Türkish Journal of Psychology. 1989;7. Available from: https://www.researchgate.net/publication/233791614_Use_of_the_Beck_Depression_Inventory_with_Turkish_University_Students_Reliability_validity_and_Factor_Analysis
12. Hisli Sahin N. Validation of the BDI with a Group of Turkish Psychiatric Outpatients. Türkish Journal of Psychology. 1988. Available from: https://www.researchgate.net/publication/233791585_Validation_of_the_BDI_with_a_Group_of_Turkish_Psychiatric_Outpatients
13. Spielberger CD, Gorsuch RL, Luschene RE. Manual for the state-trait anxiety invenntory. California: Consulting Psychologists Press; 1970.
14. Öner N, Le Compte A. Durumluk sürekli kaygı envanteri el kitabı. Istanbul: Boğaziçi Üniversitesi Yayınları; 1983.
15. Ware Jr JE, Snow KK, Kosinski M, Gandek B. SF36 Health Survey: manual and interpretation guide. Lincoln: Quality Metric Inc; 1993.
16. Kocyigit H, Aydemir O, Fisek G, Olmez N, Memis A. Validity and reliability of Turkish version of short form 36: a study of a patients with romatoid disorder. Drug Therapy. 1999;12:102-6.
17. Fugl-Meyer K, Fugl-Meyer AR. Sexual disabilities are not singularities. Int J Impot Res. 2002;14(6):487-93. https://doi.org/10.1038/sj.ijir.3900914
18. Hartmann U, Schedlowski M, Krüger THC. Cognitive and partner-related factors in rapid ejaculation: differences between dysfunctional and functional men. World J Urol. 2005;23(2):93-101. https://doi.org/10.1007/s00345-004-0490-0
19. Rowland D, Perelman M, Althof S, Barada J, McCullough A, Bull S, et al. Self-reported premature ejaculation and aspects of sexual functioning and satisfaction. J Sex Med. 2004;1(2):225-32. https://doi.org/10.1111/j.1743-6109.2004.04033.x
20. Culha MG, Tuken M, Gonultas S, Cakir OO, Serefoglu EC. Frequency of etiological factors among patients with acquired premature ejaculation: prospective, observational, single-center study. Int J Impot Res. 2020;32(3):352-57. https://doi.org/10.1038/s41443-019-0188-x
21. el-Sakka AI. Severity of erectile dysfunction at presentation: effect of premature ejaculation and low desire. Urology. 2008;71(1):94-8. https://doi.org/10.1016/j.urology.2007.09.006
22. Rowland DL, Patrick DL, Rothman M, Gagnon DD. The psychological burden of premature ejaculation. J Urol. 2007;177(3):1065-70. https://doi.org/10.1016/j.juro.2006.10.025
23. Hanafy S, Hamed AM, Samy MSH. Prevalence of premature ejaculation and its impact on the quality of life: results from a sample of Egyptian patients. Andrologia. 2019;51(8):e13298. https://doi.org/10.1111/and.13298

ORIGINAL ARTICLE

https://doi.org/10.1590/1806-9282.20220528

A comparative study of the RIPASA and Alvarado scores in geriatric patients diagnosed with acute appendicitis

Davut Tekyol[1], Rohat Ak[2*], Nihat Müjdat Hökenek[2], Mazlum Kılıç[3], Kübra Kaytaz Tekyol[4], Doğan Erdoğan[5]

SUMMARY

OBJECTIVE: While abdominal pain is one of the most prevalent reasons for seeking medical attention, diagnosing elderly adults with acute appendicitis (AA) may be difficult. In this study, Raja Isteri Pengiran Anak Saleha Appendicitis (RIPASA) and Alvarado ratings were evaluated for diagnostic accuracy in patients who reported to the emergency department complaining of abdominal pain and received surgery for AA .

METHODS: The data of patients over the age of 65 years who reported to the ER and had appendectomy after being diagnosed with AA were evaluated in this retrospective cohort study. For each patient, the diagnostic accuracy of the Alvarado and RIPASA scores was determined individually.

RESULTS: A total of 86 patients were included in the research. The average patient was 71.2 years old, with a male preponderance of 46.5%. Alvarado's score was found to have an area under the curve (AUC) of 0.799, the Youden's index of 0.549, and a p-value of 0.001 after a receiver operating characteristic (ROC) study of the Alvarado score in identifying the diagnosis of AA. The AUC was 0.886 (95%CI 0.799–0.944), the Youden's index was 0.642, and a p-value of 0.001 was found in the ROC analysis of the RIPASA score in identifying the diagnosis of AA.

CONCLUSIONS: When comparing the two scores used to diagnose AA, we found no statistically significant difference between the RIPASA and Alvarado scores (p=0.09), although the Youden's index for the RIPASA score was higher.

KEYWORDS: Elderly. Geriatrics. Appendicitis. Alvarado score. RIPASA score.

INTRODUCTION

Although acute appendicitis (AA) is a prevalent cause of abdominal pain in geriatric patients, diagnostic challenges persist[1,2]. Complication rates are particularly greater in older patients than younger individuals, who more commonly report to the emergency room with stomach discomfort and unusual symptoms[3]. Similarly, the death rate for people with AA over the age of 65 years may grow to 8%[4]. Age more than 65 years was shown to be a significant risk factor for death in a large observational study including 164,579 people diagnosed with AA[5].

Due to the fact that a delayed diagnosis of AA in senior patients increases morbidity and mortality, current evidence-based recommendations urge the adoption of scoring systems in this age range[6]. The Alvarado score, which was created in 1986, is one of the most popular of these grading systems. The Alvarado score is composed of eight components, which include patient complaints, physical examination results, and laboratory data[7]. In 2010, a new scoring system, called the Raja Isteri Pengiran Anak Saleha Appendicitis (RIPASA), was created for the diagnosis of AA, which has 15 parameters[8]. It was claimed that when applied to the Asian population, the sensitivity and specificity of this scoring system will rise[9].

The goal of this study was to compare the RIPASA and Alvarado scoring systems in patients who arrived at the emergency department with abdominal pain and had AA surgery.

METHODS

Study design

Between January 1, 2018 and January 1, 2021, this retrospective cohort study was conducted in the emergency department at the Haydarpaşa Numune Education and Research Hospital. The institutional review board authorized the analysis and waived permission (Ethics Committee Ruling number: HNEAH-KAEK 2022/88).

[1]Haydarpaşa Numune Education and Research Hospital, Department of Emergency Medicine – Istanbul, Turkey.
[2]Kartal Dr. Lütfi Kırdar City Hospital, Department of Emergency Medicine – Istanbul, Turkey.
[3]Fatih Sultan Mehmet Education and Research Hospital, Department of Emergency Medicine – Istanbul, Turkey.
[4]Kovancılar State Hospital, Department of General Surgery – Elazığ, Turkey.
[5]Haydarpaşa Numune Education and Research Hospital, Department of General Surgery – Istanbul, Turkey.
*Corresponding author: rohatakmd@gmail.com
Conflicts of interest: the authors declare there is no conflicts of interest. Funding: none.
Received on April 05, 2022. Accepted on June 30, 2022.

Selection of patients

The study population comprised all patients over the age of 65 years who attended to an emergency room with abdominal discomfort and received open or laparoscopic appendectomy throughout the study period. Histopathological studies validated the diagnosis of AA. Each patient's medical computerized data were examined retrospectively, and the Alvarado and RIPASA ratings were computed independently (Table 1). Patients with missing data necessary for the scoring criteria, as well as those under the age of 65 years, were excluded from the study. Using an area under the curve (AUC) value of at least 0.7 as the minimum needed sample size for the investigation, a minimum of 62 patients was computed.

The statistical analyses were conducted using SPSS Statistics version 19.0 (IBM Corp., Armonk, NY, USA) and MedCalc version 19. The mean, standard deviation, median, and interquartile range values were used to describe the data. The Kolmogorov-Smirnov test was used to determine if the data were normally distributed.

The receiver operating characteristic (ROC) curve analysis was utilized to estimate the Alvarado and RIPASA cutoff values for AA diagnosis prediction. The ROC curves of these scores were compared. The DeLong approach was used to compute the appropriate cutoff, 95% confidence interval (CI), AUC, positive predictive (PPV), and negative predictive (NPV) values using Youden's index (YJI). The value 0.05 was chosen as the threshold of significance.

Table 1. Comparison of Alvarado and RIPASA scoring systems.

	Alvarado score	RIPASA score
Sex	–	Female +0.5
Male +1		
Age (years)	–	<40 +1
>40 +0.5		
Duration of symptoms	–	<48 h +1
>48 h +0.5		
Anorexia	1	1
Nausea or vomiting	1	1
RIF pain/tenderness	2	0.5 +1*
Elevated temperature	1	2
Guarding	–	2
Rebound tenderness	1	1
Rovsing's sign	–	2
Migration of pain to RIF	1	0.5
Leukocytosis (>10,000)	2	1
Leukocyte left shift (>75%)	1	–
Normal urine analysis	–	1
Total	10	16
Possible diagnosis appendicitis	>6–7	>7.5

RIF: right iliac fossa. *Score combined: 0.5 point for RIF pain (symptom) and 1 point for right iliac fossa tenderness (sign).

RESULTS

The study was completed with 86 patients who met the inclusion criteria. The mean age of these patients was 71.2±5.9 years, and 46.5% were men. As a result of the statistical analysis, it was determined that the median values of the white blood cell and neutrophil counts, Alvarado, and RIPASA scores were statistically substantially higher in individuals with an appendicitis histological diagnosis compared to those without appendicitis. The negative appendectomy rate of the patients included in the study was found to be 24.4% (Table 2).

As a result of the ROC analysis of the Alvarado score in determining the diagnosis of AA, the AUC value was 0.799 (95%CI 0.698–0.877), YJI was 0.549, and the p-value was 0.001. According to the statistical analysis, the Alvarado score was statistically significant in determining the diagnosis of AA (p=0.001). At a cutoff value of >4, the Alvarado score had a sensitivity of 69.2%, specificity of 85.7%, PPV of 93.7%, and NPV of 47.4% in predicting a diagnosis of AA (Table 3).

The ROC analysis of the RIPASA score in determining the diagnosis of AA revealed that the AUC value was 0.886 (95%CI 0.799–0.944), YJI was 0.642, and the p-value was 0.001. According to the statistical analysis, the RIPASA score was statistically significant in determining the diagnosis of AA (p=0.001). At a cutoff value of >8, the RIPASA score had 78.5% sensitivity, 85.7% specificity, 94.4% PPV, and 56.2% NPV in predicting an AA diagnosis (Table 3).

When the two scoring systems' values for diagnosing AA were compared, despite the fact that the RIPASA score's YJI value was greater, there was no statistically significant difference (p=0.09) (Table 3).

DISCUSSION

This study evaluated the adequacy of the Alvarado and RIPASA scores in determining the diagnosis of AA in patients who underwent appendectomy for AA. It was concluded that both scores had high diagnostic accuracy, and neither was superior to the other.

Early detection of AA is critical in older individuals with a high rate of death and morbidity. In a study conducted in

Finland, the data of 164,579 patients who underwent appendectomy surgery over a 20-year period were examined, and it was reported that mortality increased 39 times in patients aged over 65 years. Similarly, the same study determined that negative appendectomy increased mortality fourfold[10]. In the literature, the rate of negative appendectomy in geriatric patients ranges from 17% to 31%[11-13]. In the current cohort, the rate of negative appendectomy was found to be 24.4%, which is consistent with the literature.

Due to increased life expectancy, diseases previously associated with younger populations, including AA, have a growing incidence among elderly patients[14]. Although the lifetime risk of AA is 7% for the general population, this rate can rise to 10% in the elderly population[15]. As in many diseases, the clinical diagnosis process in AA is more difficult in the geriatric population than in young people. This is partly due to pain sensations altered by changes in nerve conduction due to aging, resulting in overlooking the classical findings of AA[16]. Since a delayed diagnosis will increase mortality and morbidity, many guidelines recommend using clinical score systems in the initial evaluation process of patients[6].

Alvarado[7], a 10-point scale based on indications, symptoms, and laboratory data, is one of the most widely used and examined scoring systems for the AA assessment. A score of 5 or 6 points on the Alvarado scale is considered consistent with the diagnosis of AA; a score of 7 or 8 suggests a plausible diagnosis of AA; and a score of 9 or 10 indicates a very probable diagnosis of AA. This diagnostic score is designed to assist clinicians in making clinical decisions by objectively determining which patients should be observed and which should receive surgery. This is a limited research examining the Alvarado score's relevance in the older population. A retrospective analysis of 96 patients over the age of 65 years revealed that using the Alvarado scoring system with a cutoff value of 5 resulted in accurate findings in senior individuals. It was noted in a study that an Alvarado score of 5–10 indicated a greater risk of appendicitis in the elderly[17]. In another study, the Alvarado and Lintula scores were compared in senior patients undergoing appendectomy, and the former was shown to be a more helpful prediction tool, with an AUC value of 96.9%[18]. A research indicated that the Alvarado score is ineffective at differentiating between difficult and simple AA in older people[19].

Table 2. Comparison of some characteristics between the patients with (+) and without (−) a histopathological diagnosis of appendicitis.

		n	Mean	Median	IQR	p-value
Age	−	21	72.48	71.0	10	0.235*
	+	65	70.72	70.0	7	
Body temperature	−	21	36.39	36.4	0.2	0.146*
	+	65	36.50	36.5	0.4	
White blood cell count	−	21	9,277.14	9300	4,690	0.002*
	+	65	12,933.85	13,330	7,820	
Neutrophil count	−	21	7,201.43	6490	5,155	0.001*
	+	65	10,295.38	10,860	6,560	
Neutrophil percentage	−	21	74.40	72.1	20.8	0.286*
	+	65	77.93	79.6	12.2	
Alvarado score	−	21	3.48	3.0	1.0	0.001*
	+	65	5.29	6.0	2.5	
RIPASA score	−	21	5.90	5.5	3.3	0.001*
	+	65	9.63	10.0	2.5	

IQR: interquartile range. *Mann-Whitney U test.

Table 3. Comparison of the Alvarado and RIPASA scores in determining the diagnosis of acute appendicitis.

	AUC	Cutoff	Sensitivity	Specificity	+LR	−LR	PPV	NPV	Youden's index	p-value
Alvarado	0.799 (0.698–0.877)	>4	69.2 (56.6–80.1)	85.7 (63.7–97.0)	4.85	0.36	93.7	47.4	0.549	0.09
RIPASA	0.886 (0.799–0.944)	>8	78.5 (66.5–87.7)	85.7 (63.7–97.0)	5.49	0.25	94.4	56.2	0.642	

AUC: area under the curve; LR: likelihood ratio; PPV: positive predictive value; NPV: negative predictive value.

The RIPASA score, which we compared with the Alvarado score in our study, is one of the scoring systems developed in 2010 and has since been widely adopted. This score has 14 parameters, including clinical history, physical examination, and various laboratory data. In this scoring system, the total score varies between 3 and 16.5. A score below 7 is associated with a low AA risk, and a score of 7.5 and above is associated with a high AA risk[8]. In a study conducted in Ireland, it was reported that a RIPASA score of 7.5 and above provided higher sensitivity and specificity than the Alvarado score[20]. In a retrospective cohort of 68 patients over the age of 65 years who underwent appendectomy, the sensitivity of the RIPASA score was determined as 86.2%, specificity as 40%, PPV as 89.3%, and NPV as 33.3%[21]. In the current cohort, the RIPASA score had a sensitivity of 78.5%, specificity of 85.7%, PPV of 94.4%, and NPV of 56.2%, while for the Alvarado score, these values were 69.2%, 85.7%, 93.7%, and 47.4%, respectively.

There are some limitations to our study. First, our results cannot be generalized to the general population since they were obtained from a single center. Second, since this study was retrospective, it is possible that the results were influenced by inadequate or erroneous data in hospital records. Another disadvantage is the small patient population.

CONCLUSIONS

Diagnosing AA in the elderly continues to be difficult owing to the broad number of potential diagnoses and clinical manifestations seen in this group. It is necessary to use clinical risk scoring systems that will help identify patients with AA early. In this study, we concluded that both the RIPASA and Alvarado scores had high diagnostic accuracy in the detection of AA in the geriatric patient group, and neither had any superiority over the other.

AUTHORS' CONTRIBUTIONS

DT: Conceptualization, Data curation, Project administration, Resources, Writing – original draft, Writing – review & editing. **RA:** Conceptualization, Project administration, Writing – original draft, Writing – review & editing. **NMH:** Validation, Visualization, Writing – original draft, Writing – review & editing. **MK:** Software, Supervision, Writing – original draft, Writing – review & editing. **KKT:** Project administration, Writing – original draft, Writing – review & editing. **DE:** Project administration, Resources, Software, Supervision, Validation, Visualization.

REFERENCES

1. Tantarattanapong S, Arwae N. Risk factors associated with perforated acute appendicitis in geriatric emergency patients. Open Access Emerg Med. 2018;10:129-34. https://doi.org/10.2147/OAEM.S17393
2. Bayrak S, Tatar C, Cakar E, Colak S, Gunes ME, Tekesin K, et al. Evaluation of the predictive power of laboratory markers in the diagnosis of acute appendicitis in the elderly. North Clin Istanb. 2019;6(3):293-301. https://doi.org/10.14744/nci.2019.93457
3. Fan SM, Grigorian A, Smith BR, Kuza CM, Lekawa M, Schubl SD, et al. Geriatric patients undergoing appendectomy have increased risk of intraoperative perforation and/or abscess. Surgery. 2020;168(2):322-7. https://doi.org/10.1016/j.surg.2020.04.019
4. Kraemer M, Franke C, Ohmann C, Yang Q, Acute Abdominal Pain Study Group. Acute appendicitis in late adulthood: incidence, presentation, and outcome. Results of a prospective multicenter acute abdominal pain study and a review of the literature. Langenbecks Arch Surg. 2000;385(7):470-81. https://doi.org/10.1007/s004230000165
5. Kotaluoto S, Ukkonen M, Pauniaho SL, Helminen M, Sand J, Rantanen T. Mortality related to appendectomy; a population based analysis over two decades in Finland. World J Surg. 2017;41(1):64-9. https://doi.org/10.1007/s00268-016-3688-6
6. Fugazzola P, Ceresoli M, Agnoletti V, Agresta F, Amato B, Carcoforo P, et al. The SIFIPAC/WSES/SICG/SIMEU guidelines for diagnosis and treatment of acute appendicitis in the elderly (2019 edition). World J Emerg Surg. 2020;15(1):19. https://doi.org/10.1186/s13017-020-00298-0
7. Alvarado A. A practical score for the early diagnosis of acute appendicitis. Ann Emerg Med. 1986;15(5):557-64. https://doi.org/10.1016/s0196-0644(86)80993-3
8. Chong CF, Adi MIW, Thien A, Suyoi A, Mackie AJ, Tin AS, et al. Development of the RIPASA score: a new appendicitis scoring system for the diagnosis of acute appendicitis. Singapore Med J. 2010;51(3):220-5. PMID: 20428744
9. Ak R, Doğanay F, Akoğlu EU, Akoğlu H, Uçar AB, Kurt E, et al. Predictive value of scoring systems for the diagnosis of acute appendicitis in emergency department patients: is there an accurate one? Hong Kong Journal of Emergency Medicine. 2019;27(5):262-9. https://doi.org/10.1177/1024907919840175
10. Kotaluoto S, Ukkonen M, Pauniaho SL, Helminen M, Sand J, Rantanen T. Mortality related to appendectomy; a population based analysis over two decades in Finland. World J Surg. 2017;41(1):64-9. https://doi.org/10.1007/s00268-016-3688-6
11. Joshi MK, Joshi R, Alam SE, Agarwal S, Kumar S. Negative appendectomy: an audit of resident-performed surgery. How can its incidence be minimized? Indian J Surg. 2015;77(Suppl 3):913-7. https://doi.org/10.1007/s12262-014-1063-0
12. Chamisa I. A clinicopathological review of 324 appendices removed for acute appendicitis in Durban, South Africa: a retrospective analysis. Ann R Coll Surg Engl. 2009;91(8):688-92. https://doi.org/10.1308/003588409X12486167521677
13. Chooi WK, Brown JA, Zetler P, Wiseman S, Cooperberg P. Imaging of acute appendicitis and its impact on negative appendectomy and perforation rates: the St. Paul's experience. Can Assoc Radiol J. 2007;58(4):220-4.PMID: 18186433

14. Deiters A, Drozd A, Parikh P, Markert R, Shim JK. Use of the Alvarado score in elderly patients with complicated and uncomplicated appendicitis. Am Surg. 2019;85(4):397-402. PMID: 31043201
15. Omari AH, Khammash MR, Qasaimeh GR, Shammari AK, Yaseen MKB, Hammori SK. Acute appendicitis in the elderly: risk factors for perforation. World J Emerg Surg. 2014;9(1):6. https://doi.org/10.1186/1749-7922-9-6
16. Emektar E, Dağar S, Karaatlı RH, Uzunosmanoğlu H, Buluş H. Determination of factors associated with perforation in patients with geriatric acute appendicitis. Ulus Travma Acil Cerrahi Derg. 2022;28(1):33-8. https://doi.org/10.14744/tjtes.2020.25741
17. Shchatsko A, Brown R, Reid T, Adams S, Alger A, Charles A. The utility of the Alvarado score in the diagnosis of acute appendicitis in the elderly. Am Surg. 2017;83(7):793-8. PMID: 28738954
18. Konan A, Hayran M, Kılıç YA, Karakoç D, Kaynaroğlu V. Scoring systems in the diagnosis of acute appendicitis in the elderly. Ulus Travma Acil Cerrahi Derg. 2011;17(5):396-400. PMID: 22090323
19. Deiters A, Drozd A, Parikh P, Markert R, Shim JK. Use of the Alvarado score in elderly patients with complicated and uncomplicated appendicitis. Am Surg. 2019;85(4):397-402. PMID: 31043201
20. Malik MU, Connelly TM, Awan F, Pretorius F, Fiuza-Castineira C, El Faedy O, et al. The RIPASA score is sensitive and specific for the diagnosis of acute appendicitis in a western population. Int J Colorectal Dis. 2017;32(4):491-7. https://doi.org/10.1007/s00384-016-2713-4
21. Bardakci O, Tatli F. The effectiveness of the Raja Isteri Pengiran Anak Saleha Appendicitis Score in the diagnosis of acute appendicitis in elderly patients. Signa Vitae. 2021;17(3):214-7. https://doi.org/10.22514/sv.2021.027

ORIGINAL ARTICLE

https://doi.org/10.1590/1806-9282.20220620

Changes in the frequency and clinical features of acute rheumatic fever in the COVID-19 era: a retrospective analysis from a single center

Fuat Laloğlu[1*], Naci Ceviz[1]

SUMMARY

OBJECTIVE: Coronavirus disease 2019 (COVID-19) pandemic resulted in significant changes in the frequency of many diseases. In this study, we aimed to investigate the changes in the frequency and clinical features of acute rheumatic fever (ARF) in this period and determine the effect of health measures taken against COVID-19 on this change.

METHODS: The cases with initial attack of ARF between January 2016 and March 2022 in Ataturk University, Division of Pediatric Cardiology, were determined from the clinic's database, and case per month ratios were calculated for each period, retrospectively. Also the frequency of the clinical manifestations was compared among patients before and during the outbreak.

RESULTS: Frequency of the major clinical manifestations among patients before and during the outbreak was similar. On average, the number of cases reported per month in the years 2016, 2017, 2018, and 2019 are, respectively, 1.75, 2, 2.25, and 2.58. In the first 3 months of 2020, the average number of cases reported per month was 3.67. After the advent of the pandemic, in the period from April to December 2020 and from January to September 2021, an average of 0.56 and 0.22 cases were reported per month, respectively. The frequency of clinical features between patients diagnosed before and during the outbreak was similar.

CONCLUSIONS: Our results indicated an important decrease in frequency of ARF, but no change in the clinical features of the disease during the COVID-19 pandemic. It is thought that this is the result of health measures taken for COVID-19. Children with an increased risk of acute rheumatic fever should be encouraged in terms of wearing mask, social distance, and cleaning, especially during the seasons when upper respiratory tract infections are common. Thus, a permanent decrease in the incidence of ARF and its recurrences may be achieved.

KEYWORDS: Acute rheumatic fever. COVID-19. Children. Frequency. Mask.

INTRODUCTION

The World Health Organization declared the novel coronavirus (COVID-19) outbreak a pandemic in March 2020[1]. The disease affected all over the world and resulted in apparent changes in human behaviors. Wearing masks and complying with social distancing rules are behaviors that are generally accepted and implemented against the outbreak. Studies pointed out that the use of facial protective equipment reduces the frequency of COVID-19 infections[2,3].

With the onset of the epidemic, between April 2020 and September 2021, face-to-face education was suspended in schools in our country. While the Ministry of Health made the use of masks mandatory in schools, it encouraged the strict execution of the measures taken due to COVID-19 (e.g., cancellation of collective activities, control of cleaning practices, and continuity of the educational activities with printed materials and oral presentations). Schools resumed education in September 2021. In the COVID-19 era, the frequency of a rare clinical condition, such as multisystem inflammatory syndrome in children, increased significantly[4]. A recent study indicates a significant decrease in the frequency of pediatric rheumatic diseases[5]. Also influenza activity declined substantially in 2020 because of the measures taken for COVID-19[6]. Results of this study indicated that public health measures taken for COVID-19 are effective in reducing the spread of viral respiratory diseases[6]. To the best of our knowledge, there is no study investigating the changes in the frequency and clinical features of upper respiratory tract infections (URTIs) caused by group A beta hemolytic streptococcus (GABHS) that may result in, during COVID-19 period, acute rheumatic fever (ARF) in susceptible individuals. ARF is still one of the most important health problems in developing countries[7]. Our country is also among the countries that reported moderate-high on incidence and prevalence of ARF[7-10]. In this study, we aimed to investigate the changes in the frequency and clinical features of ARF during the COVID-19 pandemic and determine the possible effect of the measures taken against the COVID-19 pandemic on this change.

[1]Atatürk University, Faculty of Medicine, Department of Pediatrics, Division of Pediatric Cardiology – Erzurum, Turkey.
*Corresponding author: flaloglu25@hotmail.com
Conflicts of interest: the authors declare there is no conflicts of interest. Funding: none.
Received on June 20, 2022. Accepted on June 27, 2022.

METHODS

The study was performed in Ataturk University School of Medicine, Division of Pediatric Cardiology. The database in which echocardiographic data and diagnoses of all patients admitted to the pediatric cardiology outpatient clinic were entered was scanned.

The database was searched for the cases who had been diagnosed as having first attack of ARF between January 1, 2016 and March 31, 2022. The clinical features of the patients were derived from medical recordings, retrospectively.

For the diagnosis of ARF, the last guideline about Jones criteria, published by the American Heart Association in 2015[7], was used, and the criteria recommended for societies with medium-high prevalence were taken into account. Only patients with first attack of ARF were included, and patients with recurrences were not.

Patients who were diagnosed before April 1, 2020 were included into Group 1 (before the outbreak) and between April 1, 2020 and September 30, 2021 to Group 2 (during the outbreak). Frequency of clinical features was compared between the two groups. As the schools were opened again, the two cases diagnosed after September 30, 2021 were not included in this analysis. The case numbers for each year were determined, and the changes in case numbers during this period were evaluated. To depict the changes better, case number per month ratio was calculated for time periods before and during the outbreak. Data were expressed as total number and number per month.

The study commenced following receipt of approval from the Republic of Turkey, Ministry of Health COVID-19 Scientific Research Assessment Commission, and Ataturk University Medical Faculty Ethical Committee.

Statistical analysis

The data were transferred to Statistical Package for the Social Sciences pocket program (IBM SPSS Statistics version 20). Chi-square analysis was used for comparison of frequencies of the major manifestations and Student's t-test (Mann-Whitney U test) for comparison of median values between groups. A $p<0.05$ was considered significant.

RESULTS

During the study period, a total of 125 cases were diagnosed as having ARF. As they had previous attacks of ARF, three patients were excluded from the study. As two cases diagnosed after school reopening, clinical features of only the 120 patients diagnosed before and during the outbreak are used in comparisons and results are given in Table 1. Only one patient from Group 1 had severe carditis. In remaining patients, carditis was mild. The frequency of clinical features between groups was similar. In Group 1, 41 (36.2%) patients had clinical and 58 (51.3%) had silent carditis. In Group 2, same values were 1 (14.2%) and 5 (71.4%), respectively (p=0.398). In Group 1, 67 (59.2%) patients had endocarditis in one valve, and 32 (28.3%) in two valves. In Group 2, same values were 4 (57.1%) and 5 (28.5%), respectively (p=1.000).

Case numbers by years is shown in Figure 1. After the first case of COVID-19 was diagnosed in Turkey (March 2020), the case numbers of ARF decreased apparently in our clinic. On average, the number of cases reported per month in the years 2016, 2017, 2018, and 2019 are, respectively, 1.75, 2, 2.25, and 2.58. In the first 3 months of 2020, the average number of cases reported per month was 3.67. After the advent of the pandemic, in the period from April to December of 2020 and

Table 1. Clinical features of the patients with the diagnosis of first attack of acute rheumatic fever between January 1, 2016 and September 30, 2021 (n=120).

	Group 1* (n=113)	Group 2† (n=7)	p
	Median (IQR)	Median (IQR)	
Age (year, median)	12 (4)	11.5 (5)	0.578
	n (%)	n (%)	
Gender (male/female)	51/62	4/3	0.701
Major clinical features			
Carditis	99 (87.6)	6 (85.7)	1.000
Joint involvement (polyarthritis, monoarthritis, polyarthralgia)	64 (56.6)	4 (57.1)	1.000
Chorea	47 (41.6)	3 (42.9)	1.000
Patients with active inflammation	70 (61.9)	4 (57.1)	1.000

*Patients who were diagnosed before April 1, 2020 (before the outbreak); †Patients who were diagnosed between April 1, 2020 and September 30, 2021 (during the outbreak).

from January to September 2021, an average of 0.56 and 0.22 cases were reported per month, respectively. Between September 30, 2021 and March 31, 2022, only two patients (0.33 cases per month) were diagnosed as having first attack of ARF.

DISCUSSION

The COVID-19 disease is caused by a novel coronavirus named as severe acute respiratory syndrome coronavirus (SARS-CoV-2)[11]. After the first case, seen in December 2019, the disease has spread all over the world and the event is declared as a pandemic in March 2020[1]. Especially in the early period of the pandemic, there were deaths at a rate that could paralyze the current healthcare system even in the developed countries, and very strict measures were taken all over the world. While international travel has been cancelled, countries have introduced travel restrictions within themselves. Collective events were canceled and, from time to time, during the peak periods of the epidemic, full closure measures were applied for temporary periods. Schools have been suspended since the beginning of the pandemic in our country and were largely remained closed until September 30, 2021. In the meantime, broadcasts were made emphasizing the importance of using personal protective masks, complying with social distance rules and personal hygiene rules in the fight against the disease. With the widespread use of vaccines, some countries have relaxed measures. However, the new peaks that emerged with the new variants led to the tightening of the measures again.

Although vaccines have been shown to provide a significant protection, a significant reduction in the need for hospitalization and intensive care, and a significant reduction in mortality rates[11,12], uncertainty about permanent immunity[13] has increased the importance of personal protection measures, which are sloganized as mask, distance, and cleaning. These measures seem to keep their place in our lives for a long time.

ARF is a nonsuppurative complication of tonsillopharyngitis due to group A beta hemolytic streptococci (GABHS). Signs of the disease appear after a latent period of 2–4 weeks following an infection in the susceptible host[7]. Improvement of hygiene conditions in developed countries has significantly reduced the frequency of the disease. On the other hand, the frequency of first attack of ARF and recurrences are still high in developing countries and in handicapped regions of developed countries where health conditions are not good[14]. Recurrences

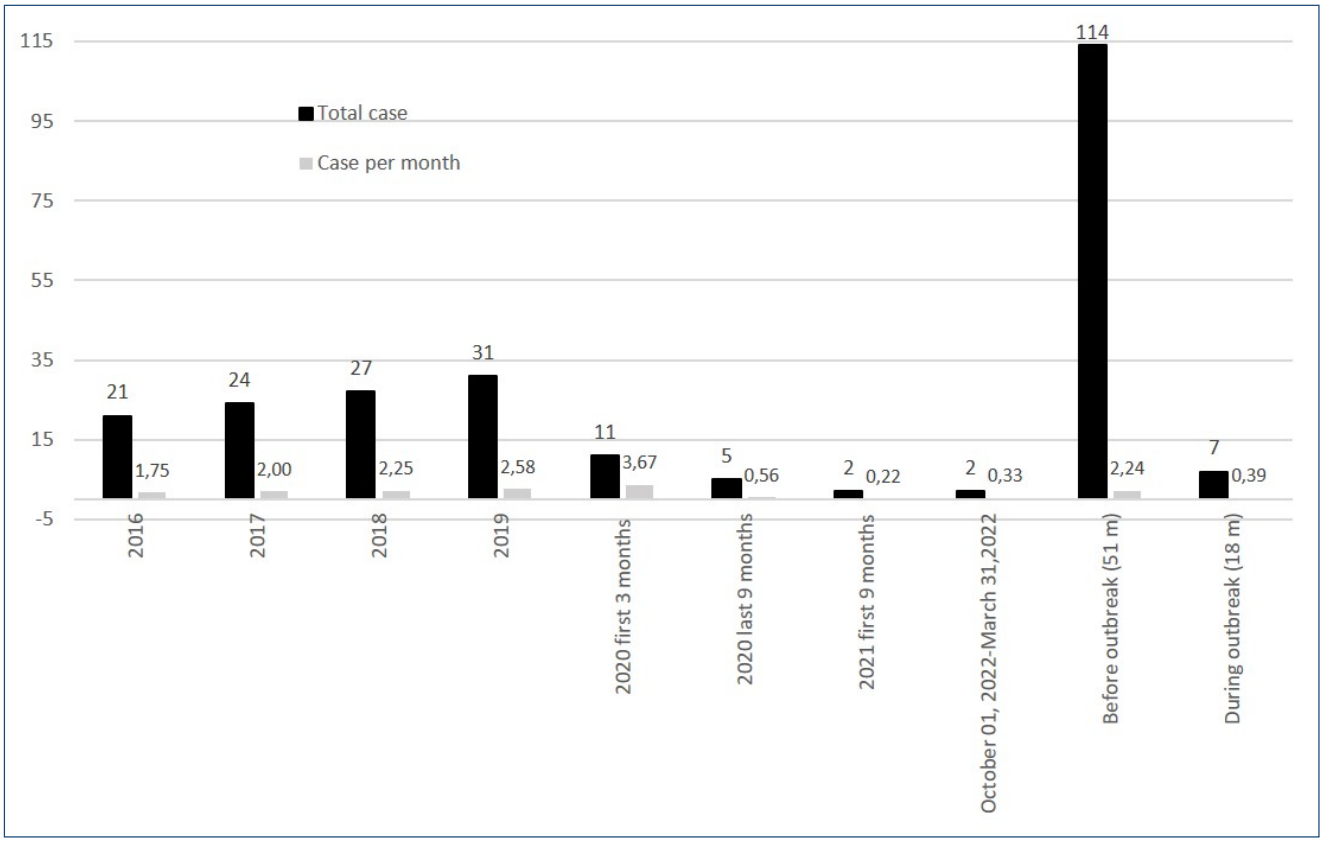


Figure 1. Case numbers and cases per month before and during the outbreak. There is a significant decrease in the number of patients with first acute rheumatic fever attack during the COVID-19 outbreak.

of new GABHS tonsillopharyngitis in children with previous rheumatic carditis are closely related to the development of chronic rheumatic heart disease (RHD). For this reason, long-acting penicillin prophylaxis is applied in patients who have had ARF[7]. Compliance with prophylaxis is the most important issue in this regard. Apart from poor compliance with prophylaxis, general economic situation and crowded living environment are seen as the most effective risk factors on ARF recurrences and RHD[14]. The disease is most common in children aged 5–15 years. The fact that this group is school-age children is important in terms of our study results. Primordial prevention reduces community-based risk factors to prevent the occurrence of a disease[15]. ARF is attributable to social determinants of health, including quality of housing, level of household occupancy, and access to health hardware including washing facilities[14,16]. Evidence on the impact of "washing people" and "reducing the negative effects of overcrowding," two of the nine Healthy Living Practices[17], on reducing streptococcal infections at the community level, is classified as "strong[15]." We believe that the increased prevalence of these two practices in our society due to the COVID-19 pandemic and schools being closed caused a decrease in the frequency of tonsillopharyngitis due to GABHS, and as a result, a significant decrease in the frequency of ARF occurred. After reopening of schools, only two children admitted with first attack ARF in 6 months. Although the class sizes were not changed, the measures against COVID-19 infection continued. We think that the low frequency after schools reopening is related to these measures. We will see in future how the frequency of ARF will be affected with full normalization.

Study limitations

- It is a fact that there has been a decrease in hospital admissions due to the fear of COVID-19 contamination during the pandemic process. This may have caused patients with relatively faint signs of ARF not to be diagnosed.
- It is possible that patients have applied to other centers. However, this probability is low, as our center was the only pediatric cardiology center unit in Erzurum city center and eight nearby provinces during the pandemic.

CONCLUSIONS

Our results are important in terms of showing the significant decrease in the frequency of ARF during the COVID-19 pandemic. It was thought that the lack of a rapid increase in the number of cases despite the reopening of the schools may be related to the fact that wearing masks is still compulsory in schools and the educations and controls on hygiene continues.

Depending on these results we offer; for children with an increased risk of first attack ARF, permanent measures should be taken in terms of mask, social distance, and cleaning in schools, especially during the seasons when URTIs are common. Thus, a permanent decrease in the incidence of ARF can be achieved. In addition to benzathine penicillin prophylaxis, mask, distance, and cleaning rules should be made permanent for children with previous ARF and their families for preventing ARF recurrences in order to reduce chronic results of the disease.

AUTHORS' CONTRIBUTIONS

FL: Conceptualization, Data curation, Formal analysis, Investigation, Project administration, Resources, Validation, Visualization, Writing – review & editing. **NC:** Conceptualization, Data curation, Formal analysis, Investigation, Methodology, Project administration, Resources, Supervision, Validation, Visualization, Writing – original draft, Writing – review & editing.

REFERENCES

1. World Health Organization. WHO Director General's opening remarks at the media briefing on COVID-19 - 11 March 2020 [cited on Apr 01, 2020]. Available from: https://www.who.int/director-general/speeches/detail/who-director-general-s-opening-remarks-at-the-media-briefing-on-covid-19---11-march-2020
2. Silva GS, Avila GO, Lubianca FN, Lubianca JPN, Michelon VMM, Kalil DP, et al. Prevalence of COVID-19 in medical school and residency in Porto Alegre, RS. Rev Assoc Med Bras (1992). 2022;68(2):206-11. https://doi.org/10.1590/1806-9282.20211114
3. Li DTS, Samaranayake LP, Leung YY, Neelakantan P. Facial protection in the era of COVID-19: a narrative review. Oral Dis. 2021;27(Suppl 3):665-73. https://doi.org/10.1111/odi.13460
4. Vukomanovic V, Krasic S, Prijic S, Ninic S, Popovic S, Petrovic G, et al. Recent experience: corticosteroids as a first-line therapy in children with multisystem inflammatory syndrome and COVID-19-related myocardial damage. Pediatr Infect Dis J. 2021;40(11):e390-e394. https://doi.org/10.1097/INF.0000000000003260
5. Soo RJJ, Chiew CJ, Ma S, Pung R, Lee V. Decreased influenza incidence under COVID-19 control measures, Singapore. Emerg Infect Dis. 2020;26(8):1933-5. https://doi.org/10.3201/eid2608.201229
6. Akca UK, Atalay E, Cuceoglu MK, Balik Z, Sener S, Ozsurekci Y, et al. Impact of the COVID-19 pandemic on the frequency of the pediatric rheumatic diseases. Rheumatol Int. 2022;42(1):51-7. https://doi.org/10.1007/s00296-021-05027-7

7. Gewitz MH, Baltimore RS, Tani LY, Sable CA, Shulman ST, Carapetis J, et al. Revision of the Jones Criteria for the diagnosis of acute rheumatic fever in the era of Doppler echocardiography: a scientific statement from the American Heart Association. Circulation. 2015;131(20):1806-18. https://doi.org/10.1161/CIR.0000000000000205
8. Gürses D, Koçak G, Tutar E, Özbarlas N, Turkish ARF study group. Incidence and clinical characteristics of acute rheumatic fever in Turkey: results of a nationwide multicentre study. J Paediatr Child Health. 2021;57(12):1949-54. https://doi.org/10.1111/jpc.15619
9. Atalay S, Tutar E, Uçar T, Topçu S, Köse SK, Doğan MT. Echocardiographic screening for rheumatic heart disease in Turkish schoolchildren. Cardiol Young. 2019;29(10):1272-7. https://doi.org/10.1017/S1047951119002075
10. Olguntürk R, Aydin GB, Tunaoğlu FS, Akalin N. Rheumatic heart disease prevalence among schoolchildren in Ankara, Turkey. Turk J Pediatr. 1999;41(2):201-6. PMID: 10770659
11. Lombardi A, Bozzi G, Ungaro R, Villa S, Castelli V, Mangioni D, et al. Mini review immunological consequences of immunization with COVID-19 mRNA vaccines: preliminary results. Front Immunol. 2021;12:657711. https://doi.org/10.3389/fimmu.2021.657711
12. Mascellino MT, Di Timoteo F, De Angelis M, Oliva A. Overview of the main anti-SARS-CoV-2 vaccines: mechanism of action, efficacy and safety. Infect Drug Resist. 2021;14:3459-76. https://doi.org/10.2147/IDR.S315727
13. Acuña-Zegarra MA, Díaz-Infante S, Baca-Carrasco D, Olmos-Liceaga D. COVID-19 optimal vaccination policies: a modeling study on efficacy, natural and vaccine-induced immunity responses. Math Biosci. 2021;337:108614. https://doi.org/10.1016/j.mbs.2021.108614
14. Coffey PM, Ralph AP, Krause VL. The role of social determinants of health in the risk and prevention of group A streptococcal infection, acute rheumatic fever and rheumatic heart disease: a systematic review. PLoS Negl Trop Dis. 2018;12(6):e0006577. https://doi.org/10.1371/journal.pntd.0006577
15. Ralph AP, Noonan S, Wade V, Currie BJ. The 2020 Australian guideline for prevention, diagnosis and management of acute rheumatic fever and rheumatic heart disease. Med J Aust. 2021;214(5):220-7. https://doi.org/10.5694/mja2.50851
16. Brown A, McDonald MI, Calma T. Rheumatic fever and social justice. Med J Aust. 2007;186(11):557-8. https://doi.org/10.5694/j.1326-5377.2007.tb01052.x
17. Health Habitat. Safety and the 9 healthy living practices [cited on Sep 30, 2020]. Available from: https://www.healthabitat.com/what-we-do/safety-and-the-9-healthy-living-practices/

ORIGINAL ARTICLE

https://doi.org/10.1590/1806-9282.20220630

Role of apparent diffusion coefficient measurement in differentiating histological subtypes of brain metastasis of lung cancer

Lutfi Incesu[1], Said Abdullayev[1], Mesut Ozturk[2*], Kerim Aslan[1], Hediye Pinar Gunbey[3]

SUMMARY

OBJECTIVE: The aim of this study was to investigate the role of apparent diffusion coefficient of diffusion-weighted imaging in differentiating histological subtypes of brain metastasis of lung cancer.

METHODS: Diffusion-weighted imaging of 158 patients (mean age: 61.2±10.68 years) with brain metastasis of lung cancer (36 small cell lung cancer and 122 non-small cell lung cancer) were retrospectively evaluated. The minimum and mean apparent diffusion coefficient values of the metastasis, apparent diffusion coefficient of edema around the metastasis, and apparent diffusion coefficient of contralateral brain parenchyma were measured. Normalized apparent diffusion coefficient was calculated by proportioning the mean apparent diffusion coefficient of the metastasis to the apparent diffusion coefficient of the contralateral brain parenchyma. Minimum and mean apparent diffusion coefficient of the metastasis, apparent diffusion coefficient of edema around metastasis, and normalized apparent diffusion coefficient were compared between small cell lung cancer and non-small cell lung cancer metastases.

RESULTS: Minimum apparent diffusion coefficient, mean apparent diffusion coefficient, and normalized apparent diffusion coefficient values of small cell lung cancer metastases ($0.43\pm0.19\times10^{-3}mm^2/s$, $0.63\pm0.20\times10^{-3}mm^2/s$, and 0.81 [0.55–1.44], respectively) were significantly lower than those of non-small cell lung cancer metastases ($0.71\pm0.26\times10^{-3}mm^2/s$, $0.93\pm0.29\times10^{-3}mm^2/s$, and 1.30 [0.60–3.20], respectively; p<0.001). Mean apparent diffusion coefficient of edema of small cell lung cancer metastases ($1.21\pm0.28\times10^{-3}mm^2/s$) was significantly lower than that of non-small cell lung cancer metastases ($1.39\pm0.26\times10^{-3}mm^2/s$, p=0.020). The best cutoff values of minimum apparent diffusion coefficient, mean apparent diffusion coefficient, normalized apparent diffusion coefficient, and apparent diffusion coefficient of edema for the differentiation of small cell lung cancer and non-small cell lung cancer were found to be $0.56\times10^{-3}mm^2/s$, $0.82\times10^{-3}mm^2/s$, 1.085, and $1.21\times10^{-3}mm^2/s$, respectively. The area under the receiver operating characteristic curve, sensitivity, and specificity values were, respectively, 0.812, 80.6, and 73.8% for minimum apparent diffusion coefficient; 0.825, 91.7, and 61.5% for mean apparent diffusion coefficient; 0.845, 80.6, and 73.8% for normalized apparent diffusion coefficient; and 0.698, 75.0, and 67.7% for apparent diffusion coefficient of edema.

CONCLUSIONS: Minimum apparent diffusion coefficient, mean apparent diffusion coefficient, normalized apparent diffusion coefficient, and apparent diffusion coefficient of edema around metastasis can differentiate histological subtypes of brain metastasis of lung cancer.

KEYWORDS: Lung cancer. Brain metastasis. Diffusion weighted MRI. Histological subtype.

INTRODUCTION

The annual incidence of primary and secondary central nervous system (CNS) tumors is 10–17 per 100,000 people, accounting for 2% of all cancers in the adult population[1-4]. Brain tumors have the lowest survival rates among malignant tumors and they benefit poorly from the current treatment options[5]. However, early diagnosis and accurate pretreatment staging significantly affect the survival rates.

Metastatic brain tumors are the most common brain tumor in adults, constituting 20–40% of all CNS tumors[4]. Lung cancer is the most common tumor that metastasizes to the brain. Lung cancer has two different histological subtypes: small cell lung carcinoma (SCLC) and non-small cell lung carcinoma (NSCLC). Treatment of lung cancer depends on the histological subtype of the tumor and its stage at the time of diagnosis. While chemotherapy or radiotherapy is used in SCLC, surgery is performed in the early stage of NSCLC and chemoradiotherapy in the advanced stage.

Diffusion-weighted imaging (DWI) is a functional imaging method that evaluates the random movement of water

[1]Ondokuz Mayis University Faculty of Medicine, Department of Radiology – Samsun, Turkey.
[2]Samsun University Faculty of Medicine, Department of Radiology – Samsun, Turkey
[3]University of Health Sciences Kartal Lutfi Kırdar Training and Research Hospital, Department of Radiology – Istanbul, Turkey.
*Corresponding author: dr.mesutozturk@gmail.com
Conflicts of interest: the authors declare there is no conflicts of interest. Funding: none.
Received on June 29, 2022. Accepted on July 04, 2022.

molecules in biological tissues[6]. There are many studies in the literature investigating the benefit of DWI in the diagnosis of brain tumors[7-12]. Low apparent diffusion coefficient (ADC) values are often associated with a poor prognosis[13-15]. Some recent studies have shown that DWI is useful for the differentiation of low-grade and high-grade glial tumors, metastases from high-grade gliomas, and posterior fossa tumors such as ependymoma and medulloblastoma[16-18]. There are also studies in the literature investigating the value of ADC measurements in metastatic brain tumors[7-11]. The development of noninvasive biomarkers in brain metastases of lung cancer is important because it helps clinicians make early diagnosis and chose appropriate treatment modalities. DWI can be used for this purpose as it is a fast imaging method and allows quantitative measurements.

This study aimed to evaluate whether ADC measurement in DWI contributes to the differentiation of the histological subtypes of brain metastasis from lung cancer.

METHODS

This retrospective study was approved by the Institutional Ethics Committee, and the requirement for informed consent was waived. The standards for reporting of diagnostic accuracy studies were used[19].

Patient selection

The hospital database was retrospectively searched to identify patients who were diagnosed with lung cancer and had metastases to the brain on magnetic resonance imaging (MRI) between January 2015 and January 2019. There were 200 patients. The histopathological diagnosis of lung cancer was made by bronchoscopy or percutaneous or surgical biopsy. In all, 10 patients with signs of intratumoral hemorrhage on conventional MRI and 32 patients who received radiotherapy for the brain metastasis before MRI were excluded. As a result, 158 patients (145 males and 13 females) were included in the study. The mean age of the patients was 61.2±10.7 years (range: 28–89). Notably, 56 patients had a single metastatic lesion and 102 patients had more than one metastatic lesion. The patients were divided into two groups according to the histopathology of lung cancer: SCLC metastasis (n=36) and NSCLC metastasis (n=122). The NSCLC group consisted of 89 adenocarcinomas and 33 squamous cell carcinomas. The diagnosis of 46 cases was made according to the histopathological evaluation of the brain tumor after an operation. The brain lesions of 112 patients were diagnosed as metastasis with clinical and radiological findings.

Magnetic resonance imaging acquisitions

MRI of patients were acquired with a 1.5-T MRI device (Philips Achieva, Koninklijke, The Netherlands) using a dedicated head coil. In our center, the routine MRI protocol of the patients who were referred to imaging with a preliminary diagnosis of metastasis included conventional MRI and DWI sequences. Conventional sequences were as follows: axial and sagittal T2W images, axial T1W images, coronal FLAIR, and axial contrast-enhanced 3D MP-RAGE. DWI was acquired using single-shot spin echo, echo planar imaging (SS SE-EPI) technique with the b values of 0 and 1,000 s/mm^2. ADC maps were automatically reconstructed at the console of the MRI device. All MRI images including DWI and ADC maps were transferred to a dedicated workstation (Philips IntelliSpace Portal version 6.0.4) for further analysis.

Image interpretation and apparent diffusion coefficient measurements

Image interpretation and ADC measurements were performed by a senior radiology resident who was blinded to the histopathological results of the cases. ADC measurements were performed by drawing manual regions of interest (ROIs) on the tumor using the ADC maps. During the measurement, ROIs were drawn on three different regions:

1. the solid component of the tumor,
2. the contralateral normal brain parenchyma, and
3. the edematous area around the metastatic tumor.

In conventional MRI sequences, the size of the mass, its location, whether it contained cystic and/or necrotic components, the presence of enhancement, and the presence of peritumoral edema were evaluated. The most enhancing region of the tumors was determined using the contrast-enhanced MRI sequence. On the ADC maps, three ROIs were placed on the tumor that corresponded to the most enhancing areas without cystic/necrotic changes. The average and the lowest ADC values in the drawn ROI were noted. The mean ADC (ADC_{mean}) and the minimum ADC (ADC_{min}) of those three ROIs were calculated. For the patients with more than one metastatic lesion, the mean of ADC_{mean} and ADC_{min} of the three largest lesions were calculated and used in statistical analysis.

Three different ROIs were placed on the perilesional edema, and the mean of these ROIs was calculated as ADC_{edema}. The mean ADC value of the contralateral normal brain parenchyma was measured. Then, normalized ADC (nADC) was obtained by proportioning the mean ADC of the tumor to the mean ADC of normal brain parenchyma. An example of the ROI placements is demonstrated in Figure 1.

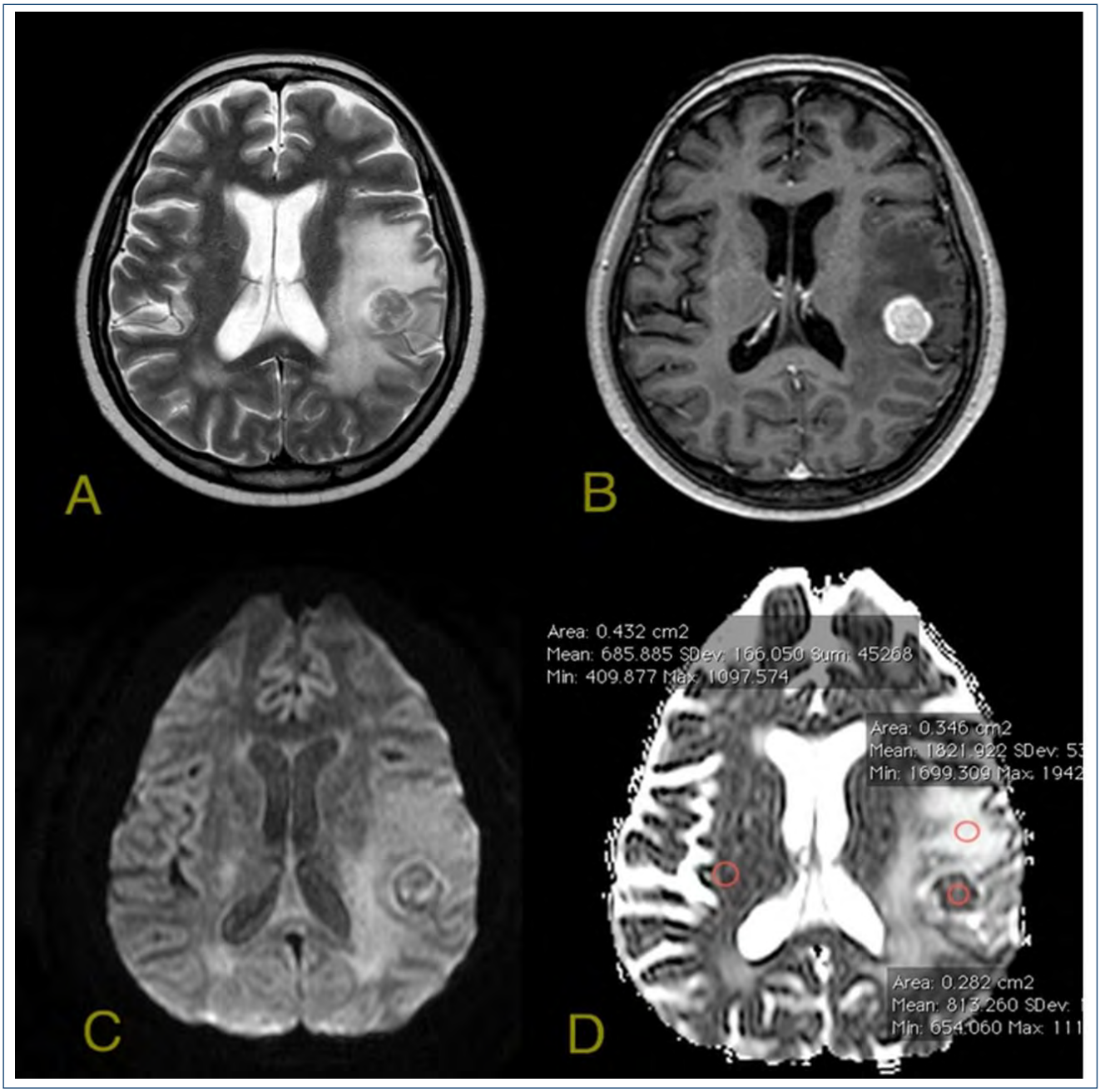


Figure 1. A metastatic lesion in left postcentral gyrus with surrounding vasogenic edema. A) T2-weighted image demonstrates metastatic lesion and peripheral edema. B) The lesion is enhancing heavily in T1-weighted contrast-enhanced images. C) On diffusion-weighted images, the lesion is heterogeneous with a low signal. D) On the apparent diffusion coefficient map, the measurements are obtained by placing regions of interests on the lesion, on the peripheral edema area, and on the contralateral white matter.

Statistical analysis

ADC_{min}, ADC_{mean}, ADC_{edema}, and nADC were compared between SCLC and NSCLC metastases. The data were analyzed with SPSS version 18.0. Continuous variables were expressed as mean and standard deviation or median and ranges as appropriate. Categorical variables were compared using Pearson's chi-square or Fisher's exact tests. Continuous variables were compared using the t-test. Receiver operating characteristics (ROC) curve analysis was used to assess the diagnostic performances of ADC values in the differentiation of SCLC and NSCLC metastases. The best cutoff values were found by maximizing the Youden's index (Youden index=-Sensitivity+specificity−1). A p-value <0.05 was indicative of statistical significance.

RESULTS

Comparison of apparent diffusion coefficient values between the histological subtypes of lung cancer metastases

The mean ADC_{min} and ADC_{mean} and the median nADC of the brain metastases of NSCLC were 0.71±0.26×10^{-3}mm^2/s, 0.93±0.29×10^{-3}mm^2/s, and 1.30 (0.60–3.20), respectively. The mean ADC_{min} and ADC_{mean} and the median nADC of the brain metastases of SCLC were 0.43±0.19 ×10^{-3}mm^2/s, 0.63±0.20 ×10^{-3}mm^2/s, and 0.81 (0.55–1.44), respectively. ADC_{min}, ADC_{mean}, and nADC of the SCLC metastases were significantly lower than those of the NSCLC metastases (p<0.001 for each, Table 1). For the NSCLC group, ADC_{mean} and ADC_{min} of the squamous cell carcinomas (0.82±0.24×10^{-3}mm^2/s and 0.60±0.19×10^{-3}mm^2/s, respectively) were significantly lower than those of the adenocarcinomas (0.97±0.29×10^{-3}mm^2/s and 0.74±0.26×10^{-3}mm^2/s, respectively; p=0.010).

In our series, 56 (35.4%) patients had a single metastatic lesion whereas 102 (64.6%) had more than one metastatic lesion. We compared the ADC_{min}, ADC_{mean}, and nADC of the patients with single metastases with those of the patients with multiple metastases. The mean ADC_{min} and ADC_{mean} and the median nADC of the single metastases (0.64±0.26×10^{-3}mm^2/s, 0.85±0.29×10^{-3}mm^2/s, and 1.20 [0.60–2.90], respectively) were not statistically different from those of the multiple metastases (0.65±0.27×10^{-3}mm^2/s, 0.87±0.30×10^{-3}mm^2/s, and 1.20 [0.55–3.20]; p=0.875, p=0.723, and p=0.923, respectively).

In 109 patients with peritumoral edema around the metastatic lesions (SCLC=16, NSCLC=93), the ADC_{edema} of SCLC metastases (1.22±0.28×10^{-3}mm^2/s) was significantly lower than the ADC_{edema} of NSCLC metastases (1.39±0.26×10^{-3}mm^2/s; p=0.020).

Receiver operating characteristic curve analyses

ROC curve analysis of ADC_{min}, ADC_{mean}, nADC, and ADC_{edema} for the differentiation of SCLC and NSCLC is demonstrated in Table 2. According to the ROC curve analysis, the best cutoff value for the ADC_{mean} in the differentiation of SCLC and NSCLC metastases was found to be 0.82×10^{-3}mm^2/s. For this cutoff value, the sensitivity, specificity, and AUC were found to be 91.7, 61.5%, and 0.825, respectively (95%CI 0.750–0.900, p<0.001). The best cutoff value for the nADC in the differentiation of SCLC and NSCLC metastases was 1.085. For this cutoff value, the sensitivity, specificity, and AUC were 80.6, 73.8%, and 0.845, respectively (95%CI 0.777–0.913, p<0.001).

DISCUSSION

The MRI device we used had 1.5-T field strength. Similar studies in the literature used the same field strength machines, and the field strength of the machine can affect DWI parameters. Jung et al.[7] also used a 3.0-T device. In our study, we tried to standardize our measurements by calculating the ratio of lesion ADC to normal parenchyma ADC (nADC). Our study results showed that nADC can also be used in the differentiation of brain metastasis of lung cancer.

Table 1. Apparent diffusion coefficient measurements of small cell lung cancer and non-small cell lung cancer metastases.

ADC parameter (×10^{-3}mm^2/s)	SCLC	NSCLC	p-value
ADC_{min}	0.43±0.19	0.71±0.26	<0.001
ADC_{mean}	0.63±0.20	0.93±0.29	<0.001
nADC	0.81 (0.55–1.44)	1.30 (0.60–3.20)	<0.001
ADC_{edema}	1.22±0.28	1.39±0.26	0.020

ADC: apparent diffusion coefficient; SCLC: small cell lung cancer; NSCLC: non-small cell lung cancer.

Table 2. Sensitivity, specificity, and area under the receiver operating characteristic curve of the best apparent diffusion coefficient cutoff values in the differentiation of small cell lung cancer and non-small cell lung cancer metastases.

ADC parameter	Cutoff	Sensitivity (%)	Specificity (%)	AUC
ADC_{min}	0.56 ×10^{-3} mm^2/s	80.6	73.8	0.812
ADC_{mean}	0.82 ×10^{-3} mm^2/s	91.7	61.5	0.825
nADC	1.085	80.6	73.8	0.845
ADC_{edema}	1.21 ×10^{-3} mm^2/s	75.0	67.7	0.698

ADC: apparent diffusion coefficient; AUC: area under the receiver operating characteristic curve.

In a study conducted on 26 patients by Hayashida et al.[8], T2W and DWI of metastatic brain lesions of lung cancer were evaluated. They reported that well-differentiated adenocarcinoma metastases demonstrated lower T2 signal intensity and higher nADC values compared to SCLC and poorly differentiated adenocarcinoma metastases. The low ADC values of poorly differentiated adenocarcinoma and SCLC metastases were attributed to high tumoral cellularity.

Duygulu et al.[9] evaluated 76 metastatic brain tumors and concluded that there was no association between primary cancer and ADC values of a metastatic lesion. Since there were only 37 lung cancer metastases in their study, the low number of cases might have led to this conclusion. The authors also emphasized that studies with larger patient groups would be beneficial.

Jung et al.[7] evaluated 74 patients and compared the ADC_{min} and nADC values of SCLC metastases with other lung cancer subtypes. The ADC_{min} was $623.02\pm163.0\times10^{-6}$ mm^2/s in adenocarcinoma metastases, $682.76\pm182.0\times10^{-6}mm^2/s$ in squamous cell carcinomas, and $531.75\pm160.12\times10^{-6}mm^2/s$ in SCLC metastases. The nADC values were found to be 1.04 in adenocarcinoma metastases, 1.11 in squamous cell carcinoma metastases, and 0.88 in SCLC metastases. Although the differences were not statistically significant (p=0.131), the numerical results of the ADC measurements of the tumors were similar to our study.

Yıldırım et al.[10] compared the ADC_{mean} and nADC of the brain metastases of 60 lung cancer patients according to the histological subtypes of the tumors. The differences were not statistically significant and these results were not consistent with our data. They also compared the ADC values of metastatic lesions according to whether they are single or multiple and found that the ADC values of the tumor were significantly lower in patients with multiple metastatic lesions compared to the patients with a single metastasis. They thought that this situation might be due to the tumor grade rather than histological diagnosis. However, in our study, we did find a significant difference between the ADC measurements of single and multiple metastases.

Peritumoral edema in noninfiltrative brain tumors such as meningioma is pure vasogenic and no tumor cells are present[11]. In high-grade gliomas, the peritumoral edema area is composed of vasogenic edema and infiltrative tumoral cells that pass through the blood-brain barrier and invade the white matter. Zakaria et al.[12] measured ADC values from the peritumoral edema of different primary tumor metastases and claimed that the difference in ADC values of the peritumoral edema in some tumor metastases may be due to the different infiltrative properties of different metastases. For example, they found that the peritumoral ADC values of melanoma metastases were significantly higher than those of NSCLC metastases. They attributed this to the fact that melanomas use existing vessels while growing, and NSCLC triggers neo-angiogenesis. In our study, peritumoral ADC values of SCLC metastases were significantly lower than the peritumoral ADC values of NSCLC. SCLCs are more aggressive tumors, and the metastatic tumor cells may infiltrate peritumoral areas.

We had some limitations. First of all, it was a retrospective study with related limitations. Second, histopathological diagnosis was obtained for only 46 of the metastatic tumors. Third, pathological grades of the adenocarcinomas (i.e., well, intermediate, or poorly differentiated) were not considered, which might affect the results of DWI parameters. Fourth, ADC measurements were performed only by one radiologist and we did not assess inter- or intraobserver variation, which might influence the level of the accuracy of ADC.

CONCLUSIONS

ADC measurements can differentiate histological subtypes of brain metastases of lung cancer. ADC_{min}, ADC_{mean}, nADC, and ADC_{edema} values of SCLC metastases are significantly lower than those of NSCLC metastases.

AUTHORS' CONTRIBUTIONS

LI: Conceptualization, Data curation, Formal analysis, Methodology, Supervision, Writing – original draft, Writing – review & editing. **SA:** Conceptualization, Data curation, Methodology, Formal analysis, Writing – original draft, Writing – review & editing. **MO:** Conceptualization, Data curation, Formal analysis, Writing – original draft, Writing – review & editing. **KA:** Conceptualization, Data curation, Formal analysis, Methodology, Supervision, Writing – original draft, Writing – review & editing. **HPG:** Conceptualization, Data curation, Formal analysis, Methodology, Supervision, Writing – original draft, Writing – review & editing.

REFERENCES

1. Wrensch M, Minn Y, Chew T, Bondy M, Berger MS. Epidemiology of primary brain tumors: current concepts and review of the literature. Neuro Oncol. 2002;4(4):278-99. https://doi.org/10.1093/neuonc/4.4.278
2. Fisher JL, Schwartzbaum JA, Wrensch M, Wiemels JL. Epidemiology of brain tumors. Neurol Clin. 2007;25(4):867-90,vii. https://doi.org/10.1016/j.ncl.2007.07.002
3. Schlehofer B, Blettner M, Becker N, Martinsohn C, Wahrendorf J. Medical risk factors and the development of brain tumors.

Cancer. 1992;69(10):2541-7. https://doi.org/10.1002/1097-0142(19920515)69:10<2541::aid-cncr2820691025>3.0.co;2-h

4. Fox BD, Cheung VJ, Patel AJ, Suki D, Rao G. Epidemiology of metastatic brain tumors. Neurosurg Clin N Am. 2011;22(1):1-6,v. https://doi.org/10.1016/j.nec.2010.08.007
5. Ryan P, Lee MW, North B, McMichael AJ. Risk factors for tumors of the brain and meninges: results from the Adelaide adult brain tumor study. Int J Cancer. 1992;51(1):20-7. https://doi.org/10.1002/ijc.2910510105
6. Le Bihan D. Looking into the functional architecture of the brain with diffusion MRI. Nat Rev Neurosci. 2003;4(6):469-80. https://doi.org/10.1038/nrn1119
7. Jung WS, Park CH, Hong CK, Suh SH, Ahn SJ. Diffusion-weighted imaging of brain metastasis from lung cancer: correlation of MRI parameters with the histologic type and gene mutation status. AJNR Am J Neuroradiol. 2018;39(2):273-9. https://doi.org/10.3174/ajnr.A5516
8. Hayashida Y, Hirai T, Morishita S, Kitajima M, Murakami R, Korogi Y, et al. Diffusion-weighted imaging of metastatic brain tumors: comparison with histologic type and tumor cellularity. AJNR Am J Neuroradiol. 2006;27(7):1419-25. PMID: 16908550
9. Duygulu G, Ovali GY, Çalli C, Kitis Ö, Yünten N, Akalin T, et al. Intracerebral metastasis showing restricted diffusion: correlation with histopathologic findings. Eur J Radiol. 2010;74(1):117-20. https://doi.org/10.1016/j.ejrad.2009.03.004
10. Yildirim I, Aktaş A. Evaluation of Solid Brain Metastases in Lung Cancers with Diffusion MRI [Akciger Kanserli Hastalarda Solid Beyin Metastazlarinin Difuzyon MRG ile Degerlendirilmesi]. Med-Science. 2014;3(1):1079-91. https://doi.org/10.5455/medscience.2013.02.8107
11. Strugar J, Rothbart D, Harrington W, Criscuolo GR. Vascular permeability factor in brain metastases: correlation with vasogenic brain edema and tumor angiogenesis. J Neurosurg. 1994;81(4):560-6. https://doi.org/10.3171/jns.1994.81.4.0560
12. Zakaria R, Das K, Radon M, Bhojak M, Rudland PR, Sluming V, et al. Diffusion-weighted MRI characteristics of the cerebral metastasis to brain boundary predicts patient outcomes. BMC Med Imaging. 2014;14:26. https://doi.org/10.1186/1471-2342-14-26
13. Zulfiqar M, Yousem DM, Lai H. ADC values and prognosis of malignant astrocytomas: does lower ADC predict a worse prognosis independent of grade of tumor?--a meta-analysis. AJR Am J Roentgenol. 2013;200(3):624-9. https://doi.org/10.2214/AJR.12.8679
14. Poussaint TY, Vajapeyam S, Ricci KI, Panigrahy A, Kocak M, Kun LE, et al. Apparent diffusion coefficient histogram metrics correlate with survival in diffuse intrinsic pontine glioma: a report from the Pediatric Brain Tumor Consortium. Neuro Oncol. 2016;18(5):725-34. https://doi.org/10.1093/neuonc/nov256
15. Nishiofuku H, Tanaka T, Marugami N, Sho M, Akahori T, Nakajima Y, et al. Increased tumour ADC value during chemotherapy predicts improved survival in unresectable pancreatic cancer. Eur Radiol. 2016;26(6):1835-42. https://doi.org/10.1007/s00330-015-3999-2
16. Rumboldt Z, Camacho DL, Lake D, Welsh CT, Castillo M. Apparent diffusion coefficients for differentiation of cerebellar tumors in children. AJNR Am J Neuroradiol. 2006;27(6):1362-9. PMID: 16775298
17. Taheri H, Tavakoli MB. Measurement of apparent diffusion coefficient (adc) values of ependymoma and medulloblastoma tumors: a patient-based study. J Biomed Phys Eng. 2021;11(1):39-46. https://doi.org/10.31661/jbpe.v0i0.889
18. Payabvash S, Tihan T, Cha S. Differentiation of Cerebellar Hemisphere Tumors: Combining Apparent Diffusion Coefficient Histogram Analysis and Structural MRI Features. J Neuroimaging. 2018;28(6):656-65. https://doi.org/10.1111/jon.12550
19. Bossuyt PM, Reitsma JB, Bruns DE, Gatsonis CA, Glasziou PP, Irwig L, et al. STARD 2015: An Updated List of Essential Items for Reporting Diagnostic Accuracy Studies. Clin Chem. 2015;61(12):1446-52. https://doi.org/10.1373/clinchem.2015.246280

ORIGINAL ARTICLE

https://doi.org/10.1590/1806-9282.20220701

A simple method for clinical implications of pain; comprehensive geriatric assessment

Eyyüp Murat Efendioğlu[1*], Ahmet Çiğiloğlu[2], Zeynel Abidin Öztürk[1]

SUMMARY

OBJECTIVE: The effect of chronic pain on the elderly population is enormous in terms of both human suffering and cost. This study aimed to investigate the factors associated with chronic low back pain in older adults by performing a comprehensive geriatric assessment.

METHODS: This cross-sectional study included 225 elderly patients admitted to a geriatric outpatient clinic. All participants underwent a comprehensive geriatric assessment, and factors related to chronic low back pain were assessed. Participants were grouped as those with and without chronic pain.

RESULTS: The mean age of the participants was 72.9±6.9 years, and 149 (66.2%) of them had chronic pain complaints. The number of chronic diseases and medications, depressive symptom scores, and sleep quality scores were higher, and quality of life (European Quality of Life-5 Dimensions index and European Quality of Life-5 Dimensions visual analog scale) and nutritional status scores were lower in the chronic pain group. The pain visual analog scale score had a statistically significant moderate negative correlation with the European Quality of Life-5 Dimensions index (r=-0.440, p=0.000) and European Quality of Life-5 Dimensions visual analog scale (r=-0.398, p=0.000) scores. The male gender was associated with a reduced risk of chronic pain, while poor sleep quality and number of comorbidities were associated with an increased risk of chronic pain (p=0.000, OR 0.20, p=0.021, OR 2.54, and p=0.010, OR 1.40, respectively).

CONCLUSION: Chronic pain is common and independently associated with poor sleep quality, an increased number of diseases, and female gender. The results of our study may guide pain management in older individuals.

KEYWORDS: Chronic pain. Elderly. Geriatric assessment. Sleep quality.

INTRODUCTION

Chronic pain is a common public health problem which has a detrimental impact on individuals' health and quality of life and poses a significant socioeconomic burden[1]. It is defined as pain that persists or recurs for more than 3 months, according to the International Classification of Diseases[2]. The prevalence of chronic pain in older adults ranges from 27–86%[3].

Biological and psychological factors associated with the development of chronic pain include genetics, age, sex, depression, anxiety, post-traumatic stress, poor concentration, cognitive impairment, sleep problems, and medication use[4]. The influence of sex hormones and the higher sensitivity of pain receptors have been identified as factors that may mediate a more painful experience in women than in men[5].

Studies have shown that chronic pain can have negative consequences on health and well-being, such as malnutrition[6] and poor sleep quality[7]. A previous study reported that most older adults with chronic pain suffered from at least one sleep problem, and short sleep duration and poor sleep quality were the most common complaints[8].

Chronic pain has been linked to restrictions on daily activities, anxiety and depressive symptoms, and poor quality of life[9]. Furthermore, it has been reported that measures of physical function, such as grip strength and lower extremity physical performance, and lower skeletal muscle mass, were associated with chronic pain in older adults[3].

Few studies have comprehensively evaluated the factors associated with chronic pain in older adults[10]. Prevention or treatment of chronic pain has great importance for healthy aging. However, less is known about the causality of chronic pain among older adults.

The purpose of this study was to identify the factors associated with chronic pain by performing a comprehensive geriatric assessment (CGA) on geriatric outpatients.

[1]Gaziantep University, Faculty of Medicine, Department of Internal Medicine, Division of Geriatric Medicine – Gaziantep, Turkey.
[2]Kahramanmaraş Necip Fazıl City Hospital, Division of Geriatric Medicine – Kahmaranmaraş, Turkey.
*Corresponding author: eefendioglu@gmail.com
Conflicts of interest: the authors declare there is no conflicts of interest. Funding: none.
Received on June 14, 2022. Accepted on July 01, 2022.

METHODS

This cross-sectional study involved 225 geriatric outpatients admitted to a university hospital between November 2020 and November 2021. To provide a more homogeneous study group, participants with only low back pain were included as chronic pain patients. Participants with diseases that affect the assessment of muscle function and pain perception (e.g., cancer, rheumatic diseases, neuromuscular diseases, immobility, neurodegenerative diseases, neuropathy, visual and hearing disorders, and peripheral artery disease) were excluded from the study.

All participants underwent a CGA including screening and evaluation of activities of daily living, depressive symptoms, nutritional status, cognitive functions, sarcopenia, sleep quality, and quality of life[11]. Participants were asked whether they had low back pain, and those with pain for 3 months or longer were considered patients with chronic pain. A horizontal visual analog scale (VAS) was used to assess pain intensity, with 0 points indicating no pain and 100 points indicating the worst imaginable pain.

Assessment of activities of daily living

The Katz Index of Activities of Daily Living (ADL) was used to assess the dependence on activities such as continence, bathing, toileting, dressing, feeding, and transferring. According to the index, the total score ranges from 0–6, with higher scores indicating greater independence.

Assessment of instrumental activities of daily living

The Lawton & Brody Index of Instrumental Activities of Daily Living (IADL) was used to measure independence on activities such as food preparation, doing laundry, shopping, using the telephone, housekeeping, taking medicine, using transportation, and managing money. The total score ranges from 0–8 and higher scores indicate greater independence.

Assessment of quality of life

The European Quality of Life-5 Dimensions (EQ-5D) questionnaire was used to assess the quality of life. In the questionnaire, individuals were asked to self-assess the status of their health (including five dimensions, namely, usual activities, self-care, mobility, anxiety/depression, and pain/discomfort). The index score is calculated according to the scores of the dimensions, and a score of 0 indicates death, 1 indicates perfect health, and negative values indicate someone is bedridden, dependent, and unconscious. The EQ-5D VAS is the second part of the questionnaire, indicating the individual's overall health on a vertical scale ranging from 0–100.

Assessment of depressive symptoms

The Geriatric Depression Scale (GDS) was used to evaluate depressive symptoms. A score of 14 and above is considered depression according to the scale.

Assessment of nutritional status

The Mini Nutritional Assessment Tool (MNA) was used to assess the nutritional status of the individuals. According to the tool, a score of <17 indicates malnutrition, 17–23.5 indicates malnutrition risk, and ≥24 indicates adequate nutritional status.

Assessment of cognitive functions

The Mini-Mental State Examination (MMSE) test was used. The reliability and validity of the test have been confirmed, and the cutoff point for the diagnosis of mild dementia in the Turkish population was found to be 23/24 over 30 points.

Assessment of sleep quality

The Pittsburgh Sleep Quality Index (PSQI) scale was used. The scale has 7 components, and each component is rated between 0 and 3 points. A total score of 5 and above indicates poor sleep quality.

Assessment of Sarcopenia

The European Working Group on Sarcopenia in Older People (EWGSOP2) criteria was used to diagnose sarcopenia. According to the EWGSOP2 criteria, low muscle strength and mass are required for the diagnosis[12]. Muscle strength was determined by measuring handgrip strength with a hydraulic hand dynamometer. A bioelectrical impedance analyzer was used to measure muscle mass.

Statistical analysis

The normality of the distribution of continuous variables was checked using the Shapiro-Wilk test. The Mann-Whitney U-test and the independent samples t-test were used to compare two independent groups. The relationship between categorical variables was assessed using the chi-square test. The correlations between continuous variables were measured using the Spearman's rank correlation coefficient. Multivariate logistic regressions were performed to determine the independent variables on chronic low back pain. SPSS version 22.0 was used and a p-value of <0.05 was considered statistically significant.

RESULTS

The mean age of the participants was 72.9±6.9 years, 61.3% were female, and 149 (66.2%) of them suffered from chronic

low back pain. The proportion of female participants and those with sarcopenia and hypertension was higher in the chronic pain group. The number of comorbidities and medications, GDS, and PSQI scores were higher, while ADL, EQ-5D index, EQ-5D VAS, and MNA scores were lower in the chronic pain group. Table 1 shows the geriatric assessment results and sociodemographic characteristics of the patients.

The pain VAS score had a statistically significant moderate negative correlation with the EQ-5D index (r=-0.440, p=0.000), EQ-5D VAS (r=-0.398, p=0.000), and skeletal muscle mass index (r=-0.316, p=0.000) scores, and a statistically significant moderate positive correlation with the GDS (r=0.316, p=0.000) and PSQI (r=0.357, p=0.000) scores (Table 2).

Variance inflation factor was calculated and the number of medications was excluded from models. The male gender was associated with a decreased risk of chronic pain, while poor sleep quality and the number of comorbidities were associated with an increased risk of chronic pain (p=0.000, OR 0.20, p=0.021, OR 2.54, and p=0.010, OR 1.40, respectively) according to multivariate logistic regression analysis (Table 3).

DISCUSSION

This study has shown that older adults with chronic low back pain are more likely to have impaired functional status, malnutrition, sarcopenia, depressive symptoms, poorer quality of life, and sleep quality. Poor sleep quality has also been found to be an independent risk factor for chronic pain.

Similar to our results, previous studies have shown that chronic pain impairs ADL[13], sleep quality[14], and quality of life[15]. A study investigating chronic pain and sleep difficulties in older adults reported strong and consistent associations between chronic pain and heterogeneous sleep complaints[16]. It has been shown that poor sleep quality is associated

Table 1. Participants' sociodemographic characteristics and comprehensive geriatric assessment results (n=225).

	Chronic pain (–) (n=76)	Chronic pain (+) (n=149)	p-value	Total (n=225)
Gender				
Female (%)	32 (42.1)	106 (71.1)	<0.001*	138 (61.3)
Male (%)	44 (57.9)	43 (28.9)		87 (38.7)
Age†	72.9±6.0	72.9±7.2	0.572	72.9±6.9
Number of comorbidities#	2 (1)	3 (2)	<0.001*	3 (2)
Number of medications#	4 (3)	5 (4)	0.042*	5 (4)
Comorbidities				
Hypertension (%)	38 (50.0)	100 (67.1)	0.013*	138 (61.3)
Diabetes mellitus (%)	39 (51.3)	88 (59.1)	0.268	127 (56.4)
Coronary artery disease (%)	16 (21.1)	50 (33.6)	0.051	66 (29.3)
Asthma/COPD (%)	11 (14.5)	32 (21.5)	0.206	43 (19.1)
ADL#	6 (1)	5 (2)	0.025*	6 (1)
IADL#	6 (3)	7 (3)	0.435	7 (3)
EQ-5D index#	0.84 (0.67)	0.42 (0.39)	<0.001*	0.53 (0.60)
EQ-5D VAS#	80 (25)	60 (30)	<0.001*	60 (30)
GDS#	7.5 (9)	12 (10)	0.001*	10 (10)
MNA#	24 (6)	22 (7.5)	0.002*	23 (7.1)
MMSE#	24 (11)	25 (10)	0.799	25 (10)
PSQI#	4 (4)	6 (4)	<0.001*	6 (4)
Sarcopenia (%)	16 (21.1)	66 (44.3)	0.002*	82 (36.4)
Gait speed (m/s)†	0.83±0.29	0.77±0.30	0.155	0.79±0.30

COPD: chronic obstructive pulmonary disease; ADL: Katz Index of Activities of Daily Living; IADL: Lawton & Brody Index of Instrumental Activities of Daily Living; EQ-5D: European Quality of Life-5 Dimensions; VAS: visual analog scale; GDS: Geriatric Depression Scale; MNA: Mini Nutritional Assessment Tool; MMSE: Mini-Mental State Examination; PSQI: Pittsburgh Sleep Quality Index. *p<0.05; †Data are presented as mean±SD. #Data are presented as median (interquartile range).

Table 2. Correlation analysis results between the variables.

		VAS	Age	Number of diseases	Number of medications	ADL	IADL	EQ-5D index	EQ-5D VAS	GDS	MNA	MMSE	PSQI	HGS	SMMI	Gait speed
VAS	r		-0.017	0.289	0.180	-0.133	-0.078	-0.440	-0.398	0.316	-0.276	0.066	0.357	-0.212	-0.316	-0.125
	p		0.802	0.000**	0.007**	0.046*	0.243	0.000**	0.000**	0.000**	0.000**	0.325	0.000**	0.002**	0.000**	0.075
Age	r			0.029	0.096	-0.252	-0.375	-0.284	-0.132	0.121	-0.074	-0.330	0.024	-0.262	-0.026	-0.439
	p			0.665	0.150	0.000**	0.000**	0.000**	0.048*	0.069	0.272	0.000**	0.724	0.000**	0.713	0.000**
Number of diseases	r				0.681	-0.239	-0.285	-0.376	-0.321	0.287	-0.157	-0.085	0.168	-0.138	-0.196	-0.161
	p				0.000**	0.000**	0.000**	0.000**	0.000**	0.000**	0.019*	0.206	0.013*	0.041*	0.005**	0.021*
Number of medications	r					-0.306	-0.286	-0.326	-0.197	0.219	-0.185	-0.152	0.100	-0.140	-0.089	-0.205
	p					0.000**	0.000**	0.000**	0.003**	0.001**	0.006**	0.023*	0.139	0.040*	0.205	0.003**
ADL	r						0.535	0.513	0.445	-0.390	0.204	0.330	-0.220	0.195	0.017	0.169
	p						0.000**	0.000**	0.000**	0.000**	0.002**	0.000**	0.001**	0.004**	0.808	0.016*
IADL	r							0.641	0.444	-0.501	0.242	0.572	-0.157	0.462	0.129	0.501
	p							0.000**	0.000**	0.000**	0.000**	0.000**	0.020*	0.000**	0.067	0.000**
EQ-5D index	r								0.631	-0.620	0.344	0.325	-0.369	0.442	0.310	0.440
	p								0.000**	0.000**	0.000**	0.000**	0.000**	0.000**	0.000**	0.000**
EQ-5D VAS	r									-0.628	0.270	0.232	-0.294	0.339	0.232	0.324
	p									0.000**	0.000**	0.000**	0.000**	0.000**	0.001**	0.000**
GDS	r										-0.345	-0.274	0.448	-0.378	-0.177	-0.253
	p										0.000**	0.000**	0.000**	0.000**	0.012*	0.000**
MNA	r											0.045	-0.309	0.120	0.013	0.198
	p											0.508	0.000**	0.079	0.858	0.005**
MMSE	r												-0.088	0.342	0.041	0.323
	p												0.196	0.000**	0.559	0.000**
PSQI	r													-0.180	-0.193	-0.118
	p													0.009**	0.007**	0.098
HGS	r														0.600	0.532
	p														0.000**	0.000**
SMMI	r															0.386
	p															0.000**
Gait speed	r															
	p															

VAS: visual analog scale pain score; ADL: katz index of activities of daily living; IADL: Lawton & Brody index of instrumental activities of daily living; EQ-5D: European quality of life-5 dimensions; GDS: geriatric depression scale; MNA: mini nutritional assessment tool; MMSE: mini-mental state examination; PSQI: Pittsburgh sleep quality index; HGS: handgrip strength; SMMI: skeletal muscle mass index. r: Spearman rank correlation coefficient; *Significant at 0.05 level; **Significant at 0.01 level.

Table 3. Multivariate logistic regression analysis results of the independent variables for chronic pain.

Variable	Chronic pain	
	OR [95%CI]	p-value
Age	0.97 [0.91–1.03]	0.344
Gender (male vs. female)	0.20 [0.09–0.45]	0.000*
Number of comorbidities	1.40 [1.09–1.82]	0.010*
ADL score	0.87 [0.61–1.22]	0.411
Malnutrition	1.06 [0.49–2.29]	0.884
Depression	1.12 [0.44–2.92]	0.802
Sarcopenia	1.04 [0.94–1.07]	0.916
Poor sleep quality	2.54 [1.15–5.58]	0.021*

CI: confidence interval; OR: odds ratio; ADL: Katz index of activities of daily living. *p<0.05 according to multivariate binary logistic regression analysis.

with increased pain complaints in older adults[17]. In a study investigating the relationship between sleep disorders and pain, sleep deprivation has been shown to increase neuronal response that causes hyperexcitability and a decrease in pain thresholds. Sleep deprivation has also been found to induce a low-grade inflammatory response, resulting in increased sensitivity to pain[18].

In our study, older adults with chronic pain had a statistically significantly higher prevalence of sarcopenia. The mean gait speed was also lower in the chronic pain group, although there was no statistically significant difference. Several studies have shown that sarcopenia can cause chronic pain[19,20]. A study conducted in Japan has reported that elderly patients with chronic pain had significantly lower skeletal muscle mass than those without chronic pain[21].

We also found that older adults with chronic pain were more likely to be malnourished. This may be explained by the fact that chronic pain is associated with decreased food intake and appetite[22]. A recent study showed that suffering from chronic pain was a predictor of malnutrition among older adults[6].

The prevalence of chronic pain in our study (66.2%) was significantly higher than that reported in previous studies[7,23]. The reason for the higher prevalence in our study may be due to the fact that it was performed in a tertiary referral hospital. In addition, different definitions of chronic pain in some studies may have led to differences in the prevalence.

Moreover, we found that chronic pain was associated with a number of comorbidities and medications in older adults. Multimorbidity, defined as two or more chronic diseases, is present in approximately 65% of older adults and it complicates pain management in individuals[24]. Therefore, coordinated management of comorbid conditions is critical for reducing chronic pain in the elderly.

Another significant finding of our study was that the female gender was an independent risk factor for chronic pain. Most previous studies revealed that women were more likely to have chronic pain, which was consistent with our study[7,25]. It is thought that women are more sensitive to pain due to differences in biological or psychological mechanisms.

Our study has some limitations. First, due to the cross-sectional nature of the study, no conclusions can be drawn about causal relationships. Second, the study was conducted on a population that may not be fully representative of the general population. Third, the classification of the pain was not done (neuropathic, nociceptive, etc.). The strengths of our study are that all the participants underwent CGA using valid tools and the exclusion of participants having diseases that may complicate the assessment of pain.

CONCLUSIONS

In this study, poor sleep quality, increased number of diseases, and female gender were found to be independent risk factors for chronic pain. We also showed that older adults with chronic pain are more likely to suffer from impaired functional status, depressive symptoms, malnutrition, sarcopenia, and poorer quality of life.

Our findings highlight the close relationship between chronic pain and other geriatric syndromes. Performing comprehensive assessment of factors that may cause pain and planning treatment strategies are important in order to ensure healthy aging and to prevent possible negative consequences.

AUTHORS' CONTRIBUTIONS

EME: Conceptualization, Writing – original draft. **AÇ:** Data curation, Formal Analysis. **ZAÖ:** Writing – review & editing.

REFERENCES

1. Clauw DJ, Essex MN, Pitman V, Jones KD. Reframing chronic pain as a disease, not a symptom: rationale and implications for pain management. Postgrad Med. 2019;131(3):185-98. https://doi.org/10.1080/00325481.2019.1574403
2. Treede RD, Rief W, Barke A, Aziz Q, Bennett MI, Benoliel R, et al. Chronic pain as a symptom or a disease: the IASP classification of chronic pain for the international classification of diseases (ICD-11). Pain. 2019;160(1):19-27. https://doi.org/10.1097/j.pain.0000000000001384
3. Patel KV, Guralnik JM, Dansie EJ, Turk DC. Prevalence and impact of pain among older adults in the United States: findings from the 2011 National Health and Aging Trends Study. Pain. 2013;154(12):2649-57. https://doi.org/10.1016/j.pain.2013.07.029
4. Cohen SP, Vase L, Hooten WM. Chronic pain: an update on burden, best practices, and new advances. Lancet. 2021;397(10289):2082-97. https://doi.org/10.1016/S0140-6736(21)00393-7
5. Bartley EJ, Fillingim RB. Sex differences in pain: a brief review of clinical and experimental findings. Br J Anaesth. 2013;111(1):52-8. https://doi.org/10.1093/bja/aet127
6. Abdu AO, Yimamu ID, Kahsay AA. Predictors of malnutrition among older adults aged above 65 years in eastern Ethiopia: neglected public health concern. BMC Geriatr. 2020;20(1):497. https://doi.org/10.1186/s12877-020-01911-2
7. Si H, Wang C, Jin Y, Tian X, Qiao X, Liu N, et al. Prevalence, factors, and health impacts of chronic pain among community-dwelling older adults in China. Pain Manag Nurs. 2019;20(4):365-72. https://doi.org/10.1016/j.pmn.2019.01.006
8. Zaidel C, Musich S, Karl J, Kraemer S, Yeh CS. Psychosocial factors associated with sleep quality and duration among older adults with chronic pain. Popul Health Manag. 2021;24(1):101-9. https://doi.org/10.1089/pop.2019.0165
9. Gureje O, Von Korff M, Simon GE, Gater R. Persistent pain and well-being: a World Health Organization Study in Primary Care. JAMA. 1998;280(2):147-51. https://doi.org/10.1001/jama.280.2.147
10. Liberman O, Freud T, Peleg R, Keren A, Press Y. Chronic pain and geriatric syndromes in community-dwelling patients aged ≥65 years. J Pain Res. 2018;11:1171-80. https://doi.org/10.2147/JPR.S160847
11. Parker SG, McCue P, Phelps K, McCleod A, Arora S, Nockels K, et al. What is Comprehensive Geriatric Assessment (CGA)? An umbrella review. Age Ageing. 2018;47(1):149-55. https://doi.org/10.1093/ageing/afx166
12. Cruz-Jentoft AJ, Bahat G, Bauer J, Boirie Y, Bruyère O, Cederholm T, et al. Sarcopenia: revised European consensus on definition and diagnosis. Age Ageing. 2019;48(4):601. https://doi.org/10.1093/ageing/afz046
13. Eggermont LHP, Penninx BWJH, Jones RN, Leveille SG. Depressive symptoms, chronic pain, and falls in older community-dwelling adults: the MOBILIZE Boston Study. J Am Geriatr Soc. 2012;60(2):230-7. https://doi.org/10.1111/j.1532-5415.2011.03829.x
14. Miu DKY, Chan KC. Under-detection of pain in elderly nursing home residents with moderate to severe dementia. J Clin Gerontol Geriatr. 2013;5(1):23-7. https://doi.org/10.1016/j.jcgg.2013.09.001
15. Bernfort L, Gerdle B, Rahmqvist M, Husberg M, Levin LÅ. Severity of chronic pain in an elderly population in Sweden--impact on costs and quality of life. Pain. 2015;156(3):521-7. https://doi.org/10.1097/01.j.pain.0000460336.31600.01
16. Chen Q, Hayman LL, Shmerling RH, Bean JF, Leveille SG. Characteristics of chronic pain associated with sleep difficulty in older adults: the Maintenance of Balance, Independent Living, Intellect, and Zest in the Elderly (MOBILIZE) Boston study. J Am Geriatr Soc. 2011;59(8):1385-92. https://doi.org/10.1111/j.1532-5415.2011.03544.x
17. Sampaio RA, Sewo Sampaio PY, Yamada M, Tsuboyama T, Arai H. Self-reported quality of sleep is associated with bodily pain, vitality and cognitive impairment in Japanese older adults. Geriatr Gerontol Int. 2014;14(3):628-35. https://doi.org/10.1111/ggi.12149
18. Nijs J, Mairesse O, Neu D, Leysen L, Danneels L, Cagnie B, et al. Sleep disturbances in chronic pain: neurobiology, assessment, and treatment in physical therapist practice. Phys Ther. 2018;98(5):325-35. https://doi.org/10.1093/ptj/pzy020
19. Scott D, Blizzard L, Fell J, Jones G. Prospective study of self-reported pain, radiographic osteoarthritis, sarcopenia progression, and falls risk in community-dwelling older adults. Arthritis Care Res (Hoboken). 2012;64(1):30-7. https://doi.org/10.1002/acr.20545
20. Scott D, Blyth F, Naganathan V, Le Couteur DG, Handelsman DJ, Seibel MJ, et al. Prospective associations of chronic and intrusive pain with sarcopenia and physical disability amongst older Australian men: the concord health and ageing in men project. Exp Gerontol. 2021;153:111501. https://doi.org/10.1016/j.exger.2021.111501
21. Sakai Y, Matsui H, Ito S, Hida T, Ito K, Koshimizu H, et al. Sarcopenia in elderly patients with chronic low back pain. Osteoporos Sarcopenia. 2017;3(4):195-200. https://doi.org/10.1016/j.afos.2017.09.001
22. Bosley BN, Weiner DK, Rudy TE, Granieri E. Is chronic nonmalignant pain associated with decreased appetite in older adults? Preliminary evidence. J Am Geriatr Soc. 2004;52(2):247-51. https://doi.org/10.1111/j.1532-5415.2004.52063.x
23. Li X, Zhu W, Li J, Huang C, Yang F. Prevalence and characteristics of chronic Pain in the Chinese community-dwelling elderly: a cross-sectional study. BMC Geriatr. 2021;21(1):534. https://doi.org/10.1186/s12877-021-02432-2
24. Wolff JL, Starfield B, Anderson G. Prevalence, expenditures, and complications of multiple chronic conditions in the elderly. Arch Intern Med. 2002;162(20):2269-76. https://doi.org/10.1001/archinte.162.20.2269
25. Satghare P, Chong SA, Vaingankar J, Picco L, Abdin E, Chua BY, et al. Prevalence and correlates of pain in people aged 60 years and above in singapore: results from the WiSE study. Pain Res Manag. 2016;2016:7852397. https://doi.org/10.1155/2016/7852397

ORIGINAL ARTICLE

https://doi.org/10.1590/1806-9282.20220758

The effectiveness of berberine on noise-induced hearing loss: a rat model

Korhan Kilic[1*], Muhammed Sedat Sakat[1], Abdulkadir Sahin[1], Serkan Yildirim[2], Muhammet Bahaeddin Dortbudak[2]

SUMMARY

OBJECTIVE: Noise-induced hearing loss is a preventable form of hearing loss that has serious social and economic impacts. This study aimed to investigate the protective effect of berberine, a potent antioxidant and anti-inflammatory agent, against Noise-induced hearing loss.

METHODS: After applying distortion product otoacoustic emission, 28 female Sprague-Dawley rats were randomly divided into four groups. Group 1 was designated as acoustic trauma group, and rats in this group were exposed to white noise for 12 h at an intensity of 4 kHz 110 dB sound pressure level. Group 2 was the control group. Group 3 was designated as the berberine group, and 100 mg/kg of berberine was administered to rats in this group by intragastric lavage for five consecutive days. Group 4 was designated as the acoustic trauma+berberine group. distortion product otoacoustic emission was repeated on the 6th day of the study and cochlear tissues of rats were dissected for histopathological and immunohistochemical analyses after sacrificing rats.

RESULTS: The distortion product otoacoustic emission results showed a significant decrease in signal-noise ratio values at higher frequencies in rats of the trauma group compared to those in other groups. Acoustic trauma caused severe histopathological impairment at cochlear structures together with severe 8-hydroxy-2-deoxyguanosine expression. Rats in the acoustic trauma+berberine group showed mild histopathological changes with mild 8-hydroxy-2-deoxyguanosine expression and better signal-noise ratio values.

CONCLUSION: The histopathological and audiological findings of this experimental study showed that berberine provides protection in Noise-induced hearing loss and may have the potential for use in acoustic trauma-related hearing losses.

KEYWORDS: Acoustic trauma. Berberine. Noise-induced hearing loss.

INTRODUCTION

Noise can be defined as unwanted and uncomfortable sound, causing various psychological and physiological effects in humans and adversely affecting the quality of life. Noise is an agent to which individuals are exposed during much of modern life, and that can cause various pathological effects throughout the body. The most important of these effects is seen in the auditory system, the first site impacted by noise[1].

The mechanism underlying noise-related hearing losses is not yet fully understood. However, a combination of apoptosis, oxidative stress, and genetic, physical, and environmental factors is thought to be involved. Oxidative stress is characterized by the presence of DNA damage and lipid peroxidation, generally resulting from the development of free radicals. Noise-induced damage to the cochlea results from degeneration in support cells, afferent nerve fibers, and particularly outer hair cells[2].

The importance of oxidative stress in the pathogenesis of this damage led to the idea of employing antioxidants to prevent it. Various agents have been used for this purpose in the literature[3-7]. Berberine is an alkaloid with a broad pharmacological spectrum and particularly with antioxidant and anti-inflammatory effects[8].

Distortion product otoacoustic emissions (DPOAE) were used to demonstrate noise-related hearing damage. DPOAE are highly sensitive in showing noise-related damage in the inner ear in rats and can yield an earlier response than the auditory brain stem response test[9].

The purpose of this study was to investigate the protective efficacy of the powerful antioxidant and anti-inflammatory agent berberine on noise-related hearing losses using histopathological and immunohistochemical methods and DPOAE.

[1]Ataturk University, Faculty of Medicine, Department of Otorhinolaryngology – Erzurum, Turkey.
[2]Ataturk University, Faculty of Veterinary, Department of Pathology – Erzurum, Turkey.
*Corresponding author: Korhankilic@gmail.com

Conflicts of interest: the authors declare there is no conflicts of interest. Funding: This work was supported by Research Fund of the Ataturk University. Project Number: TAB-2021-9273.
Received on June 23, 2022. Accepted on July 04, 2022.

METHODS

This study was approved by the Ataturk University animal experiments ethical committee with number 2021;1:4. The study was conducted at the Ataturk University experimental research laboratory.

Animals

The study protocol was established with 28 female Sprague-Dawley rats weighing 220–260 g. The Care and Use of Laboratory Animals guideline was implemented throughout the study. Rats were housed in separate cages in a 12:12 h light:dark system. The cages were designed to allow ad libitum access to food and water. The room temperature was set to 22°±2° and the humidity to 50±5%. Environmental noise was kept below 50 dB SPL.

Study design

Before the study, general anesthesia was applied to all rats using 40 mg/kg ketamine hydrochloride + 10 mg/kg xylazine hydrochloride via the intraperitoneal (i.p.) route. The tympanic membranes of both ears of all rats were subjected to otoscopic examination under general anesthesia. DPOAE was then applied to all rats. Rats with tympanic membrane perforation, findings of otitis media, or failing the DPOAE test were excluded from the study.

The saline solution and berberine used in the study were administered in a single dose by intragastric lavage once daily for 5 days. Saline was administered at a dosage of 8 mg/kg and berberine (Santa Cruz Biotechnology, Inc., Texas, USA) at a dosage of 100 mg/kg. Rats were exposed to acoustic trauma on day 3 of the study. DPOAE measurements were repeated on day 6, and all rats were sacrificed under general anesthesia. The rats' cochlear tissues were excised and set aside for histopathological and immunohistochemical examination.

Experimental Protocol

Rats were randomized into four groups of seven animals each.

Group 1 was designated as the acoustic trauma group. Rats in this group received 8 mg/kg of saline solution by orogastric lavage together with acoustic trauma.

Group 2 was designated as the control group. No drug or acoustic trauma was applied to this group.

Group 3 was designated as the berberine group. The rats in this group received 100 mg/kg berberine dissolved in saline solution in a single dose once daily for 5 days by intragastric lavage.

Group 4 was designated as the acoustic trauma+berberine group. Together with the acoustic trauma, the rats in this group received 100 mg/kg of berberine in a single dose once daily for 5 days via intragastric lavage.

Acoustic Trauma Model

The acoustic trauma was applied to rats in groups 1 and 4 on the 3rd day of the study. For this, the rats were placed into a silent booth inside their cages, equidistant from two speakers. The rats were then exposed to white noise for 12 h at an intensity of 4 kHz 110 dB SPL in a free environment using a GSI Audiostar Pro audiometer (Grason-Stadler, Eden Prairie, Minnesota, USA).

Distortion product otoacoustic emissions

DPOAE measurements were performed on all experimental animals under general anesthesia before (on day 1) and after (on day 6) noise exposure. The test was conducted following an otoscopic examination in a silent environment using a Madsen Capella 2 (GN Otometrics, Denmark) measurement device, and an appropriate probe was applied to the outer ear canals. DPgram measurements were carried out at 10 frequencies between 2002 and 10000 Hz. Signal-noise ratios (SNR) were compared in the measurement results for days 1 and 6.

Histopathological examination

Following fixation in 10% formalin solution for 48 h, tissues were allowed to soften for 96–120 h in the Osteosoft decalcification solution (Merck, HC313331, Germany). After softening, the tissue was washed under running water for 24 h. Tissues were then passed through routine processes and then were embedded in paraffin blocks. Sections of 4 µm in thickness were taken and placed onto glass slides. Preparates made ready for histopathological examination were stained with hematoxylin-eosin and examined under a light microscope. These sections were classified based on the presence of lesions as none (–), mild (+), moderate (++), and severe (+++), and they were photographed. Hyperemia in stria vascularis was determined by the diameter of the vessels (<1 µm is defined as none, 1–2 µm as mild, 3–5 µm as moderate, and >5 µm as severe). The degeneration of spiral ganglia was determined by the degenerated cell number (0 is defined as none, 3–5 cells as mild, 6–10 cells as moderate, and >10 cells severe). Structural impairment in outer hair cells was determined by the impaired cell number (0 as none, 3–5 cells as mild, 6–10 cells as moderate, and >10 cells as severe).

Immunohistochemical examination

All sections placed onto adhesive-containing slides (poly-L-lysine) for immunoperoxidase examination were passed through xylol and alcohol series. After washing with phosphate-buffered saline, endogenous peroxidase inactivation was established by keeping the sections in 3% H_2O_2 for 10 min. Following

treatment in a microwave with an antigen retrieval solution for 2×5 min at 500 watts for antigen detection, tissues were left to cool and treated in a microwave. Tissues were then incubated with 8-hydroxy-2-deoxyguanosine (8-OHdG) (catalog no. sc-66036, Santa Cruz, USA) at 37°C for 60 min. Procedures were carried out in compliance with the immunohistochemistry kit instructions (Abcam HRP/DAB Detection IHC kit). 3-3′ Diaminobenzidine was used as the chromogen. Background staining was applied with hematoxylin. To determine the intensity of positive staining from the obtained images, five random areas were selected from each image. As a result of the antibody staining used for the evaluation process, the positive/total area was measured using the ZEISS Zen Imaging Software program.

Statistical Analysis

Statistical analysis was conducted using the SPSS 20.0 software. Data distribution was checked using the Shapiro-Wilk test. One-way ANOVA and the post-hoc Tukey's test were employed for comparisons of DPOAE results, immunoreactive cells, and immunopositive stained areas of positive antibodies in immunochemical analyses in the case of normal distribution. The nonparametric Kruskal-Wallis test was applied in the analysis of intergroup differences among semi-quantitatively obtained non-normally distributed data at histopathological examination, while the Mann-Whitney U-test was employed for two-way examination. For all tests, a p-value of <0.05 was considered significant.

RESULTS

Distortion product otoacoustic emissions results

No difference was observed in SNR values of the control, berberine, and berberine+trauma groups on the 6th day compared to those on the 1st day. No significant difference was observed in SNR values of the trauma group at 2002 and 2383 Hz frequencies on day 6 compared to day 1 values, but significant decreases were determined in SNR values on day 6 at all higher frequencies. This shows that acoustic trauma leads to cochlear damage, particularly at high frequencies. Comparison of post-exposure DPOAE results between groups showed higher SNR values in the berberine+trauma group compared to those in the trauma group, while no significant difference was observed between the berberine+trauma group and the control group. This shows that berberine exhibits effective protection against acoustic trauma in the cochlea. The results of DPOAE are given in Figure 1.

Histopathological and immunochemical findings

Acoustic Trauma Group: Cochlear tissues exhibited degeneration and necrosis in the spinal ganglia, severe erosion in outer hair

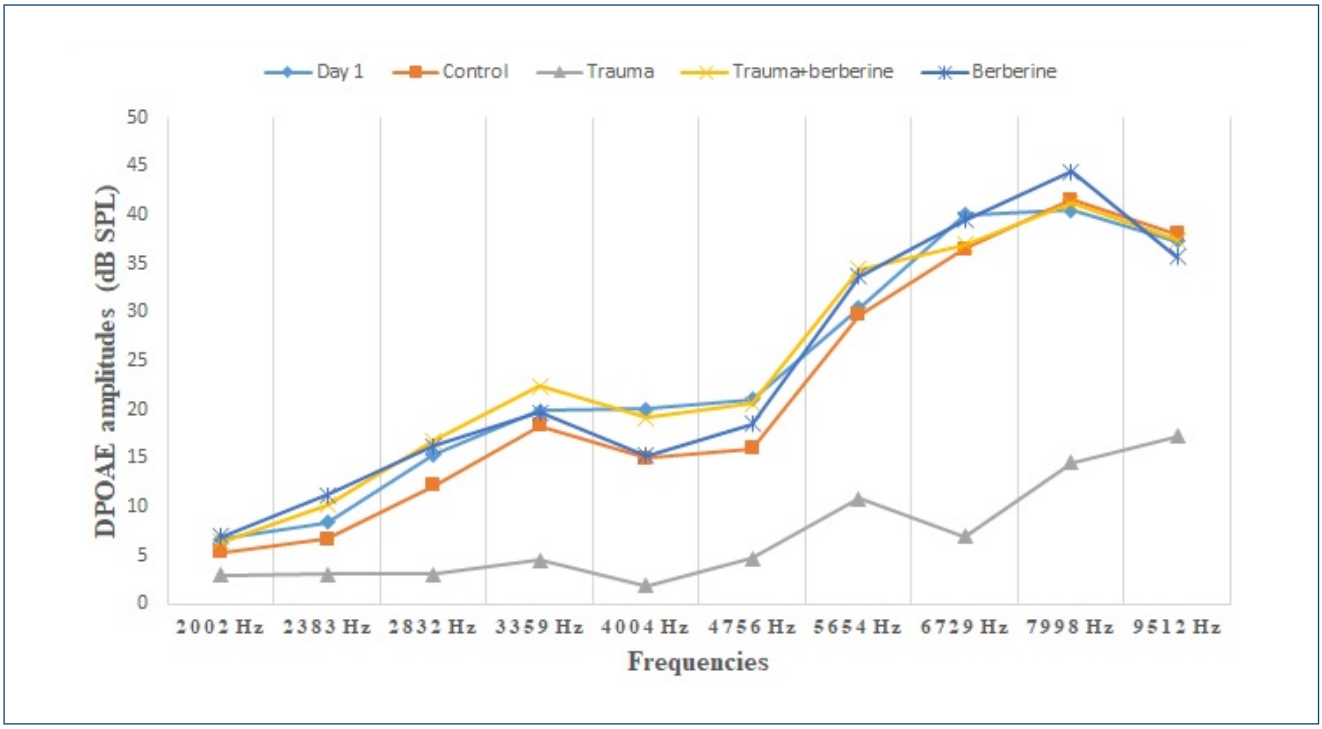


Figure 1. Results of distortion product otoacoustic emissions tests before (day 1) and after (day 6) noise exposure. Control, trauma, trauma+berberine, and berberine groups mean the results of distortion product otoacoustic emissions of these groups, performed on day 6.

cells and decreased numbers due to desquamation, and hyperemia in the stria vascularis (Figure 2-A). Immunohistochemical examination of cochlear tissues revealed severe 8-OHdG expression in the spinal ganglia and outer hair cells (Figure 2-E).

Control and Berberine Groups: Cochlear tissues exhibited a normal histological appearance in the stria vascularis, spinal ganglia, and outer hair cells (Figure 2-B, C). Immunohistochemical examination revealed negative 8-OHdG expression (Figure 2-F, G).

Acoustic Trauma+Berberine Group: Cochlear tissues exhibited mild degeneration in spinal ganglia, mild erosion in outer hair cells, desquamation, and an associated mild decrease in numbers, and moderate hyperemia in the stria vascularis (Figure 2-D). Immunohistochemical examination of cochlear tissues revealed mild cytoplasmic 8-OHdG expression in the spinal ganglia and outer hair cells (Figure 2-H). A statistically significant difference was observed compared with the acoustic trauma group in terms of histopathological and immunochemical results ($p<0.05$). The histopathological and immunohistochemical findings are summarized in Table 1.

DISCUSSION

Exposure to noise is one of the most common causes of hearing loss. Noise-induced hearing loss (NIHL) is a preventable form of hearing loss involving both genetic and environmental factors. Research has shown that measures taken in the prevention of NIHL are most effective and economical than treatment. Sufficient understanding of the pathophysiology of the disease is important for NIHL to be prevented and even treated. Studies to date have shown that oxidative stress is the most important mechanism in the pathophysiology of NIHL[10].

Under normal physiological conditions, oxidants and antioxidants in the body are maintained in balance. However, increased reactive oxygen species (ROS) following the exposure to noise results in that balance being impaired in favor of oxidants. Increased ROS production also causes apoptotic and necrotic cell death in the cochlea, associated with collapse in support cells and stria edema, dendrite breakdown, and stereocilia defects[11]. The outer hair cells are the first structures affected by exposure to noise in the cochlea. Due to their motility, the outer hair cells are highly energy-dependent. On account of their energy dependency, greater oxygen is used in the mitochondria in case of noise exposure, and more ROS is produced as a side product[12]. Increasing ROS production triggers cell death as a cause of DNA damage and the breakdown of lipid and protein molecules[13]. 8-OHdG is a predominant form that occurs as a result of free radical-induced oxidative lesion of nuclear and mitochondrial DNA. Numerous studies have revealed that 8-OHdG is an important marker of oxidative DNA damage. Semenova et al. stated that 8-OHdG is an important indicator of oxidative DNA damage and an important marker in aging and sleep-wake cycle[14]. Chen et al. also found that 8-OHdG levels increased in the cochlear tissue after noise exposure[15]. In this study, increased expression of 8-OHdG was demonstrated in the cochlear tissue after acoustic trauma.

Several molecules have been employed in research for the purpose of halting or neutralizing this physiological cascade at any stage. This study employed histopathological and audiological methods to determine the impact of berberine in an acoustic trauma model. The effect mechanisms of berberine in diseases derive from its antioxidant and anti-inflammatory properties[16]. Berberine shows its antioxidant and anti-inflammatory effects in three main ways:

1. the inhibition of nicotinamide adenine dinucleotide phosphate (NADPH) oxidase,
2. the activation of the Nrf2 pathway, and
3. the inhibition of the NF-kB pathway. With all these effects, it shows antioxidant and anti-inflammatory activity[17].

It has also been shown that berberine inhibits apoptosis caused by oxidative stress by modulating Ca^{2+} deregulation[18].

NADPH stimulation via cytokines, the mitochondrial electron transport chain, and xanthine oxidase generally result in oxidative stress as a cause of ROS overproduction[15]. Berberine reduces this overproduction by inhibiting the NADPH pathway. Jang et al. showed that berberine exhibits a high hydroxyl radical scavenging effect[19]. In this study, the administration of berberine decreased the expression of 8-OHdG in cochlear tissue.

The immunohistochemical and audiological findings of the present experimental study showed that, thanks to its excellent antioxidant and apoptotic effects, berberine exhibited a protective effect on the inner ear in an acoustic trauma model. Studies in the literature have also shown that berberine is used in humans. Jiang et al. reported that berberine is a safe and effective drug in patients with colorectal cancer and is beneficial in the treatment of these patients[20]. Similarly, human studies have shown that berberine is an effective agent in neurodegenerative disorders such as the Parkinson's and Alzheimer's diseases due to its potent antioxidant effect[21]. As oxidative stress is one of the most important steps in the underlying mechanism of NIHL, we predict that berberine can also be used for NIHL in humans with its strong antioxidant activity.

The principal limitation of this study is that biochemical investigation showing oxidative and antioxidative values was not

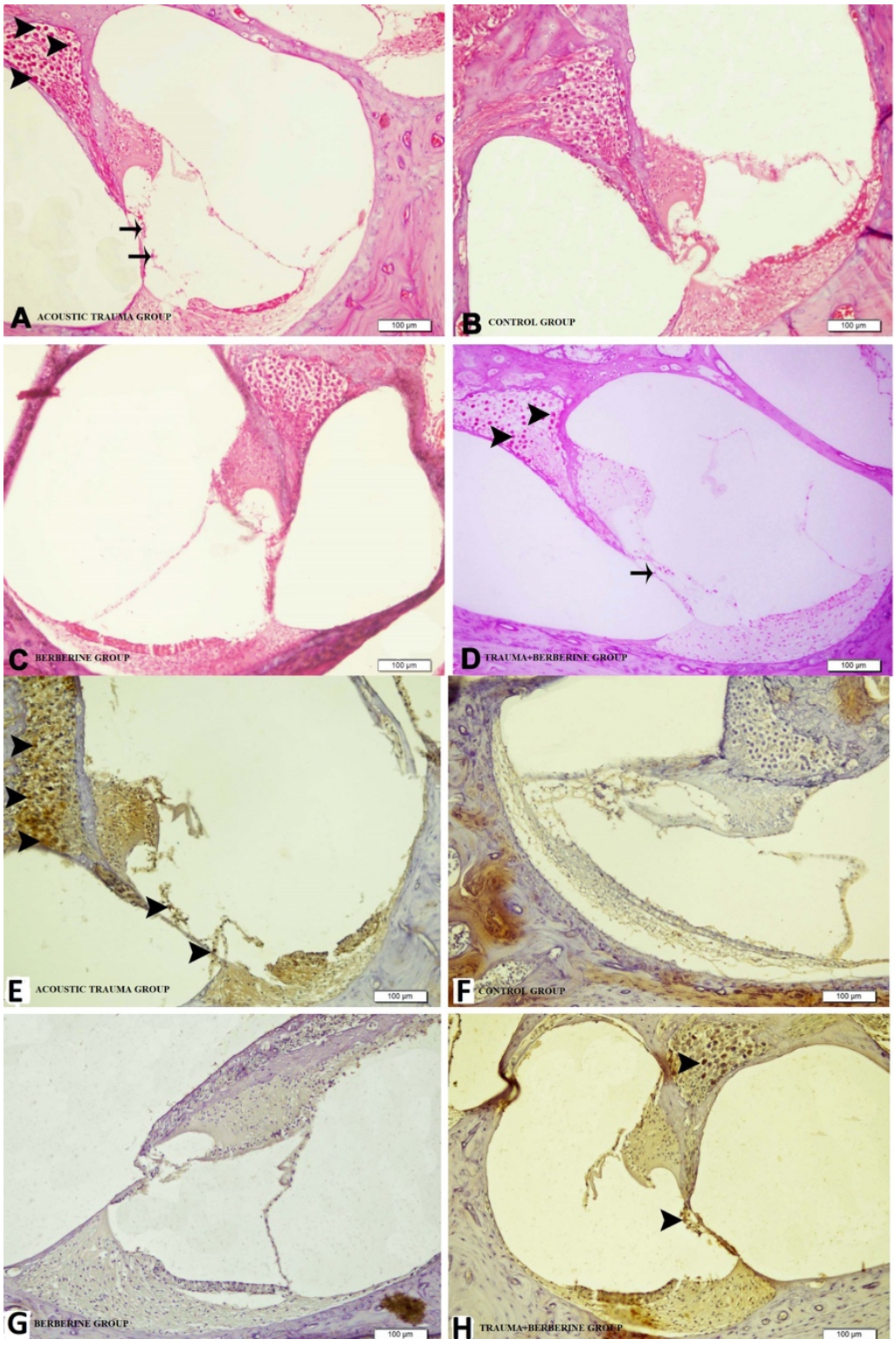


Figure 2. Histopathological appearance of cochlear tissues. (A) Acoustic Trauma Group. Degeneration and necrosis in ganglia (arrow heads), desquamation, and severe decrease in number of outer hair cells (arrows). (B) Control Group. Normal histological appearance. (C) Berberine Group. Normal histological appearance. (D) Acoustic Trauma+Berberine Group. Degeneration in ganglia (arrow heads), mild desquamation, and decrease in number of outer hair cells (arrows). Hematoxilen & eosine, Bar: 100 µm. Immunohistochemical appearance of cochlear tissues. (E) Acoustic Trauma Group. Severe cytoplasmic 8-hydroxy-2-deoxyguanosine expression in ganglia and outer hair cells (arrow heads). (F) Control Group. Negative 8-hydroxy-2-deoxyguanosine expression. (G) Berberine Group. Negative 8-hydroxy-2-deoxyguanosine expression. (H) Acoustic Trauma+Berberine Group. Mild 8-hydroxy-2-deoxyguanosine expression in ganglia and outer hair cells (arrow heads). Immunohistochemistry-peroxidase, Bar: 100 µm.

Table 1. Histopathological and immunochemical results of cochlear tissues

	Acoustic Trauma	Control	Berberine	Acoustic Trauma+ Berberine
Hyperemia in the stria vascularis	+++	–	–	++
Decreased outer hair cells	+++	–	–	+
Degeneration and necrosis in spinal ganglion cells	+++	–	–	+
8-OHdG expression (mean±SD)	63.21±3.23[a]	20.51±6.42[b]	21.47±5.96[b]	41.53±5.81[c]

[a, b, c]different letters show statistically significance ($p<0.05$). Presence of lesions as none (–), mild (+), moderate (++), and severe (+++).

performed. However, 8-OHdG, an important marker of oxidative stress, reduces the scale of that limitation in immunohistochemical terms. As this is an experimental study, there should be difficulties in methodological design and transposing data to human beings.

CONCLUSIONS

To the best of our knowledge, this is the first study in the literature to show the protective efficacy of berberine in an acoustic trauma model. The histopathological and audiological findings of this experimental study showed that berberine provides protection in acoustic trauma. Berberine may therefore have the potential for use in acoustic trauma-related hearing losses. However, as this is an experimental study, further research is needed on the use of berberine in humans.

AUTHORS' CONTRIBUTIONS

KK: Conceptualization, Data curation, Formal Analysis, Writing – original draft. **MSS**: Conceptualization, Data curation, Formal Analysis, Writing – original draft. **AS**: Data curation, Formal Analysis, Writing – original draft. **SY:** Data curation, Formal Analysis, Writing – original draft. **MBD:** Data curation, Formal Analysis, Writing – original draft.

REFERENCES

1. Ozdogan F, Ensari S, Cakir O, Ozcan KM, Koseoglu S, Ozdas T, et al. Investigation of the cochlear effects of intratympanic steroids administered following acoustic trauma. Laryngoscope. 2012;122(4):877-82. https://doi.org/10.1002/lary.23185
2. Ada S, Hanci D, Ulusoy S, Vejselova D, Burukoglu D, Muluk NB, et al. Potential protective effect of N-acetyl cysteine in acoustic trauma: An experimental study using scanning electron microscopy. Adv Clin Exp Med. 2017;26(6):893-7. https://doi.org/10.17219/acem/64332
3. Kopke RD, Weisskopf PA, Boone JL, Jackson RL, Wester DC, Hoffer ME, et al. Reduction of noise-induced hearing loss using L-NAC and salicylate in the chinchilla. Hear Res. 2000;149(1-2):138-46. https://doi.org/10.1016/s0378-5955(00)00176-3
4. Bas E, Martinez-Soriano F, Láinez JM, Marco J. An experimental comparative study of dexamethasone, melatonin and tacrolimus in noise-induced hearing loss. Acta Otolaryngol. 2009;129(4):385-9. https://doi.org/10.1080/00016480802566279
5. Zhou Y, Zheng H, Shen X, Zhang Q, Yang M. Intratympanic administration of methylprednisolone reduces impact of experimental intensive impulse noise trauma on hearing. Acta Otolaryngol. 2009;129(6):602-7. https://doi.org/10.1080/00016480802342424
6. Fetoni AR, Paciello F, Rolesi R, Eramo SL, Mancuso C, Troiani D, et al. Rosmarinic acid up-regulates the noise-activated Nrf2/HO-1 pathway and protects against noise-induced injury in rat cochlea. Free Radic Biol Med. 2015;85:269-81. https://doi.org/10.1016/j.freeradbiomed.2015.04.021
7. Heinrich UR, Fischer I, Brieger J, Rümelin A, Schmidtmann I, Li H, et al. Ascorbic acid reduces noise-induced nitric oxide production in the guinea pig ear. Laryngoscope. 2008;118(5):837-42. https://doi.org/10.1097/MLG.0b013e31816381ae
8. Wang Z, Chen Z, Chen T, Yi T, Zheng Z, Fan H, et al. Berberine Attenuates Inflammation Associated with Delayed-Type Hypersensitivity via Suppressing Th1 Response and Inhibiting Apoptosis. Inflammation. 2017;40(1):221-31. https://doi.org/10.1007/s10753-016-0472-6
9. Fraenkel R, Freeman S, Sohmer H. The effect of various durations of noise exposure on auditory brainstem response, distortion product otoacoustic emissions and transient evoked otoacoustic emissions in rats. Audiol Neurootol. 2001;6(1):40-9. https://doi.org/10.1159/000046807
10. Ohinata Y, Miller JM, Altschuler RA, Schacht J. Intense noise induces formation of vasoactive lipid peroxidation products in the cochlea. Brain Res. 2000;878(1-2):163-73. https://doi.org/10.1016/s0006-8993(00)02733-5
11. Plontke S, Zenner HP. Current aspects of hearing loss from occupational and leisure noise. GMS Curr Top Otorhinolaryngol Head Neck Surg. 2004;3:Doc06. PMID: 22073048
12. Kamogashira T, Fujimoto C, Yamasoba T. Reactive oxygen species, apoptosis, and mitochondrial dysfunction in hearing loss. Biomed Res Int. 2015;2015:617207. https://doi.org/10.1155/2015/617207
13. Nasezadeh P, Shahi F, Fridoni M, Seydi E, Izadi M, Salimi A. Moderate O3/O2 therapy enhances enzymatic and non-enzymatic antioxidant in brain and cochlear that protects noise-induced hearing loss. Free Radic Res. 2017;51(9-10):828-37. https://doi.org/10.1080/10715762.2017.1381695
14. Semenova NV, Madaeva IM, Brichagina AS, Kolesnikov SI, Kolesnikova LI. 8-Hydroxy-2'-Deoxyguanosine as an oxidative stress marker in insomnia. Bull Exp Biol Med. 2021;171(3):384-7. https://doi.org/10.1007/s10517-021-05233-0

15. Chen L, Han M, Lu Y, Chen D, Sun X, Yang S, et al. Molecular mechanisms underlying the protective effects of hydrogen-saturated saline on noise-induced hearing loss. Acta Otolaryngol. 2017;137(10):1063-8. https://doi.org/10.1080/00016489.2017.1328743

16. Wang K, Feng X, Chai L, Cao S, Qiu F. The metabolism of berberine and its contribution to the pharmacological effects. Drug Metab Rev. 2017;49(2):139-57. https://doi.org/10.1080/03602532.2017.1306544

17. Ma X, Chen Z, Wang L, Wang G, Wang Z, Dong X, et al. The Pathogenesis of Diabetes Mellitus by Oxidative Stress and Inflammation: Its Inhibition by Berberine. Front Pharmacol. 2018;9:782. https://doi.org/10.3389/fphar.2018.00782

18. Luo R, Liao Z, Song Y, Yin H, Zhan S, Li G, et al. Berberine ameliorates oxidative stress-induced apoptosis by modulating ER stress and autophagy in human nucleus pulposus cells. Life Sci. 2019;228:85-97. https://doi.org/10.1016/j.lfs.2019.04.064

19. Jang MH, Kim HY, Kang KS, Yokozawa T, Park JH. Hydroxyl radical scavenging activities of isoquinoline alkaloids isolated from Coptis chinensis. Arch Pharm Res. 2009;32(3):341-5. https://doi.org/10.1007/s12272-009-1305-z

20. Jiang X, Jiang Z, Jiang M, Sun Y. Berberine as a Potential Agent for the Treatment of Colorectal Cancer. Front Med (Lausanne). 2022;9:886996. https://doi.org/10.3389/fmed.2022.886996

21. Cheng Z, Kang C, Che S, Su J, Sun Q, Ge T, et al. Berberine: a promising treatment for neurodegenerative diseases. Front Pharmacol. 2022;13:845591. https://doi.org/10.3389/fphar.2022.845591

ORIGINAL ARTICLE

https://doi.org/10.1590/1806-9282.20220806

Epidemiological study on the lip and oral cavity cancer in Brazil: connecting science and clinical applicability

Isnaya Almeida Brandão Lima[1], Rodrigo José Lima Almeida[2], André Pontes-Silva[3]*, Bruno Ferreira Ribeiro[4], Francisco Winter dos Santos Figueiredo[5], Fernando Rodrigues Peixoto Quaresma[1], Erika da Silva Maciel[1]

SUMMARY

OBJECTIVE: The aim of this study was to describe and discuss the epidemiological indicators of lip and oral cavity cancer in Brazil, in 2017, according to data from the Global Burden of Disease data.

METHODS: This is a descriptive study reported according to STROBE guidelines. We identified epidemiological indicators using the Global Burden of Disease results tool. Mortality/incidence rates were described per 100,000 population. Global Burden of Disease 2017 reviews were completed using Python version 2.7, Stata version 13.1, and R version 3.3.

RESULTS: In 2017, there were 5,237 deaths from the lip or oral cavity cancer in Brazil, most of them were males aged between 50 and 69 years (2,730 cases, which was equivalent to 52% of the universe of deaths resulting from this cause). Regarding the burden of lip and oral cavity cancer, per 100,000 Brazilians, we observed an incidence of 3.99, prevalence of 15.46, and mortality of 2.29 (with higher indicators in the South and Southeast regions of the country).

CONCLUSIONS: Epidemiological indicators of lip and oral cavity cancer were higher in men, with higher mortality indicators in individuals aged 50–69 years, and higher rates (incidence, prevalence, and mortality) in the South and Southeast regions of Brazil. From 2002–2015, there was a reduction in mortality; however, in the period from 2015–2017, there was a resumption in the growth of this indicator.

KEYWORDS: Epidemiology. Mortality. Mouth neoplasms.

INTRODUCTION

In Europe, mortality rates from the lip and oral cavity cancer have been decreasing since 1970. In contrast, Latin American countries, such as Chile, have shown increased rates since 1980[1]. Brazil followed this trend until 2002, and then, until 2015, it showed stability or reduction in its rates[2]. This coincides with the implementation of public policies on oral health in our country: inclusion of oral health in the Family Health Strategy at the end of 2000; regulation of the actions of oral health teams in the Family Health Strategy (2001); completion of the national epidemiological survey of oral health (2003); and launch of the guidelines of the National Oral Health Policy (*Brasil Sorridente, 2004*)[3].

In Brazil, 15,290 new cases of that disease were recorded in 2014 and 15,490 in 2015[4]. Therefore, Brazil was the country with the highest number of contributing cases in Latin America (33,925 deaths attributed to oral and pharyngeal cancer in 2015)[5]; thus, future longevity gains will depend on the adoption of health policies focused on the management of chronic conditions, which requires studies and analyses of these conditions[6]; however, no study investigated the epidemiological profile of oral cancer in the Brazilian region in 2017.

Despite the known action of smoking and alcohol in the etiology of this disease, epidemiological studies have shown that, even after adjusting for these risk factors, there is still a residual effect of social conditions on the risk of oral cancer. Thus, the findings of this study investigate whether socioeconomic conditions interfere with the prognosis of the disease. This study aimed to describe and discuss the epidemiological indicators of lip and oral cavity cancer in Brazil, in 2017, according to the Global Burden of Disease (GBD) data.

[1]Universidade Federal do Tocantins, Postgraduate Program in Science and Health Teaching – Palmas (TO), Brazil.
[2]Universidade Federal do Tocantins, Graduate Program in Regional Development – Palmas (TO), Brazil.
[3]Universidade Federal de São Carlos, Postgraduate Program in Physiotherapy – São Carlos (SP), Brazil.
[4]Universidade Federal do Tocantins, School of Physical Education – Miracema do Tocantins (TO), Brazil.
[5]Faculdade de Medicina do ABC, Postgraduate Program in Health Sciences – Santo André (SP), Brazil.
*Corresponding author: contato.andrepsilva@gmail.com
Conflicts of interest: the authors declare there is no conflicts of interest. Funding: none.
Received on June 06, 2022. Accepted on July 07, 2022

METHODS

This is a descriptive study with data on the estimated burden of lip and oral cavity cancer in Brazil in GBD 2017. GBD Brazil is a partnership, started in 2014, and involves the Institute for Health Metrics and Evaluation, Ministry of Health, local universities, and researchers from around the world[7].

GBD study conducted in 2017 aimed to determine the incidence, prevalence, mortality, and disability-adjusted life years (DALYs) of 359 diseases and injuries, and 84 risk factors by age and sex in 195 countries and territories[8]. It provides a comprehensive assessment of cause-specific mortality for 282 causes from 1980–2017[9]. In addition, more indicators from the United Nations Sustainable Development Goals were examined, and forecasting methods were used to generate projections through 2030 and assess the pace of change needed to achieve them.

The GBD 2017 study investigated:

a. all causes, risks, etiologies, disabilities, injuries by nature, and aggregates of GBD sequelae;
b. measures: deaths, years of life lost (YLLs), years lived with disability (YLDs), DALYs, prevalence, incidence, life expectancy, probability of death, health-adjusted life expectancy, the maternal mortality rate, and summary exposure value;
c. metrics (units): number, rate, percentage, years, probability of death;
d. years: 1990–2017;
e. annual results for all measures;
f. all GBD age groups;
g. sexes: males, females, both sexes;
h. locations: super-regions, regions, GBD countries, sub-national units, and custom regions.

We started with the identification of the epidemiological indicators of lip and oral cavity cancer in Brazil in 2017, according to sex, age group, and region of the country, through the GBD results tool (http://ghdx.healthdata.org/gbd-results-tool). For the composition of its database, the GBD uses multiple sources from all countries such as vital statistics, censuses, administrative databases, publications, surveys, cancer records, police records (external causes), and environmental data[7].

The following data sources were used in Brazil – a) epidemiological surveys: Vigitel (*Vigilância de fatores de risco e proteção para doenças crônicas por Inquérito Telefônico*), PNAD (*Pesquisa Nacional por Amostra de Domicílios*), and PeNSE (*Pesquisa Nacional de Saúde do Escolar*); b) vital records: SIM (*Sistema de Informação sobre Mortalidade*) and DATASUS (*Departamento de Informática do Sistema Único de Saúde*); and c) sources of epidemiological surveillance: SIA-SUS (*Sistema de Informação Ambulatorial do Sistema Único de Saúde*), SISVAN (*Sistema de Vigilância Alimentar e Nutricional*), and SINAN (*Sistema de Informação de Agravos de Notificação*) – the main source of mortality data. The database of the Mortality Information System of the Ministry of Health (SIM) was used.

Analysis of these data generated indicators of mortality and YLLs due to premature death, which, in addition to the information on morbidity and the number of YLDs, provided the measure of the GBD: the YLLs due to premature death, or disability (DALYs).

Mortality/incidence rates (MIR) were described per 100,000 people. GBD 2017 analyses were completed using Python version 2.7, Stata version 13.1, and R version 3.3[9]. Data are presented as absolute frequency and relative frequency.

RESULTS

The study variables related to lip and oral cavity cancer were mortality, incidence, prevalence, DALYs, YLD, and YLL. The ratio between the mortality rate and the incidence rate generated an indicator called the MIR, which was used to estimate the 5-year survival of cancer of the lip or oral cavity. These data were considered according to gender, age group (15–49, 50–69, and ≥70 years), and Brazilian region (North, Northeast, Southeast, South, and Midwest) of cases that occurred in 2017, and all data were expressed as a number per 100,000 inhabitants.

In 2017, there were 5,237 deaths from cancer of the lip or oral cavity in Brazil. Most of them were male (3,864 deaths, corresponding to approximately 74% of the total) and aged between 50 and 69 years (2,730 cases, which was equivalent to 52% of the universe of deaths resulting from this cause) (Table 1).

Regarding the burden of lip and oral cavity cancer per 100,000 Brazilian inhabitants in 2017, we observed an incidence of 3.99, a prevalence of 15.46, mortality of 2.29, 57.78 DALYs, 1.64 YLD, and 56.14 YLL (Table 2). Regarding the

Table 1. Deaths from cancer of the lip or oral cavity in Brazil in 2017

Deaths	n	%
Total	5,237	100
Sex		
Female	1,373	26.22
Male	3,864	73.78
Age group (years)		
15–49	683	13.04
50–69	2,730	52.13
70>	1,824	34.83

geographic region, the numbers indicated higher mortality, incidence, and prevalence in the South and Southeast regions of the country (Table 3). Regarding lip and oral cavity cancer in Brazil (with reference to the period from 2002 to 2017), there was a balanced reduction in mortality until 2015, when there was a resumption in its growth.

DISCUSSION

Other studies confirm the fact that all epidemiological indicators of oral cancer are higher in men than in women. The National Cancer Institute estimated, for the year 2016, 11,140 new cases of oral cavity cancer in men and 4,350 in women. The values correspond to an estimated risk of 11.27 new cases per 100,000 men and 4.21 per 100,000 women[4].

Thus, the epidemiological profile of the individuals most affected by the disease would be characterized by men, aged between 50 and 70 years, workers exposed to the sun, and chronic users of cigarettes and/or alcohol, habits more common among men[10,11]. Consequently, the mortality rate from these neoplasms in men is significantly higher than in women, reaching a ratio of 4/1[2].

Previous research identified the age group from 60–69 years as the most prone to this type of cancer[12]. however, the GBD data showed a change in relation to the age group, bringing higher rates for individuals aged more than 70 years. As for the rate of YLLs (potential YLLs due to cancer of the mouth and pharynx) in the country, there was an upward trend between 1979 and 2013 in both sexes[5].

When analyzing its distribution throughout the entire territorial extension of Brazil, it is observed that for mouth cancer, the Northeast region presented one of the lowest average coefficients for the period from 2002–2013 (1.6/100,000 inhabitants), but with an average annual increase in mortality of 6.9%. The Southeast region, in turn, had the second-highest average coefficient (2.04); however, it was the only region in which there was a reduction in mortality rates. It is known that tobacco is the main risk factor for cancer of the mouth and pharynx and that the South and Southeast regions have the highest consumption of tobacco in Brazil[13]. Between 1989 and 2010, the drop in the percentage of smokers in Brazil was 46%[14], reflecting the reduction in mortality observed in recent years.

From 1979–2002, the average mortality rate from oral cancer in Brazil was 2.7/100,000 inhabitants[5]. Between 2002 and 2013, the rate dropped to 1.87/100,000 inhabitants[2], remaining stable in this period. The GBD data confirm a reduction in mortality between 2002 and 2015 and a resumption in the growth of this indicator from then on. It is estimated that, in

Table 2. Epidemiology of lip and oral cavity cancer in Brazil in 2017.

Indicators	General	Sex		Age group (years)		
		Male	Female	15–49	50–69	≥70
Incidence	3.99	6.03	2.25	1.55	12.7	21.94
Prevalence	15.46	22.36	9.55	7.22	49.99	72.97
Mortality	2.29	3.69	1.1	0.6	7.14	15.2
MIR	0.57	0.61	0.49	0.39	0.56	0.69
DALYs	57.78	96.4	23.88	27.59	213.12	199.02
YLD	1.64	2.45	0.93	0.7	5.25	8.34
YLL	56.14	93.94	22.95	26.89	207.87	190.68

MIR: mortality/incidence rates; DALYs: disability-adjusted life years; YLD: years lived with disability; YLL: years of life lost.

Table 3. Epidemiology of lip and oral cavity cancer in Brazilian region in 2017.

Indicators	North	Northeast	Southeast	South	Midwest
Incidence	3.03	3.78	4.23	4.26	3.59
Prevalence	11.73	14.69	16.44	16.41	13.89
Mortality	1.8	2.25	2.39	2.41	2.04
MIR	0.59	0.6	0.56	0.57	0.57
DALYs	43.59	56.3	61.23	60.97	49.66
YLD	1.25	1.55	1.73	1.74	1.48
YLL	42.34	54.74	59.5	59.23	48.18

MIR: mortality/incidence rates; DALYs: disability-adjusted life years; YLD: years lived with disability; YLL: years of life lost.

2020, more than 21,000 new cases presented with oral and pharyngeal cancer and more than 10,000 of them died in Brazil[15].

This discrepancy in rates between the sexes is observed not only in Brazil but also worldwide. The increase in the longevity of the Brazilian population has caused a demographic and epidemiological transition[13]. This process encompasses the following three basic changes: replacement of communicable diseases by non-communicable diseases and external causes; transformation from a situation in which mortality predominates to one in which morbidity is dominant; and shifting the burden of morbidity and mortality from younger groups to older groups[16] (which justifies the significant increase in the incidence of oral cancer cases in elderly individuals).

The differences in the behavior of the main types of cancer, with a decrease mainly in the more developed regions and an increase in the less developed regions of the country, seem to reflect both socioeconomic inequalities and access to health services by the Brazilian population[17]. In addition, it may suggest an improvement in the information systems in the period studied (which would justify the registration of a greater number of deaths for the calculation).

A possible reduction in oral cancer mortality in recent years may be related to the efforts undertaken to provide access to early diagnosis and treatment for the main types of cancer, in line with the National Oral Health Policy and the National Oncology Care Policy.

In terms of clinical applicability, knowledge about the pathology brings more chances of an early diagnosis, thus avoiding mutilating treatments that impact the quality of life of patients (and unnecessary expenses in public health). As such, discussing the pathology to highlight the high rates of morbidity and mortality will make health professionals, especially doctors and dentists, reflect on their responsibilities in carrying out health education and screening for lip and oral cavity cancer.

In terms of scientific applicability, our results highlight the difficulties in establishing public policies aimed at the main risk factors related to the occurrence of oral malignancy. In this way, researchers in the area of epidemiology and clinical applicability will be encouraged to deepen the studies on the relationship between the factors associated with this disease, the future perspectives for the studied indices, the importance of policies already implemented, and the social and economic impact caused by high rates of oral cancer morbidity.

The high rates of mortality and morbidity due to oral cancer indicate that this disease constitutes a public health problem both in developed and developing countries. The possibility of reducing the incidence of oral cancer is related to the knowledge and control of risk factors that lead to the development of the disease. Therefore, the more the topic is discussed, the more information based on scientific evidence is disseminated.

There is still no evidence that a visual examination, as part of a population-based screening program, reduces the mortality rate from lip and oral cavity cancer. Thus, there is a need for longitudinal studies that can analyze this relationship. There is also a need to produce scientific evidence that supports actions that demonstrate a real impact on the epidemiological indicators of oral cancer to the detriment of isolated, voluntary, and disconnected actions of public action, especially at the local level. Hence, extensive research should be carried out in order to show the burden that social conditions exert on the complex causal chain of lip and oral cavity cancer.

This study has limitations that must be addressed. The first one is that we use secondary data, which may be outdated from state and/or national databases. The second refers to the study design (cross-sectional), which has no explanatory power in terms of cause and effect. Therefore, we suggest conducting a longitudinal study to provide additional information about this disease over time.

CONCLUSIONS

Epidemiological indicators of lip and oral cavity cancer were higher in men, with higher mortality indicators in individuals aged 50–69 years and higher rates (incidence, prevalence, and mortality) in the South and Southeast regions of Brazil. From 2002–2015, there was a reduction in mortality; however, in the period from 2015–2017, there was a resumption in the growth of this indicator.

ACKNOWLEDGMENT

We thank the Dean of Postgraduate (PROPESQ) and the Universidade Federal do Tocantins for their support and encouragement to this research.

AUTHORS' CONTRIBUTIONS

IABL: Conceptualization, Data curation, Formal analysis, Investigation, Methodology, Project administration, Resources, Supervision, Validation, Visualization, Writing – original draft, Writing – review & editing. **RJLA:** Validation, Visualization, Writing – original draft, Writing – review & editing. **APS:** Validation, Visualization, Writing – original draft, Writing – review & editing. **BFR:** Validation, Visualization, Writing – original draft, Writing – review & editing. **FWSF:** Validation, Visualization, Writing – original

draft, Writing – review & editing. **FRPQ:** Validation, Visualization, Writing – original draft, Writing – review & editing. **ESM:** Conceptualization, Data curation, Formal analysis, Investigation, Methodology, Project administration, Resources, Supervision, Validation, Visualization, Writing – original draft, Writing – review & editing.

REFERENCES

1. Riera P, Martínez B. Morbilidad y mortalidad por cáncer oral y faríngeo en Chile [Morbidity and mortality for oral and pharyngeal cancer in Chile]. Rev Med Chil. 2005;133(5):555-63. http://doi.org/10.4067/s0034-98872005000500007
2. Perea LME, Peres MA, Boing AF, Antunes JLF. Tendência de mortalidade por câncer de boca e faringe no Brasil no período. Rev Saúde Pública. 2018;52(10):1-10. https://doi.org/10.11606/S1518-8787.2018052000251
3. Ely HC, Carvalho DQ, Santos M. Políticas de Saúde Bucal. 2006 [cited on Jun 6, 2022]. Available from: https://www.nescon.medicina.ufmg.br/biblioteca/imagem/2200.pdf
4. Brasil. Estimativa 2016: incidência de câncer no Brasil. 2016 [cited on Jun 6, 2022]: 126. Available from: https://santacasadermatoazulay.com.br/wp-content/uploads/2017/06/estimativa-2016-v11.pdf
5. Perea LME, Boing AC, Peres MA, Boing AF. Anos potenciais de vida perdidos por câncer de boca e faringe no Brasil : 1979 a 2013. Rev Saúde Pública. 2019;53(67):1-11. https://doi.org/10.11606/s1518-8787.2019053001054
6. Calazans JA, Queiroz BL. O perfil da mortalidade adulta por idade e causas básicas de óbito na América Latina e Caribe (2000 – 2010). 2015 [cited on Jun 6, 2022]:1-20. Available from: https://repositorio.ufmg.br/bitstream/1843/42789/1/julia%20almeida%20calazans.pdf
7. Murray CJ, Ezzati M, Flaxman AD, Lim S, Lozano R, Michaud C, et al. GBD 2010: design, definitions, and metrics. Lancet. 2012;380(9859):2063-6. https://doi.org/10.1016/S0140-6736(12)61899-6
8. GBD 2017 Mortality Collaborators. Global, regional, and national age-sex-specific mortality and life expectancy, 1950-2017: a systematic analysis for the Global Burden of Disease Study 2017. Lancet. 2018;392(10159):1684-735. https://doi.org/10.1016/S0140-6736(18)31891-9
9. GBD 2017 Causes of Death Collaborators. Global, regional, and national age-sex-specific mortality for 282 causes of death in 195 countries and territories, 1980-2017: a systematic analysis for the Global Burden of Disease Study 2017. Lancet. 2018;392(10159):1736-88. https://doi.org/10.1016/S0140-6736(18)32203-7
10. Freitas RM, Rodrigues AMX, Matos Júnior AF, Oliveira GAL. Fatores de risco e principais alterações citopatológicas do câncer bucal: uma revisão de literatura. RBAC. 2016 [cited on Jun 6, 2022];48(1):13-8. Available from: http://www.rbac.org.br/wp-content/uploads/2016/05/ARTIGO-2_VOL-48_1_2016-ref-120.pdf
11. Domingos PAS, Passalacqua MLC, Oliveira ALBM. Câncer bucal: um problema de saúde pública. Rev Odontol Univ Cid São Paulo. 2014 [cited on Jun 6, 2022];26(1):46-52. Available from: https://arquivos.cruzeirodosuleducacional.edu.br/principal/old/revista_odontologia/pdf/janeiro_abril_2014/Odonto_26_2014.pdf#page=46
12. Martins JD, Andrade JOM, Freitas VS, Araújo TM. Determinantes sociais de saúde e a ocorrência de câncer oral: uma revisão sistemática de literatura. Rev Salud Pública. 2014;16(5):786-98. http://doi.org/10.15446/rsap.v16n5.40083
13. Btasil. Prevalência de tabagismo no Brasil: dados dos inquéritos epidemiológicos em capitais brasileiras. 2004 [cited on Jun 6, 2022]:15. Available from: https://bvsms.saude.gov.br/bvs/publicacoes/tabaco_inquerito_nacional_070504.pdf
14. Levy D, de Almeida LM, Szklo A. The Brazil SimSmoke policy simulation model: the effect of strong tobacco control policies on smoking prevalence and smoking-attributable deaths in a middle income nation. PLoS Med. 2012;9(11):e1001336. http://doi.org/10.1371/journal.pmed.1001336
15. Bray F, Ferlay J, Soerjomataram I, Siegel RL, Torre LA, Jemal A. Global cancer statistics 2018: GLOBOCAN estimates of incidence and mortality worldwide for 36 cancers in 185 countries. CA Cancer J Clin. 2018;68(6):394-424. http://doi.org/10.3322/caac.21492
16. Schramm JMA, Oliveira AF, Leite IC, Valente JG, Gadelha AMJ, Portela MC, et al. Transição epidemiológica e o estudo de carga de doença no Brasil. Cien Saúde Colet. 2004;9(4):897-908. https://doi.org/10.1590/S1413-81232004000400011
17. Guerra MR, Bustamante-Teixeira MT, Corrêa CSL, Abreu DMX, Curado MP, Mooney M, et al. Magnitude e variação da carga da mortalidade por câncer no Brasil e Unidades da Federação, 1990 e 2015. Rev Bras Epidemiol. 2017;20(1):102-17. https://doi.org/10.1590/1980-5497201700050009