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 11
November, 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 11, November, 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

https://doi.org/10.1590/1806-9282.2EDITR11

May isoflavones prevent breast cancer risk?

Adriana Aparecida Ferraz Carbonel[1,2], Ricardo Santos Simões[3], Gisela da Silva Sasso[1], Renata Ramos Vieira[1], Patricia Azevedo Lima[4], Manuel de Jesus Simões[1,3], José Maria Soares Júnior[3*]

Breast cancer still represents a challenge in Brazil, as it is the most frequent malignant neoplasm with more than 14,000 deaths recorded in 2014. It is the leading cause of death in the female population[1]. It is also commonly diagnosed among women in Western countries as the second leading cause of cancer[2]. It is the sixth leading cause of mortality among women, after acute myocardial infarction, pneumonia, diabetes, stroke, and chronic obstructive pulmonary disease. Breast cancer is a heterogeneous disease and can be classified by clinical, histopathological, and molecular parameters[3]. In this classification, the estrogen receptors play an important role and seem to influence the development of breast neoplasms or response to treatment[4]. However, women with breast cancer face the consequences of hypoestrogenism due to chemotherapy treatment or being postmenopausal. Thus, several substances are being suggested to reduce the vasomotor symptoms that appear in these women.

The effects of soy isoflavones, due to their structural similarity and molecular size that resemble estrogens, have the ability to bind with greater affinity to estrogen beta-receptors; for this reason, they are called phytoestrogens[5-7]. The binding of phytoestrogen to the receptor can result in partial activation of the receptor (agonist effect) or displacement of estrogen molecules, thus reducing receptor activation (antagonistic effect)[8].

Intake of soy at high dosages may have a statistically significant reduction in breast cancer risk[9]. Epidemiological studies show that soy consumption is associated with low incidences of hormone-dependent cancers, including breast and prostate cancer in Western countries[10]. However, there are other components in soy that can also have a biological effect and there is a substitution in these countries of animal protein for soy protein. Therefore, this is still a controversial point[11].

Soy contains large amounts of isoflavones, such as genistein and daidzein. Genistein, one of the predominant soy isoflavones, may inhibit several steps involved in carcinogenesis by targeting estrogen- and androgen-mediated signaling pathways in carcinogenesis processes, in addition to its antioxidant properties showing to be a potent inhibitor of angiogenesis and metastasis[12,13]. In vivo and in vitro studies have clearly shown that genistein is a promising reagent for the chemoprevention and/or treatment of cancer. However, results are still conflicting and there is still no consensus on its effectiveness on the breast cancer risk[11,14,15].

Prospective cohort meta-analysis studies suggest that high soy intakes may statistically reduce the risk of breast cancer[9], other systematic and meta-analysis reviews conclude that there is a lack of evidence as the benefit would be small and irrelevant in clinical practice[16]. Thus, further prospective cohort studies are needed to determine the causality of this relationship, as well as to explain the mechanisms involved in the association between isoflavones and breast cancer[9].

A randomized, double-blind, placebo-controlled clinical trial conducted by Delmanto et al.[17] determined the effect of soy isoflavones on breast density and breast parenchyma assessed by mammography in 80 postmenopausal women. After 10 months of isoflavone supplementation, it was found that daily intake of 100 mg isoflavones did not affect breast density (assessed by mammography) and breast tissues (assessed by ultrasound).

Khan et al.[18] evaluated the effect of soy isoflavone supplementation on breast epithelial proliferation and other biomarkers in high-risk, healthy Western women. The breast cell proliferation is an intermediate marker of breast cancer risk generally considered more reflective of risk than mammographic density. Cells were examined for Ki-67 labeling index and atypia. The study involved 98 pre- and postmenopausal women. After 6

[1]Universidade Federal de São Paulo, Escola Paulista de Medicina, Department of Morphology and Genetics – São Paulo (SP), Brazil.
[2]Universidade Federal de São Paulo, Escola Paulista de Medicina, Department of Gynecology – São Paulo (SP), Brazil.
[3]Universidade de São Paulo, School of Medicine, Hospital das Clínicas, Department of Gynecology and Obstetrics – São Paulo (SP), Brazil.
[4]Department of Medicine, Queen's Cardio-Pulmonary Unit – Kingston (ON), Canada.
*Corresponding author: jsoares415@hotmail.com
Conflicts of interest: the authors declare there is no conflicts of interest. Funding: none.
Received on July 18, 2022. Accepted on July 31, 2022.

months of isoflavone supplementation, the authors found that daily intake of 235 mg of isoflavones did not increase cell proliferation in pre- and postmenopausal women compared with placebo. In contrast, a hormone therapy combination increased breast cell proliferation in postmenopausal womenhan[19].

Although there is a greater consumption of soy and isoflavones worldwide, it is still too early to understand the real impact of these substances on the reduction of the risk of incidence, recurrence, and mortality from breast cancer. There is no enough evidence in the literature of serious adverse effects such as increased risk for breast cancer and cardiovascular disease with the use of isoflavones in high doses (≤100 mg)[20]. Although studies on herbal medicine are still in progress, there are only a few still many myths to overcome[21].

The extramammary benefits of soy are evident as in vasomotor symptoms[22], skin[23], bone mass[24], and genital tract[25]. However, the risk of breast cancer needs to be better explored and evaluated, mainly in the long term, and there are still risks that should be better evaluated, such as metabolic ones. In addition, the indication of isoflavone extracts should be individualized, as estroprogestative hormone therapy in the climacteric[26], guiding the patient on the benefits and risks, as well as respecting the individual preferences of postmenopausal women until new evidences in the literature.

AUTHORS' CONTRIBUTIONS

AAFC: Conceptualization, Writing – original draft, Writing – review & editing. **RSS:** Conceptualization, Resources, Validation. **GSS:** Supervision, Validation. **PAL:** Writing – original draft. **MJS:** Supervision, Writing – review & editing. **JMSJ:** Supervision, Writing – review & editing.

REFERENCES

1. Instituto Nacional De Câncer José Alencar Gomes Da Silva. Atlas da mortalidade. Rio de Janeiro: Instituto Nacional De Câncer José Alencar Gomes Da Silva; 2020. Available from: https://www.inca.gov.br/app/mortalidade
2. Harbeck N, Penault-Llorca F, Cortes J, Gnant M, Houssami N, Poortmans P, et al. Breast cancer. Nat Rev Dis Primers. 2019;5(1):66. https://doi.org/10.1038/s41572-019-0111-2
3. DATASUS. Informações de saúde. Available from: http://www2.datasus.gov.br
4. Liang J, Shang Y. Estrogen and cancer. Annu Rev Physiol. 2013;75:225-40. https://doi.org/10.1146/annurev-physiol-030212-183708
5. K?ížová L, Dadáková K, Kašparovská J, Kašparovský T. Isoflavones. Molecules. 2019;24(6):1076. https://doi.org/10.3390/molecules24061076
6. Chen MN, Lin CC, Liu CF. Efficacy of phytoestrogens for menopausal symptoms: a meta-analysis and systematic review. Climacteric. 2015;18(2):260-9. https://doi.org/10.3109/13697137.2014.966241
7. Messina M, Nagata C, Wu AH. Estimated Asian adult soy protein and isoflavone intakes. Nutr Cancer. 2006;55(1):1-12. https://doi.org/10.1207/s15327914nc5501_1
8. Castelo-Branco C, Cancelo Hidalgo MJ. Isoflavones: effects on bone health. Climacteric. 2011;14(2):204-11. https://doi.org/10.3109/13697137.2010.529198
9. Zhao TT, Jin F, Li JG, Xu YY, Dong HT, Liu Q, et al. Dietary isoflavones or isoflavone-rich food intake and breast cancer risk: a meta-analysis of prospective cohort studies. Clin Nutr. 2019;38(1):136-45. https://doi.org/10.1016/j.clnu.2017.12.006
10. Pabich M, Materska M. Biological effect of soy isoflavones in the prevention of civilization diseases. Nutrients. 2019;11(7):1660. https://doi.org/10.3390/nu11071660
11. Kaari C, Haidar MA, Júnior JM, Nunes MG, Quadros LG, Kemp C, et al. Randomized clinical trial comparing conjugated equine estrogens and isoflavones in postmenopausal women: a pilot study. Maturitas. 2006;53(1):49-58. https://doi.org/10.1016/j.maturitas.2005.02.009
12. Varinska L, Gal P, Mojzisova G, Mirossay L, Mojzis J. Soy and breast cancer: focus on angiogenesis. Int J Mol Sci. 2015;16(5):11728-49. https://doi.org/10.3390/ijms160511728
13. Sarkar FH, Li Y. Soy isoflavones and cancer prevention. Cancer Invest. 2003;21(5):744-57. https://doi.org/10.1081/cnv-120023773
14. Bedell S, Nachtigall M, Naftolin F. The pros and cons of plant estrogens for menopause. J Steroid Biochem Mol Biol. 2014;139:225-36. https://doi.org/10.1016/j.jsbmb.2012.12.004
15. Carbonel AA, Santos RH, Simões RS, Silva RF, Soares JM Jr, Baracat EC, et al. Efeitos de altas doses de genisteína sobre o epitélio mamário de ratas [Effects of high doses of genistein on mammary gland of female rat]. Rev Bras Ginecol Obstet. 2011;33(9):264-9. https://doi.org/10.1590/s0100-72032011000900008
16. Qiu S, Jiang C. Soy and isoflavones consumption and breast cancer survival and recurrence: a systematic review and meta-analysis. Eur J Nutr. 2019;58(8):3079-90. https://doi.org/10.1007/s00394-018-1853-4
17. Delmanto A, Nahas-Neto J, Traiman P, Uemura G, Pessoa EC, Nahas EA. Effects of soy isoflavones on mammographic density and breast parenchyma in postmenopausal women: a randomized, double-blind, placebo-controlled clinical trial. Menopause. 2013;20(10):1049-54. https://doi.org/10.1097/GME.0b013e3182850270
18. Khan SA, Chatterton RT, Michel N, Bryk M, Lee O, Ivancic D, et al. Soy isoflavone supplementation for breast cancer risk reduction: a randomized phase II trial. Cancer Prev Res (Phila). 2012;5(2):309-19. https://doi.org/10.1158/1940-6207.CAPR-11-0251
19. Murkes D, Conner P, Leifland K, Tani E, Beliard A, Lundstrom E, et al. Efeitos da progesterona oral-estradiol percutânea versus estrogênios equinos conjugados orais-acetato de medroxiprogesterona na proliferação de células mamárias e BCL-2 proteína em mulheres saudáveis. Fértil Esteril. 2011;95(3):1188-91. https://doi.org/10.1016/j.fertnstert.2010.09.062
20. Fritz H, Seely D, Flower G, Skidmore B, Fernandes R, Vadeboncoeur S, et al. Soy, red clover, and isoflavones and breast cancer: a systematic review. PLoS One. 2013;8(11):e81968. https://doi.org/10.1371/journal.pone.0081968

21. Lopes CMC, Lima SMRR, Veiga ECA, Soares-Jr JM, Baracat EC. Phytotherapeutic medicines: reality or myth? Rev Assoc Med Bras (1992). 2019;65(3):292-4. https://doi.org/10.1590/1806-9282.65.3.292

22. Han KK, Soares JM Jr, Haidar MA, de Lima GR, Baracat EC. Benefits of soy isoflavone therapeutic regimen on menopausal symptoms. Obstet Gynecol. 2002;99(3):389-94. https://doi.org/10.1016/s0029-7844(01)01744-6

23. Accorsi-Neto A, Haidar M, Simões R, Simões M, Soares J Jr, Baracat E. Effects of isoflavones on the skin of postmenopausal women: a pilot study. Clinics (Sao Paulo). 2009;64(6):505-10. https://doi.org/10.1590/s1807-59322009000600004

24. Carbonel AAF, Vieira MC, Simões RS, Lima PDA, Fuchs LFP, Girão ERC, et al. Isoflavones improve collagen I and glycosaminoglycans and prevent bone loss in type 1 diabetic rats. Climacteric. 2020;23(1):75-83. https://doi.org/10.1080/13697137.2019.1627314

25. Franco PC, Simões RS, Carbonel AAF, Sasso GRDS, Florencio-Silva R, Baracat EC, et al. The influence of phytoestrogens or estrogens on the proliferation of the rat endocervical mucosa. Rev Assoc Med Bras (1992). 2020;66(2):174-9. https://doi.org/10.1590/1806-9282.66.2.174

26. Soares Júnior JM, Sorpreso IC, Baracat EC. Is hormone therapy during climacteric for all? Rev Assoc Med Bras (1992). 2015;61(3):191-2. https://doi.org/10.1590/1806-9282.61.03.191

https://doi.org/10.1590/1806-9282.222D6811

Nitinol double-layer stent versus closed single-layer stent: a systematic review

Antonio Silvinato[1], Idevaldo Floriano[2], Wanderley Bernardo[3*]

INTRODUCTION

The Guidelines Project, an initiative of the Brazilian Medical Association, aims to combine information from the medical field to standardize how to conduct and to assist in the reasoning and decision-making of doctors. The information provided by this project must be critically evaluated by the physician responsible for the conduct that will be adopted, depending on the conditions and the clinical condition of each patient.

About 10–15% of all ischemic strokes (STROKES) originate from stenosis at the level of the internal carotid artery. In patients with carotid disease, the goal of carotid revascularization is the prevention of stroke (recurrent). For more than 50 years, carotid endarterectomy (CEA) has been considered the standard treatment for severe asymptomatic and symptomatic carotid stenoses. The carotid artery stent (CAS) has emerged in the past 20 years as a minimally invasive alternative to surgery[1]. It is recognized that the stent itself can substantially increase embolic protection in CAS through adequate plate scaffolding, since the distal embolic protection device (EPD) has been removed. The ideal properties of a carotid stent are a well-balanced blend of high flexibility and conformability, accommodating tortuous anatomy, as well as high plate coverage, preventing delayed embolization of debris. The structure of the stents is characterized by annular rings sequentially aligned by bridges, and the drawing can be open cell or closed cell, depending on the density of the bridges between the rings. Open-cell design stents present some free segments of adjacent rings, allowing greater adaptation to vessel anatomy, but with lower plate coverage and increased risk of tissue prolapse. Closed-cell design stents are characterized by higher bridge interconnection density, which reduces their conformability and increases the likelihood of bed position, but at the same time offers greater plate coverage. A hybrid configuration with an open-cell design of the proximal and distal segments combined with a closed-cell design of the central segments was also developed[2-5].

Another carotid double-layer mesh stent design allows high flexibility to accommodate tortuous anatomies while conveying the properties of the scaffold for optimal plate coverage. This technology is characterized by an internal layer of micromesh for plate coverage and an outer layer of self-expanding nitinol for scaffolding, offering the flexibility that characterizes open-cell design stents[2].

The impact of the design of the self-expanding stent on the clinical outcome after CAS is the objective of this evaluation.

OBJECTIVE

This study aimed to evaluate the efficacy and safety of carotid angioplasty stent micromesh design and double layer of nickel/titanium alloy (nitinol) implantation, with closed-cell stent (single-layer) of nitinol or stainless steel, both procedures using distal EPDs.

METHODS

Clinical doubt: What is the impact of stent design on clinical outcome after CAS with EPD, comparing double-layer nitinol stent versus closed-cell stent (single layer), nitinol or stainless steel?

The eligibility elements of the studies are as follows:

1. Patient with carotid stent and indication of CAS.

[1]Associação Médica Brasileira, Medicina Baseada em Evidências – São Paulo (SP), Brazil.
[2]Cooperativa Baixa Mogiana, Medicina Baseada em Evidências – Mogi Guaçu (SP), Brazil.
[3]Universidade de São Paulo, Faculdade de Medicina – São Paulo (SP), Brazil.
*Corresponding author: wmbernardo@usp.br
Guideline conclusion: 29 August 2022.
Societie: Associação Médica Brasileira.
Conflicts of interest: the authors declare there is no conflict of interest. Funding: none.
Received on August 01, 2022. Accepted on October 01, 2022.

2. CAS with EPD, use of double-layer stent (nitinol) compared with closed-cell stent (single layer) of nitinol or stainless steel.
3. Outcomes—new brain lesions detected and adverse events (neurological and cardiac complications) related to procedure.
4. Excluding outcomes—intermediaries.
5. Phase III randomized controlled trial (RCT) or cohort studies.
6. No period or language limit.
7. Full-text available for access.
8. Follow-up time: 1-month post-procedure.

The search for evidence will be carried out in the Virtual Scientific Information Base MEDLINE using the following search strategy: (Carotid Stenosis OR Carotid Stenoses OR Carotid Artery Diseases) AND (Carotid Stenting OR Stent*) AND (nitinol OR dual-layer OR double layer OR double layer OR micromesh OR Casper OR Roadsaver) AND Random*; CENTRAL/Cochrane: (Carotid Stenosis OR Carotid Stenoses OR Carotid Artery Diseases) AND (Carotid Stenting OR Stent*) AND (nitinol OR dual-layer OR double layer OR double layer OR micromesh OR Casper OR Roadsaver); and ClinicalTrials.gov: (Carotid Stenting OR Stent) AND (nitinol).

The search was carried out until June 2022, and a systematic review was carried out according to PRISMA recommendations[6].

Two authors independently performed the data extraction, followed by a cross-check of the data. From the studies, the following data were extracted: author's name and year of publication, study population, intervention and comparison methods, absolute number of events, number and average size of new ischemic brain lesions, mean number of microembolic signs (MES), adverse events, and follow-up time.

We assessed the risk of bias for RCTs level using the RoB 2 tool[7], plus other key elements, and expressed it as very severe, severe, or non-severe. For cohort studies, the tool ROBINS-I (Risk of Bias In Non-randomized Studies of Interventions), recommended by the Cochrane Collaboration, was used to assess the risk of bias in estimates of effectiveness and safety in non-randomized intervention studies[8]. ROBINS-I evaluates seven domains of bias, classified by the moment of occurrence. The bias risk assessment was conducted by two independent reviewers (AS and IF), and in case of disagreements, a third reviewer (WB) deliberated on the assessment. The quality of the evidence was extrapolated from the risk of bias, and it was obtained from the study/studies (if was or no meta-analysis) using the terminology GRADE[9] through the GRADEpro software[10] for very low, low, moderate, and high degree of evidence.

The results for categorical outcomes were expressed as the difference in risk (DR) between the CAS procedure with EPD between double-layer nitinol stent and closed-cell stent (single layer) of nitinol or stainless steel. If DR between the groups was significant, the result was expressed with 95% confidence interval (95%CI) and the number needed to treat (NNT) or number needed to harm (NNH). For continuous measurements, the results were the difference of the mean (DM) with 95%CI.

If more than one study was included with common outcomes, the results were aggregated through the meta-analysis, using the RevMan 5.4 software[11], and the overall DR or DM, with 95%CI as the final measure used to support the synthesis of evidence, which answers the clinical doubt of this evaluation. The estimated size of the combined effects was performed by a model of fixed effect ($I^2 \leq 50\%$) or random effect ($I^2 > 50\%$) after the evaluation of heterogeneity results. Heterogeneity was also calculated using the I^2 value.

STUDIES INCLUDED

Database searching identified 16 citations. We removed 14 records, and we selected 2 studies with regard to title and abstract[12,13], which evaluated the CAS with EPD with double-layer nitinol stent and closed-cell stent (single layer) of nitinol or stainless steel. The two studies were assessed since they met the eligibility criteria for analysis of the full text. Both were RCTs and were included to support this evaluation, whose characteristics are described in ANNEX Table 1. The number of excluded studies and the reasons are available in Figure 1.

The population included was 140 participants in the 2 RCTs, submitted to carotid angioplasty with stent implantation and distal brain protection device. This population was followed to measure the outcomes such as new ischemic brain lesions assessed by a diffusion-weighted resonance imaging (DW-MRI); average number of new ischemic brain lesions; average (mm) size of new ischemic brain lesions; brain microembolization in the stages of stent implantation, dilation and recovery of EPD; major adverse cardiac and cerebrovascular events (MACCE); and restenosis in-stent, in a follow-up of 1, 3, and 6 months after the procedure (ANNEX Table 2).

Regarding the risk of bias of the 2 RCTs (12–13) included, a study by Montorsi et al.(13) did not describe randomization;

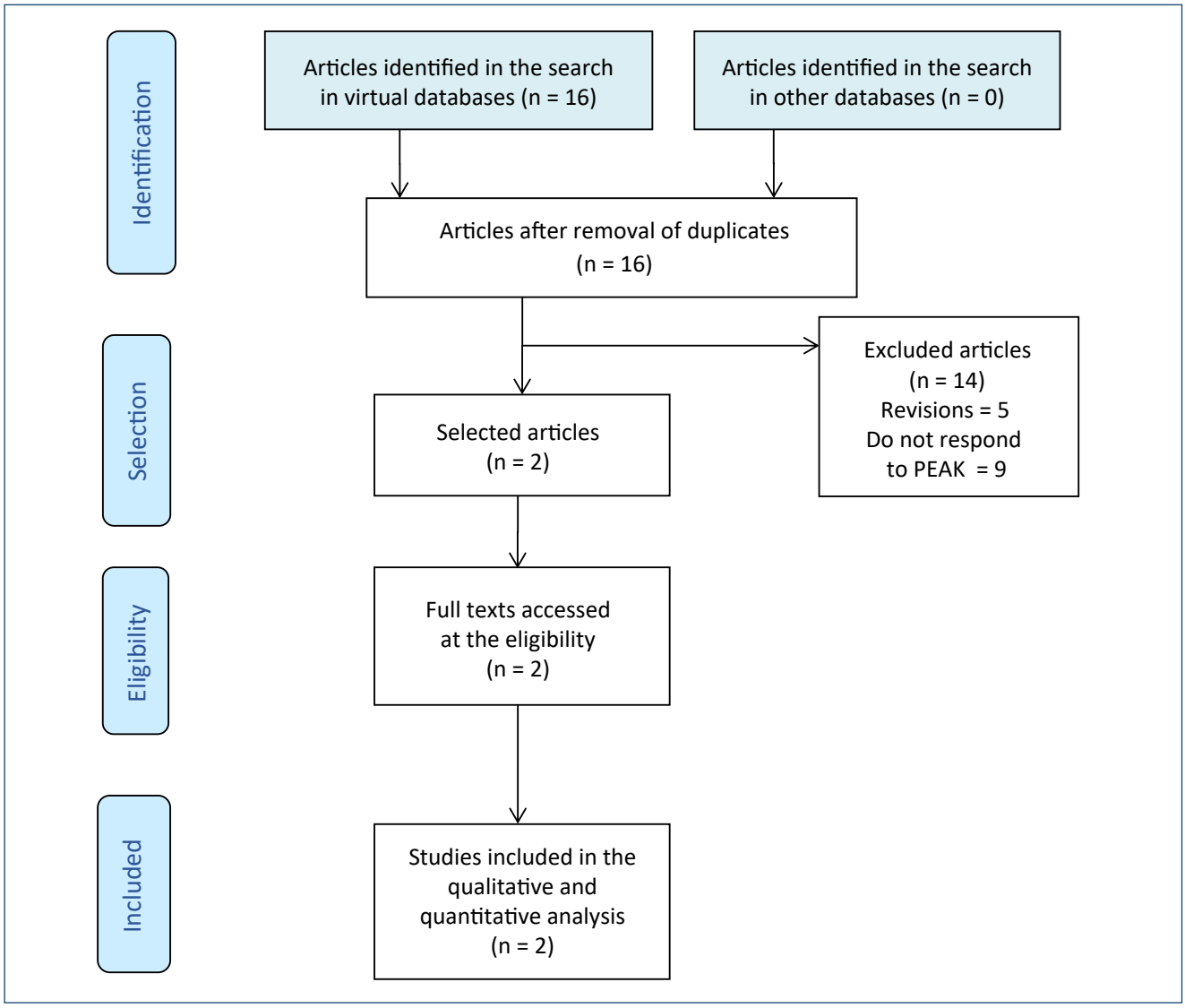

Figure 1. Evidence retrieval and selection diagram. Moher D, Liberati A, Tetzlaff J, Altman DG, The PRISMA Group. Preferred Reporting Items for Systematic Reviews and Meta-Analyses: The PRISMA Statement. PLoS Med. 2009;6(7):e1000097. https://doi.org/10.1371/journal.pmed1000097

Table 1. Risk of bias from randomized controlled trials included.

Risk of bias in randomized clinical trials										
Study	Random	Blind-folded allocation	Double blind	Appraiser blinding	Losses <20%	Characteristic prognostic	Outcome	Intention-to-treatment	Simple size calculation	Early interruption
Vanzin et al.[12]										
Montorsi et al.[13]										

Biases of the included ECRs: red indicates absence; green indicates presence; yellow indicates risk of unclear bias.

it had uncertain blinded allocation, was not blinded to the evaluator, and did not analyze by intention-to-treat (ITT); while Vanzin et al. did not show bias. The overall risk of bias could be considered non-severe (Table 1).

RESULTS OF THE STUDIES INCLUDED

One study[12], with a total of 88 participants, compared the double-layer nitinol stent (n=41) and single-layer closed-cell stent (n=47), plus EPD, evaluating the efficacy and safety in a follow-up of up to 3 months.

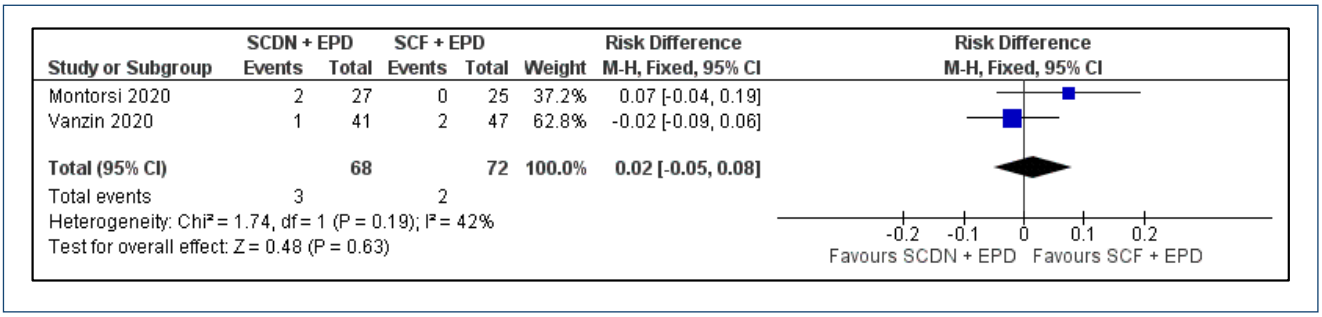

Figure 2. Forest plot comparison: double-layer stent of nitinol versus closed-cell stent, outcome: 1.5.

There was no difference in the risk of new ischemic brain lesions evaluated by magnetic resonance imaging in the diffusion sequence (DWI-MR) (RD=-0.06, 95%CI -0.26 to 0.15; NNT=NS; p=0.59).

There was also no difference in the outcomes such as mean number of new ischemic brain lesions (RD=-0.40, 95%CI -1.09 to 0.29; p=0.26) and average (in mm) size of new ischemic brain lesions (RD=-1.10, 95%CI -3.20 to 1.00; p=0.30).

One study[13] including a total of 52 participants compared the double-layer nitinol stent (n=27) and closed-cell stent (n=25), plus EPD, with outcome measurements at 24 h, 30 days, and 6 months after CAS.

There was no difference in the mean number of cerebral microembolization [mean (SD)], evaluated by monitoring with transcranial Doppler (number of MES), in the stages of stent implantation, dilation, and recovery of the distal EPD, including spontaneous MES (29% of patients) (RD=-2.80, 95%CI -5.96 to 0.36; p=0.08).

There was also no difference in the risk of significant in-stent restenosis (PSV>330 cm/s with stenosis >80% of the diameter) at 6 months (RD=-0.04, 95%CI -0.14 to 0.06, NNT=NS, p=0.44).

Two studies[12,13] that compared the double-layer nitinol stent (n=25) and single-layer closed-cell stent (n=47), plus EPD, presented data for the outcome MACCE (ipsilateral stroke, transient ischemic event, and myocardial infarction) at follow-up of 3–6 months. There was no difference in MACCE risk (RD=0.02, 95%CI -0.05 to 0.08, NNH=NS, p=0.63, I^2=42%) (Figure 2).

Summary of evidence and quality of evidence: TOOL GRADE

In patients with carotid stenosis, angioplasty with nitinol double-layer stent implantation versus stent (nitinol or chromium-cobalt alloy) single closed-cell layer are adopted, both procedures using distal brain protection device.

Showed no difference

- At the risk of new ischemic brain damage up to 3 months. High evidence quality.
- At the average number of brain microembolizations in the stages of stent implantation, dilation, and recovery of EPD, including spontaneous MES. Moderate evidence quality.
- At the risk of significant in-stent restenosis at 6 months. Moderate evidence quality.
- At the risk of MACCE (ipsilateral stroke, transient ischemic event, and myocardial infarction) at 3- to 6-month evaluations. High evidence quality.
- At the average number of new ischemic brain lesions at 3 months. High evidence quality.
- At the average size of new ischemic brain lesions up to 3 months. High evidence quality.

CONCLUSION

The double-layer nitinol stents showed no difference in the outcomes that evaluated efficacy and safety when compared to closed-cell stents during CAS under distal EPD.

AUTHORS' CONTRIBUTIONS

AS, IF, and WMB contributed to study conception, data collection, statistical analysis, and data interpretation. **AS and IF** contributed to manuscript writing. **AS, IF, and WMB** contributed to critical review and approval of the final version.

REFERENCES

1. Roffi M, Mukherjee D, Clair DG. Carotid artery stenting vs. endarterectomy. Eur Heart J. 2009;30(22):2693-704. https://doi.org/10.1093/eurheartj/ehp471
2. Bosiers M, de Donato G, Deloose K, Verbist J, Peeters P, Castriota F, et al. Does free cell area influence the outcome in carotid artery stenting? Eur J Vasc Endovasc Surg. 2007;33(2):135-41; discussion 142-3. https://doi.org/10.1016/j.ejvs.2006.09.019
3. Bosiers M, Deloose K, Verbist J, Peeters P. Carotid artery stenting: which stent for which lesion? Vascular. 2005;13(4):205-10. https://doi.org/10.1258/rsmvasc.13.4.205
4. Jim J, Rubin BG, Landis GS, Kenwood CT, Siami FS, Sicard GA, SVS Outcomes Committee. Society for vascular surgery vascular registry evaluation of stent cell design on carotid artery stenting outcomes. J Vasc Surg. 2011;54(1):71-9. https://doi.org/10.1016/j.jvs.2010.12.054

5. Timaran CH, Rosero EB, Higuera A, Ilarraza A, Modrall JG, Clagett GP. Randomized clinical trial of open-cell vs closed-cell stents for carotid stenting and effects of stent design on cerebral embolization. J Vasc Surg. 2011;54(5):1310-6.e1; discussion 1316. https://doi.org/10.1016/j.jvs.2011.05.013
6. Page MJ, McKenzie JE, Bossuyt PM, Boutron I, Hoffmann TC, Mulrow CD, et al. The PRISMA 2020 statement: an updated guideline for reporting systematic reviews. BMJ. 2021;372:n71. https://doi.org/10.1136/bmj.n71
7. Sterne JAC, Savović J, Page MJ, Elbers RG, Blencowe NS, Boutron I, et al. RoB 2: a revised tool for assessing risk of bias in randomised trials. BMJ. 2019;366:l4898. https://doi.org/10.1136/bmj.l4898.
8. Sterne JAC, Hernán MA, Reeves BC, Savović J, Berkman ND, Viswanathan M, et al. ROBINS-I: a tool for assessing risk of bias in non-randomized studies of interventions. BMJ. 2016;355:i4919. https://doi.org/10.1136/bmj.i4919
9. GRADE Working Group. Available from: https://www.gradeworkinggroup.org/. Accessed: August 2021
10. GRADEpro GDT. GRADEpro Guideline Development Tool [Software]. Hamilton, ON: McMaster University; 2020 (developed by Evidence Prime, Inc.). Available from: gradepro.org.
11. Cochrane Collaboration. Review Manager (RevMan) [Computer program]. Version 5.4. London: The Cochrane Collaboration; 2020.
12. Vanzin JR, de Castro-Afonso LH, Santos MN, Manzato LB, Nakiri GS, Monsignore LM, et al. Casper vs. closed-cell stent: carotid artery stenting randomized trial. Clin Neuroradiol. 2021;31(3):843-52. https://doi.org/10.1007/s00062-020-00937-8
13. Montorsi P, Caputi L, Galli S, Ravagnani PM, Teruzzi G, Annoni A, et al. Carotid wallstent versus roadsaver stent and distal versus proximal protection on cerebral microembolization during carotid artery stenting. JACC Cardiovasc Interv. 2020;13:403-14. https://doi.org/10.1016/j.jcin.2019.09.007

ANNEXES

Table 1. Characteristics of the included studies.

Descriptive table of the characteristics of studies in therapy					
Study	**Population**	**Intervention**	**Comparison**	**Outcome**	**Follow-up Time**
Vanzin et al.[12]	Study with a total of 88 patients; age in years: 73.5±6.9; symptomatic ICA stenosis ≥50%*, asymptomatic ICA stenosis ≥70%*, symptoms defined as ischemic stroke, TIA, or amaurosis. Excluded: Total occlusion of the target carotid artery; ischemic stroke <14 days before CAS; MI <6 months; major surgery 30 days before or planned for 30 days after stent; severe CRF; intractable hemorrhagic diathesis or hypercoagulability state; high or medium risk for cardioembolism and contraindication for antiplatelet therapy.	Double-layer nitinol stent+EPD (n=41)	Single-layer stent, closed cell+EPD (n=47)	Primary: Incidence, number, and size of new ischemic brain lesions. Secondary: Stroke, TIA, and MI (up to 3 months).	MRI and neurological evaluation between 06:00 and 24:00 after the procedure. A new neurological evaluation was performed at a 3-month follow-up.
Montorsi et al.[13]	Included 104 patients (age 72.4±9) at high risk, with lipid-rich plaque; de novo carotid artery stenosis either symptomatic (Doppler peak systolic velocity [PSV] ≥130 cm/s and >50% stenosis) or asymptomatic (Doppler PSV≥230 cm/s and >70% stenosis). Excluded: Evolving acute or recent disabling stroke, history of major disabling stroke (modified Rankin scale score ≥3), acute MI 72 h before CAS, and concomitant sources of potential cerebral embolization that would confound neurological assessment. Anatomic exclusion criteria were contralateral carotid occlusion without detectable ipsilateral posterior communicating artery, isolated hemisphere of the target vessel, target vessel ECA occlusion, intracranial, significant (>50%) stenosis of the ipsilateral CCA, and/or CCA >50% stenosis below bifurcation.	**GROUP 1** Double-layer nitinol stent+EPD (n=27) GROUP 3 Double-layer nitinol stent+proximal protection (n=27)	**GROUP 2** Single-layer stent (chromium-cobalt alloy) and closed cell+EPD (n=25) GROUP 4 Single-layer stent (chromium-cobalt alloy) and closed cell+proximal protection (n=25)	Primary: Cerebral microembolization evaluated by monitoring with TCD (number of microembolic signals). Secondary: End points included in-hospital and 30-day MACCE (death, all stroke, retinal embolism, and MI), technical and clinical success, target vessel ECA patency on angiography at the end of CAS and on Doppler ultrasound at 1, 30, and 180 days of follow-up, and significant in-stent restenosis at 6 months.	The measurements of the outcomes were repeated within 24 h, 30 days, and 6 months post-CAS.

*Based on the criteria defined by NASCET. ECA: external carotid artery; CCA: common carotid artery; ICA: internal carotid artery; MI: myocardial infarction; TCD: transcranial Doppler; MACCE: major adverse cardiac and cerebrovascular events; EPD: embolic protection device; TIA: transient ischemic attack; DW-MRI: diffusion-weighted magnetic resonance imaging; CRF: chronic renal failure; MRI: magnetic resonance imaging.

Table 2. Summary of evidence and quality of evidence: TOOL GRADE.

Summary of results: Double-layer nitinol+EPD stent compared to closed-cell stent+EPD for carotid stenosis					
Participants or population: Carotid stenosis **Context:** Efficacy and safety **Intervention:** Double-layer stent of nitinol+EPD **Comparison:** Closed-cell stent+EPD					
Outcome no. of participants (studies)	**Relative effect (95%CI)**	**Anticipated absolute effects (95%CI)**			**Certainty**
		Control	**Intervention**	**Difference**	
New ischemic brain lesions (DW-MRI). Number of participants: 88 (1 ECR)	**RR 0.87** (0.53 para 1.44)	44.7%	**38.9%** (23.7 para 64.3)	**5.8% less** (21 less to 19.7 more)	⨁⨁⨁⨁ High
Average number of new ischemic brain lesions in the number of participants: 88 (1 ECR)	–	–	–	MD **0.4 lower** (1.09 lower to 0.29 higher)	⨁⨁⨁⨁ High
Average size (mm) of new ischemic brain lesions in participants: 88 (1 ECR)	–	–	–	MD **1.1 smaller** (3.2 lower to 1 higher)	⨁⨁⨁⨁ High
Cerebral microembolization Nº of participants: 52 (1 ECR)	–	–	–	MD **2.8 lower** (5.96 lower to 0.36 higher)	⨁⨁⨁◯ Moderate[a]
Major adverse cardiac and cerebrovascular events (MACCE) In the participants: 140 (2 ECRs)	**RR 1.46** (0.28 para 7.52)	2.8%	**4.1%** (0.8 para 20.9)	**1.3% more** (2 less to 18.1 more)	⨁⨁⨁⨁ High
Significant in-stent restenosis no. of participants: 52 (1 ECR)	**RR 0.31** (0.01 para 7.26)	4.0%	**1.2%** (0 for 29)	**2.8% less** (4 less to 25 more)	⨁⨁⨁◯ Moderate[a]

*The risk in the intervention group (and its 95%CI) is based on the assumed risk in the comparison group and the relative effect of the intervention (and its 95%CI). CI, confidence interval; MD: mean difference; RR: risk ratio.

GRADE: Working group grades of evidence.

High certainty: We are very confident that the true effect lies close to that of the estimate of the effect.

Moderate certainty: We are moderately confident in the effect estimate: the true effect is likely to be close to the estimate of the effect, but there is a possibility that it is substantially different.

Low certainty: Our confidence in the effect estimate is limited: the true effect may be substantially different from the estimate of the effect.

Very low certainty: We have very little confidence in the effect estimate: the true effect is likely to be substantially different from the estimate of effect.

https://doi.org/10.1590/1806-9282.20220948

Comment on "Artificial intelligence and machine learning in pediatrics and neonatology healthcare"

Fernando Korn Malerbi[1*], Marcio Krakauer[2], Beatriz Schaan[3]

Dear Editor,

We read with interest the article entitled "Artificial intelligence and machine learning in pediatrics and neonatology healthcare" by Matsushita et al.[1]. We agree with the authors on the huge potential of artificial intelligence/deep learning (AI/DL) systems in improving healthcare, especially on the management of chronic diseases. Many countries and multilateral forums are currently developing strategies for AI/DL legal regulation, involving system's design, validation, implementation, and postmarketing monitoring[2], while taking steps to avoid biased data sets that will negatively impact the system's performance and potentially increase health inequalities[3]. Due to their theoretically unlimited scalability, the risk of such systems should be dimensioned accordingly[3]. Safety and efficacy evaluation demands well-designed studies with a rigorous methodology that is proportional to the sensitivity of data and the risk of patient damage; for risk stratification, regulatory policies could be inspired, for example, on the existing legislation on data protection and the biosecurity classification for laboratories[4]. The adoption of such technologies will also demand societal decisions which involve local conditions such as the availability of healthcare personnel and economic factors. An example is the screening of diabetic retinopathy, a major cause of preventable blindness: how should one health system calibrate the trade-off between sensitivity and specificity? Cost-effectiveness, constrained workforces, and current workflows are some of the variables of this equation[5].

Regulation should balance safety guarantees and the support for innovations and should engage all the stakeholders, including medical and scientific societies, the academia, and the final user, in order to increase public confidence[3]. Given the expected overwhelming demand in the near future, centralized regulation is unlikely to adequately ensure the safety, efficacy, and equity of implemented systems; possible answers to such challenges may involve a decentralized approach with local evaluation, as well as the proposed creation of the new medical specialty of clinical AI[6].

The cooperation among developers, ethic experts, physicians, patients, and regulatory agencies is essential for the rapid adoption and successful implementation of AI/DL in health, with an enormous potential of improving healthcare, increasing access, reducing costs, and promoting equity. Scientific and medical societies should participate actively in the formulation of best practices and in the prospective validation of AI systems.

ACKNOWLEDGMENTS

The authors thank Pamela Ferreira Todendi for the assistance with the final formatting of the manuscript.

AUTHORS' CONTRIBUTIONS

FKM: Conceptualization, Investigation, Methodology, Supervision, Writing – original draft, Writing – review & editing. **MK:** Conceptualization, Investigation, Methodology, Supervision, Writing – original draft, Writing – review & editing. **BS:** Conceptualization, Investigation, Methodology, Supervision, Writing – original draft, Writing – review & editing.

REFERENCES

1. Matsushita FY, Krebs VLJ, Carvalho WB. Artificial intelligence and machine learning in pediatrics and neonatology healthcare. Rev Assoc Med Bras. 2022;68(6):745-50. https://doi.org/10.1590/1806-9282.20220177

2. Murphy K, Di Ruggiero E, Upshur R, Willison DJ, Malhotra N, Cai JC, et al. Artificial intelligence for good health: a scoping review of the ethics literature. BMC Med Ethics. 2021;22(1):14. https://doi.org/10.1186/s12910-021-00577-8

[1]Universidade Federal de São Paulo, Departamento de Oftalmologia e Ciências Visuais, – São Paulo (SP), Brazil.
[2]Sociedade Brasileira de Diabetes, Departamento de Saúde Digital, Telemedicina e Inovação – São Paulo (SP), Brazil.
[3]Universidade Federal do Rio Grande do Sul, Hospital de Clínicas de Porto Alegre – Porto Alegre (RS), Brazil.
*Corresponding author: fernandokmalerbi@gmail.com

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

3. Abràmoff MD, Cunningham B, Patel B, Eydelman MB, Leng T, Sakamoto T, et al. Foundational considerations for artificial intelligence using ophthalmic images. Ophthalmology. 2022;129(2):e14-32. https://doi.org/10.1016/j.ophtha.2021.08.023
4. Gruson D, Helleputte T, Rousseau P, Gruson D. Data science, artificial intelligence, and machine learning: opportunities for laboratory medicine and the value of positive regulation. Clin Biochem. 2019l;69:1-7. https://doi.org/10.1016/j.clinbiochem.2019.04.013
5. Ruamviboonsuk P, Tiwari R, Sayres R, Nganthavee V, Hemarat K, Kongprayoon A, et al. Real-time diabetic retinopathy screening by deep learning in a multisite national screening programme: a prospective interventional cohort study. Lancet Digit Health. 2022;4(4):e235-e244. https://doi.org/10.1016/S2589-7500(22)00017-6
6. Panch T, Duralde E, Mattie H, Kotecha G, Celi LA, Wright M, et al. A distributed approach to the regulation of clinical AI. Plos Digit Health. 2022;1(5):e0000040. https://doi.org/10.1371/journal.pdig.0000040

https://doi.org/10.1590/1806-9282.20211099

Comment on "Protective effect of dexmedetomidine on perioperative myocardial injury in patients with Stanford type-A aortic dissection"

Chuanding Li[1], Shigao Wang[2*], Man Wang[3]

Dear Editor,

We have perused with interest the article entitled "Protective effect of dexmedetomidine on perioperative myocardial injury in patients with Stanford type-A aortic dissection" in which Wang et al.[1] found that dexmedetomidine treatment may alleviate perioperative myocardial injury in patients with Stanford type-A aortic dissection by resisting inflammatory response and oxidative stress. However, there are still more issues in our opinion.

First, 86 patients were randomly divided into dexmedetomidine (Dex) group and control group, with 43 cases in each group. However, random grouping method should be provided in this study. There was no significant difference in gender, age, BMI, smoking history, hypertension history, diabetes mellitus history, ASA grade, anesthesia duration, cardiopulmonary bypass duration, or surgery duration between Dex and control groups. Basic information on the demographics of Dex and control groups should also be given, especially for statistical values and p-values.

Second, it is not clear whether the article is based on a retrospective study or a prospective study. If this article is based on a prospective study, there might be some patients who refused to cooperate with the researcher. Also, this study involved a small sample. Hence, sample size power estimation is needed in "Methods" section.

In "Results" section, the study found that the heart rate and mean arterial pressure in the Dex group were significantly lower than those in the control group at t2 and t3. We were surprised to find that the standard deviation of heart rate and mean arterial pressure is about 50% of the mean heart rate and mean arterial pressure. Therefore, these results should be considered with caution and need further confirmation.

AUTHORS' CONTRIBUTIONS

MW: Data curation, Formal Analysis, Writing – original draft. **SW:** Conceptualization, Data curation. **CL:** Conceptualization, Writing – review & editing.

REFERENCE

1. Wang D, Lin Q, Du M, Zheng G, Xu W, Zhang H, et al. Protective effect of dexmedetomidine on perioperative myocardial injury in patients with Stanford type-A aortic dissection. Rev Assoc Med Bras (1992). 2020;66(12):1638-44. https://doi.org/10.1590/1806-9282.66.12.1638

[1]Jingmen Recovery Hospital, Department of Anesthesiology – Jingmen, China.
[2]Jingmen Traditional Chinese Medicine Hospital, Department of Anesthesiology – Jingmen, China.
[3]Yingshan People's Hospital, Department of Anesthesiology – Huanggang, China.
*Corresponding author: Shigaowang886@163.com

Conflicts of interest: the authors declare there is no conflicts of interest. Funding: none.
Received on October 28, 2021. Accepted on November 18, 2021.

ORIGINAL ARTICLE

https://doi.org/10.1590/1806-9282.20220854

Total cholesterol/high-density lipoprotein and inflammatory parameters in patients with polycystic ovary syndrome

Selim Gülücü[1*], İlkin Seda Can[2]

SUMMARY

OBJECTIVE: In this study, the hormone profile, lipid profile, and inflammatory parameters of patients with polycystic ovary syndrome were compared with those of non-polycystic ovary syndrome patients to determine predictive markers in young polycystic ovary syndrome patients who have not yet had children.

METHODS: Patients' age, height, weight, body mass index, waist circumference, degree of hirsutism, and ultrasound findings were recorded. Hormone profile, lipid levels, ratio of complete blood count parameters, monocyte/high-density lipoprotein ratio, and total cholesterol/high-density lipoprotein ratio were compared between groups.

RESULTS: No statistically significant differences were found between groups in terms of age, weight, waist circumference, body mass index, and dysmenorrhea ($p>0.05$). A significant relationship was found between the height and the degree of hirsutism in the groups ($p<0.05$). It was found that prolactin, total testosterone, and dehydroepiandrosterone sulfate levels were statistically significantly higher in the polycystic ovary syndrome group compared to the control group. The polycystic ovary syndrome group had hemoglobin, leukocytes, lymphocytes, neutrophils, platelets, and statistically higher ratios of total cholesterol/high-density lipoprotein, Low-density lipoprotein/high-density lipoprotein, and triglycerides/high-density lipoprotein. No statistically significant relationships were found between homeostatic model assessment insulin resistance, neutrophil-to-lymphocyte ratio, and monocyte-to-high-density lipoprotein ratio between the groups ($p<0.05$). There was no significant difference in systemic immune inflammation index values between the groups.

CONCLUSION: Polycystic ovary syndrome patients are at risk for short- and long-term complications, and the use of the total cholesterol/high-density lipoprotein, Low-density lipoprotein/high-density lipoprotein, and triglycerides/high-density lipoprotein ratios in clinical practice during the follow-up of these patients may allow easy follow-up for patients. The health status of polycystic ovary syndrome patients can be objectively determined by tracking these outcomes at regular intervals.

KEYWORDS: Polycystic ovary syndrome. Inflammation. Lipoprotein. Cholesterol. Monocyte. Neutrophils.

INTRODUCTION

Polycystic ovary syndrome (PCOS) is a common endocrinologic pathology in women of reproductive age with symptoms including menstrual cycle irregularity, hirsutism, hyperandrogenism, and infertility. It is closely related to many clinical conditions such as insulin resistance (IR), hyperinsulinemia, glucose intolerance, dyslipidemia, hypertension, obesity, hyperandrogenism, endothelial dysfunction, and chronic low-grade inflammation[1]. White blood cell subtype ratios are important in identifying low-grade inflammation, and neutrophil-to-lymphocyte ratios (NLR), platelet-to-lymphocyte ratios (PLR), and lymphocyte-to-monocyte ratios (LMR) are used to evaluate the prognosis in some diseases[1,2]. Chronic low-grade inflammation is also known to have a stimulatory effect on the development of endothelial disease and atherosclerosis[2]. High-density lipoproteins (HDL) play a role in reducing atherosclerosis and cardiovascular complications. Markers such as total cholesterol (TC)/HDL, low-density lipoprotein (LDL)/HDL, and triglycerides (TG)/HDL can provide information about long-term PCOS complications.

The study compared hormone profiles, lipid profiles, and inflammatory parameters of PCOS patients with those of non-PCOS patients and examined predictive markers in young PCOS patients who have not yet had children.

METHODS

A total of 46 women with the diagnosis of PCOS and 41 healthy women who applied to the Tokat Gaziosmanpaşa University Research and Application Hospital Gynecology and Obstetrics

[1]Gaziosmanpaşa University, Department of Obstetrics and Gynecology – Tokat, Turkey.
[2]Sivas Cumhuriyet University, Department of Obstetrics and Gynecology – Sivas, Turkey.
*Corresponding author: selim.gulucu@gop.edu.tr
Conflicts of interest: the authors declare there is no conflicts of interest. Funding: none.
Received on June 20, 2022. Accepted on July 08, 2022.

Clinic were included in the study. Informed consent was obtained from all participants. Approval was obtained from the Faculty Ethics Committee before the start of the study (dated: October 15, 2020, project number: 20-KAEK-263).

The Rotterdam criteria (clinical or biochemical hyperandrogenism, anovulation or oligomenorrhea, and sonographically polycystic appearance of the ovaries) were used to diagnose PCOS[3], and if at least two of the three major criteria were present, the diagnosis was made. The presence of hirsutism, which is one of the findings of hyperandrogenism, was also evaluated using the Ferriman-Gallwey scoring system[4] and score above 8 was considered hyperandrogenism. The patients' age, height, weight, body mass index (BMI), waist circumference (WC), degree of hirsutism, and ultrasonographic findings were recorded. The examinations, pelvic ultrasound, and peripheral venous blood sampling of the participants were performed between days 2 and 4 of the menstrual cycle. All women underwent transabdominal pelvic ultrasonography with a 1.4–5 MHz (GE Logiq P5, GE Healthcare, USA) 4C Convex probe by the same gynecologist. A regularly maintained device (Mindray BC-6800, China) was used for complete blood count. A regularly maintained Roche Cobas e601 (Roche Diagnostics GmbH, Germany) device was used for other tests. The parameters of complete blood count, follicle-stimulating hormone (FSH), luteinizing hormone (LH), serum estradiol (E2), thyroid stimulating hormone (TSH), free thyroxine (T4), prolactin, total testosterone, DHEA-SO_4, glucose, insulin, TC, TG, LDL, cholesterol, and HDL cholesterol levels were measured. A HOMA-IR (fasting blood glucose mg/dL × fasting insulin mIU/L/405) value of ≥2.5 was considered the presence of IR. TC/HDL, TG/HDL, LDL/HDL, NLR, monocyte/high-density lipoprotein (MHR), monocyte/PLT, PLT/lymphocyte ratio (PLR), LMR, and systemic immune-inflammation index (SII/SIRS) parameters (NLR×PLT; NLR/PLR) were also calculated.

Patients with chronic diseases (e.g., congenital adrenal hyperplasia, Cushing's syndrome, and androgen-secreting tumors), taking medications (diabetic, antihypertensive, antilipidemic, oral contraceptives), who gave birth, and who had a history of surgery were excluded from the study.

Power analysis was performed using G-Power 3.1.9.7. It was found that at least 64 subjects were required, with an effect size of 0.80, a margin of error of 0.05, and a power of 0.80 (80%). The SPSS (Statistical Package for Social Sciences) program for Windows 22.0 (IBM SPSS, USA) was used for statistical analysis. The statistical methods used were the t-test for the variables with a normal distribution, the significance test for the difference between two means, and the Mann-Whitney U test for the variables that did not have a normal distribution. The chi-square test was used for the comparison of categorical variables. A Pearson's correlation analysis was performed to determine the relationship between variables. The statistical significance level was accepted as $p<0.05$.

RESULTS

The demographic characteristics of the cases are shown in Table 1. A statistically significant difference was found between the values of height, weight, BMI, WC, and hirsutism scores of the groups ($p<0.05$) (Table 1).

The results of hormone profiles and biochemical parameters of PCOS patients and control group are shown in Table 2. Although fasting glucose level was similar between the groups ($p=0.946$), insulin and IR levels calculated using HOMA-IR were significantly higher ($p=0.001$) in the PCOS patients (Table 2). IR defined as HOMA-IR ≥2.1 was present in 41 (63.1%) patients with PCOS. The Pearson's correlation analysis of the PCOS group revealed a negative correlation between

Table 1. Comparison of baseline characteristics between the study and control group.

Hormonal parameters	PCOS (n=41)(mean±SD)	Control (n=46)(mean±SD)	p
Age (years)	22.5±1.58	22.6±1.63	0.930[a]
Height (m)	1.62±0.55	1.65±0.56	**0.048**[b]
Weight (kg)	63.1±7.29	58.83±9.87	**0.001**[a]
BMI (kg/m^2)	23.8±2.69	21.5±3.46	**0.001**[b]
WC (cm)	81.5±8.59	76.4±8.34	**0.005**[a]
Hirsutism score			
Mild (%)	17 (28.3)	43 (71.7)	**0.001**[c]
Moderate (%)	24 (88.9)	3 (11.1)	

PCOS: polycystic ovary syndrome; BMI: body mass index; WC: waist circumference. Bold indicates statistical significance: $p<0.05$. [a]Mann-Whitney U test for continuous variables. [b]Pairwise t-test for continuous variables. [c]χ^2 for categorical variables. Data were given as mean±standard deviation or number (%).

T4 and weight, BMI, and WC (r=-0.421, p=0.004; r=-0.374, p=0.010; r=-0.389, p=0.008, respectively). When comparing the SIRS parameters (NLR×PLT; NLR/PLR) between the control and PCOS groups, no statistically significant differences were found (p=0.185; p=0.580).

HDL cholesterol levels were found to be statistically significantly lower in the PCOS group (p=0.001). The PCOS group had hemoglobin, leukocytes, lymphocytes, neutrophils, platelets, and statistically higher ratios of TC/HDL, LDL/HDL, and TG/HDL (Table 2). The Pearson's correlation analysis showed a positive correlation between the TC/HDL ratio and the parameters TG/HDL, LDL/HDL, insulin, HOMA-IR, LDL, and triglycerides in the patients of the PCOS group (Table 3). When monocyte/HDL ratios were evaluated, a positive correlation between monocyte, TC/HDL, TG/HDL, LDL/HDL, and TG levels was found in the Pearson's correlation (Table 3).

Table 2. Comparison of hormonal and biochemical parameters between the study and control group.

Hormonal parameters	PCOS (n=41)(mean±SD)	Control (n=46)(mean±SD)	p-value
FSH (mIU/mL)	5.46±0.96	5.87±1.00	0.055[b]
LH (mIU/mL)	9.88±6.47	5.49±2.02	**0.001[b]**
E2 (pg/mL)	47.13±30.54	40.05±12.59	0.153[b]
Total testosterone (ng/dL)	0.43±0.19	0.31±0.21	**0.007*[b]**
Prolactin (ng/mL)	21.43±9.30	18.97±8.82	0.210[b]
DHEA-SO_4 (µg/dL)	316.81±118.98	262.37±62.77	0.011[b]
Insulin (µIU/mL)	20.29±3.84	11.93±10.79	**0.001*[b]**
HOMA-IR	4.51±0.96	2.70±2.66	**0.001*[b]**
HOMA-IR >2.1 (%)	41 (63.1)	24 (36.9)	**0.001*[c]**
TSH (µIU/L)	1.60±0.68	1.80±0.96	0.272[b]
T4 (µg/dL)	1.27±0.19	1.28±0.16	0.817[b]
Biochemical parameters			
Glucose (mg/dL)	89.87±7.26	89.77±6.18	0.946[b]
Triglyceride (mg/dL)	81.24±29.84	74.60±30.45	0.307[b]
Total cholesterol (mg/dL)	157.05±20.92	158.67±29.02	0.764[b]
HDL cholesterol (mg/dL)	49.66±9.25	61.33±13.82	**0.001*[b]**
LDL cholesterol (mg/dL)	91.15±19.25	91.83±23.62	0.884[b]
WBC (10^3/mL)	7.67±1.70	7.77±1.88	0.806[b]
Neutrophils (10^3/mL)	4.78±1.48	4.59±1.27	0.521[b]
Lymphocytes (10^3/mL)	2.33±1.58	2.17±0.51	0.522[b]
PLT (10^3/mL)	313.27±76.56	289.01±70.02	0.126[b]
Hemoglobin (g/dL)	13.42±1.02	13.12±1.15	0.218[b]
Monocyte (10^3/mL)	598.54±178.54	683.04±213.12	0.049[b]
MPV	9.12±1.27	9.39±1.14	0.292[b]
Neutrophil/lymphocyte ratio	2.34±1.01	2.18±0.67	0.367[b]
PLT/lymphocyte ratio	151.45±47.79	138.49±42.78	0.185[b]
MHR	12.68±4.96	11.56±3.99	0.249[b]
Total cholesterol /HDL	3.25±0.68	2.66±0.56	**0.001*[b]**
Monocyte/PLT	0.0020±0.000	0.0025±0.001	0.052[b]
Lymphocytes/monocyte	4.38±4.07	3.42±1.23	0.171[a]
LDL/HDL ratio	1.90±0.56	1.57±0.50	**0.004*[b]**
TG/HDL ratio	1.74±0.90	1.31±0.68	**0.011*[a]**

PCOS: polycystic ovary syndrome; FSH: follicle-stimulating hormone; LH: luteinizing hormone; E2: estradiol; DHEA-SO_4: dehydroepiandrosterone sulfate; HOMA-IR: homeostatic model assessment insulin resistance; TSH: thyroid-stimulating hormone; T4: thyroxine; 25OHD: 25-hydroxy vitamin D; HDL: high-density lipoprotein; LDL: low-density lipoprotein; TG: triglyceride; WBC: white blood cells; PLT: platelet; MPV: mean platelet volume; MHR: monocyte/high-density lipoprotein ratio. [a]Mann-Whitney U test for continuous variables. [b]Pairwise t-test for continuous variables. [c]χ^2 test for categorical variables, Data were given as mean±standard deviation or number (%). Bold indicates statistical significance: p<0.05.

DISCUSSION

PCOS is a common disease at reproductive age and it negatively affects women's health with its long-term effects. It can cause diseases such as coronary heart disease, impaired glucose tolerance, type 2 diabetes, endometrial cancer, and breast cancer[5]. PCOS is also associated with increased oxidative stress and low-grade chronic inflammation (CI)[6]. CI affects the clinical findings and complications of PCOS[7]. It is already known that IR is associated with low-grade CI. Hyperandrogenism and IR are common findings in women with PCOS[8]. In this study, the values for weight, BMI, WC, IR, and hirsutism scores were higher in the PCOS group than those in the control group, which is consistent with the literature data.

HDL cholesterol has anti-inflammatory, antioxidant, and antithrombotic effects[9]. Monocyte/HDL is a marker that has previously been associated with cardiovascular events[10]. In a study on 61 PCOS patients conducted by Usta et al, monocyte/HDL was found to be a useful marker for diagnosing PCOS and predicting cardiovascular complications[11]. Another study reported that the monocyte/HDL ratio was significantly higher in PCOS patients compared with the control group[12]. In contrast to reports in the literature, no significant differences in monocyte/HDL were found between the PCOS and control groups in this study. The measurement of ApoA/ApoB, which is one of the best known atherogenic and thus cardiovascular disease risk indicators, is the most studied[13]. The ratio of TC/HDL or LDL/HDL is the surrogate for ApoB/ApoA[14]. In a study of 99 PCOS patients conducted by Cakir and Simsek, the ratio of TC/HDL was significantly higher[9]. In this study, the ratios of TC/HDL and LDL/HDL were significantly higher in the PCOS group than those in the control group. It has been shown that the TG/HDL ratio can be used to define insulin-resistant individuals[15]. In this study, the TG/HDL ratio was found to be significantly higher in the PCOS group than that in the control group. This result was similar to the literature.

NLR is a peripheral blood marker associated with inflammation and has been used in many studies as a potential biomarker to reflect the inflammatory status of the body and evaluate disease prognosis[16]. Yılmaz et al. found that NLR was higher in the PCOS group than that in the control group[17]. Another study reported that NLR was significantly higher[9]. In this study, no significant differences were found for NLR between the PCOS and control groups. The greater the platelet volume, the easier the release of inflammatory factors. Based on this information, some studies have found that PLR and MPV can be used as markers to detect inflammation[18]. In a study of 48 PCOS patients, Kebapcilar et al. reported that WBC and MPV values were higher in the PCOS group than those in the group without PCOS[19]. In another study, MPV was found to be higher in the PCOS group than that in the control group[17]. In this study, no significant differences were found between the PCOS and control groups in terms of MPV values. SII/SIRS is defined as NLR×platelets and is another effective indicator of inflammatory status that has been widely used to predict disease prognosis in recent studies[20]. In a case-control study with 527 participants, it was found that patients with PCOS had higher NLR, PLR, and SII ratios than those in the control group, which indicated that PCOS patients were in an inflammatory state[18]. In this study, there was no difference in SII values between groups, which was due to the small number of patients in the study. The fact that the monocyte/HDL, NLR, MPV, and SII/SIRS values in our study were similar in the PCOS and control groups, in contrast to the literature, is probably because the patient population was young and had not given birth to children, and the number of patients was small. The limitations of this study were the relatively small number

Table 3. The Pearson correlation results between the hormone values, hemogram, and blood lipid ratios of the polycystic ovary syndrome group.

	TG/HDL		LDL/HDL		MPV		NLR/PLR	
	r	p	r	p	r	p	R	p
BMI	-0.034	0.833	-0.127	0.429	-0.243	0.126	0.171	0.286
Insulin	0.303	0.054	0.302	0.055	-0.249	0.117	-0.121	0.449
HOMA-IR	0.433	**0.005**	0.326	**0.037**	-0.254	0.109	-0.092	0.565
DEAS-SO_4	-0.084	0.603	-0.089	0.579	-0.173	0.280	-0.014	0.929
FSH	0.058	0.720	-0.103	0.524	-0.297	0.059	0.100	0.534
LH	-0.147	0.358	-0.237	0.136	0.261	0.099	-0.051	0.752
Testosterone	-0.197	0.218	-0.212	0.184	-0.207	0.194	-0.086	0.594

BMI: body mass index; HOMA-IR: homeostatic model assessment insulin resistance; HDL: high-density lipoprotein; LDL: low-density lipoprotein; TG: triglyceride; FSH: follicle-stimulating hormone; LH: luteinizing hormone; DHEA-SO4: dehydroepiandrosterone sulfate; MPV: mean platelet volume; PLR: platelet lymphocyte ratio; NLR: neutrophil/lymphocyte ratio. Bold indicates statistical significance: p<0.05.

of patients and the retrospective design. The strength of the study was that the hematologic parameters and lipid parameters were presented together in the same study.

CONCLUSIONS

PCOS patients are at risk of short- and long-term complications, and the practical use of the TC/HDL, LDL/HDL, and TG/HDL ratios in the follow-up of these patients may allow for easy patient follow-up. The health status of PCOS patients can be objectively determined by monitoring these results at regular intervals. Prospective studies with a large number of participants need to be conducted to obtain clearer results.

AUTHORS' CONTRIBUTIONS

SG: Conceptualization, Data curation, Formal analysis, Investigation, Resources, Writing – original draft, Writing – review & editing. **ISC:** Conceptualization, Formal analysis, Writing – original draft, Writing – review & editing.

REFERENCES

1. Yildiz BO, Bozdag G, Yapici Z, Esinler I, Yarali H. Prevalence, phenotype and cardiometabolic risk of polycystic ovary syndrome under different diagnostic criteria. Hum Reprod. 2012;27(10):3067-73. https://doi.org/10.1093/humrep/des232
2. Yayla Ç, Akboğa MK, Gayretli Yayla K, Ertem AG, Efe TH, Şen F, et al. A novel marker of inflammation in patients with slow coronary flow: lymphocyte-to-monocyte ratio. Biomark Med. 2016;10(5):485-93. https://doi.org/10.2217/bmm-2016-0022
3. Fauser BC, Tarlatzis BC, Rebar RW, Legro RS, Balen AH, Lobo R, et al. Consensus on women's health aspects of polycystic ovary syndrome (PCOS): the Amsterdam ESHRE/ASRM-Sponsored 3rd PCOS Consensus Workshop Group. Fertil Steril. 2012;97(1):28-38.e25. https://doi.org/10.1016/j.fertnstert.2011.09.024
4. Garzia E, Galiano V, Marfia G, Navone S, Grossi E, Marconi AM. Hyperandrogenism and menstrual imbalance are the best predictors of metformin response in PCOS patients. Reprod Biol Endocrinol. 2022;20(1):6. https://doi.org/10.1186/s12958-021-00876-0
5. Eslamian G, Hekmatdoost A. Nutrient patterns and risk of polycystic ovary syndrome. J Reprod Infertil. 2019;20(3):161-8. PMID: 31423419
6. Szczuko M, Hawryłkowicz V, Kikut J, Drozd A. The implications of vitamin content in the plasma in reference to the parameters of carbohydrate metabolism and hormone and lipid profiles in PCOS. J Steroid Biochem Mol Biol. 2020;198:105570. https://doi.org/10.1016/j.jsbmb.2019.105570
7. Rudnicka E, Suchta K, Grymowicz M, Calik-Ksepka A, Smolarczyk K, Duszewska AM, et al. Chronic low grade inflammation in pathogenesis of PCOS. Int J Mol Sci. 2021;22(7):3789. https://doi.org/10.3390/ijms22073789
8. Ebejer K, Calleja-Agius J. The role of cytokines in polycystic ovarian syndrome. Gynecol Endocrinol. 2013;29(6):536-40. https://doi.org/10.3109/09513590.2012.760195
9. Çakir I, Simsek Y. Total cholesterol/HDL cholesterol ratio and monocyte/HDL cholesterol ratio are related with subclinical hypothyroidism in polycystic ovary syndrome. Turk J Biochem. 2021;47(1):1-5. https://doi.org/10.1515/tjb-2021-0050
10. Vahit D, Akboga MK, Samet Y, Hüseyin E. Assessment of monocyte to high density lipoprotein cholesterol ratio and lymphocyte-tomonocyte ratio in patients with metabolic syndrome. Biomark Med. 2017;11(7):535-40. https://doi.org/10.2217/bmm-2016-0380
11. Usta A, Avci E, Bulbul CB, Kadi H, Adali E. The monocyte counts to HDL cholesterol ratio in obese and lean patients with polycystic ovary syndrome. Reprod Biol Endocrinol. 2018;16(1):34. https://doi.org/10.1186/s12958-018-0351-0
12. Herkiloglu D, Gokce S. Correlation of monocyte/HDL ratio (MHR) with inflammatory parameters in obese patients diagnosed with polycystic ovary syndrome. Ginekologia polska. 2021;92(8):537-43. https://doi.org/10.5603/GP.a2020.0191
13. Yusuf S, Hawken S, Ounpuu S, Dans T, Avezum A, Lanas F, et al. Investigators IS. Effect of potentially modifiable risk factors associated with myocardial infarction in 52 countries (the INTERHEART study): case-control study. Lancet. 2004;364(9438):937-52. https://doi.org/10.1016/S0140-6736(04)17018-9
14. Wild RA. Dyslipidemia in PCOS. Steroids. 2012;77(4):295-9. https://doi.org/10.1016/j.steroids.2011.12.002
15. McLaughlin T, Abbasi F, Cheal K, Chu J, Lamendola C, Reaven G. Use of metabolic markers to identify overweight individuals who are insulin resistant. Ann Intern Med. 2003;139(10):802-9. https://doi.org/10.7326/0003-4819-139-10-200311180-00007
16. Fest J, Ruiter TR, Koerkamp BG, Rizopoulos D, Ikram MA, van Eijck CH, et al. The neutrophil-to-lymphocyte ratio is associated with mortality in the general population: The Rotterdam Study. Eur J Epidemiol. 2019;34(5):463-70. https://doi.org/10.1007/s10654-018-0472-y
17. Yilmaz MA, Duran C, Basaran M. The mean platelet volume and neutrophil to lymphocyte ratio in obese and lean patients with polycystic ovary syndrome. J Endocrinol Invest. 2016;39(1):45-53. https://doi.org/10.1007/s40618-015-0335-2
18. Wang Q, Sun Y, Xu Q, Liu W, Wang P, Yao J, et al. Higher dietary inflammation potential and certain dietary patterns are associated with polycystic ovary syndrome risk in China: a case–control study. Nutr Res. 2022;100:1-18. https://doi.org/10.1016/j.nutres.2021.12.006
19. Kebapcilar L, Taner CE, Kebapcilar AG, Sari I. High mean platelet volume, low-grade systemic coagulation and fibrinolytic activation are associated with androgen and insulin levels in polycystic ovary syndrome. Arch Gynecol Obstet. 2009;280(2):187-93. https://doi.org/10.1007/s00404-008-0884-0
20. Nøst TH, Alcala K, Urbarova I, Byrne KS, Guida F, Sandanger TM, et al. Systemic inflammation markers and cancer incidence in the UK Biobank. Eur J Epidemiol. 2021;36(8):841-8. https://doi.org/10.1007/s10654-021-00752-6

ORIGINAL ARTICLE

https://doi.org/10.1590/1806-9282.20220961

Revisiting surgical management of breast cancer in a geriatric population

Tugrul Kesicioglu[1], Ilker Sengul[1,2*], Ismail Aydın[1], Selahattin Vural[1], Demet Sengul[3]

SUMMARY

OBJECTIVE: Breast cancer is a leading cause of death not only in the young population but also in the elderly. There are no consensus treatment guidelines for elderly breast cancer patients. We purposed to discuss surgical treatment options for breast cancer cases over 80 years concerning morbidity and mortality.

METHODS: This retrospective study includes 58 patients over 80 years of age at the time of surgery for breast cancer between 2006 and 2017. A sum of 58 cases (54 females and 4 males), over 80 years of age, with an average age of 84.5±4.07 (80–94) years were included in the study. The modified radical mastectomy was the most common surgical modality in 30 (51.7%) cases, and the axillary intervention was performed on 41 (70.7%). Axillary dissection and sentinel lymph node biopsy were performed for 30 (51.7%) and 11 (18.9%) cases, respectively.

RESULTS: Minor and major complications were observed in 8 (13.8%) cases. The average follow-up period of the patients was 37.5 (1–120) months. During the follow-up period, breast cancer-related mortality was observed in 9 (15.52%) cases. No statistical differences were detected in mortality with/without axillary intervention and chosen surgical modality.

CONCLUSIONS: Comorbidity, the American Society of Anesthesiologists score, and life expectancy should be considered in the management and surgical planning of patients over 80 years of age with breast cancer. Minimally invasive approaches should be preferred for the elderly whenever feasible and applicable in the light of oncologic surgery principles in order to reduce complications and mortality rates.

KEYWORDS: Breast. Breast cancer. Geriatrics. Elderly. Pathology.

INTRODUCTION

Increasing life standards, widespread screening tests, and improved treatment options lead to an increased length of human life worldwide. The number of elderly people is estimated to be more than double by 2040 to 1.3 billion and 14% of the world population will be of pensionable age. The United Nations definition of "very old population" is the proportion of the elderly in a country that exceeds 10% of the total[1].

Breast cancer is the most common cancer in the world and one of the leading causes of cancer death in women, accounting for 23% of total cases and 14% of all cancer-related mortalities[2]. The most common type of cancer in women in our country is breast cancer. According to 2014 data, a sum of 16,646 women were diagnosed with breast cancer within 1 year and one out of every four women was diagnosed with that[2].

The median age is defined as 60 years, and over 40% of women with newly diagnosed breast cancer are aged 65 years or older. The risk is present in 15 out of 1000 women in the fifth decade and 43 out of 1000 women in the age range of 70–80. Even though about two-fifths of breast cancer is seen over the age of 65, no standard consensus on breast cancer treatment in elderly cases has been reported[3]. Hutchins et al.[4] demonstrated that only 9% of those over 65 years were represented in cancer studies. We purposed to describe the general characteristics of elderly breast cancer cases over 80 years and discuss surgery for elderly over 80 with breast cancer whose numbers are increasing in society.

METHODS

This retrospective study includes the medical data of 58 patients who had been operated on for breast cancer diagnosis at the age of 80 years and older in our Department between 2006 and 2017. The patients' data were evaluated regarding the age, sex, breast cancer type, tumor size, tumor spread, surgical approach, axillary intervention, anesthesia, complication, hormonal status

[1]Giresun University, Faculty of Medicine, Department of General Surgery – Giresun, Turkey.
[2]Giresun University, Faculty of Medicine, Division of Endocrine Surgery – Giresun, Turkey.
[3]Giresun University, Faculty of Medicine, Department of Pathology – Giresun, Turkey.
*Corresponding author: demet.sengul.52@gmail.com
Conflicts of interest: the authors declare there is no conflicts of interest. Funding: none.
Received on July 15, 2022. Accepted on July 21, 2022.

of the tumor, neoadjuvant and adjuvant treatment, follow-up period, recurrence status, and mortality. Descriptive statistics for continuous variables in our study were expressed as the mean±-standard deviation, and categorical variables were expressed as numbers and percentages. The Kolmogorov-Smirnov test was applied to test the normal distribution of continuous variables. The distributions of nonparametric variables were compared using the Kruskal-Wallis test and Mann-Whitney U test, chi-square test, and Fisher's exact test was used to determine the relationship between categorical variables. The Kaplan-Meier test was performed for survival. Statistical significance was accepted as $p<0.05$. A statistical package program SPSS (IBM SPSS for Windows, version 24) was used for the calculations.

RESULTS

Of 58 patients diagnosed with breast cancer, 54 (93.1%) were female and 4 (6.9%) were male, and the mean age was 84.5±4.07 (80–94) years. The mean tumor diameter was 32.6±2.66 (8–100) mm, and 51 (87.9%) cases were diagnosed by physical examination and 7 (12.1%) by breast ultrasonography and mammography. Axillary lymph nodes were clinically detected in 14 (24.1%) of the cases while not in 44 (75.9%). Notably, 53 (91.4%) cases had undergone surgery under general anesthesia and 5 (8.6%) were under local anesthesia. The American Society of Anesthesiologists (ASA) scores of the patients were as follows: 38 patients had ASA-2, 18 had ASA-3, and 2 had ASA-4 without perioperative mortality. The demographic and clinical data of the patients are given in Table 1.

The modified radical mastectomy (MRM) was performed for 30 (51.7%) of 58 cases, while the segmental mastectomy for 11 (19%), simple mastectomy for 6 (10.3%), mastectomy with sentinel lymph node biopsy (SLNB) for 4 (6.9%), and breast-conserving surgery (BCS) with SLNB for 7 (12.1%). The axillary intervention was performed on 41 (70.7%) while not on 17 (29.3%) patients. SLNB was performed on 11 (26.8%) of 41 with axillary intervention. The remaining 30 (73.2%) underwent axillary dissection (AD) without SLNB. The axillary interference was completed to levels I-II AD due to the metastatic lymph nodes detection in the axilla of 4 (36.4%) of 11 patients who underwent SLNB. The metastatic lymph nodes were positive in 23 (56.1%) of 41 with the axillary intervention and in 19 (63.3%) of the cases who had AD.

Histopathologically, breast cancer was revealed as the invasive ductal cancer in 41 (70.7%) cases while invasive lobular cancer in 7 (12.1%), mucinous cancer in 3 (5.2%), and papillary carcinoma in 3 (5.2%), apocrine cancer in 1 (1.7%), neuroendocrine cancer in 1 (1.7%), medullary cancer in 1 (1.7%), and adenoid cystic carcinoma in 1 (1.7%) case. The presence of estrogen receptor (ER), progesterone receptor (PR), and human epidermal growth factor receptor (Her2/Neu) was analyzed in 49 (84.5%) of the 58 patients; however, 9 (15.5%) patients' data were not available. ER (+) was found in 35 (71.4%) patients, ER (–) in 14 (28.6%), PR (+) in 29 (59.2%), PR (–) in 20 (40.8%), Her2/Neu (+) in 21 (42.9%), and Her2/Neu (–) in 28 (57.1%) patients.

The analysis of chemotherapy (CT), radiotherapy (RT), and hormonotherapy (HT) treatments in the postoperative period revealed that 14 (28.57%) of 49 patients were treated without any treatment and 35 (72.43%) were treated with one or several cycles of CT, RT, and HT treatments. Of 49 patients whose data were obtained, 11 (22.4%) received CT, 6 (12.2%) RT, and 31 (63.3%) HT. In detail, 5 (10.2%) patients received CT and HT, 4 (8.16%) patients received RT and HT, and 2 (4.08%) patients received RT, CT, and HT. Only 4 (8.16%) cases received CT and 20 (40.81%) received HT. Only two cases received CT as neoadjuvant therapy.

The average follow-up period was 37.5 (1–120) months and the disease-free survival time of the operated patients was 36.6 (1–120) months. Recurrence was observed in 3 (5.2%) of 58 patients. No significant difference was revealed in the effect of the axillary intervention and surgical modalities on disease-free survival. During follow-up, 14 (24.14%) of 58 patients died: 9 (15.5%) were due to breast cancer, and 5 (8.6%) were due to other causes. The average life span was 44.11 (12–85) months for those who died due to breast cancer, while 51 (3–120) months for those who died from other causes. No statistical differences were detected in mortality with/without axillary intervention and chosen surgical modality.

DISCUSSION

The incidence of breast cancer increases with age and peaks in the oldest-old group of patients. Despite this, there is no standard approach to managing breast cancer in the elderly. In the treatment strategy of elderly patients, some factors are different from younger ones. All elderly should undergo a pretreatment evaluation, including age and comorbidities, threatening their health and life expectancy, which may have a decisive impact on surgery[5].

Chronological age, per se, is not an appropriate criterion on which to decide the treatment strategy. Instead, biological age, which reflects the presence of comorbid diseases, and the general fitness or health of a patient should be considered. Comorbidities increase with age, and cancer patients in their 70s may be expected to have at least three comorbid conditions[5,6]. Regardless of the age, the greater

Table 1. The demographic characteristics, diagnostic and surgical modalities, histopathologic evaluations, and survival of the cases.

Age (years)			84.5±4.07 (80–94)
Sex, n (%)			Female: 54 (93.1)
			Male: 4 (6.9)
Diameter of the tumor (mm)			32.6±2.66 (8-100)
Clinical axillary lymph nodes, n (%)			(+): 13 (22.4)
			(–): 44 (75.9)
			Unknown: 1 (2.7)
Diagnostic method, n (%)			CE: 51 (87.9)
			Screening: 7 (12.1)
Neoadjuvant treatment, n (%)			(+): 2 (3.4)
			(–): 56 (96.6)
Type of anesthesia, n (%)			Local: 5 (8.6)
			General: 53 (91.4)
Axillary intervention, n (%)			Yes: 41 (70.7)
			No: 15 (25.8)
			Unknown: 2 (3.5)
Sentinel lymph node biopsy, n (%)			Malignancy (+): 4 (36.4)
			Malignancy (–): 7 (63.6)
Axillary dissection, n (%)			Malignancy (+): 19 (63.3)
			Malignancy (–): 11 (36.7)
Surgical modalities, n (%)		MRM	30 (51.7)
		Segmental mastectomy	11 (19.0)
		Simple mastectomy	6 (10.3)
		Mastectomy+SLNB	4 (06.9)
		BCS+SLNB	7 (12.1)
Postoperative complication, n (%)		SLNB	Minor: 1 (14.3)
			Major: 0 (0.0)
		AD	Minor: 5 (71.4)
			Major: 1 (14.3)
		No intervention	Minor: 0 (0.0)
			Major: 0 (0.0)
Histopathology, n (%)		Invasive ductal carcinoma	41 (70.7)
		Invasive lobular carcinoma	7 (12.1)
		Mucinous carcinoma	3 (5.2)
		Papillary carcinoma	3 (5.2)
		Apocrine carcinoma	1 (1.7)
		Neuroendocrine carcinoma	1 (1.7)
		Medullary carcinoma	1 (1.7)
		Adenoid cystic carcinoma	1 (1.7)
Receptor status, n (%)	ER	35 (71.4) (+)	14 (28.6) (–)
	PR	29 (59.2) (+)	20 (40.8) (–)
	Her2/Neu	21 (42.9) (+)	28 (57.1) (–)
Adjuvant treatment,	n (%) CT	11 (22.4) (+)	38 (77.6) (–)
	RT	6 (12.2) (+)	43 (87.8) (–)
	HT	31 (63.3) (+)	18 (36.7) (–)
Recurrence, n (%)			3 (5.2) (+)
			55 (94.8) (–)
Causes of death, n (%)	Breast cancer		9 (15.5)
	Other causes		5 (8.6)
Disease-free survival (month)			36.6 (1–120)
Mean follow-up time (month)			37.5 (1–120)

CE: clinical examination; SLNB: sentinel lymph node biopsy; MRM: modified radical mastectomy; BCS: breast-conserving surgery; AD: axillary dissection; ER: estrogen receptor; PG: progesterone receptor; Her2/Neu: human epidermal growth factor receptor 2; CT: chemotherapy; RT: radiotherapy; HT: hormonotherapy.

the number of additional diseases, the greater the likelihood of death due to non-breast cancer causes[7]. No matter how the chronological age of breast cancer patients is advanced, an important part of them dies from breast cancer. Besic et al.[8] reported that 31% of cases, over 80 years, died from breast cancer during the mean follow-up period of 5.3 years. In the United Kingdom, breast cancer-related mortality in women aged 80 years or older was 39% between 1999 and 2009[9]. In our study, 15.5% of patients died due to breast cancer during the mean follow-up period of 37.5 months.

In the elderly, the biological features of breast cancer are more innocent than the younger patient. Breast cancer in elderly women expresses ER and/or PR more often than in younger and tumors show lower proliferative indices and less HER2 overexpression[10]. In the present study, ER (+) was detected in 71.4% while PR (+) in 59.2%, and Her2/Neu (+) in 42.9%. Although the tumor's biological features are better than those of younger people, the prognosis of breast cancer is worse in older patients. The screening of breast cancer in the elderly is still controversial, and there is no consensus on annual mammography screening[11]. The breast cancers were revealed by clinical examination and imaging in 82 and 18%, respectively[8].

Blair et al.[12] examined 2947 cases in order to investigate the treatment of breast cancer over 80 years and reported the 2169 surgical approach (mastectomy or BCS) as the most common choice of treatment. No specific recommendations in the literature regarding the extent of surgery in breast cancer cases over 80 years[13]. Surgical treatment extends from local excision to s segmental resection, quadrantectomy, and total or partial removal of the mammary gland and axillary lymph nodes, id est, MRM, or BCS[14]. In the present study, 51.7% of the 58 had MRM, while 19% had a segmental mastectomy, 10.3% simple mastectomy, 6.9% mastectomy+SLNB, and 12.1% BCS+SLNB.

German pathologist Rudolf Virchow's hypothesis revealed that breast cancer is primarily spread on axillary lymph nodes and passes through other places when the lymph nodes are filled with the tumor[15]. AD demonstrates the status of the lymph nodes and helps determine the adjuvant treatment and control the disease. Lymphedema may cause many morbidities, such as pain, paresthesia, limitation of limb movements, altered quality of life, and weakness[16]. Lymph node involvement is a major prognostic factor in breast cancer, even in the elderly. The presence of axillary metastasis suggests a reduction in disease-free survival and overall survival rates[17]. Histopathologic examination of lymph nodes after AD in approximately 70% of patients with T1/T2 tumors exhibits negative[18]. In the axillary SLNB negativity estimation model based on the criteria of patient age, tumor diameter, and palpability, 5% of the cases had positive SLNB even in the lowest risk group. Regardless of the age of the patient, it is important to at least stage the axillary with SLNB in all cases where it is thought that adjuvant systemic therapy will be determined[19,20].

CONCLUSIONS

The elderly population is increasing rapidly all over the world and the incidence of breast cancer is also increasing in them. Providers should consider their additional diseases, ASA score, and life expectancy while planning the surgical approach. Similar surgical modalities may be administrated to the elderly like the youngers in case of possessing healthy status. Ad hoc elderly with severe comorbidities and limited life expectancy, avoiding surgery may be useful. Of note, minimally invasive techniques should be applied to the elderly as much as possible in order to attenuate morbidity and even mortality. *Nulla tenaci invia est via.*

ACKNOWLEDGMENT

We thank all the study participants.

AUTHORS' CONTRIBUTIONS

TK: Conceptualization, Data curation, Formal analysis, Investigation, Methodology, Project administration, Resources, Software, Validation, Visualization, Writing – original draft. **IS:** Investigation, Methodology, Software, Supervision, Visualization, Writing – original draft, and Writing – review & editing. **IA:** Investigation, Methodology, Validation, Visualization, Writing – original draft. **SV:** Investigation, Validation, Visualization. **DS:** Investigation, Methodology, Software, Supervision, Writing – original draft, Writing – review & editing.

REFERENCES

1. Swaminathan D, Swaminathan V. Geriatric oncology: problems with under-treatment within this population. Cancer Biol Med. 2015;12(4):275-83. 10.7497/j.issn.2095-3941.2015.0081
2. Jemal A, Bray F, Center MM, Ferlay J, Ward E, Forman D. Global cancer statistics. CA Cancer J Clin. 2011;61(2):69-90. https://doi.org/10.3322/caac.21262
3. Halter JB, Ouslander JG, Tinetti ME, Studenski S, High KP, Asthana S, editors. Hazzard's geriatric medicine and gerontology. 6th ed. New York: McGraw-Hill; 2015.
4. Hutchins LF, Unger JM, Crowley JJ, Coltman Junior CA, Albain KS. Underrepresentation of patients 65 years of age or older in cancer treatment trials. New Eng J Med. 1999;341(27):2061-7. https://doi.org/10.1056/NEJM199912303412706

5. Rao V, Jameel JK, Mahapatra T, McManus PL, Fox JN, Drew PJ. Surgery is associated with lower morbidity and longer survival in elderly breast cancer patients over 80. Breast J. 2007;13(4):368-73. https://doi.org/10.1111/j.1524-4741.2007.00444.x
6. Keats AS. The ASA classification of physical status – a recapitulation. Anesthesiology. 1978;49(4):233-6. https://doi.org/10.1097/00000542-197810000-00001
7. Yancik R, Wesley MN, Ries LA, Havlik RJ, Edwards BK, Yates JV. Effect of age and comorbidity in postmenopausal breast cancer patients aged 55 years and older. JAMA. 2001;285(7):885-92. https://doi.org/10.1001/jama.285.7.885
8. Besic N, Besic H, Peric B, Pilko B, Petric R, Zmuc J, et al. Surgical treatment of breast cancer in patients aged 80 years or older–how much is enough? BMC Cancer. 2014;14:700. https://doi.org/10.1186/1471-2407-14-700
9. Ali AMG, Greenberg D, Wishart GC, Pharoah P. Patient and tumour characteristics, management, and age-specific survival in women with breast cancer in the East of England. Br J Cancer. 2011;104(4):564-70. https://doi.org/10.1038/bjc.2011.14
10. Gennari R, Curigliano G, Rotmensz N, Robertson C, Colleoni M, Zurrida S, et al. Breast carcinoma in elderly women: features of disease presentation,choice of local and systemic treatments compared with younger postmenopausal patients. Cancer. 2004;101(6):1302-10. https://doi.org/10.1002/cncr.20535
11. Pace LE, Keating NL. A systematic assessment of benefits and risks to guide breast cancer screening decisions. JAMA. 2014;311(13):1327-35. https://doi.org/10.1001/jama.2014.1398
12. Blair S, Robles J, Weiss A, Ward E, Unkart J. Treatment of breast cancer in women aged 80 and older: a systematic review. Breast Can Curr Res. 2016;1(4):1000115. https://doi.org/10.4172/2572-4118.1000115
13. Van Leeuwen BL, Rosenkranz KM, Feng LL, Bedrosian I, Hartmann K, Hunt KK, et al. The effect of under-treatment of breast cancer in women 80 years of age and older. Crit Rev Oncol Hematol. 2011;79(3):315-20. https://doi.org/10.1016/j.critrevonc.2010.05.010
14. Sakorafas GH, Farley DR, Peros G. Recent advances and current controversies in the man- agement of DCIS of the breast. Cancer Treat Rev. 2008;34(6):483-97. https://doi.org/10.1016/j.ctrv.2008.03.001
15. Virchow RLK. Cellular pathology as based upon physiological and pathological histology. 2nd ed. Philadelphia: JB Lippincott; 1863.
16. Soares EWS, Nagai HM, Bredt LC, Cunha Júnior AD, Andrade RJ, Soares GVS, et al. Morbidity after conventional dissection of axillary lymph nodes in breast cancer patients. World J Surg Oncol. 2014;12:67. https://doi.org/10.1186/1477-7819-12-67
17. Inal A, Akman T, Yaman S, Ozturk SC, Geredeli C, Bilici M, et al. Is lymph node ratio prognostic factor for survival in elderly patients with node positive breast cancer? The Anatolian Society of Medical Oncology. Ann Ital Chir. 2013;84(2):143-8. PMID: 23698146
18. Pijpers R, Meijer S, Hoekstra OS, Collet GJ, Comans EF, Boom RP, et al. Impact of lymphoscintigraphy on sentinel node identification with technetium-99m-colloidal albumin in breast cancer. J Nucl Med. 1997;38(3):366-8. PMID: 9074519
19. Chagpar AB, McMasters KM, Edwards MJ, North American Fareston Tamoxifen Adjuvant Trial. Can sentinel node biopsy be avoided in some elderly breast cancer patients? Ann Surg 2009;249(3):455-60. https://doi.org/10.1097/SLA.0b013e318194d16b
20. McMahon LE, Gray RJ, Pockaj BA. Is breast cancer sentinel lymph node mapping valuable for patients in their seventies and beyond? Am J Surg. 2005;190(3):366-70. https://doi.org/10.1016/j.amjsurg.2005.03.028

ORIGINAL ARTICLE

https://doi.org/10.1590/1806-9282.20210300

Access to antiviral therapy for chronic hepatitis B during COVID-19

Marilia Rocha Bertolli[1], Priscilla Alves Rocha[1*], Vanusa Barbosa Pinto[1], Suzane Kioko Ono[2]

SUMMARY

OBJECTIVE: Hepatitis B is an important public health concern. Currently, the COVID-19 pandemic is a major challenge for health systems, and the access to pharmacologic and non-pharmacologic treatment of chronic diseases, such as hepatitis B, may have been affected due to the contingency measures. This study aimed to evaluate the access to antiviral therapy during the ongoing pandemic.

METHODS: This was a descriptive analysis of the access to treatment for chronic hepatitis B at a tertiary-level university hospital in São Paulo, integrated with the Brazilian health system. The study was conducted from April to December 2020.

RESULTS: Access to antiviral therapy for 225 patients was assessed. The majority of the population was male (59%). The main type of service was the *Programa Medicamento em Casa* (Home Medication Delivery Program), which was availed by 144 (64%) patients. Women had poorer access to antiviral therapy (56%, p<0.05), and patients registered in the HMDP (68%, p<0.05) had better access. The age group of >48 years represented 70% of the group without access to antiviral therapy. Twenty-two pharmaceutical appointments were conducted through phone calls with patients without access to antiviral therapy.

CONCLUSION: This study contributes to the rationalization of efforts in a public health crisis through the identification of groups with the highest risk of poor access to antiviral therapy and the demonstration of the benefits of a medication delivery system.

KEYWORDS: Hepatitis B. Antiviral agents. COVID-19. Public health.

INTRODUCTION

Hepatitis B is an important public health issue with significant morbidity and mortality rates. Since the beginning of the century, mortality due to viral hepatitis has increased by 22%, which is expected to increase in the absence of adequate diagnosis and treatment. Globally, hepatitis B is responsible for approximately 800,000 deaths from complications such as cirrhosis and hepatocellular carcinoma, and 3.5% of the world population is estimated to have chronic hepatitis B[1,2]. In Brazil, 9,938 new cases and 1,728 deaths from hepatitis B were recorded in 2018[3].

The main goal of antiviral therapy against hepatitis B is to achieve viral suppression to slow disease progression and prevent complications, increasing survival and quality of life[4,5]. Currently, the Ministry of Health offers five oral drugs for the treatment of chronic hepatitis B: tenofovir (TDF), entecavir (ETV), and lamivudine (3TC)[6]. Ford et al. reported treatment adherence as one of the main factors that define the success of antiviral therapy and discussed the presence of numerous barriers, such as lack of medication. Adverse reactions can also be a barrier to adherence[2,7]. Abreu et al. identified an unsatisfactory rate of non-adherence (43%) when compared with experimental models, which associated rates below 65% with an additional 2.6 million deaths in a 15-year period. In a prospective study, for 3 consecutive years, a significant increase in the rate of adherence after health education to patients was noted[8,9].

Since March 2020, the COVID-19 pandemic has become a global challenge to health systems. The restriction measures and mobilization of health professionals may have impaired the management of chronic diseases. Supplying medications for chronic use is a priority of health services and, by extension, of the pharmaceutical service[10,11]. The pharmacist plays an important role in fostering adherence and monitoring the efficacy and safety of current therapy to avoid unnecessary hospital visits[10,12].

Therefore, according to the recommendations of the official entities in the State of São Paulo, the Hospital das Clínicas of the Faculty of Medicine of the University of São Paulo instituted contingency measures on March 18, 2020, aimed at ensuring medical care to patients through the program "HC at home"

[1]Universidade de São Paulo, Faculty of Medicine, Hospital das Clínicas, Pharmacy Division – São Paulo (SP), Brazil.
[2]Universidade de São Paulo, Faculty of Medicine, Hospital das Clínicas, Department of Gastroenterology, Division of Gastroenterology and Clinical Hepatology – São Paulo (SP), Brazil.
*Corresponding author: priscilla.alves@hc.fm.usp.br
Conflicts of interest: the authors declare there is no conflicts of interest. Funding: none.
Received on March 29, 2021. Accepted on May 02, 2021.

with the postponement of in-person medical consultations and extension of the validity of medical prescriptions.

In the midst of the COVID-19 pandemic, access to drugs may be hampered due to the adopted contingency measures and, consequently, impair the treatment of chronic diseases.

Regular and continued use of medications is essential for the success of therapy in hepatitis B. Therefore, it is necessary to investigate the access to antiviral therapy during the pandemic period and the current public health situation.

METHODS

This was a descriptive analysis of patients undergoing treatment for chronic hepatitis B who continued and discontinued antiviral therapy, given the contingency measures adopted secondary to the COVID-19 pandemic.

This study was conducted in a tertiary-level university hospital in São Paulo integrated into the Unified Health System. Patients aged >18 years, diagnosed with chronic hepatitis B, using antiviral therapy (e.g., TDF, ETV, or 3TC), and in outpatient follow-up were included. Patients co-infected with hepatitis C and human immunodeficiency virus were excluded.

Data were collected from patients regarding the prescribed antiviral therapy (e.g., TDF, ETV, or 3TC) between October 1, 2019, and April 1, 2020, and medications were dispensed by the pharmacy from April 1 to 30, 2020, through an institutional computerized system of medical records. After confirming the withdrawal or delivery of drugs, two groups were identified: group with access to antiviral therapy and group without access to antiviral therapy (Figure 1).

The members of the group without access to antiviral therapy were evaluated for possible failures in the dispensing process and were the candidates for distanced pharmaceutical consultation through phone calls. The distance pharmaceutical consultation form was applied individually and recorded in electronic medical records. After 30 days from the date of consultation and registration in the institutional system, a favorable (i.e., dispensation of treatment and continuity of antiviral therapy) or unfavorable outcome (i.e., probable treatment abandonment) was assessed.

Quantitative variables are presented as absolute values and mean±standard deviation, and qualitative variables are presented as absolute frequency (n) and relative frequency (%). The association between qualitative variables was assessed by the chi-square statistical test, with a significance set at $p<0.05$.

According to the opinion no. 4.157.514 of the Research Ethics Committee of the institution, the study was exempt from the requirement of the informed consent form.

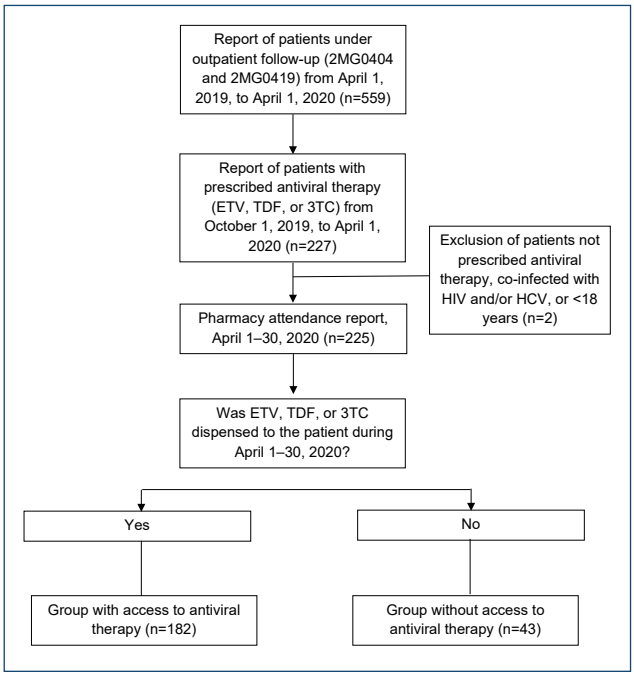

Figure 1. Flowchart of the patient enrollment process.

RESULTS

The study analyzed 225 patients who were prescribed antiviral therapy regarding their access to the prescribed medication in the proposed period. A total of 182 (80.9%) patients were identified to have access to the prescribed treatment, whereas 43 (19.1%) patients did not have access to the drug.

The general characteristics of the study participants are shown in Table 1. The largest percentage of the population is male (59%). The mean age was 55.11±14.20 years. The most prescribed drug was tenofovir, being given to 181 (80.4%) patients. The main type of care in the pharmacy was the Home Medication Delivery Program (HMDP), an institutional program for the delivery of medicines at home, to 144 (64%) patients.

When analyzing the association between gender and access to antiviral therapy (Table 2), we confirmed that women had less access than men to antiviral therapy (56 vs. 44%, $p<0.05$) during the study period.

Similarly, when comparing the groups with and without access to antiviral therapy regarding the type of care, access was higher in the group that received the drug through the HMDP, corresponding to 68% ($p<0.05$) among those who had guaranteed access to antiviral therapy (Table 3).

The analysis of the group without access to antiviral therapy revealed that 30% experienced access failure due to the

inefficiency of the measures during the pandemic. The remaining 70% was attributed to patient non-adherence. The age group of 48–77 years corresponded to 70% of the patients in the group without access to antiviral therapy.

The pharmaceutical consultations conducted from August to December 2020 recorded the reasons reported by 22 (47%) of the 43 patients without access to antiviral therapy (Table 4): 9 (41%) did not reside in São Paulo (capital); 15 (68%) mainly used public transportation; 14 (64%) had remaining medications at home; and 5 (23%) had a "fear of leaving home."

Table 1. General characteristics of patients with chronic hepatitis B treated with antiviral therapy at an outpatient gastroenterology clinic.

Characteristics	Total (N=225)
Sex, n (%)	
Female	93 (41.33)
Male	132 (58.67)
Age (years), mean±SD	55.11±14.20
Medications, n (%)	
Tenofovir	184 (81.78)
Entecavir	36 (16.00)
Lamivudine (tablet)	3 (1.33)
Lamivudine (suspension)	2 (0.89)
Care offered by pharmacy, n (%)	
In-person	81 (36)
Home medicine program	144 (64)

SD: standard deviation.

Table 2. Comparison of groups with and without access to antiviral therapy by sex.

Sex	With access to antiviral therapy		Without access to antiviral therapy		p-value
	n	%	n	%	
Female	69	38	24	56	0.031
Male	113	62	19	44	0.031

Table 3. Comparison of groups with and without access to antiviral therapy by care offered.

Care provided by pharmacy	With access to antiviral therapy		Without access to antiviral therapy		p-value
	N	%	N	%	
In-person	58	32	23	53	0.007
Home medicine program	124	68	20	47	0.007

DISCUSSION

The data from this study were collected at the beginning of the COVID-19 pandemic, in which there were numerous changes in social mobility due to the establishment of control measures, particularly social distancing[13]. The results indicate the difficulty of access to medications for a significant proportion of patients.

Table 4. Distance pharmaceutical consultations and responses from patients in the without access to antiviral therapy group (n=22).

Remote pharmaceutical consultations		n	%
Performed		22	51
Not performed		21	49
In which city do you currently live?	Sao Paulo	11	50
	Other	11	50
How long does it take you to travel to the Hospital das Clínicas?	30 min	1	5
	1 h	11	50
	>1 h	10	45
What means of transportation do you use to travel to the Hospital das Clínicas?	Own	7	32
	Public	15	68
Do you live alone?	Yes	10	45
	No	12	55
What medication are you using for the treatment of chronic hepatitis B?	TDF	13	59
	ETV	6	27
	3TC	0	0
	Don't know	3	14
Are you responsible for your pharmacotherapy?	Yes	22	100
	No	0	0
You were not given the drug in April for the treatment of chronic hepatitis B. Why did you not come to the Hospital das Clínicas to receive the drug?	Fear of leaving home	5	23
	Strictly complied with the social isolation recommendations	2	9
	I didn't know the pharmacy was open	0	0
	I used leftover drug at home	14	64
	Distance from hospital	0	0
	Lack of transportation	1	5
	Other	0	0
Did you have to seek emergency medical care with symptoms of COVID-19?	Yes, needed hospitalization for >24 h	1	5
	Yes, but did not need hospitalization	2	9
	No	19	86
Remote post-consultation situation	Continue antiviral therapy	20	91
	Failure to access/likely abandonment	2	9

In a survey conducted between May and June 2020 in Nigeria among study participants with chronic conditions, there was an increase from 10.6 to 35.2% in patients who had difficulty obtaining access to medications[14]. In Italy, the impact of COVID-19 on the management of liver diseases, including viral hepatitis, was reported, and in 23% of the patients, the onset of viral hepatitis treatment was postponed[15].

Medication access hampered by the COVID-19 pandemic is an additional challenge to the WHO's target of eliminating viral hepatitis[1]. Mobility restrictions and suspension of medical care during this pandemic may have contributed to poor access. In a survey by the World Hepatitis Alliance, 52% of frontline health professionals reported that patients undergoing treatment for viral hepatitis did not have access to the drug[16].

Levorato et al. reported that women, in general, more frequently seek health services[17]. In the United States and other English-speaking European countries, men exhibit less compliance than women on the recommendations for social distancing, and those aged >45 years exhibited greater adherence to social distancing measures during this pandemic[18]. In this study, females and patients aged >48 years were predominant in the group without access to antiviral therapy, which may be related to better adherence to pandemic measures.

The difficulty of access was greater in those who receive the drug in person at the pharmacy, as well as in the age groups of 41–50 and 61–70 years. These data may be related to the context of the pandemic and restriction measures. The study does not exactly provide the reasons for not accessing the drug but suggests that the number of reduced medical visits and strict compliance with social distancing may have influenced the findings. The generalizability of our results is subject to limitations such as the limited study duration and lack of data regarding the consequences of the COVID-19 pandemic on disease progression. Further investigations involving the same study population are required.

CONCLUSION

The findings from this study can contribute to the identification and monitoring of high-risk populations and those with potential difficulty in accessing treatment during a public health crisis. The efficiency of the established pandemic contingency plans was not evaluated; however, beneficial results were evident in the drug delivery system that can be expanded in similar contexts to ensure access to all patients.

ACKNOWLEDGMENTS

MRB thanks the Ministry of Health for the residency grant (Hospital and Clinical Pharmaceutical Care). SKO thanks the National Council for Scientific and Technological Development—CNPq (PQ 308609/2018-2).

AUTHORS' CONTRIBUTIONS

MRB: Conceptualization, Data curation, Formal Analysis, Investigation, Methodology, Writing – original draft, Writing – review & editing. **PAR:** Conceptualization, Data curation, Formal Analysis, Investigation, Methodology, Writing – original draft, Writing – review & editing. **SKO:** Conceptualization, Formal Analysis, Supervision, Validation, Writing – review & editing. **VBP:** Validation, Writing – review & editing.

REFERENCES

1. World Health Organization (WHO). Global hepatitis report, 2017. WHO | World Health Organization, January 01, 2017. [cited on May 02, 2020]. Available from: www.who.int/hepatitis/publications/global-hepatitis-report2017/en/
2. Ford N, Scourse R, Lemoine M, Hutin Y, Bulterys M, Shubber Z, et al. Adherence to nucleos(t)ide analogue therapies for chronic hepatitis b infection: a systematic review and meta-analysis. Hepatol Commun. 2018;2(10):1160-7. https://doi.org/10.1002/hep4.1247
3. TabNet Win32 3.0. Casos confirmados notificados no sistema de informação de agravos de notificação - São Paulo. Brasil. n.d. [cited on May 17, 2020]. Available from: http://tabnet.datasus.gov.br/cgi/deftohtm.exe?sinannet/cnv/hepasp.def
4. Lieveld FI, van Vlerken LG, Siersema PD, van Erpecum KJ. Patient adherence to antiviral treatment for chronic hepatitis B and C: a systematic review. Ann Hepatol. 2013;12(3):380-91. PMID: 23619254
5. Ha NB, Trinh HN, Rosenblatt L, Nghiem D, Nguyen MH. Treatment outcomes with first-line therapies with entecavir and tenofovir in treatment-naive chronic hepatitis B patients in a routine clinical practice. J Clin Gastroenterol. 2016;50(2):169-74. https://doi.org/10.1097/MCG.0000000000000345
6. Brasil. Ministério da Saúde. Protocolo Clínico e Diretrizes Terapêuticas para Hepatite B e Coinfecções. Brasília, DF: Ministério da Saúde; 2016. [cited on May 2, 2020]. Available from http://www.aids.gov.br/pt-br/pub/2016/protocolo-clinico-e-diretrizes-terapeuticas-para-hepatite-b-e-coinfeccoes.
7. de Fraga RS, Van Vaisberg V, Mendes LCA, Carrilho FJ, Ono SK. Adverse events of nucleos(t)ide analogues for chronic hepatitis B: a systematic review. J Gastroenterol. 2020;55(5):496-514. https://doi.org/10.1007/s00535-020-01680-0
8. Abreu RM, da Silva Ferreira C, Ferreira AS, Remor E, Nasser PD, Carrilho FJ, et al. Assessment of adherence to prescribed therapy in patients with chronic hepatitis B. Infect Dis Ther. 2016;5(1):53-64. https://doi.org/10.1007/s40121-015-0101-y

9. Abreu RM, Bassit LC, Tao S, Jiang Y, Ferreira AS, Hori PC, et al. Long-term virological and adherence outcomes to antiviral treatment in a 4-year cohort chronic HBV study. Antivir Ther. 2019;24(8):567-79. https://doi.org/10.3851/IMP3338
10. Zheng S-Q, Yang L, Zhou P-X, Li H-B, Liu F, Zhao R-S. Recommendations and guidance for providing pharmaceutical care services during COVID-19 pandemic: a China perspective. Res Soc Adm Pharm. 2021;17(1):1819-24. https://doi.org/10.1016/j.sapharm.2020.03.012
11. Kretchy IA, Asiedu-Danso M, Kretchy JP. Medication management and adherence during the COVID-19 pandemic: perspectives and experiences from low-and middle-income countries. Res Soc Adm Pharm. 2020;17(1):2023-6 https://doi.org/10.1016/j.sapharm.2020.04.007
12. Cadogan CA, Hughes CM. On the frontline against COVID-19: community pharmacists' contribution during a public health crisis. Res Soc Adm Pharm. 2021;17(1):2032-5. https://doi.org/10.1016/j.sapharm.2020.03.015
13. Aquino EML, Silveira IH, Pescarini JM, Aquino R, Souza-Filho JA, Rocha AS, et al. Social distancing measures to control the COVID-19 pandemic: potential impacts and challenges in Brazil. Ciên Saúde Colet. 2020;25(suppl. 1):2423-46. https://doi.org/10.1590/1413-81232020256.1.10502020
14. Emmanuel Awucha N, Chinelo Janefrances O, Chima Meshach A, Chiamaka Henrietta J, Ibilolia Daniel A, Esther Chidiebere N. Impact of the COVID-19 pandemic on consumers' access to essential medicines in Nigeria. Am J Trop Med Hyg. 2020;103(4):1630-4. https://doi.org/10.4269/ajtmh.20-0838
15. Aghemo A, Masarone M, Montagnese S, Petta S, Ponziani FR, Russo FP. Assessing the impact of COVID-19 on the management of patients with liver diseases: a national survey by the Italian association for the study of the Liver. Dig Liver Dis. 2020;52(9):937-41. https://doi.org/10.1016/j.dld.2020.07.008
16. The Lancet Gastroenterology Hepatology. Eliminating viral hepatitis in the COVID-19 era: weighing challenge and opportunity. Lancet Gastroenterol Hepatol. 2020;5(9):789. https://doi.org/10.1016/S2468-1253(20)30237-5
17. Levorato CD, Mello LM de, Silva AS da, Nunes AA, Levorato CD, Mello LM de, et al. Fatores associados à procura por serviços de saúde numa perspectiva relacional de gênero. Ciên Saúde Colet. 2014;19(04):1263-74. https://doi.org/10.1590/1413-81232014194.01242013
18. Coroiu A, Moran C, Campbell T, Geller AC. Barriers and facilitators of adherence to social distancing recommendations during COVID-19 among a large international sample of adults. PLoS One. 2020;15(10):e0239795. https://doi.org/10.1371/journal.pone.0239795

ORIGINAL ARTICLE

https://doi.org/10.1590/1806-9282.20220113

Surgeon experience, robotic perioperative outcomes, and complications in gynecology

Bruna Bottura[1*], Beatriz Porto[2], Renato Moretti-Marques[2], Gustavo Barison[2], Eduardo Zlotnik[2], Sergio Podgaec[2], Mariano Tamura Vieira Gomes[2]

SUMMARY

OBJECTIVE: Robotic surgery is currently on the rise and has been widely applied all over the world. Gynecology offers great opportunities for the development of innovative techniques due to the magnitude of surgical needs. The aim of this study was to correlate perioperative complications, surgical time, and length of hospital stay with surgical diagnosis, procedure performed, and surgeon experience in robot-assisted gynecological surgeries in a 10-year period.

METHODS: This was a retrospective, transversal, cross-sectional study involving 632 patients who underwent robotic gynecological surgery from January 2008 to December 2017 in a community hospital in Sao Paulo, Brazil. Medical records of robot-assisted gynecological operations were searched for perioperative complications, operative time, and length of hospital stay, correlating these outcomes with surgical diagnosis, procedure performed, and surgeon experience, considering those with 20 or less robotic procedures and surgeons with more than 20 cases in their career as in-training or qualified surgeons, respectively.

RESULTS: Endometriosis (381 cases) was the most common surgical indication, followed by uterine myoma (171 patients). Qualified surgeons had 64% less complications than in-training surgeons (p=0.03) and achieved 20% lower surgical time and 15% shorter length of hospital stay.

CONCLUSION: In this study, qualified surgeons with more than 20 robotic procedures had better perioperative outcomes and less complications than in-training surgeons during their first 20 robotic surgeries.

KEYWORDS: Complications. Endometriosis. Fibroid tumor. Robotics. Surgeons.

INTRODUCTION

Robotic surgery is currently on the rise and has been widely applied all over the world[1]. At present, there are more than 50,000 certified surgeons and more than 6,730 robots distributed across 69 countries[2,3]. Gynecology offers many opportunities for the development of innovative techniques due to the magnitude of benign and malignant diagnoses with surgical needs[1,4]. To date, 84 hospitals in Brazil have the robotic daVinci system and these institutions, as well as medical associations and regulatory entities, have been searching and working for the safety in the use of this technology and its association with good results for the patient[3]. On this topic, we recently published an article on the importance of proctors in robotic gynecological procedures when surgeons are performing their first procedures, providing a learning curve without increasing risks to the patient[5]. But the literature is scarce, and there is no global credentialing rules to assure the best and safest outcomes to patients[1,4,6]. Barbash and Glied have recommended a minimum of 150–200 procedures for the surgeon to become skilled in the use of robotics, and Lenihan Jr described a shorter surgical time after 50 hysterectomies[7,8]. In contrast, Geller et al. showed consistent improvement in surgical time and robotic suture time after 20 procedures, including hysterectomies and sacrocolpopexies[4].

To seek for possible differences after some experience with the technology, we arbitrarily divided surgeons into two groups: those with more than 20 robotic procedures (qualified surgeons) and those with 20 or less procedures (in-training surgeons). Our goal was to correlate perioperative outcomes such as surgical time, complications, and length of hospital stay, with the surgical diagnosis, procedure performed, and surgeon experience.

METHODS

This was a cross-sectional, retrospective survey, including an analysis of 632 medical records from patients who underwent robotic gynecological surgeries from January 2008 to December 2017. All procedures were performed at the Hospital Israelita

[1]Hospital Israelita Albert Einstein, Medical Residency Program in Obstetrics and Gynecology – São Paulo (SP), Brazil.
[2]Hospital Israelita Albert Einstein, Department of Obstetrics and Gynecology – São Paulo (SP), Brazil.
*Corresponding author: brunabottura_26@hotmail.com
Conflicts of interest: the authors declare there is no conflicts of interest. Funding: none.
Received on June 02, 2022. Accepted on August 15, 2022.

Albert Einstein (HIAE), Brazil. Cases in which the main procedure was not gynecological were not considered in our analysis. This study was approved by the Institutional Research Ethics Committee (no. 38045414.7.0000.007).

We collected information on the number of surgeries per year, patient's age, body mass index (BMI), diagnoses, procedures performed, surgical time, length of hospital stay, and complications, such as intraoperative injuries, transfusions, and conversions. Comorbidities and previous surgeries were not evaluated.

Surgeries included in the study were composed of those for benign and malignant pathologies. Surgical time was determined as the time for the whole surgical act, including the docking and undocking of the robot, but not the time for the anesthetic induction. Perioperative complications were identified, evaluated one by one, and divided into three major groups: perioperative injuries, transfusions, and conversions. Perioperative injuries that need extra care or treatment for correction were considered. The prescription of blood cell transfusion was individualized on a case-by-case basis, based on patient's background, bleeding amount, and decision of the surgical team. Conversions of robot-assisted laparoscopy, when necessary, took place for conventional laparoscopy or open surgery.

All the participating gynecological surgeons were board certified by the National Obstetrics and Gynecology Association (FEBRASGO) and the first six robotic procedures of each surgeon were always leaded by a proctor, with recognized experience in robotic surgery, according to the local protocol. We analyzed the results of 32 surgeons who were divided into two groups as follows: qualified (>20 previous robotic surgeries) and in-training surgeons (≤20 previous robotic surgeries). With these criteria, 9 qualified surgeons were responsible for 475 surgeries in the period (75% of the total), while the remaining 157 surgeries were performed by 23 in-training surgeons (25% of the total). We first considered those surgeons qualified in robotics who had done at least 20 procedures before the study period, considering that when reaching the preestablished threshold (20 cases) during the time of the study, the new surgical data had been changed to the qualified group from the next case on. Therefore, the initial 20 records were counted as in-training and from case 21 onward as qualified group.

Sample size was defined as the total number of surgeries performed in an established period of time, i.e., 10 years. Comparisons among surgeon experience, length of hospital stay, and duration of the surgery were performed using linear mixed models applied to the log-transformed data. The results are presented as mean ratios and p-values.

We used mixed logistic regression models, accounting for the dependence between different surgeries performed by the same surgeon. Results were expressed as odds ratios with 95% confidence intervals. All analyses were performed considering the level of significance as 5% (p=0.05).

RESULTS

The analyzed sample consisted of 632 robot-assisted gynecological surgeries performed at HIAE from January 2008 to December 2017. In the study period, the number of surgeries consistently increased. The number of surgeries performed in 2017 was 50 times higher than that in 2008, which confirmed a significant growth in the adoption of this technology by the gynecological surgeons at the institution over the years.

Patients' age ranged from 19 to 84, with a mean of 39 years old, and an interquartile range (IQR) of 34–46 years. BMI ranged from 16 to 49, with a median of 23 kg/m^2. A total of 632 patients underwent robotic surgery, with 756 main diagnoses. In total, 1,929 procedures were performed, since several patients underwent two or more procedures at the same time. Of the 756 indications for surgery, we observed 381 cases of endometriosis, which corresponded to 50.4% of the total, being the most common diagnosis in our sample. The same predominance was observed in the frequency of procedures, with endometriosis treatment representing 19.7% of the total, as other procedures often compose those patients' surgeries.

Surgical time varied from 30 to 600 min, with a median of 205 min (IQR: 135–270 min), and the length of hospital stay ranged from <1 to 13 days, with a median of 2 days (IQR: 2–4 days). Patients who underwent surgery with qualified surgeons had a shorter surgical time (p<0.001) and shorter hospitalization (p=0.005), compared with patients operated on by in-training surgeons (Table 1).

In the present study, we aimed to measure the incidence of perioperative complications, such as perioperative injuries, transfusions, and conversions. In 632 patients, we had 20 complications, corresponding to 3.2% of the total, composed by 1.6% incidence of blood cell transfusions, 1.1% of perioperative injuries, and 0.5% of surgical conversion. We tested the correlation of adverse events with the most relevant clinical categories such as indication of surgery, type of procedure, and surgeon qualifying status.

In the set of cases, it should be noted that the 3 of 632 conversions were necessary either because of heavy bleeding that made it difficult to continue the procedure or due to technical limitations to handle big fibroids robotically. The need for transfusion could be associated with patient's previous hemoglobin level. Therefore,

we considered perioperative complication as only the cases where excess of bleeding in the procedure resulted in the need for blood transfusion (10 cases). It is also worth highlighting the perioperative injuries found in this 10-year period: one ureter injury, one intraperitoneal hematoma, one vaginal cuff dehiscence, one rectovaginal fistula, one abdominal bleeding, one hemorrhagic shock, and one post-spinal anesthesia headache (7/632).

Table 2 presents the analysis, in a multiple model, for these categories: qualified surgeon (yes vs. no), indication of surgery (endometriosis or myoma vs. other), procedure (hysterectomy vs. myomectomy vs. other), and endometriosis treatment (yes vs. no). We observed that qualified surgeons had 64% less adverse outcomes than in-training surgeons (p=0.038). Regarding the indication of surgery, no relation with perioperative complications was noted (p=0.654). When myomectomy was compared to hysterectomy, we found a 4.78 times higher probability of perioperative complications in patients who underwent myomectomy than in those who underwent hysterectomy (p=0.029). Regarding the endometriosis treatment, no difference was noted (p=0.480).

Considering perioperative complications, only blood cell transfusion had enough events to allow individualized statistical analysis. We used the simple mixed model and observed that in the qualified surgeons' procedures the percentage of blood transfusion was 79% lower (p=0.018), as can be seen in Table 3. Concerning the indication of surgery and procedures performed, no difference in the frequency of blood transfusion was noted in our set of cases.

DISCUSSION

Robotic surgery is a substantial breakthrough in the field of minimally invasive surgery, and this type of intervention has shown a large growth in the past decade[1,2,7]. There are more than 6,730 robots over 69 countries[2,3]. In the United States, there has been a 23% increase rate per year in the number of procedures using robotics[3]. In our hospital, in Sao Paulo / Brazil, this percentage growth was even higher in the past few years, with the number of robotic procedures increasing around 42% every year from 2008 to 2017.

Table 1. Surgical time and length of hospital stay *based on* surgeon experience.

Outcomes	Estimated mean (estimated standard error)		*MR (95%CI)	p-value
	In-training surgeons	Qualified surgeons		
Length of hospital stay, days	2.22 (1.09)	1.89 (1.10)	0.85 (0.77–0.95)	0.005
Surgical time, min	211.51 (1.08)	169.13 (1.09)	0.80 (0.73–0.88)	<0.001

*MR is the ratio between the mean surgical time and the length of hospitalization with qualified or in-training surgeons. The "in-training surgeons" is the reference category.

Table 2. Logistic regression analysis in a multiple model for adverse outcomes.

	Perioperative complications		Multiple model	p-value
	No	Yes	Odds ratio (95%CI)	
Qualified surgeon				
No	149	8	1.0	0.03
Yes	464	11	0.36 (0.13–0.94)	
Indication of surgery				
Other	156	4	1.0	0.654
Endometriosis or myoma	457	15	0.74 (0.20–2.77)	
Procedure				
Hysterectomy	211	4	1.0	
Myomectomy	128	10	4.78 (1.17–19.44)	0.029
Other	274	5	1.08 (0.26–5.10)	0.921
Endometriosis treatment				
No	246	6	1.0	0.480
Yes	367	13	1.56 (0.45–5.40)	

CI: confidence interval. Total of perioperative complications=20. Total of patients with perioperative complications=19 (one had both perioperative injury and need for transfusion).

Table 3. Simple mixed logistic regression models for blood transfusion.

	Blood transfusion		Odds ratio (95%CI)	p-value
	No	Yes		
Qualified surgeon				
No	151	6	1.0	0.018
Yes	471	4	0.21 (0.05–0.6)	
Surgical indication				
Other	157	3	1.0	0.732
Endometriosis or myoma	465	7	0.79 (0.20–3.08)	
Procedure				
Hysterectomy	212	3	1.0	
Myomectomy	133	5	2.66 (0.64–11.29)	0.186
Other	277	2	0.51 (0.07–3.08)	0.463
Endometriosis treatment				
No	248	4	1.0	0.993
Yes	374	6	0.99 (0.28–3.56)	

CI: confidence interval.

In this 10-year period, the most frequent diagnosis for surgery was endometriosis, representing 381 (50.4%) cases. Previous studies have shown benefits in the use of robotics for the endometriosis treatment, given its extension, depth, and complexity[1,9]. Advantages go beyond ergonomics, with more precise identification of lesions, as confirmed by Mosbrucker et al. showing a significantly higher rate of confirmed diagnosis in patients treated with robotic technology[9]. The robotic-assisted approach seems to better preserve ovarian function in patients with bilateral ovarian endometrioma when compared to traditional laparoscopy, based on AMH levels before and after ovarian cystectomy[10]. However, this growth in the adoption of the technology raises concerns regarding safety and surgical training[4,6,8].

There is no consensus on the minimum number of procedures to achieve good surgical performance[6,8]. Barbash and Glied, who evaluated robotic surgery in different specialties, concluded that 150–200 procedures were the requirements for a surgeon to become proficient[7]. Woelk et al. claimed that 91 cases are needed to reach feasibility in robotic hysterectomy, while Lenihan mentioned 50 as the number of procedures required to develop enough competence in the same procedure, according to suture and surgical time[8,11]. Geller et al. demonstrated improvements in surgical time for robotic hysterectomy after 20 cases, which is in accordance with the data presented on different procedures comparing surgeons with more than 20 robotic surgeries to those with 20 or less[4]. Qualified surgeons (>20 robotic surgeries) had a 20% decreasing in surgical time and 15% in length of hospital stay. Regarding the occurrence of unfavorable outcomes, these qualified surgeons had 64% less complications than in-training ones (≤20 robotic surgeries).

Comparison between robotic myomectomy and hysterectomy showed that patients who underwent myomectomy had risk of complications four times higher, therefore reflecting the complexity of myomectomy and enforcing the need of this procedure to be performed by a qualified surgeon with the most appropriate therapeutic tools. The number of perioperative complications was low, represented by 20 in total, making individual parameters difficult to be analyzed. No statistical significance was noted when comparing perioperative injuries and conversions due to the small number of occurrences, and a larger set of cases would be necessary to compare those numbers. Transfusion rate was the only adverse event with sufficient numbers to be separately analyzed and patients operated on by qualified surgeons had 79% less transfusions than those by in-training surgeons.

Taking into account patient safety priorities, although considering that our study has limitations of a retrospective descriptive noncontrolled trial, we present relevant data for establishing policies regarding the minimum number of procedures that a surgeon should perform under supervision of a proctor to assure low risks of perioperative complications to the gynecological patient. By adding suitable training to

safety protocols and development of technology, robotics can be a very useful tool in the operating room. It is worth to highlight that this article has limitations, as only one medical institution was evaluated. In addition, there was no standardization on surgical technique and extension of procedures when gynecological surgeries were compared. There was a wide range of surgical complexity as endometriosis treatment, myomectomy, and oncological procedures are usually more complicated than benign hysterectomies and adnexal procedures.

CONCLUSION

Qualified surgeons with more than 20 robotic surgeries may have better perioperative results and less complications than in-training surgeons during their 20 initial robotic procedures.

AUTHORS' CONTRIBUTIONS

BB: Conceptualization. **BP:** Methodology. **RMM:** Visualization. **GB:** Formal Analysis. **EZ:** Funding acquisition. **SP:** Resources. **MTVG:** Supervision.

REFERENCES

1. Rivas-López R, Sandoval-García-Travesí FA. Robotic surgery in gynecology: review of literature. Cir Cir. 2020;88(1):107-16. https://doi.org/0.24875/CIRU.18000636
2. Intuitive. 2021 [cited on May 07, 2022]. Available from: https://www.intuitive.com/en/about-us/company
3. Strattner. 2020 [cited on May 07, 2022]. Available from: http://www.strattner.com.br
4. Geller EJ, Lin FC, Matthews CA. Analysis of robotic performance times to improve operative efficiency. J Minim Invasive Gynecol. 2013;20(1):43-8. https://doi.org/10.1016/j.jmig.2012.08.774
5. Gomes MTV, Costa Porto BTD, Parise Filho JP, Vasconcelos AL, Bottura BF, Marques RM. Safety model for the introduction of robotic surgery in gynecology. Rev Bras Ginecol Obstet. 2018;40(7):397-402. https://doi.org/10.1055/s-0038-1655746
6. Heit M. Surgical proctoring for gynecologic surgery. Obstet Gynecol. 2014;123(2 Pt 1):349-52. https://doi.org/10.1097/AOG.0000000000000076
7. Barbash GI, Glied SA. New technology and health care costs – the case of robot-assisted surgery. N Engl J Med. 2010;363(8):701-4. https://doi.org/10.1056/NEJMp1006602
8. Lenihan JP Jr. How to set up a robotic-assisted laparoscopic surgery center and training of staff. Best Pract Res Clin Obstet Gynaecol. 2017;45:19-31. https://doi.org/10.1016/j.bpobgyn.2017.05.004
9. Mosbrucker C, Somani A, Dulemba J. Visualization of endometriosis: comparative study of 3-dimensional robotic and 2-dimensional laparoscopic endoscopes. J Robot Surg. 2018;12(1):59-66. https://doi.org/10.1007/s11701-017-0686-0
10. Lee HJ, Lee JS, Lee YS. Comparison of serum antimüllerian hormone levels after robotic-assisted vs. laparoscopic approach for ovarian cystectomy in endometrioma. Eur J Obstet Gynecol Reprod Biol. 2020;249:9-13. https://doi.org/10.1016/j.ejogrb.2020.04.010
11. Woelk JL, Casiano ER, Weaver AL, Gostout BS, Trabuco EC, Gebhart JB. The learning curve of robotic hysterectomy. Obstet Gynecol. 2013;121(1):87-95. https://doi.org/10.1097/aog.0b013e31827a029e

ORIGINAL ARTICLE

https://doi.org/10.1590/1806-9282.20220215

Evaluation of pulmonary nodules by magnetic resonance imaging sequences: which sequence will replace computed tomography?

Hüseyin Alper Kızıloğlu[1*], Adem Karaman[2], Okan Dilek[3], Kamber Kasali[4], Fatih Alper[2]

SUMMARY

OBJECTIVE: This study aimed to determine the role of magnetic resonance imaging in minimizing radiation exposure, especially in the follow-up of pulmonary nodules.

METHODS: Patients who applied to our hospital between April 2013 and August 2018 for various reasons and had lung-mediastinal dynamic magnetic resonance imaging and thoracic computed tomography were included in the study. A total of 194 patients were included in the study, involving 84 females and 110 males. Scanning of the nodules was done retrospectively. This study was conducted by two readers: a thoracic radiologist with 15 years of experience and a nonspecific radiologist with 4 years of experience. Evaluations were made using the double-blind method.

RESULTS: Of the 194 patients, 84 (43.3%) were female and 110 (56.7%) were male. For the first reader, 135 (69.5%) nodules were detected in postcontrast T1 vibe images, 130 (67%) in T2 fast spin echo, 128 (66%) in precontrast T1 vibe, and 98 (50.5%) in T2 turbo inversion recovery magnitude sequence. For the second reader, 133 (68%) nodules were detected in postcontrast T1 vibe images, 120 (61.9%) in T2 fast spin echo, 122 (62.9%) in precontrast T1 vibe, and 99 (51%) in T2 turbo inversion recovery magnitude sequence. Capability levels were examined in detecting nodules between the first and second readers, and the ratios were reached at 0.92 in T2 fast spin echo, 0.81 in postcontrast T1 vibe images, 0.93 in precontrast T1 vibe, and 0.96 in T2 turbo inversion recovery magnitude sequence.

CONCLUSION: In this study of detecting pulmonary nodules by magnetic resonance imaging, which we performed with two different readers, one of whom was an experienced thoracic radiologist, both readers found the highest detection rate in the postcontrast T1 vibe sequence.

KEYWORDS: Magnetic resonance imaging. Radiation exposure. Lung.

INTRODUCTION

A pulmonary nodule is less than 3 cm in diameter and is surrounded by lung parenchyma. They are focal single lesions with oval or round walls which are not accompanied by pathologies such as atelectasis, lymphadenopathy, or pneumonia[1,2]. Larger diameter nodular lesions, also called masses, do not fall into this definition, because most of the nodules larger than 3 cm are malignant[3,4].

There are many pathologies that can cause pulmonary nodules, the most common being granulomas, lung cancer, and hamartomas[5,6]. The radiological properties of nodules are as follows: its size, whether it contains calcification, in which part of the nodule calcification is located; the contour characteristics; the presence of satellite lesions; and, most importantly, whether the size and nature change are detected in the follow-up images. These features have made computed tomography (CT) the gold standard imaging method in detection and follow-up of lung nodules. Although ionizing radiation dose exposure has been reduced with the developing technology, it could not be reset. The detection, scanning, and follow-up of these nodules are performed by CT. These procedures cause cumulative radiation exposure to the patient and, in some cases, even the development of radiation-related malignancies. The use of magnetic resonance imaging (MRI) in the thorax is to primarily detect mediastinal and thoracic wall invasions of masses. Indications for the use of MRI in the thorax are increasing[5,6].

In this study, we aimed to determine the location of MRI, which is an imaging method that does not contain ionizing radiation, in order to reduce the exposure dose in the detection and follow-up of nodules. In this context, a retrospective study was conducted to determine the sensitivity of MRI in detecting nodules. In addition, our study aimed to show the detectability rather than the size difference between MRI and CT.

[1]Tokat Gaziosmanpaşa Üniversitesi, Faculty of Medicine, Department of Radiology – Tokat, Turkey.
[2]Atatürk University, Faculty of Medicine, Department of Radiology – Erzurum, Turkey.
[3]Adana City Hospital, Department of Radiology – Adana, Turkey.
[4]Atatürk University, Faculty of Medicine, Department of Statistic – Erzurum, Turkey.
*Corresponding author: alperkzloglu@hotmail.com
Conflicts of interest: the authors declare there is no conflicts of interest. Funding: none.
Received on July 27, 2022. Accepted on August 15, 2022.

METHODS

Ethical approval was obtained by the Ethics Committee of the Ataturk Faculty of Medicine Clinical Research with decision number 16, dated September 28, 2017.

Patient selection and evaluation

Patients who applied to our hospital between April 2013 and August 2018 for nodules examination or other reasons (e.g., invasion of the masses in the mediastinum and thoracic wall, mediastinal masses, metastasis, and rheumatoid nodules) and had lung-mediastinal dynamic MRI and thoracic CT were included in the study. In the evaluation of these patients, oval or round lesions smaller than 3 cm in diameter were considered. A total of 194 patients (84 females and 110 males) were included, with the mean age of 18 years. Patients with an examination time of 3 months or less between CT and MRI were included in the study. Scanning of the nodules was done retrospectively. Consent was not obtained from the patients participating in the clinical trial due to the review being done retrospectively. This study was conducted by two readers: a thoracic radiologist with 15 years of experience and a nonspecific radiologist with 4 years of experience. The readers evaluated the nodules by analyzing the MRI sequences, but not the CT images. Then, 1 month after the evaluation of MR images, both radiologists viewed the CT images.

Magnetic resonance imaging and computed tomography techniques

The evaluation of the patients was performed with 256-slice dual-energy CT (Somatom Flash, Siemens) and 3 Tesla (Skyra, Siemens) devices. CT images were obtained as nonenhanced HRCT (high-resolution computed tomography). All patients underwent HRCT and a 1-mm-thick section was taken for HRCT. Images for HRCT were taken with a bone algorithm. MR images with gadolinium with intravenous contrast, precontrast T1 volumetric interpolated breath-hold examination (vibe), three-dimensional (3D) gradient-echo (GRE), T2-weighted half-Fourier acquisition single-shot turbo spin-echo (HASTE), fast spin echo (FSE), T2 turbo inversion recovery magnitude (TIRM), and parenchymal phase contrast dynamic T1 vibe taken at 90 s were used as imaging sequences. For MRI, 0.5 and 1 mmol/mL solution preparations containing gadolinium were used as contrast. The MRI parameters are as follows: T1 vibe: TR/TE 3,1/1,1; slice thickness, 5 mm; slice gap value, 1 mm; matrix value, 256×256; and field of view (FOV), 350–400 mm for axial images. T2 HASTE: TR/TE 1,400/100; slice thickness, 5 mm; slice gap value, 1 mm; matrix value, 256×256; and FOV, 350–400 mm for axial images. T2 TIRM: TR/TE 3030/107; inversion time, 160 ms; slice thickness, 5 mm; slice gap value, 1 mm; matrix value, 256×256; and FOV, 350–400 mm for axial images.

Image evaluation

Solid density nodules were included in our study for CT. In addition, the nodules were evaluated according to their lung lobes, detection rates in size ranges, and contrast material factor for MRI. In measuring the nodule size, mean measurements of the longest and shortest diameter parallel to the long axis of the thorax were taken in the parenchyma window in axial sections on CT. On the MR images, precontrast T1 vibe, contrast-enhanced T1 vibe in the parenchyma phase, T2-weighted, T2 TIRM, and detectable nodules were also measured parallel to the long axis of the thorax.

Statistical analysis

The SPSS 23.0 package program was used for the statistical analysis of the data. Categorical measurements were summarized as numbers and percentages, and continuous measurements as mean, deviation, and minimum-maximum. The Pearson's chi-square test was used to compare categorical variables. The Cohen's kappa test was used to determine the level of compatibility between readers. Readers made independent evaluations of each other. ANOVA was applied to more than two variables by controlling the distributions in the comparison of continuous measurements between the groups. A statistical significance level was set at 0.05 in all tests.

RESULTS

Between April 2013 and August 2018, 194 patients who applied to our hospital for pulmonary nodule research or other reasons were included in this study. In the study, 84 (43.3%) patients were female and 110 (56.7%) were male. The age range of the patients was between 18 and 83 years. The mean age of the patients was 58.35±15.29 years. The average size of nodules detected on CT was 10.67±7.23. Considering CT as the gold standard modality for the detection of nodules (1–30 mm) in this study, for the first reader, 135 (69.5%) nodules were detected in postcontrast T1 vibe images, 130 (67%) in T2 FSE, 128 (66%) in precontrast T1 vibe, and 98 (50.5%) nodules in the T2 TIRM sequence. For the second reader, 133 (68%) nodules were detected in postcontrast T1 vibe images, 120 (61.9%) in T2 FSE, 122 (62.9%) in precontrast T1 vibe, and 99 (51%) nodules in the T2 TIRM sequence. For both readers, the highest percentage of detection of nodules was observed in the postcontrast T1 vibe images and the lowest detection percentage in the T2 TIRM sequence. Capability levels were

examined in detecting nodules between the first and second readers, and the ratios of 0.92 in T2 FSE, 0.81 in postcontrast T1 vibe images, 0.93 in precontrast T1 vibe, and 0.96 in T2 TIRM sequence were obtained. According to both radiologists, the compatibility between the postcontrast T1 vibe, T2 FSE, and T2 TIRM sequences was very good. In the precontrast T1 vibe sequence, a medium level of capability was noted.

The percentages of readers to detect nodules between sequences, kappa compliance levels between readers, and the sensitivity, specificity, positive predictive value (PPV), and negative predictive value (NPV) for the study sequences are shown in Table 1.

In the follow-up of 194 nodules, 168 (86.6%) remained stable; therefore, a noninvasive intervention was performed. An invasive procedure was applied to 26 (13.4%) nodules. Pathological results showed 17 (8.7%) nodules as benign and 9 (4.6%) in a malignant nature. Histopathological results confirmed 7 (3.6%) nodules as metastasis and 2 (1%) as primary lung adenocarcinoma.

CT and MR images of a 44-year-old female patient are shown in Figures 1 and 2, respectively.

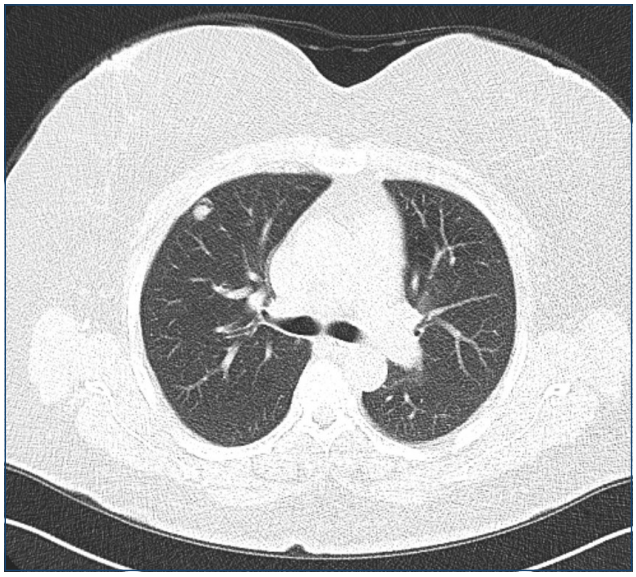

Figure 1. Thoracic computed tomography of a 44-year-old female patient. A solid density nodule is observed in the right lung upper lobe anterior segment.

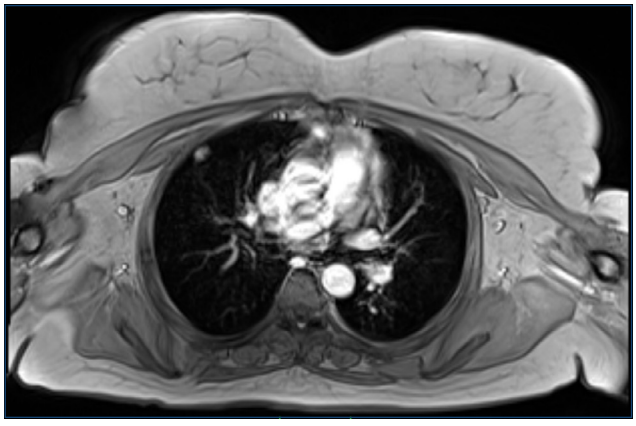

Figure 2. Magnetic resonance imaging of a 44-year-old female patient showing postcontrast T1 vibe sequence.

DISCUSSION

With increasing research on the use of MRI in the detection of pulmonary nodules, a greater understanding of the limitations and areas of use has increased[7]. In this study, we aimed to determine which MRI sequences are easier to detect nodules. The findings showed that the highest nodules were detected in the T1 vibe sequence, attributing this to the fact that most of the nodules are solid, thereby causing a significant contrast difference from the pulmonary parenchyma, and that T1 vibe images can show very good edge sharpness.

Table 1. Percentages of readers to detect nodules between sequences, kappa compliance levels between readers, and the sensitivity, specificity, positive predictive value, and negative predictive value for the study sequences.

		Group		Kappa	Sensitivity (95%CI)	Specificity (95%CI)	PPV (95%CI)	NPV (95%CI)
		Reader 1	Reader 2					
Postcontrast T1 vibe	Not seen	59 (30.4%)	61 (31.4%)	0.826	65.9% (58.8–72.6)	35.6% (30.8–40.6)	33.9% (31.1–36.7)	67.6% (62.3–72.6)
	Seen	135 (69.6%)	133 (68.6%)					
T2 FSE	Not seen	64 (33%)	74 (38.1%)	0.881	70.1% (63.1–76.5)	35.6% (30.8–40.6)	35.2% (32.6–38.0)	70.4% (64.9–75.4)
	Seen	130 (67%)	120 (61.9%)					
Precontrast T1 vibe	Not seen	66 (34%)	72 (37.1%)	0.525	71.7% (64.8–77.9)	30.9% (26.4–35.8)	34.2% (31.7–36.7)	68.6% (62.5–74.1)
	Seen	128 (66%)	122 (62.9%)					
T2 TIRM	Not seen	96 (49.5%)	95 (49%)	0.919	52.6% (45.3–59.8)	49.2% (44.1–54.3)	34.1% (30.5–37.9)	67.5% (63.4–71.3)
	Seen	98 (50.5%)	99 (51%)					

CI: confidence interval.

An MRI examination has been routinely used to detect mediastinal, chest wall, and vascular invasion of mass lesions due to its ability to provide high resolution for soft tissue. However, studies on diagnosis and follow-up of pulmonary nodules and lung parenchymal diseases are still ongoing. A multi-detector CT is considered the gold standard modality in diagnosis and follow-up. In addition, research on reducing radiation exposure is ongoing[8,9]. There are only a few indications that lung-mediastinal MRI replaces CT such as thoracic wall and mediastinal pathologies, vascular invasion, and its role in staging of oncological patients. Although CT provides optimal spatial resolution, it creates limited soft-tissue contrast. The use of MRI in the lung is limited by motion artifact (cardiac and respiratory origin), sensitivity artifact (due to multiple artifacts and interfaces), and low proton amount. However, it has advantages such as high resolution for soft tissue, the absence of ionizing beam, and not requiring a contrast agent in most examinations[10]. In this study, we first examined the detectability of the nodule, the degree of spatial and geometric resolution of MRI regardless of the size, and the differences and limits between sequences. We found the highest detection rate in the T1 vibe sequence for both readers, attributing this ratio to the higher spatial resolution of the T1 vibe sequence and hence the clearer edge sharpness. The vibe sequence is a 3D volumetric GRE sequence. This sequence produces T1-weighted 3D images using interpolation and/or partial Fourier techniques. Vibe sequences are a sequence that allows high-resolution imaging at a 30-s breath-hold time. Semelka et al stated that at a very high rate, nodules can be detected at a 3-mm threshold value in 3D GRE MRI sequences[11]. In our study, both readers detected the lowest rate of nodules in the T2 TIRM sequence, attributing this to the high rate of background noise in the lung tissue of the T2 TIRM sequence. TIRM sequences are inversion recovery sequences, regardless of longitudinal magnetization phase/polarity.

However, it may be an advantage to observe pronounced hyperintense in nodules with high fluid content in T2-weighted images. We noticed that the use of contrast agents in the T1 vibe sequence did not make a statistically significant difference in detecting nodules for both readers. In a study of oncological patients with lung nodules, the T2-weighted PROPELLER sequence showed no statistically significant difference in detecting nodules 10 mm or larger from HRCT[12].

The limitations of our study are the inability to optimize the image quality and artifacts secondary to retrospective scanning and to include patients with an optimal number of nodules for each subgroup. The longer duration of MRI examination compared to CT has caused an increase in arteries and difficulties in the study, especially in patients who have difficulties in respiratory control. Another limitation is the possibility of differences in the CT dimensions of the nodules due to the acquisition of images by CT and HRCT techniques.

CONCLUSION

In this study, which we conducted with two different readers, one of whom was an experienced thoracic radiologist, to detect pulmonary nodules by MRI, both readers detected the highest rate in the T1 vibe sequence and the lowest rate in the T2 TIRM sequence. In addition, the kappa compatibility levels were very good in the postcontrast T1 vibe and T2 FSE sequences.

AUTHORS' CONTRIBUTIONS

HAK: Conceptualization, Data curation, Writing – original draft, Writing – review & editing. **AK:** Supervision. **OD:** Conceptualization, Data curation. **KK:** Formal Analysis. **FA:** Supervision.

REFERENCES

1. Midthun DE, Swensen SJ, Jett JR. Approach to the solitary pulmonary nodule. Mayo Clin Proc. 1993;68(4):378-85. https://doi.org/10.1016/s0025-6196(12)60136-0
2. Winer-Muram HT. The solitary pulmonary nodule. Radiology. 2006;239(1):34-49. https://doi.org/10.1148/radiol.2391050343
3. Zerhouni EA, Stitik FP, Siegelman SS, Naidich DP, Sagel SS, Proto AV, et al. CT of the pulmonary nodule: a cooperative study. Radiology. 1986;160(2):319-27. https://doi.org/10.1148/radiology.160.2.3726107
4. Holin SM, Dwork RE, Glaser S, Rikli AE, Stocklen JB. Solitary pulmonary nodules found in a community-wide chest roentgenographic survey: a five-year follow-up study. Am Rev Tuberc. 1959;79(4):427-39. https://doi.org/10.1164/artpd.1959.79.4.427
5. Bateson EM. An analysis of 155 solitary lung lesions illustrating the differential diagnosis of mixed tumors of the lung. Clin Radiology. 1965;16(1):51-65. https://doi.org/10.1016/s0009-9260(65)80033-2
6. Murthy SC, Rice TW. The solitary pulmonary nodule: a primer on differential diagnosis. Semin Thorac Cardiovasc Surg. 2002;14(3):239-49. https://doi.org/10.1053/stcs.2002.34450
7. Kurihara Y, Matsuoka S, Yamashiro T, Fujikawa A, Matsushita S, Yagihashi K, et al. MRI of pulmonary nodules. AJR Am J Roentgenol. 2014;202(3):W210-6. https://doi.org/10.2214/AJR.13.11618
8. Wormanns D. Abklärung von Lungenrundherden: Management durch Früherkennungsuntersuchungen detektierter pulmonaler Rundherde [Diagnostic work-up of pulmonary nodules: management of pulmonary nodules detected with low-dose CT screening]. Radiologe. 2016;56(9):803-9. German. https://doi.org/10.1007/s00117-016-0150-6
9. Ohno Y, Koyama H, Seki S, Kishida Y, Yoshikawa T. Radiation dose reduction techniques for chest CT: principles and clinical results. Eur J Radiol. 2019;111:93-103. https://doi.org/10.1016/j.ejrad.2018.12.017
10. Vogt FM, Herborn CU, Hunold P, Lauenstein TC, Schröder T, Debatin JF, et al. HASTE MRI versus chest radiography in the detection of pulmonary nodules: comparison with MDCT. AJR Am J Roentgenol. 2004;183(1):71-8. https://doi.org/10.2214/ajr.183.1.1830071

11. Semelka RC, Cem Balci N, Wilber KP, Fisher LL, Brown MA, Gomez-Caminero A, et al. Breath-hold 3D gradient-echo MR imaging of the lung parenchyma: evaluation of reproducibility of image quality in normals and preliminary observations in patients with disease. J Magn Reson Imaging. 2000;11(2):195-200. https://doi.org/10.1002/(sici)1522-2586(200002)11:2<195::aid-jmri18>3.0.co;2-q

12. de Galiza Barbosa F, Geismar JH, Delso G, Messerli M, Huellner M, Stolzmann P, et al. Pulmonary nodule detection in oncological patients - Value of respiratory-triggered, periodically rotated overlapping parallel T2-weighted imaging evaluated with PET/CT-MR. Eur J Radiol. 2018;98:165-70. https://doi.org/10.1016/j.ejrad.2017.11.010

ORIGINAL ARTICLE

https://doi.org/10.1590/1806-9282.20220345

Violence against health personnel before and during the COVID-19 pandemic

Jorge Luiz Lozinski Musse[1,2*], Fernanda Cristina Coelho Musse[1,2], Sandra Marisa Pelloso[1,2], Maria Dalva de Barros Carvalho[1,2]

SUMMARY

OBJECTIVE: Violence in the workplace has been an alarming phenomenon around the world. The aim of this study was to analyze the frequency of violence against health personnel in urgent and emergency departments, before and during the COVID-19 pandemic.

METHODS: This is an exploratory cross-sectional study including a structured online survey with the approval of the Research Ethics Committee. The sample was composed of health personnel over 18 years old who work in urgent and emergency departments. The survey was structured with sections: sociodemographic data, detailing of occupational data, and a survey of physical, verbal, sexual, and racial violence. Descriptive statistics included absolute frequencies and percentages for categorical variables and means with standard deviation for continuous variables.

RESULTS: A total of 114 participants, aged between 20 and 60 years, answered the questionnaire; 68.4% of them were women. Most of them were white (71.9%), married or living with a partner (70.2%), residing in the south or southeast regions (85.1%) of Brazil, 56.1% doctors, 11.4% nurses, and 12.3% nursing technicians. The incidence of violence before the COVID-19 pandemic was 60%. During the pandemic, the incidence suffered low variation, being 57.9%. Only 37.7% said that their workplace offers some procedure/routine to report acts of violence suffered at work. Verbal violence was the most reported among the participants. Anxiety, tiredness, fear, low self-esteem, loss of concentration, and stress are the most frequent consequences of aggression.

CONCLUSION: Our results suggest that the COVID-19 pandemic did not potentiate the episodes of violence; however, episodes of violence continue to occur, and so management and prevention measures must be implemented.

KEYWORDS: Aggression. COVID-19. Emergency service, hospital. Health personnel.

INTRODUCTION

Violence in the workplace has been an alarming phenomenon around the world, with health personnel working in urgent and emergency departments at greater risk of suffering aggression[1,2,3,4]. Emergency department health personnel are frequent victims of violence perpetrated by visitors and patients, resulting in injuries, acute stress, and loss of productivity[3]. Violence against health personnel is a complex problem, and rigorous research is lacking to address this issue[5,6,7,8].

In 2020 and 2021, with the explosion of the COVID-19 pandemic—in which a new virus with high morbidity and mortality and still untreated profoundly modified human relationships—health personnel figured as heroes amid the initial health demands[9]. On the contrary, as months passed and less was known about COVID-19 treatments, the appreciation for the efforts and contributions of doctors, nurses, and other health personnel began to aggravate the population's distrust of these professionals, with the emergence of reports of increased violence against them[10,11,12].

According to the World Health Organization (WHO), approximately 8–38% of health personnel experienced physical violence prior to the COVID-19 pandemic, with a much higher number of reports of verbal abuse or various threats[7]. There is a lack of data in scientific research on the incidence and characteristics of injuries suffered within this complex occupational problem before and currently during the beginning of the pandemic.

The objective of this study was to analyze the frequency of violence against health personnel in urgent and emergency departments in Brazil, before and during the COVID-19 pandemic, in order to be an instrument for health management systems that work in the planning of care for health personnel.

METHODS

This study was registered on Plataforma Brasil under the number 40969320.0.0000.0104 and approved by the Ethics and

[1]Universidade Estadual de Maringá, Faculty of Medicine, Health Sciences Program – Maringá (PR), Brazil.
[2]Centro Universitário Ingá, Faculty of Medicine – Maringá (PR), Brazil.
*Corresponding author: jorgemusse@gmail.com
Conflicts of interest: the authors declare there is no conflicts of interest. Funding: none.
Received on March 04, 2022. Accepted on July 31, 2022.

Research Committee of the State University of Maringá—Paraná—Brazil, number 4.473.891 on December 18, 2020.

Participants and procedures

The sample was composed of participants over 18 years old who work in urgent and emergency departments. Participants were invited to respond to an online survey entitled "Survey with health personnel." The access link to the structured questionnaire, along with the free and informed consent form, was released on social media between February and May 2021. Initially, the access link to the survey was launched for groups of family members, students, members of churches, multidisciplinary health groups, teachers, a group of daycare parents, and several other groups that replicated the link through Facebook and other social networks. The survey included questions subdivided into seven sections. Participation was voluntary and anonymous, through an online Google Form. Individuals were able to actively participate and invite other participants, either by individual or collective calls (broadcast groups).

Study design and instruments

This is an exploratory cross-sectional study including a structured survey developed by the researchers.

The survey was structured with the following sections: (1) adherence to the survey, (2) selection of participants with occupation in urgent and emergency departments, (3) sociodemographic data, (4) detailing of occupational data, (5) workplace physical violence, (4) workplace verbal violence, (6) workplace sexual violence, and (7) workplace racial violence.

Participants were asked about episodes of violence at work before the COVID-19 pandemic and whether there were changes in the frequency and types of violence suffered after the start of the pandemic. In case of violence, details of the episode were requested, such as the use of weapons or other instruments in the violent act, whether the event was common in the workplace, who would have attacked them (patient, companion, co-worker, superiors/management, and others), the sex of the aggressor, the time close to the event and the day of the week it happened, and the consequences of the aggression suffered.

Statistical analysis

Descriptive statistics included absolute frequencies and percentages for categorical variables and means with standard deviation for continuous variables. To compare proportions and test associations between groups, the chi-square test was used. Analyses were performed with IBM SPSS Statistics, version 26[13].

RESULTS

Sample characteristics

A total of 144 Brazilian participants answered the questionnaire, considering 114 participants in the studied sample who had occupational positions in urgent and emergency departments. Most of them were between 30 and 39 years old, and 68.4% were women. Most of them were white (71.9%), married or living with a partner (70.2%), residing in the south or southeast regions (85.1%) of Brazil, and declared themselves as Christians (71%). Just over 70% receive more than five salaries; 64% have postgraduate/residence education, with less than 2% having only elementary education. Doctors totaled 56.1% of respondents, 11.4% nurses, and 12.3% nursing technicians. One-third have between 1 and 5 years of experience in urgent and emergency services, and 28.9% have between 6 and 10 years of experience. Workers in public hospitals totaled 45.6%, 36.8% work in the public and private sectors, and only 16.7% work only in the private sector; 39.5% work between 21 and 40 h/week, 23.7% work up to 20 h/week; and 48.2% work in the day and night shifts, which account for 28.1% of respondents (Tables 1 and 2).

Procedure/routine for reporting acts of violence

Only 43 (37.7%) said that their workplace offers some procedure/routine to report acts of violence suffered at work. Of these, only 25 (58.1%) know how to use the procedure/routine in episodes of violence. Of those interviewed, 68.4% said there was no encouragement to report violence in the workplace, and of the 36 who reported some encouragement, only 15 (41.7%) indicated their manager as encouraging.

Episodes of violence before and during the COVID-19 pandemic

The incidence of violence against health personnel in urgent and emergency departments evaluated before the COVID-19 pandemic was around 60%. During the pandemic, the incidence suffered less variation, being 57.9% in the analyzed data. This ratio changed slightly before and during the pandemic, and to see if this change was significant, we ran a two-ratio comparison test. A test for comparing two proportions was generated (Z=0.2691, p=0.7879), indicating that the proportion of violence against professionals before the pandemic is the same as the proportion of violence during the COVID-19 pandemic.

Before the pandemic, 68 participants remember having suffered some types of violence; during the pandemic, this number drops to 66 participants. Note that the types of violence

remain close, with verbal violence being the most reported among the participants, occurring either alone or in combination with other types of aggression. The report of sexual, physical, or racial violence was infrequent. Anxiety, tiredness, fear, low self-esteem, loss of concentration, and stress are the most frequent consequences of aggression both before and during the COVID-19 pandemic. The time and gender characteristics of the aggressor are listed in Table 3.

DISCUSSION

This is one of the first studies to analyze episodes of violence against health personnel from urgent and emergency departments before and during the COVID-19 pandemic in a Brazilian sample. The main results found were maintenance of the frequency of violence against health personnel in urgent and emergency departments before and during the pandemic, however, with high numbers of aggressions suffered, especially

Table 1. Types of violence against health personnel before the COVID-19 pandemic by sociodemographic data.

	Episode of violence N (%)		Verbal violence N (%)	Physical violence N (%)	Sexual violence N (%)	Racial violence N (%)
	Yes	No				
Gender (N=113)[a]						
Women	49 (62.8)	29 (37.2)	43 (55.1)	0 (0.0)	2 (2.6)	2 (2.6)
Men	18 (51.4)	17 (48.6)	13 (37.1)	1 (2.9)	0 (0.0)	0 (0.0)
Age (N=113)[a]						
20–29	8 (53.3)	7 (46.7)	6 (40.0)	0 (2.0)	1 (6.7)	1 (6.7)
30–39	36 (70.6)	15 (29.4)	30 (58.8)	1 (0.0)	0 (0.0)	1 (2.0)
40–49	14 (60.9)	9 (39.1)	11 (47.8)	0 (0.0)	0 (0.0)	0 (0.0)
50–59	6 (37.5)	10 (62.5)	6 (37.5)	0 (0.0)	1 (6.3)	0 (0.0)
60 or above	3 (37.5)	5 (62.5)	3 (37.5)	0 (0.0)	0 (0.0)	0 (0.0)
Ethnicity (N=113)[a]						
White	51 (62.2)	31 (37.8)	45 (54.9)	0 (0.0)	1 (1.2)	1 (1.2)
Brown	15 (55.6)	12 (44.4)	10 (37.0)	1 (3.7)	0 (0.0)	1 (3.7)
Other	1 (33.3)	2 (66.7)	1 (33.3)	0 (0.0)	1 (33.3)	0 (0.0)
Marital status (N=114)						
Single	13 (54.2)	11 (45.8)	12 (50.0)	0 (0.0)	1 (4.2)	0 (0.0)
Married	37 (56.9)	28 (43.1)	33 (50.8)	0 (0.0)	1 (1.5)	1 (1.5)
Living together	12 (80.0)	3 (20.0)	7 (46.7)	0 (0.0)	0 (0.0)	1 (6.7)
Other	5 (55.6)	4 (44.4)	4 (44.4)	1 (11.1)	0 (0.0)	0 (0.0)
Region of Brazil (N=114)						
South	40 (63.5)	23 (36.5)	35 (55.6)	0 (0.0)	1 (1.6)	2 (3.2)
Southeast	21 (61.8)	13 (38.2)	16 (47.1)	1 (2.9)	1 (2.9)	0 (0.0)
Midwest	2 (33.3)	4 (66.7)	1 (16.7)	0 (0.0)	0 (0.0)	0 (0.0)
North	0 (0.0)	2 (100.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)
Northeast	4 (50.0)	4 (50.0)	4 (50.0)	0 (0.0)	0 (0.0)	0 (0.0)
Religion (N=114)						
No religion	9 (56.3)	7 (43.7)	5 (37.3)	0 (0.0)	0 (0.0)	1 (6.3)
Catholic	40 (61.5)	25 (38.5)	35 (53.8)	1 (1.5)	2 (3.1)	1 (1.5)
Evangelical	9 (56.3)	7 (43.7)	8 (50.0)	0 (I0.0)	0 (0.0)	0 (0.0)
Kardecism	8 (57.1)	6 (42.9)	8 (57.1)	0 (0.0)	0 (0.0)	0 (0.0)
Afro-Brazilian traditions	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)
Other	1 (50.0)	1 (50.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)

One participant did not respond about gender, age, and ethnicity.

verbal aggression, and the fact that a minority of workplaces were cited as offering some procedure/routine to report acts of violence suffered at work.

At the start of the COVID-19 pandemic, healthcare workers figured as heroes amid initial healthcare demands[9]. On the contrary, as months passed and less was known about COVID-19 treatments, the appreciation for the efforts and contributions of doctors, nurses, and other health personnel began to aggravate the population's distrust of these professionals, with the emergence of reports of increased violence against them[10,11,12]. Devi et al.[12] reinforced an exacerbation of violence with the COVID-19 pandemic, reporting a case in Bangladesh where bricks were thrown at a doctor's home after he tested positive for COVID-19 and that a team of health care workers was verbally and physically attacked after a patient died from COVID-19[12].

Table 2. Types of violence against health personnel during the COVID-19 pandemic by sociodemographic data.

	Episode of violence N (%)		Verbal violence N (%)	Physical violence N (%)	Sexual violence N (%)	Racial violence N (%)
	Yes	No				
Gender (N=113)						
Women	48 (61.5)	30 (38.5)	47 (60.2)	6 (7.7)	5 (6.4)	4 (5.1)
Men	17 (48.6)	18 (51.4)	17 (48.6)	4 (11.4)	0 (0.0)	0 (0.0)
Age (N=113)						
20–29	10 (66.7)	5 (33.3)	10 (66.7)	2 (13.3)	2 (13.3)	1 (6.7)
30–39	34 (66.7)	17 (33.3)	33 (64.7)	4 (7.8)	3 (5.9)	1 (2.0)
40–49	12 (52.1)	11 (47.9)	12 (52.2)	4 (17.4)	0 (0.0)	1 (4.4)
50–59	6 (37.5)	10 (62.5)	6 (37.5)	0 (0.0)	0 (0.0)	1 (6.3)
60 or above	3 (37.5)	5 (62.5)	3 (37.5)	0 (0.0)	0 (0.0)	0 (0.0)
Ethnicity (N=113)						
White	48 (58.5)	34 (41.5)	48 (58.5)	7 (8.5)	3 (3.7)	1 (1.2)
Brown	17 (63.0)	10 (37.0)	16 (59.3)	3 (11.1)	2 (7.4)	3 (11.1)
Other	0 (0.0)	4 (100.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)
Marital status (N=113)						
Single	15 (62.5)	9 (37.5)	15 (62.5)	2 (8.3)	2 (8.3)	0 (0.0)
Married	35 (53.9)	30 (46.1)	35 (53.9)	5 (7.7)	2 (3.1)	1 (1.5)
Living together	11 (73.3)	4 (26.7)	11 (73.3)	3 (20.0)	0 (0.0)	1 (6.7)
Other	4 (44.4)	5 (55.6)	3 (33.3)	0 (0.0)	1 (11.1)	2 (22.2)
Region of Brazil (N=113)						
South	36 (57.1)	27 (42.9)	35 (55.6)	7 (11.1)	3 (4.8)	3 (4.8)
Southeast	18 (52.9)	16 (47.1)	18 (52.9)	3 (8.8)	1 (2.9)	1 (2.9)
Midwest	5 (83.3)	1 (16.7)	5 (83.3)	0 (0.0)	1 (16.7)	0 (0.0)
North	2 (100.0)	0 (0.0)	2 (100.0)	0 (0.0)	0 (0.0)	0 (0.0)
Northeast	4 (50.0)	4 (50.0)	4 (50.0)	0 (0.0)	0 (0.0)	0 (0.0)
Religion (N=113)						
No religion	10 (62.5)	6 (37.5)	9 (56.3)	1 (6.3)	1 (6.3)	2 (12.5)
Catholic	37 (56.9)	28 (43.1)	37 (56.9)	6 (9.5)	3 (4.6)	1 (1.5)
Evangelical	7 (43.8)	9 (56.20	7 (43.8)	2 (12.5)	1 (6.3)	0 (0.0)
Kardecism	11 (78.6)	3 (21.4)	11 (78.6)	1 (7.1)	0 (0.0)	1 (7.1)
Afro-Brazilian traditions	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)
Other	0 (0.0)	2 (100.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)

One participant did not respond about data during the pandemic.

Table 3. Characteristics of episodes of violence during the COVID-19 pandemic.

Characteristics of episodes of violence	Absolute number of occurrences
Aggressor's sex	
Even if the victim	49
Opposite sex of victim	50
Time of day	
Morning	34
Afternoon	35
Night	31
Dawn	12
Day of the week	
Monday to Friday	35
Weekend (Saturday and Sunday)	9
Do not remember	34

These studies have led to increased research on the situation of violence against health personnel during the pandemic. In our research, the frequency of violence before and during the pandemic in urgent and emergency departments against health personnel did not change.

In 2019, in a systematic review and meta-analysis, with 253 prepandemic studies of COVID-19, that sought to evidence the prevalence rates of violence provoked by patients and visitors against health personnel, the authors found 61.9% of exposure reports to any form of violence[4]. The frequency of violence before and after the pandemic was very close in our study. We also found the highest number of reports among doctors and nurses with reports of aggression among professionals in urgent and emergency departments[4].

A prepandemic study with health personnel in Turkey, using the online Health Sector Workplace Violence Case Study Questionnaire, with a sample of 447 participants including doctors, nurses, and emergency technicians, found that 36.7% of participants reported exposure to physical violence and 88.8% reported exposure to verbal abuse, at least once during their working life[2]. Our data suggested high percentages but lower than those observed in Turkey, even before the pandemic. On the other hand, in this study, the authors also found that the performance of management with support for employees made them safer in their workplaces, contrary to our Brazilian study, in which participants did not feel stimulated by management, which could be a fact of the perpetuation of violence in our midst[2].

Palma et al.[14] in a systematic review on occupational violence in the health area, pre-COVID-19 pandemic, with 23 articles in the analysis, concluded that the facilitators of violence against health personnel are related to the nature of work, and the consequences most commonly studied are related to the mental health of health personnel[14]. The report of sexual, physical, or racial violence was infrequent in our study, and, in fact, anxiety, tiredness, fear, low self-esteem, loss of concentration, and stress appeared more frequently as consequences of aggression for both before and during the pandemic.

The limitations of this study refer to selection bias. We describe a nonprobabilistic sample that included mainly women who responded to an online survey. It is possible that men are underrepresented. The other potential limitation is memory bias, where participants need to recall past and present episodes of violence.

CONCLUSION

Our results suggest that the COVID-19 pandemic did not potentiate the episodes of violence suffered by health personnel in urgent and emergency departments; however, episodes of violence continue to occur, and so prevention measures must be implemented.

ETHICAL ASPECTS

We certify that this manuscript represents an original study and that neither it, in part or in full, nor any other study with substantially similar content has been published or is being considered for publication in another journal, whether in print or in online electronic format.

This study was registered on Plataforma Brasil under the number 40969320.0.0000.0104 and approved by the Ethics and Research Committee of the State University of Maringá—Paraná—Brazil, number 4.473.891 on December 18, 2020.

AUTHORS' CONTRIBUTIONS

JLLM: Conceptualization, Data curation, Formal Analysis, Resources, Writing – original draft, Writing – review & editing. **FCCM:** Conceptualization, Data curation, Formal Analysis, Resources, Writing – original draft, Writing – review & editing. **SMP:** Conceptualization, Data curation, Formal Analysis, Resources, Writing – original draft, Writing – review & editing. **MDBC:** Conceptualization, Data curation, Formal Analysis, Resources, Writing – original draft, Writing – review & editing.

REFERENCES

1. D'Ettorre G, Pellicani V, Mazzotta M, Vullo A. Preventing and managing workplace violence against healthcare workers in Emergency Departments. Acta Biomed. 2018;89(4-S), 28-36. https://doi.org/10.23750/abm.v89i4-S.7113
2. Hamzaoglu N, Türk B. Prevalence of physical and verbal violence against health care workers in Turkey. Int J Health Serv. 2019;49(4):844-61. https://doi.org/10.1177/0020731419859828
3. Kowalenko T, Gates D, Gillespie GL, Succop P, Mentzel TK. Prospective study of violence against ED workers. Am J Emerg Med. 2013;31(1):197-205. https://doi.org/10.1016/j.ajem.2012.07.010
4. Liu J, Gan Y, Jiang H, Li L, Dwyer R, Lu K, et al. Prevalence of workplace violence against healthcare workers: a systematic review and meta-analysis. Occup Environ Med. 2019;76(12):927-37. https://doi.org/10.1136/oemed-2019-105849
5. Rodríguez-Bolaños R, Cartujano-Barrera F, Cartujano B, Flores YN, Cupertino AP, Gallegos-Carrillo K. The urgent need to address violence against health workers during the COVID-19 pandemic. Med Care. 2020;58(7):663. https://doi.org/10.1097/MLR.0000000000001365
6. Phillips JP. Workplace violence against health care workers in the United States. N Engl J Med. 2016;374(17):1661-9. https://doi.org/10.1056/NEJMra1501998
7. Singh M. Intolerance and violence against doctors. Indian J Pediatr. 2017;84(10):768-73. https://doi.org/10.1007/s12098-017-2435-9
8. Heckemann B, Zeller A, Hahn S, Dassen T, Schols JM, Halfens RJ. The effect of aggression management training programmes for nursing staff and students working in an acute hospital setting. A narrative review of current literature. Nurse Educ Today. 2015;35(1):212-9. https://doi.org/10.1016/j.nedt.2014.08.003
9. McKay D, Heisler M, Mishori R, Catton H, Kloiber O. Attacks against health-care personnel must stop, especially as the world fights COVID-19. Lancet. 2020;395(10239):1743-5. https://doi.org/10.1016/S0140-6736(20)31191-0
10. Gan Y, Chen Y, Wang C, Latkin C, Hall BJ. The fight against COVID-19 and the restoration of trust in Chinese medical professionals. Asian J Psychiatr. 2020;51:102072. https://doi.org/10.1016/j.ajp.2020.102072
11. Mello MM, Greene JA, Sharfstein JM. Attacks on Public Health Officials During COVID-19. JAMA. 2020;324(8):741-2. https://doi.org/10.1001/jama.2020.14423
12. Devi S. COVID-19 exacerbates violence against health workers. Lancet. 2020;396(10252):658. https://doi.org/10.1016/S0140-6736(20)31858-4
13. IBM Corp. Released 2017. IBM SPSS Statistics for Windows, Version 25.0. Armonk, NY: IBM Corp.
14. Palma A, Ansoleaga E, Ahumada M. Violencia laboral en trabajadores del sector salud: revisión sistemática [Workplace violence among health care workers]. Revista medica de Chile. 2028;146(2):213-2. https://doi.org/10.4067/s0034-98872018000200213

ORIGINAL ARTICLE

https://doi.org/10.1590/1806-9282.20220360

Capoeira: hypothesis on health rehabilitation and quality-of-life maintenance

Sérgio R. Moreira[1,2,3,4*], Ariel Custódio de Oliveira II[1,2], Anderson Armstrong[4,5,6]

SUMMARY

OBJECTIVE: The aim of this work was to present hypotheses supporting capoeira as an activity aimed at health rehabilitation and maintenance of quality of life.

METHODS: Capoeira players (n=245), residing in Brazil and abroad, were evaluated for quality of life (physical, social, psychological, and environmental domains from WHOQOL-bref). The capoeira players' quality of life scores were compared to normative values and reference values in martial arts. Besides, studies involving capoeira (Medline/Embase/Cinahl/SportDiscus) were also reviewed for health-related hypotheses, describing population, intervention, comparator, and outcome.

RESULTS: There are hypotheses on capoeira improving health through (1) body composition, addressed by two studies investigating waist circumference, bone, and muscle mass; (2) functional capacity, investigated by three studies considering performance variables; (3) metabolism, in two studies demonstrating triglycerides and blood glucose reduction, and an enhancement of anaerobic glycolysis; and (4) cardiovascular parameters, addressed by two studies highlighting an increase in maximal oxygen consumption, heart rate, and rate of pressure product reduction, as well as an increase in parasympathetic activity at rest. The sample of this study had higher quality of life scores when compared to normative values for Brazilians, similar quality of life when it comes to social relationships, higher quality of life in the psychological and environmental domains, and lower quality of life in the physical domain when compared to practitioners of other combat sports/martial arts.

CONCLUSION: An analysis of the impacts of capoeira resulted in hypotheses on the rehabilitation of players' biological health. Although the individuals were evaluated within the pandemic period, their quality of life domains were similar or superior to normative or reference values found by studies from before the pandemic.

KEYWORDS: Martial arts. Health. Quality of life.

INTRODUCTION

Capoeira, which is an athletic performance system consisting of attack and defense[1], is, perhaps, the most original manifestation of body culture in Brazil. Due to its motor demands, capoeira is a complex sport that requires coordination and body expression, and it is supposed to involve capacities in its practice such as strength, resistance, flexibility, power, and agility[2].

Given the widely acknowledged relationship between well-being and physical performance[3], players need to be fully aware of their health condition and quality of life (QoL)[4]. The perception of a better QoL has been associated with performance in physical activities[5]. Furthermore, aging has its impacts on physical performance, which could negatively affect individuals' health and QoL, especially in conditions of physical inactivity[6]. In contrast, studies involving experienced capoeira players have shown that both men[7] and women[8] have reduced performance declines with age. Such results suggest that the pattern of reduction in capoeira players' performance with aging, associated with other benefits from the practice of capoeira[9-11], may be related to health variables and the practitioners' QoL.

Studies evaluating QoL in capoeira players and associating it with a strategic practice focused on health are still necessary, aiming at contributing to technical, scientific, and cultural perspectives related to helping in the control and treatment of diseases based on the Brazilian fighting art capoeira. Thus, the objective of this work was to present hypotheses supporting capoeira as an activity aimed at human health rehabilitation and maintenance of QoL. Therefore, applied studies involving

[1]Universidade Federal do Vale do São Francisco, Postgraduate Program in Physical Education – Petrolina (PE), Brazil.
[2]Universidade Federal do Vale do São Francisco, Tutorial Education Program in Physical Education – Petrolina (PE), Brazil.
[3]Associação Brasileira de Apoio e Desenvolvimento da Arte-Capoeira – Rio de Janeiro (RJ), Brazil.
[4]Universidade Federal do Vale do São Francisco, Postgraduate Program in Health and Biological Sciences – Petrolina (PE), Brazil.
[5]Universidade Federal do Vale do São Francisco, College of Medicine – Petrolina (PE), Brazil.
[6]Universidade do Estado da Bahia, Graduate Program in Human Ecology – Salvador (BA), Brazil.
*Corresponding author: sergio.moreira@univasf.edu.br
Conflicts of interest: the authors declare there is no conflicts of interest. Funding: none.
Received on July 22, 2022. Accepted on August 15, 2022.

capoeira players were analyzed in the generation of health-oriented hypotheses. The work also investigated the QoL profile of capoeira players in comparison to the normative values of Brazilians and practitioners of other combat sports/martial arts.

METHODS

Study design and ethical aspects

A cross-sectional study of the QoL domains of capoeira players was carried out, and evidence was reviewed for hypotheses supporting capoeira in human health. The recruitment of volunteers took place between January 22, 2021, and February 21, 2021 (pandemic period). Data collection was carried out remotely, with questionnaires made available on the Google Forms platform. Links were sent through email using a contact list from the Associação Brasileira de Apoio e Desenvolvimento da Arte Capoeira. The research was approved by the Research Ethics and Deontology Committee of the Universidade Federal do Vale do São Francisco (UNIVASF) under protocol number: 3.576.805 (CAAE: 18145719.5.0000.5196) and is in accordance with Normative Act no. 466/12 of the National Health Council.

Participants

Capoeira players of both sexes living in Brazil and abroad participated in the study (Table 1). Sample calculation was performed

Table 1. Characterization of capoeira practitioners as a function of graduation technical level (n=245). Data collected during the COVID-19 pandemic.

	General	Technical level				
		Graduate I (n=96)	Graduate II (n=61)	Instructor (n=54)	Professor (n=26)	Master (n=08)
	f (%)	f (%)	f (%)	f (%)	f (%)	f (%)
Sex						
Male	192 (78.4)	70 (72.9)	53 (86.9)	40 (74.1)	23 (88.5)	6 (72.0)
Female	53 (21.6)	26 (27.1)	8 (13.1)	14 (25.9)	3 (11.5)	2 (25.0)
Capoeira training						
Weekly frequency						
<2 times	11 (4.5)	6 (6.3)	2 (3.3)	2 (3.7)	1 (3.8)	0 (0.0)
2 times	59 (24.1)	28 (29.2)	13 (21.3)	13 (24.1)	4 (15.4)	1 (12.5)
3 times	100 (40.8)	39 (40.6)	25 (41.0)	22 (40.7)	11 (42.3)	3 (37.5)
4 times	42 (17.1)	12 (12.5)	16 (26.2)	5 (9.3)	6 (23.1)	3 (37.5)
≥5 times	33 (13.5)	11 (11.5)	5 (8.2)	12 (22.2)	4 (15.4)	1 (12.5)
Classes duration						
30–45 min	8 (3.3)	4 (4.2)	1 (1.6)	1 (1.9)	1 (3.8)	1 (12.5)
46–60 min	56 (22.9)	27 (28.1)	14 (23.0)	10 (18.5)	3 (11.5)	2 (25.0)
61–90 min	122 (49.8)	43 (44.8)	32 (52.5)	29 (53.7)	14 (53.8)	4 (50.0)
>90 min	59 (24.1)	22 (22.9)	14 (23.0)	14 (25.9)	8 (30.8)	1 (12.5)
Classes intensity						
Light	4 (1.6)	1 (1.1)	1 (1.6)	2 (3.7)	0 (0.0)	0 (0.0)
Moderate	153 (62.4)	68 (70.8)	36 (59.0)	24 (44.4)	17 (65.4)	8 (100.0)
Vigorous	88 (35.9)	27 (28.1)	24 (39.3)	28 (51.9)	9 (34.6)	0 (0.0)
	Mean±SD (95%CI)	Mean±SD (95%CI)	Mean±SD (95%CI)	Mean±SD (95%CI)	Mean±SD (95%CI)	Mean±SD (95%CI)
Age (years)	38.4±9.6 (37.2; 39.6)	36.0±10.2 (33.9; 38.9)	37.2±9.0 (34.9; 39.5)	38.7±7.3 (36.7; 40.7)	44.0±6.1 (41.5; 46.4)	55.7±3.9 (52.4; 59.1)
Whole practice in the capoeira (years)	20.5±8.8 (19.4; 21.6)	15.0±6.3 (13.7; 16.3)	19.4±5.7 (18.0; 20.9)	24.3±6.8 (22.4; 26.1)	29.0±7.5 (26.0; 32.1)	41.5±5.3 (37.0; 46.0)
Working time in the capoeira (years)	6.9±9.6 (5.7; 8.1)	1.7±4.0 (0.9; 2.5)	3.9±5.5 (2.5; 5.3)	9.0±7.5 (6.9; 11.0)	20.2±7.6 (17.1; 23.2)	35.0±5.8 (30.1; 39.8)

f: absolute frequency; %: relative frequency; SD: standard deviation; CI: confidence interval of 95%.

using G*Power version 3.1.9.2, adopting an effect size of 0.010 for QoL[12], considering an alpha error of 0.05 and statistical power (1–β) of 0.80. A necessary total of 171 individuals was obtained; however, the sample had 245 participants, increasing statistical power (1–β) to 0.93. As inclusion criteria, capoeira players above 18 years old and those who have blue belt level were included. As exclusion criterion, filling out the questionnaires in a wrong, confusing, or incomplete way was considered.

Procedures

To devise the hypotheses, studies on capoeira and/or with individuals exposed to capoeira for a long time were reviewed. The inclusion criterion was based on the analysis of health-related variables. The descriptors ^capoeira^ and ^health^ were used in Medline, Embase, Cinahl, and SportDiscus databases. Population, intervention, comparator, and outcome were considered for composing the results. The hypotheses were devised through the analysis of health variables, and the results were divided by the aspects of (1) body composition, (2) functional capacity, (3) metabolism, and (4) cardiovascular system.

The QoL of study participants was assessed using the WHOQOL-bref[4] questionnaire, assessing the physical, social, psychological, and environmental domains[13]. Each question had scores ranging from 1 to 5 on a Likert-type scale, transformed into a linear scale that ranged from 0 to 100, with "0" representing a lower QoL and "100" representing a higher QoL[13]. Furthermore, the studies by Cruz et al.[13] with normative values of Brazilians and by Schwartz et al.[12] with male combat sports/martial arts practitioners were adopted in the comparisons with the investigated capoeira players.

Statistical analysis

Descriptive statistics were performed with absolute (f) and relative (%) frequency, mean, standard deviation, and confidence interval (95%CI). Levene's test was used to verify homogeneity. Two-way ANOVA with repeated measures and Bonferroni post-hoc test were adopted. The significance level was set at $p<0.05$ using SPSS version 25.0.

RESULTS

Frame 1 presents the studies reviewed and the hypotheses devised. It highlights the results of variables related to health regarding body composition, functional capacity, metabolism, and the cardiovascular system.

Regarding the capoeira players evaluated in this study, it is noteworthy that the general characteristics (Table 1) are similar between men and women in terms of training variables (frequency, intensity, and duration), age, whole practice, and working time ($p>0.05$). There were no significant differences in QoL domains between the different graduation technical levels for both sexes evaluated ($p>0.05$).

The QoL scores of the sample are shown in Table 2 and compared to the normative values of Brazilians[13]. Since the sample of the reference study by Schwartz et al.[12] was composed exclusively of men, the results of the QoL scores of female capoeira players (n=53) were compared only with normative values of Brazilian women[13] and with male capoeira players. There was an effect between groups [$F(4, 7652)=218.20$; $p<0.001$] and interaction group vs. QoL domains [$F(12, 7652)=26.52$; $p<0.001$], where for QoL within the physical domain, male capoeira players had a higher score compared to the normative value of Brazilians ($p<0.001$) and lower compared to practitioners of other fights ($p<0.001$). Regarding the psychological and environmental domains, male capoeira players had higher scores compared to normative values ($p<0.001$) and to practitioners of other combat sports ($p<0.001$). As for the social relationship domain, there was a difference between male capoeira players and Brazilian normative values ($p<0.001$). Furthermore, it was evidenced that female capoeira players had a higher QoL score in the physical domain compared to the normative value of Brazilian women ($p<0.001$), with no difference when compared to the score of male capoeira players ($p=0.999$). Regarding the psychological domain, female capoeira players had a higher score compared to the normative value of Brazilian women ($p<0.001$) and a lower score compared to male capoeira players ($p<0.01$). Regarding the social relationship domain, there was no difference when comparing the scores of female capoeira players to the normative values of Brazilian women ($p=0.094$) and male capoeira players ($p=0.999$). Finally, regarding the environmental domain, female capoeira players had a higher score compared to the normative values of Brazilian women ($p<0.001$), with no difference for male capoeira players ($p=0.999$).

DISCUSSION

The main results evidence capoeira as a possible intervention strategy aimed at human health with hypotheses about improving body composition (waist circumference, bone, and muscle mass), functional capacity, metabolic aspects with chronic reduction in plasma triglycerides and acute reduction in blood glucose, and potentiation of the anaerobic pathway, in addition to improving parameters of the cardiovascular system with increased maximal oxygen consumption, reduced heart rate, and double pressure product at rest and increased parasympathetic

Frame 1. Hypotheses of the possible effects of capoeira on human health regarding body composition, functional capacity, and metabolic and cardiovascular systems.

Study	Population	N/Sex/Age	Intervention or Exposition	Comparator	Outcome
Body Composition					
Nogueira et al.[14]	Young physically active schoolchildren from two schools in Australia	85/M+F/12.3±0.6 years (control group) 155/M+F/12.2±1.0 years (INTERVENTION group)	Capoeira program at school during 9 months, 3 times a week with 10 min each session (movements with upper and lower limbs emphasizing high speed and associated with jumping with medium and high impact)	Comparison with the control school in a school physical education routine paired with the school in the intervention group	**Control group** Waist circumference: Δ=5.9% CBU: Δ=1.4% **Intervention group** Waist circumference: Δ=2.4% CBU: Δ=4.1% *p*<0.05 between groups
Guimarães Almeida et al.[15]	Capoeira players of various nationalities, being athletes at international level	15/M/32.8±7.2 years (light category) 25/M/34.3±5.3 years (medium category) 10/M/36.1±4.8 years (heavy category)	Exposure to capoeira practice: Light category: 20.7±6.2 years Medium category: 21.3±4.6 years Heavy category: 24.3±6.3 years	Assessment and/or comparison between weight categories	**Somatotype:** MESOMORFY predominance in all categories Body fat light category: 9.8±3.4% Body fat medium category: 11.9±3.6% Body fat heavy category: 12.5±5.9% *p*>0.05 for categories in the body fat
Hypothesis: Capoeira protects against increased adiposity, improves bone mass, and promotes body composition with muscle predominance in humans.					
Functional capacity					
Vale et al.[16]	Previously sedentary Brazilian elderly	10/F/67.3±6.6 years (control group) 13/F/69.3±6.4 years (Intervention group)	Capoeira program in a care center for the elderly, during 12 weeks, twice a week with 60 min each session (moderate intensity in the program: 13.3±0.9 a.u. in RPE 6-20)	Comparison with paired control group in anthropometric and cardiovascular characteristics and pre-training functional capacity (p>0.05)	**Control group** GFI: Δ 4 weeks= −6.2% GFI: Δ 8 weeks= −5.2% GFI: Δ 12 weeks= −7.6% **Intervention group** GFI: Δ 4 weeks=17.6% GFI: Δ 8 weeks=28.0% GFI: Δ 12 weeks=29.7% *p*<0.001 between groups
Moreira et al.[17]	Previously sedentary Brazilian adults	08/M+F/27.1±10.5 years (control group) 13/M+F/26.1±7.2 years (intervention group)	Capoeira program in a training center, during 8 weeks, twice a week with 60 minutes each session (moderate intensity)	Comparison with paired control group in anthropometric characteristics and pre-training flexibility (p>0.05)	**Control group** PThf: Δ 8 weeks=5.7% MRhf: Δ 8 weeks=-5.3% **Intervention group** PThf: Δ 8 weeks=46.2% MRhf: Δ 8 weeks=22.4% *p*≤0.01 between groups
Guimarães Almeida et al.[15]	Capoeira players of various nationalities, being athletes at international level	15/M/32.8±7.2 years (light category) 25/M/34.3±5.3 years (medium category) 10/M/36.1±4.8 years (heavy category)	Exposure to capoeira practice: Light category: 20.7±6.2 years Medium category: 21.3±4.6 years Heavy category: 24.3±6.3 years	Assessment and/or comparison between weight categories	**Tests –** Upper limb strength/ abdominal endurance/flexibility: All tests with excellent rating according to normative parameters *p*>0.05 between weight categories in functional capacity tests
Hypothesis: Capoeira promotes general functionality and angular flexibility and maintains human with satisfactory levels of motor performance.					
Metabolism					
Conceição and Moreira[18]	Previously sedentary Brazilian elderly	7/M+F/82.4±13.6 years (control group) 7/M+F/79.4±6.9 years (intervention group)	Capoeira program in a long-stay institution for the elderly, during 12 weeks, twice a week with 60 min each session (light to moderate intensity)	Comparison with a control group paired for age and anthropometry. Total energy intake, as well as for each macronutrient, did not differ within or between groups during the intervention (p>0.05)	**Control group** Plasma triglycerides: Δ 12 weeks= −18% **Intervention group** Plasma triglycerides: Δ 12 weeks= −37% *p*<0.01 between groups

Continue.

Frame 1. Continuation.

Study	Population	N/Sex/Age	Intervention or Exposition	Comparator	Outcome
Moreira et al.[19]	Brazilian capoeira players at recreational level with 10.7±5.8 years of practice in the modality	11/M/33.0±7.3 years	Acute sessions with 90 s of capoeira game, on different days and at three randomized intensities: **1. Angola** (67±12% of maximum HR) **2. Benguela** (82±6% of maximum HR) **3. São Bento** (95±3% of maximum HR)	Acute comparison of the lowest value for blood glucose concentration and the highest value for blood lactate concentration in the recovery period of capoeira sessions	**Angola session*** Blood glucose: Δ= −15.4% Blood lactate: Δ=5.7 mM **Benguela session***† Blood glucose: Δ=−6.8% Blood lactate: Δ=8.3 mM **São Bento session†** Blood glucose: Δ=11.5% Blood lactate: Δ=14.6 mM *p<0.05 for São Bento in glucose †p<0.05 for others in blood lactate
Hypothesis: Capoeira at light and moderate intensities chronically reduces triglycerides and acutely reduces blood glucose. In addition, with a greater intensity of practice in capoeira, greater activation of anaerobic glycolysis occurred, which could be chronically reflected in better indices of anaerobic fitness in humans.					
Cardiovascular system					
Nogueira et al.[14]	Young physically active schoolchildren from two schools in Australia	85/M+F/12.3±0.6 years (control group) 155/M+F/12.2±1.0 years (intervention group)	Capoeira program at school for 9 months, 3 times a week with 10 min each session (movements with upper and lower limbs emphasizing high speed and associated with jumping with medium and high impact)	Comparison with the control school in a school physical education routine paired with the school in the intervention group	**Control group** VO_2max: Δ=0.0% **Intervention group** VO_2max: Δ=7.1% p<0.05 between groups
Moreira et al.[20]	Previously sedentary Brazilian adults	08/M+F/29.6±3.3 years (control group) 10/M+F/25.4±3.3 years (intervention group)	Capoeira program in a training center, during 10 weeks, once a week with 90 min each session (moderate intensity)	Comparison with paired control group in pre-training anthropometric and cardiovascular characteristics (p>0.05)	**Control group** HR: Δ 10 weeks=−0.7% RPP: Δ 10 weeks=−2.3% RRi: Δ 10 weeks=0.9% rMSSD: Δ 10 weeks=2.9% SD1: Δ 10 weeks=6.5% pNN50: Δ 10 weeks=0.3% **Intervention group** HR: Δ 10 weeks=−8.6% RPP: Δ 10 weeks=−12.2% RRi: Δ 10 weeks=10.1% rMSSD: Δ 10 weeks=37.8% SD1: Δ 10 weeks=37.7% pNN50: Δ 10 weeks=96.2% p<0.05 between groups, except to RPP variable which was p=0.06
Hypothesis: Capoeira promotes improvement in parameters of the cardiovascular system and increases aerobic fitness (maximum oxygen consumption) in humans.					

Δ: variation from pre- to post-intervention; CBU: calcaneal bone ultrasound; RPE: rate of perceived exertion; GFI: general functionality index obtained in a battery with five tests of functional capacity specific to the elderly; PThf: passive joint tension in hip flexion; MRhf: maximum joint range in hip flexion; HR: heart rate; RPP: rate pressure product (myocardial overload rate); RRi: absolute mean of R-R interval sets at rest (HR variability); rMMSD: square root of the mean of the sum of the squares of differences between adjacent RRi (parasympathetic activity); SD1: standard deviation of instantaneous beat-to-beat RRi variability (parasympathetic activity); pNN50: RRi pairs count differing by more than 50 ms divided by the total number of RRi and multiplied by 100; VO_2max: maximum oxygen consumption.

Table 2. Normative values for the quality of life domains (WHOQOL-bref) for Brazilian men (n=288) and Brazilian women (n=463), male combat sports/martial arts practitioners (n=922), and male capoeira practitioners (n=192) and female capoeira practitioners in this study (n=53).

	Physical domain	Psychological domain	Social relationship domain	Environmental domain
Normative values of male[a]	60.3±9.9	65.9±10.8	73.50±18.4	62.9±13.8
Normative values of female[a]	57.8±10.5	62.2±12.5	71.9±19.7	59.7±16.2
Male combat sports and martial arts practitioners[b]	75.0±16.0	75.0±12.0	77.0±16.0	65.0±13.0
Male capoeira practitioners	**67.4±9.4***#	**82.4±8.6***#	**78.9±12.5***	**73.8±11.2***#
Female capoeira practitioners	**65.9±9.8***	**75.2±13.2***	**77.2±14.2**	**70.6±14.3***

[a]Cruz et al.[13]; [b]Schwartz et al.[12]. *p<0.001 for significant difference from normative values; #p<0.001 for significant difference from male combat sports/martial arts practitioners. Data are represented as mean±standard deviation.

nervous activity at rest (Frame 1). In addition, it was possible to verify in the sample of capoeira players in this study that, despite the pandemic, the QoL domains presented values similar or superior to other samples of normative or reference studies carried out before the pandemic (Table 2). Such results can be explained by the routine maintained by the sample, in which, although remotely, they kept doing capoeira training. Most of them would do it two to three times a week, in sessions lasting between 46 and 90 min, with moderate intensity (Table 1).

Corroborating the findings of this study, other authors[21] have shown that athletes in combat sports have higher scores in the domains of QoL compared to the general population. In fact, the evaluated sample of capoeira players showed better perceptions in all domains of QoL when compared to the normative values of Brazilians[13], suggesting that capoeira seems to satisfactorily maintain the QoL scores of its players, even in the pandemic period. Besides, although combat sports and martial arts show benefits in the QoL of their practitioners, capoeira seems to have a potentiated effect, with additional benefits in psychological and environmental aspects when compared to other combat sports[12].

From a scientific point of view, Kotarska et al.[22] stated that combat sports/martial arts help develop practitioners' personalities, leading them to an improvement in physical apparatus, mental resistance, and courage and also contributing to attenuating negative emotions. Furthermore, these authors[22] investigated the relationship between QoL and healthy behaviors in 543 Polish individual practitioners of fight and demonstrated positive correlations between practice of fights, health behaviors, and higher QoL scores. These findings, in addition to supporting the relationship between capoeira and the maintenance of QoL (Table 2), reinforce the hypotheses devised in this study (Frame 1). Thus, suggesting capoeira as a form of systematic physical activity, in programs aimed at human health rehabilitation, corroborates other controlled studies adopting conventional physical training (aerobic or resistance), which demonstrated important effects in the treatment of overweight and obesity[23], systemic arterial hypertension[24], and type 2 diabetes associated with functional disability[25].

Regarding the limitations faced by this study, it is important to highlight that the results presented, especially in the QoL of capoeira players, which was evaluated transversally, do not create a cause-and-effect relationship and, therefore, longitudinal studies are recommended for this purpose.

CONCLUSION

This study devised hypotheses on the rehabilitation of biological human health (body composition, functional capacity, and metabolic and cardiovascular systems) through capoeira intervention. In addition, even though QoL was evaluated during the pandemic, capoeira players had higher scores when compared to the normative values of Brazilians outside the pandemic. When compared to practitioners of other combat sports/martial arts, capoeira players showed similar results in the social relationship domain, higher in the psychological and environmental domains, and lower in the physical domain. Finally, longitudinal studies are encouraged to test the hypotheses generated in this study regarding the causal relationship between capoeira and health rehabilitation processes and QoL in different populations, especially individuals with chronic degenerative diseases that involve the aforementioned aspects.

AUTHORS' CONTRIBUTIONS

SM: Conceptualization, Data curation, Formal Analysis, Methodology, Writing – original draft, Writing – review & editing, Project administration. **AA:** Conceptualization, Data curation, Formal Analysis, Methodology, Writing – original draft, Writing – review & editing, Project administration. **ACOII:** Data curation, Formal Analysis, Methodology, Writing – original draft.

REFERENCES

1. Campos JWS, Dibai-Filho AV, Cordeiro MEC, Mariano ER, Souza SAR. Disability and pain in capoeira practitioners. Rev Assoc Med Bras. 2021;67(11):1692-5. https://doi.org/10.1590/1806-9282.20210740
2. Zakharov, AA. Ciência do treinamento desportivo. Traduzido por: Gomes AC. Rio de Janeiro: Grupo Palestra Sport; 1992.
3. Laborde S, Dosseville F, Allen MS. Emotional intelligence in sport and exercise: a systematic review. Scand J Med Sci Sports. 2016;26(8):862-74. https://doi.org/10.1111/sms.12510
4. Fleck M, Louzada S, Xavier M, Chachamovich E, Vieira G, Santos L, et al. Aplicação da versão em português do instrumento abreviado de avaliação da qualidade de vida "WHOQOL-bref". Rev Saúde Pública. 2000;34(2):178-83. https://doi.org/10.1590/S0034-89102000000200012
5. Bermejo-Cantarero A, Álvarez-Bueno C, Martinez-Vizcaino V, García-Hermoso A, Torres-Costoso AI, Sánchez-López M. Association between physical activity, sedentary behavior, and fitness with health related quality of life in healthy children and adolescents: a protocol for a systematic review and meta-analysis. Medicine. 2017;96(12):e6407. 10.1097/MD.0000000000006407
6. Korhonen MT, Cristea A, Alén M, Häkkinen K, Sipilä S, Mero A, et al. Aging, muscle fiber type, and contractile function in sprint-trained athletes. J Appl Physiol (1985). 2006;101(3):906-17. https://doi.org/10.1152/japplphysiol.00299.2006

7. Numata Filho ES, Santos GA, Moreira SR. Idade: é um fator relevante para o desempenho esportivo do capoeirista? In: Moreira SR, Oliveira SRL, Brito AC, editors. Anais do V AbadÁcadêmico: Encontro Técnico-Científico de Capoeira. 5th ed. Univasf; 2020. p. 184-90.
8. Barros LK, Numata Filho ES, Moreira SR. Influência da idade no desempenho esportivo de mulheres competidoras dos jogos mundiais da escola ABADA-Capoeira. In: Moreira SR, Oliveira SRL, Brito AC, editors. Anais do VI AbadÁcadêmico: Encontro Técnico-Científico de Capoeira. 6th ed. Univasf; 2021. p. 96-104.
9. Moreira SR, Teixeira-Araujo AA, Camara MV, Carvalho FO, Bezerra TA, Filho ANS. Heart rate, a rating of perceived exertion and basic affective responses during different moments of a single capoeira progressive training session (CPTS). Arch Budo. 2017;13:153-63.
10. Lima R. Balance assessment in deaf children and teenagers prior to and post capoeira practice through the Berg Balance Scale. Int Tinnitus J. 2017;21(2):77-82. 10.5935/0946-5448.20170016
11. Esatbeyoglu F, Kirk TN, Haegele JA. "Like I'm flying": capoeira dance experiences of youth with visual impairments. Brit J Vis Impair. 2021:02646196211059756. https://doi.org/10.1177/02646196211059756
12. Schwartz J, Takito M, Warburton D, Antonietti L, Franchini E. Quality of life in Brazilian martial arts and combat sports practitioners. Biomed Hum Kinet. 2021;13(1):212-20. https://doi.org/10.2478/bhk-2021-0026
13. Cruz LN, Polanczyk CA, Camey SA, Hoffmann JF, Fleck MP. Quality of life in Brazil: normative values for the WHOQOL-bref in a southern general population sample. Qual Life Res. 2011;20(7):1123-9. https://doi.org/10.1007/s11136-011-9845-3
14. Nogueira RC, Weeks BK, Beck B. One-year follow-up of the CAPO Kids trial: are physical benefits maintained? Pediatr Exerc Sci. 2017;29(4):486-95. https://doi.org/10.1123/pes.2017-0044
15. Guimarães Almeida L, Numata Filho ES, dos Santos GA, Carneiro Cardoso JT, Moreira SR. Anthropometric profile and functional performance of Capoeira competitors in the world games. Int J Morphol. 2021;39(4):969-76. http://doi.org/10.4067/S0717-95022021000400969
16. Vale TS, Santana MS, Moreira DVS, Moreira SR. Índice geral de capacidade funcional de idosos após 12 semanas de treinamento de capoeira. In: Moreira SR, Oliveira SRL, Brito AC, editors. Anais do VI AbadÁcadêmico: Encontro Técnico-Científico de Capoeira. 6th ed. Univasf; 2021. p. 80-94.
17. Moreira SR, Carvalho FO, de Moraes JFVN, da Silva Carvalho RG, de Araújo RC, Teixeira-Araújo AA, Okano AH. Eight weeks of Capoeira progressive training program increases flexibility of beginners. Sport Sci Health. 2016;12(3):329-37. https://doi.org/10.1007/s11332-016-0292-y
18. Conceição AJ, Moreira SR. Perfil lipídico de idosos institucionalizados após três meses de treinamento de capoeira. In: Moreira SR, Numata Filho ES, Souza GA, editors. Anais do III AbadÁcadêmico: Encontro Técnico-Científico de Capoeira. 3rd ed. Univasf; 2018. p.18-22.
19. Moreira SR, Teixeira-Araujo AA, Numata Filho ES, Moraes MR, Simões HG. Psychophysiological characterization of different capoeira performances in experienced individuals: a randomized controlled trial. PLoS One. 2018;13(11):e0207276. https://doi.org/10.1371/journal.pone.0207276
20. Moreira SR, Teixeira-Araujo AA, Dos Santos AO, Simões HG. Ten weeks of capoeira progressive training improved cardiovascular parameters in male practitioners. J Sports Med Phys Fitness. 2017;57(3):289-98. https://doi.org/10.23736/s0022-4707.16.06030-8
21. Dall'Agnol C, Silva R, Del Vecchio F. Quality of life of male amateur athletes from Pelotas, Brazil. Rev Bra Ativ Fís Saúde. 2017;22(2):147-54. https://doi.org/10.12820/rbafs.v.22n2p147-154
22. Kotarska K, Nowak L, Szark-Eckardt M, Nowak M. Selected healthy behaviors and quality of life in people who practice combat sports and martial arts. Int J Eenviron Res Public Health. 2019;16(5):875. https://doi.org/10.3390/ijerph16050875
23. Wewege M, van den Berg R, Ward RE, Keech A. The effects of high-intensity interval training vs. moderate-intensity continuous training on body composition in overweight and obese adults: a systematic review and meta-analysis. Obes Ver. 2017;18(6):635-46. https://doi.org/10.1111/obr.12532
24. Palmeira AC, Farah BQ, Silva GOD, Moreira SR, Barros MVG, Correia MA, et al. Effects of isometric handgrip training on blood pressure among hypertensive patients seen within public primary healthcare: a randomized controlled trial. Sao Paulo Med J. 2021;139(6):648-56. https://doi.org/10.1590/1516-3180.2020.0796.R1.22042021
25. Melo KCB, Araújo FS, Cordeiro Júnior CCM, de Andrade KTP, Moreira SR. Pilates method training: functional and blood glucose responses of older women with type 2 diabetes. J Strength Cond Res. 2020;34(4):1001-7. https://doi.org/10.1519/JSC.0000000000002704

ORIGINAL ARTICLE

https://doi.org/10.1590/1806-9282.20220479

Evaluation of platelet indices and pro-inflammatory cytokines in type 2 diabetic patients with retinopathy

Irfan Kucuk[1], Ersin Tural[2], Betül Doğantekin[3], Aysin Tuba Kaplan[4*], Egemen Kucuk[5], Mehmet Emin Onde[6]

SUMMARY

OBJECTIVE: The aim of this study was to investigate whether platelet parameters and pro-inflammatory cytokines associated with platelet activation could be surrogate markers of the diabetic retinopathy stages in type 2 diabetic patients.

METHODS: This prospective case-control study included 108 type 2 diabetes mellitus patients and 48 healthy controls. After fundoscopic examination, patients were divided into three groups: no retinopathy, nonproliferative diabetic retinopathy, or proliferative retinopathy. Platelet selectin, interleukin-1alpha, and interleukin-6 values were measured by the enzyme-linked immunosorbent assay method. Homeostatic Model Assessment for Insulin Resistance formula was used to assess insulin resistance in patients.

RESULTS: Mean platelet volume was lower and interleukin-1alpha was higher in the patients compared to the healthy controls ($p=0.046$ and $p<0.001$, respectively). In addition, a positive correlation between the platelet distribution width and HbA1C levels was observed in the patients ($r=0.334$, $p<0.001$).

CONCLUSION: In the studies evaluating the utility of platelet indices and the associated cytokines in diabetic retinopathy, there is a need for the standardization of the measurements. All medications that can affect platelet activation should be taken into consideration.

KEYWORDS: Diabetic retinopathy. Platelet activation. Interleukin-1alpha. Interleukin-6. p-selectin.

INTRODUCTION

Nearly 4% of the world's population has diabetes mellitus (DM) and half of these patients have varying degrees of diabetic retinopathy (DR)[1]. Nonproliferative diabetic retinopathy (NPDR) and proliferative retinopathy (PDR) are the two main stages of DR. Microaneurysms, retinal hemorrhages, soft and hard exudates, and venous beadings are the common features of NPDR. PDR is characterized by neovascularization, vitreous hemorrhages, fibrovascular bands, and tractional retinal detachment[2]. Functional changes in platelets also play roles in DR pathogenesis[3].

Platelets mediate the leukocyte recruitment during inflammation[4]. Large platelets are more reactive in the inflammatory processes[5]. Platelet selectin (p-selectin) is a structural molecule that leads platelets to interact with leukocytes and the damaged vessel wall[6,7].

Diagnostic strategies with the possibility of therapeutic intervention can be developed by identifying practical and objective new biochemical markers that may be associated with the development of DR. In the present study, we compared platelet indices, serum p-selectin, interleukin-1alpha (IL-1α) and IL-6 levels, and insulin resistance in type 2 diabetic patients with retinopathy and healthy controls. We also aimed to delineate whether these parameters could be surrogate markers for DR stages.

METHODS

Study population

The patients admitted to the internal diseases and ophthalmology outpatient clinics between February 2008 and October 2008 were

[1]Sultan 2. Abdulhamid Han Training and Research Hospital, University of Health Sciences, Department of Gastroenterology – Istanbul, Turkey.
[2]Sultan 2. Abdulhamid Han Training and Research Hospital, University of Health Sciences, Department of Pediatrics – Istanbul, Turkey.
[3]Sultan 2. Abdulhamid Han Training and Research Hospital, University of Health Sciences, Department of Internal Medicine – Istanbul, Turkey.
[4]University of Health Sciences, Kartal Dr. Lutfi Kirdar City Hospital, Department of Ophtalmology – Istanbul, Turkey.
[5]Sakarya University Training and Research Hospital, Department of Emergency Medicine – Sakarya, Turkey.
[6]Bayındır Içerenköy Hastanesi, Department of Endocrinology and Metabolism – Istanbul, Turkey.
*Corresponding author: aysintuba@yahoo.com

Conflicts of interest: the authors declare there is no conflicts of interest. Funding: This study was approved by The Epidemiological Research Committee and supported by fund from The Revolving Fund Management Department of the University of Health Sciences, Haydarpasa Training Hospital under grant number 06.07.2007/1491-454-07. Materials used for the enzyme-linked immunosorbent assay (ELISA) study were also supplied by The Revolving Fund Management Department of the University of Health Sciences, Haydarpasa Training Hospital, Istanbul, Turkey.
Received on July 24, 2022. Accepted on August 15, 2022.

enrolled in the study. A study group of 108 type 2 diabetic patients with retinopathy (56 females and 52 males) and 48 nondiabetic healthy controls (29 females and 19 males) were the subject (Table 1). The local ethics committee of our institute approved the study (06.07.2007/1491-454-07). Participants with severe organ failure, any malignancies, chronic inflammatory and autoimmune diseases, thrombocytopenia (<100,000/mm^3), severe anemia and leukopenia (Hb<9 g/dl, leukocyte count <3,000 mm^3), any hematological disease, and history of cerebrovascular accident (CVA) and coronary heart disease were excluded from the study. In addition, patients taking corticosteroids, nonsteroidal anti-inflammatory drugs, and anticoagulant drugs which can potentially affect mean platelet volume (MPV) were excluded from the study.

Study design

After overnight fasting, 5 mL of venous blood samples were drawn from each participant, and samples were collected in a tube with ethylenediaminetetraacetic acid (EDTA) for complete blood count assessed with CELL-DYN Sapphire auto-analyzer (PN9231319A Abbott, USA). Plasma for p-selectin, IL-1α, and IL-6 was separated after centrifugation of the blood sample with EDTA at 5,000 g for 10 min at 30°C, and the supernatant plasma was stored at -40°C.

The IL-1α level was determined using ELISA kits (Bender MedSystems, catalog number: BMS243/2) by following the instructions of the manufacturer. IL-6 level was determined using ELISA kits (BioSource Immunoassay, catalog number: KHC0061: 1 plate, KHC0062: 2 plates, KHC0061: 5 plates). Bender MedSystems ELISA kits (catalog number: BMS219/3) were used for the measurement of p-selectin.

To overcome the interobserver variability, the indirect stereoscopic retinal examinations of all the diabetic patients were carried out by the same ophthalmologist. Fundus photography and fundus fluorescein angiography procedures were also applied. The "Early Treatment Diabetic Retinopathy Study" (ETDRS) classification was used for the staging of DR in the patients[8,9]. At the end of fundoscopic examinations, the patients were classified into three groups: no DR, NPDR, and PDR groups.

For the assessment of insulin resistance in both groups, HOMA-IR (Homeostatic Model Assessment for Insulin Resistance) calculation was used: HOMA-IR=Fasting plasma insulin (U/mL)×fasting blood glucose (mg/dL)/405. HOMA-IR values of ≥2.7 were accepted as the presence of insulin resistance[10].

Statistical analysis

Data analysis was performed using MedicReS E-PICOS AI Smart Biostatistics Software® (version 21.3; New York, NY, USA). Descriptive statistics were reported as mean and standard deviation for continuous variables, whereas ratios (%) were used for categorical variables. The continuous and categorical

Table 1. Clinical characteristics and laboratory results of all participants.

		Type 2 diabetics	Healthy controls		p
		n (%)	n (%)		
Gender	Male	52 (48.15)	19 (39.58)		0.321
	Female	56 (51.85)	29 (60.47)		
	n	Mean±SD	N	Mean±SD	p
Age (years)	108	54.18±9.61	48	50.04±8.93	0.012
DM duration (years)	108	8.02±8.34			
HOMA-IR	106	5.55±6.37	48	2.66±1.43	<0.001
HbA1C (%)	108	8.63±2.08			
PLT (bin/mm^3)	108	268.30±72.34	48	290.85±60.32	0.061
MPV (fL)	108	7.70±1.34	48	8.06±0.88	0.046
PDW (%)	106	16.02±1.32	48	16.15±0.84	0.438
PTC (%)	106	0.20±0.06	48	0.23±0.04	<0.001
IL-1α (pg/mL)	108	1.97±1.16	48	1.23±0.70	<0.001
IL-6 (pg/mL)	100	5.86±4.52	48	6.87±3.66	0.178
p-Selectin (ng/mL)	105	15.78±11.05	47	13.76±13.51	0.333

SD: standard deviation; DM: diabetes mellitus; HOMA-IR: Homeostatic Model Assessment for Insulin Resistance; LDL-K: low density lipoprotein-cholesterol; PLT: platelet; MPV: mean platelet volume; PDW: platelet distribution width; PTC: platecrit; IL-1α: interleukin-1alpha; IL-6: interleukin-6; p-selectin: platelet selectin.

variables were compared by Student's t-test and the chi-square test, respectively. Pearson's correlation test was used to reveal any relationship between continuous variables. The confidence level of 95% was determined for statistical significance ($p<0.05$).

RESULTS

The demographic and clinical characteristics of the patients and the control groups are presented in Table 1. The average ages of the patients and the controls were different (54.18±9.61 and 50.04±8.93 years, respectively, p=0.012). The patient group had a higher HOMA-IR index compared to the control group (5.55±6.37 and 2.66±1.43, respectively, $p<0.001$).

There was no significant difference between the patients and the controls in terms of the platelet counts and the platelet distribution width (PDW) (p=0.061 and p=0.438, respectively). MPV was lower in the type 2 DM patients than in the controls (7.7±1.34 and 8.06±0.88, respectively, p=0.046). Platecrit (PTC) level was also lower in the patient group ($p<0.001$). The IL-1α level was higher in the patients than in the controls (1.97±1.16 and 1.23±0.70, respectively, $p<0.001$). IL-6 and p-selectin levels were not different between the two groups (Table 1).

There were positive correlations between p-selectin and MPV (r=0.246, p=0.011) and between PDW and glycated hemoglobin (HbA1C) (r=0.334, $p<0.001$) in the patients (Table 2). No statistically significant difference was found between the patients with (n=11) and without DR (n=36), and statistical analysis did not reveal any difference between the patients with NPDR and PDR.

DISCUSSION

Since platelet indices are cheap and easily interpreted laboratory tests, they have attracted clinicians so far. Although there are controversies about the diagnostic and prognostic utilities of these tests, they can provide valuable information about several critical conditions[11].

In this study, we aimed to evaluate the platelet indices, pro-inflammatory cytokines, p-selectin, and insulin resistance in type 2 DM patients and compared them with the healthy controls. In addition, correlations to DR stages were evaluated.

The differences between the patients and healthy controls were not statistically significant except for serum IL-1α level, which was higher in the patients. Statistical analyses also did not reveal any correlation between the stages of DR and the other investigated parameters. According to our results, the platelet count and PTC and MPV values were lower in type 2 diabetics. Although most of the studies declared higher MPV values in type 2 diabetic patients[11,12], reports revealing no difference between these patients and controls or reports with lower values in DM patients also exist[13-15].

The wide range of normal values is an important limitation in clinical studies, and they cannot be standardized among the laboratories. Anticoagulants, the interval between venipuncture, and the laboratory analysis can also influence platelet size. Using EDTA instead of citrate as an anticoagulant can result in a 30% increase in MPV[16]. Blood/citrate solution at a concentration of 0.12 mol/L (4/1) was previously proposed as an ideal anticoagulant for MPV measurement[17]. All these factors limit the usefulness of MPV.

Drugs can influence platelet activation, so the value of the platelet indices may be different depending on the treatment options[11-13]. In terms of the medications, insulin and/or oral antidiabetic drugs that lower blood glucose and acetylsalicylic acid (ASA) and/or clopidogrel that inhibits platelet function could have altered the results[14,15]. ASA has direct antiplatelet activity. Statins also decrease the MPV values[18].

Table 2. Correlations between p-selectin, HbA1C, platelet indices, and the pro-inflammatory cytokines in the patients with type 2 diabetes mellitus.

	P-selectin			HbA1C		
	N	r	p	N	r	p
p-Selectin (ng/mL)				105	-0.035	0.726
IL-1α (pg/mL)	105	0.023	0.816	108	0.164	0.089
IL-6 (pg/mL)	97	0.068	0.508	100	-0.041	0.682
MPV (fL)	105	0.246	0.011	108	0.072	0.461
PDW (%)	103	-0.121	0.222	106	0.334	<0.001
PTC (%)	103	0.049	0.625	106	0.141	0.151
HOMA-IR	105	0.082	0.404	108	-0.045	0.645
HbA1C (%)	105	-0.035	0.726			

p-Selectin: platelet selectin; MPV: mean platelet volume; PDW: platelet distribution width; PTC: platecrit; IL-1α: interleukin-1alpha; IL-6: interleukin-6; HOMA-IR: Homeostatic Model Assessment for Insulin Resistance.

Insulin therapy is likely to reduce insulin resistance and prevent osmotic changes due to hyperglycemia. In a previous study, diabetics were categorized according to the treatments and the MPV value was the lowest in the insulin treatment group, having the best glycemic control[19].

In our study, as stated in previous reports, a positive correlation was found between PDW and HbA1C levels[20,21]. An increase in PDW indicates heterogeneity in platelet morphology. Osmotic changes due to hyperglycemia could lead to an increase in PDW, and hyperglycemia can also induce inflammation, which can explain the heterogeneity[5].

P-selectin is located in the alpha granules of platelets and endothelial cells. The expression of p-selectin increases inflammation and helps the adhesion of platelets, endothelial cells, and neutrophils. P-selectin indicates an increased risk of vascular disease[6,22]. In our study, p-selectin levels were similar between the patients and controls, but there was a significant correlation between p-selectin and MPV in the patient group. This result supports the inflammation-related activation of MPV and p-selectin. However, statistical analysis did not reveal any correlation between MPV, p-selectin, and the DR stages.

Bavbek et al.[13] studied MPV and p-selectin levels in type 2 diabetics with and without DR and found no significant correlation between these variables in patients with and without DR. Koskela et al.[22] compared vitreous-plasma concentrations of adhesion molecules and cytokines in DR with nondiabetic controls. P-selectin was not different between the two groups in vitreous and plasma, but the other molecules were higher in DR[22]. Although these results can partly be ascribed to the small sample sizes of the study groups, serum p-selectin level may not be an indicator of the DR stage.

Koskela et al.[22] showed that IL-6 level was significantly higher in the vitreous fluid of the patients with PDR compared to healthy controls, but there was no difference in the serum IL-6 levels between the two groups. Previous studies also reported that IL-6 produced by the retinal pigment epithelium against the inflammatory stimuli increased the disease activity in the vitreous fluid of the patients with PDR[3,23]. In our results, serum IL-6 was not different in the diabetics with or without DR, and no association was found with the DR stages. Thus, IL-6 activation induced by DM was limited in the retina locally, and it was not detected in the peripheral blood. Serum IL-1α level was higher in the diabetics compared to controls, and this can explain the inflammatory nature of DM. However, IL-1α did not correlate with the DR stages.

The important limitations of this study are the differences in the average age of the two groups and unequal numbers of the cases classified according to DR stages. Additionally, the drug use that could affect the platelet parameters and the cytokines was not evaluated, and it is also thought of as an important limiting factor.

CONCLUSION

The platelet indices and related cytokines cannot be used to assess the DR stages. Further studies including more patients in DR stages might exhibit significant results. It should also be emphasized that in the studies about platelet parameters, all factors that exert an influence on platelet activation should be taken into consideration.

ETHICS COMMITTEE APPROVAL

The study was approved by the Local Ethics Committee of the University of Health Sciences Ankara Gulhane Training Hospital (06.07.2007/1491-454-07).

INFORMED CONSENT

Written informed consent was obtained from all participants.

ACKNOWLEDGMENTS

The data in this article have been extracted from the internal disease specialty thesis of Dr. İrfan KÜÇÜK, who is a gastroenterology specialist at the University of Health Sciences Sultan 2, Abdulhamid Han Training and Research Hospital, İstanbul, Turkey. Additionally, the special acknowledgment should be dedicated to the staff members of the ophthalmology clinics of the University of Health Sciences Haydarpaşa Training Hospital who carried out the fundoscopic examinations and the members of the central biochemistry laboratory who performed all measurements of the serum parameters included in the study.

AUTHORS' CONTRIBUTIONS

IK: Conceptualization, Data curation, Funding acquisition, Investigation, Methodology, Project administration, Writing – original draft, Writing – review & editing. **ATK:** Data curation, Methodology, Project administration, Visualization. **MEO:** Formal Analysis, Validation. **ET:** Software. **EK:** Supervision, Writing – original draft. **BD:** Resources, Writing – review & editing.

REFERENCES

1. Williams R, Airey M, Baxter H, Forrester J, Kennedy-Martin T, Girach A. Epidemiology of diabetic retinopathy and macular edema: a systematic review. Eye (Lond). 2004;18(10):963-83. https://doi.org/10.1038/sj.eye.6701476
2. Singh R, Ramasamy K, Abraham C, Gupta V, Gupta A. Diabetic retinopathy: an update. Indian J Ophthalmol. 2008;56(3):178-88. PMID: 18417817
3. Rema M, Pradeepa R. Diabetic retinopathy: an Indian perspective. Indian J Med Res. 2007;125(3):297-310. PMID: 17496357
4. Ed Rainger G, Chimen M, Harrison MJ, Yates CM, Harrison P, Watson SP, et al. The role of platelets in the recruitment of leukocytes during vascular disease. Platelets. 2015;26(6):507-20. https://doi.org/10.3109/09537104.2015.1064881
5. Breimo ES, Østerud B. Studies of biological functions in blood cells from individuals with large platelets. Platelets. 2003;14(7-8):413-9. https://doi.org/10.1080/02697450310001632597
6. Barale C, Russo I. Influence of cardiometabolic risk factors on platelet function. Int J Mol Sci. 2020;21(2):623. https://doi.org/10.3390/ijms21020623
7. Kaushansky K. The molecular mechanisms that control thrombopoiesis. J Clin Invest. 2005;115(12):3339-47. https://doi.org/10.1172/JCI26674
8. Ophthalmology. Grading diabetic retinopathy from stereoscopic color fundus photographs--an extension of the modified Airlie House classification. ETDRS report number 10. Early Treatment Diabetic Retinopathy Study Research Group. Ophthalmology. 1991;98(5 Suppl):786-806. PMID: 2062513
9. Shukla UV, Tripathy K. Diabetic retinopathy. In: StatPearls [Internet]. Treasure Island, FL: StatPearls Publishing; 2021. PMID: 32809640. Bookshelf ID: NBK560805.
10. Bilge U, Gültekin G, Bilgin M, Ünlüoğlu İ. Homeostatic model assessment insulin resistance (HOMA-IR) Değerleri ile Glomerüler Filtrasyon Hızları Arasındaki İlişki: Retrospektif Bir Çalışma. Ankara Med J. 2015;15(4):220-5. https://doi.org/10.17098/amj.18395
11. Korniluk A, Koper-Lenkiewicz OM, Kamińska J, Kemona H, Dymicka-Piekarska V. Mean platelet volume (mpv): new perspectives for an old marker in the course and prognosis of inflammatory conditions. Mediators Inflamm. 2019;2019:9213074. https://doi.org/10.1155/2019/9213074
12. Papanas N, Symeonidis G, Maltezos E, Mavridis G, Karavageli E, Vosnakidis T, et al. Mean platelet volume in patients with type 2 diabetes mellitus. Platelets. 2004;15(8):475-9. https://doi.org/10.1080/09537100420002677O7
13. Bavbek N, Kargili A, Kaftan O, Karakurt F, Kosar A, Akcay A. Elevated concentrations of soluble adhesion molecules and large platelets in diabetic patients: are they markers of vascular disease and diabetic nephropathy? Clin Appl Thromb Hemost. 2007;13(4):391-7. https://doi.org/10.1177/1076029607303615
14. Rocca B, Santilli F, Pitocco D, Mucci L, Petrucci G, Vitacolonna E, et al. The recovery of platelet cyclooxygenase activity explains interindividual variability in responsiveness to low-dose aspirin in patients with and without diabetes. J Thromb Haemost. 2012;10(7):1220-30. https://doi.org/10.1111/j.1538-7836.2012.04723.x
15. Akinsegun A, Akinola Olusola D, Sarah JO, Olajumoke O, Adewumi A, Majeed O, et al. Mean platelet volume and platelet counts in type 2 diabetes mellitus on treatment and non-diabetic mellitus controls in Lagos, Nigeria. Pan Afr Med J. 2014;18:42. https://doi.org/10.11604/pamj.2014.18.42.3651
16. Threatte GA, Adrados C, Ebbe S, Brecher G. Mean trombosit volume: the need for reference method. Am J Clin Pathol. 1984;81(6):769-72. https://doi.org/10.1093/ajcp/81.6.769
17. Bath PM, Butterworth RJ. Platelet size: measurement, physiology and vasculer disease. Blood Coagul Fibrinolysis. 1996;7(2):157-61. PMID: 8735807
18. Ji S, Zhang B, Wang X, Shi H, Yu L, Wang X. Effects of statin therapy on mean platelet volume in patients with risk of cardiovascular diseases: a systematic review and meta-analysis. Biosci Rep. 2019;39(7):BSR20190180. https://doi.org/10.1042/BSR20190180
19. Vernekar PV, Vaidya KA. Comparison of mean platelet volume in type 2 diabetics on insulin therapy and on oral hypoglycaemic agents. J Clin Diagn Res. 2013;7(12):2839-40. https://doi.org/10.7860/JCDR/2013/7636.3771
20. Wu M, Xiao L, Yang X. Positive relationship of platelet volume indices with HbA1c in unselected type-2 diabetes mellitus patients. Clin Lab. 2019;65(8). https://doi.org/10.7754/Clin.Lab.2019.190101
21. Walinjkar RS, Khadse S, Kumar S, Bawankule S, Acharya S. Platelet indices as a predictor of microvascular complications in type 2 diabetes. Indian J Endocrinol Metab. 2019;23(2):206-10. https://doi.org/10.4103/ijem.IJEM_13_19
22. Ridker PM, Buring JE, Rifai N. Soluble P-selectin and the risk of future cardiovascular events. Circulation. 2001;103(4):491-5. https://doi.org/10.1161/01.cir.103.4.491
23. Abu el Asrar AM, Maimone D, Morse PH, Gregory S, Reder AT. Cytokines in the vitreous of patients with proliferatif diabetic retinopathy. Am J Opthalmol. 1992;114(6);731-6. https://doi.org/10.1016/s0002-9394(14)74052-8

ORIGINAL ARTICLE

https://doi.org/10.1590/1806-9282.20220492

Effect of patellar resurfacing surgery on bleeding in total knee arthroplasty

Sefa Akti[1*], Deniz Cankaya[2], Seyran Kilinc[1], Zekeriya Oztemur[1], Hayati Ozturk[1], Okay Bulut[1]

SUMMARY

OBJECTIVE: Postoperative bleeding is one of the most important factors affecting clinical and functional results in total knee arthroplasty. Therefore, many studies have been conducted on bleeding in arthroplasty patients. However, there are very few reports investigating the effect of patellar surface replacement on bleeding in knee arthroplasty. We, therefore, aimed to investigate the effect of patellar surface replacement on postoperative bleeding.

METHODS: In this retrospective study, 30 with patellar resurfacing were compared with 39 without patellar resurfacing among patients who had undergone total knee replacement due to primary osteoarthritis. Demographic data, amount of transfusion, preoperative and postoperative hemoglobin and hematocrit values, and total, visible, and hidden blood loss values were recorded.

RESULTS: No statistical difference was found between the two groups in terms of demographic values. There was no significant difference between the groups in terms of the amount of blood in the drain, total blood loss, hidden blood loss, and blood transfusion in patients who had and had not undergone patellar resurfacing. A positive significant correlation was found between postoperative drainage volume and total blood loss.

CONCLUSION: Patellar component application in patients who had undergone total knee arthroplasty does not change the blood loss of the patients.

KEYWORDS: Arthroplasty, replacement, knee. Postoperative hemorrhage. Patella. Hemarthrosis.

INTRODUCTION

Background

One of the important factors affecting the clinical and functional results of patients after total knee arthroplasty (TKA) operation is the amount of postoperative bleeding[1]. Blood loss after TKA can lead to postoperative anemia, need for transfusion and its related systemic complications, as well as complications affecting functional outcomes such as delayed mobilization and decreased knee flexion[2]. The number of studies on the reduction of postoperative bleeding after TKA is gradually increasing. Considering all types of arthroplasty, the number of articles examining postoperative bleeding and published in PubMed was 19 in 2010, while this number increased to 454 in 2020[3]. The main ones of these studies are those on the use of tourniquets, hypotensive anesthesia, as well as agents such as systemic or local tranexamic acid (TXA) and lidocaine-containing epinephrine[4,5].

Another factor affecting the functional results after the operation is the patellar resurfacing performed in TKA. However, there is still no consensus on whether patellar resurfacing should be routinely performed in every patient[6]. In this regard, surgeons are divided into three groups: routinely performing patellar resurfacing, not performing it routinely, and performing it in a selected patient group[7]. Although resurfacing has advantages such as reduction in anterior knee pain and reoperation rates, it has main disadvantages such as patellar fracture that may occur during the operation and loosening of the patellar component[8]. While there are articles stating that patellar resurfacing reduces revision surgery rates and has better results, there are articles claiming that complication rates increase by 10% due to patellar resurfacing alone[9,10].

Although the factors related to the attachment of the implant to the bone tissue come to the fore while evaluating the complications related to the use of the patellar component, the additional bleeding that will occur should also be considered[11]. It is expected that patellar resurfacing will not cause significant bleeding, but we could find very few studies investigating the effect of patellar resurfacing on bleeding[6,12,13]. We think that these studies do not provide sufficient evidence. Therefore, we planned our study with the hypothesis that patellar resurfacing would not cause significant bleeding in knee replacement patients.

METHODS

Study design and setting

We started the study after receiving ethics committee approval. Patients who had undergone total knee replacement (TKR)

[1]Cumhuriyet University, Department of Orthopaedics and Traumatology – Sivas, Turkey.
[2]Gulhane Teaching and Research Hospital, Department of Orthopaedics and Traumatology – Ankara, Turkey.
*Corresponding author: sefa.akti@gmail.com

Conflicts of interest: the authors declare there is no conflicts of interest. Funding: none.
Received on July 22, 2022. Accepted on August 17, 2022.

for primary knee osteoarthritis between June 2015 and June 2021 were included. A total of 103 patients operated by a single orthopedic surgeon using the same standard surgical procedures were included in this study. Thirty-four patients with a history of deep vein thrombosis (DVT) or pulmonary embolism (PE), bleeding diathesis, a history of renal failure, cardiovascular disease, a history of TXA allergy, a history of malignancy, hemorrhagic diathesis and coagulopathy, receiving anticoagulant therapy, preoperative hemoglobin values below 10 g/dl, traumatic osteoarthritis or inflammatory arthritis, peripheral vascular disease, liver failure, and a history of stroke were excluded from this study according to the exclusion criteria. Comparison was made between 30 patients who had undergone patellar resurfacing during the operation and 39 patients who had not.

First-generation cephalosporins reportedly had been given to all patients as 1 g just before the operation and 1 g every 8 h for every 24 h. Operations had been performed under spinal/epidural and general anesthesia. Cemented femoral component and cemented tibial component had been used in all patients. The cemented patellar component was additionally used in patients who underwent polyethylene insert patellar resurfacing. Notably, 10 mg/kg intraoperative TXA was administered intravenously to all patients, and the same dose was repeated at the third postoperative hour. At the end of the operation, a 10-gauge drain was placed intra-articularly. Surgical folds passed through the incision were closed in order anatomically. At the 24th postoperative hour, the drain was removed. The amount of blood accumulated in the drain reservoir was measured and recorded. Intraoperative blood loss was calculated as zero because tourniquets were used in all patients. Of note, 4,000 IU low-molecular-weight heparin (Oksapar; Kocak Farma, Turkey) was administered subcutaneously to all patients daily for thrombosis prophylaxis, and it was continued for 4 weeks. On the first postoperative day, they were mobilized with as much weight as they tolerated.

Patients' age, surgical side, body mass index (BMI, kg/m^2), the amount of transfusion, preoperative and postoperative hemoglobin (Hgb), hematocrit (Hct) values on the first, second, and third days, and the amount of blood from the postoperative drain were recorded. Total blood volume (TBV) was calculated as described by Nadler et al.[14]. Total blood loss (TBL) was calculated using the Gross[15] formula as follows:

TBL=TBV × (preoperative Hct – postoperative day 3 Hct) / Mean Hct

The amount of erythrocyte suspension (200 mL each) given to the patients in the postoperative period was added to the amount of TBL. Hidden blood loss (HBL) volume was obtained by subtracting the visible blood loss (VBL) volume from the TBL volume (Figure 1). Iron or

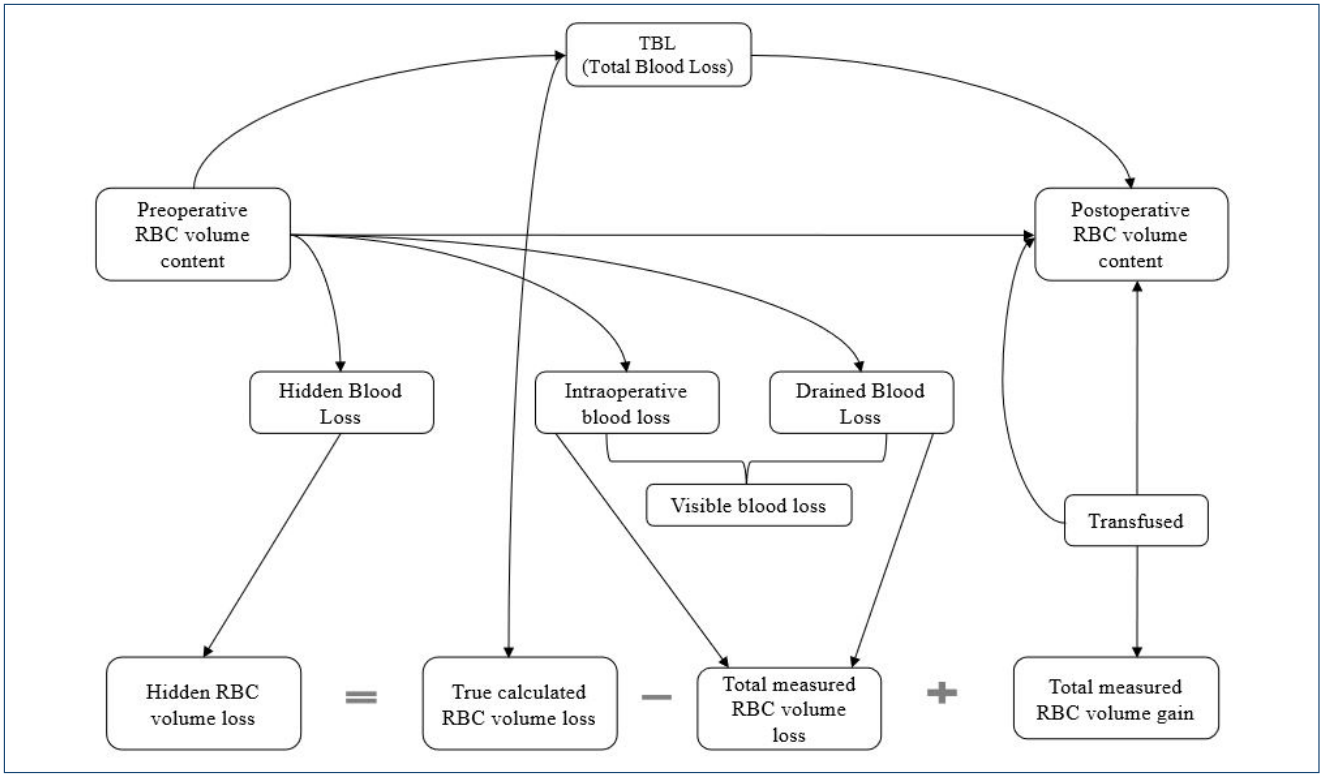

Figure 1. Flowchart of the movement of blood between compartments and calculation of blood loss parameters.

erythropoietin preparations were not used in any of the patients. In case of hemogram (Hgb) values being <8.5 g/dl in the follow-up of the patients or in clinical cases showing symptoms of tachycardia, hypotension, or anemia, blood transfusion was performed in consultation with the anesthesia team.

Statistical analysis

The Gpower (G*Power version 3.1.9.6; Germany) software was used for the adequacy test of the sample size. For calculation, data from a recently published similar article about bleeding[5] were used. In the 95% power and effect size range of 1.15, a minimum of 18 patients from both groups was calculated as a sufficient value (the number of patients in the groups in our study was 30 and 39). Statistical analysis was performed using IBM SPSS for Windows 23.0 software (IBM Corp., Armonk, NY, USA). Descriptive statistics for numerical variables were expressed as mean and standard deviation. Parametric test procedures on normal distribution were used in the Kolmogorov-Smirnov test. Independent two-sample t-tests were used to determine the relationships between parameters. Chi-square analysis was used to determine the relationship between categorical data. The correlation analysis between TBL and VBL and postoperative drainage volume was evaluated using the Pearson correlation coefficient. The results were evaluated within the 95% confidence interval, and $p<0.05$ was considered statistically significant.

RESULTS

Demographic data of the patients included in this study are given in Table 1. There was no statistically significant difference between the groups with and without patellar resurfacing in terms of age, operation side, BMI, TBV, preoperative Hgb values, and the type of anesthesia administered. There was no statistically significant difference between the hemoglobin values of the groups in the mean hemogram values on the first, second, and third postoperative days (Table 1).

There was no statistically significant difference between the groups in terms of the amount of blood in the drain, TBL, and VBL of the patients participating in this study. There was no statistically significant difference between the groups in terms of blood transfusion (Table 2). When the correlation between postoperative drainage volume and VBL was evaluated, there was no significant correlation ($r=0.025$, $p=0.837$), but a positive significant correlation was found between postoperative drainage volume and TBL ($r=0.262$, $p=0.029$).

DISCUSSION

The most important finding of our study is that no significant effect of patellar component change on TBL, VBL, and HBL was observed in patients who had undergone TKA. In the current literature, there are very few studies investigating the effect of patellar resurfacing on bleeding, and their results are inconsistent. In a comparative study investigating the effect of patellar resurface surgery on bleeding in patients undergoing TKA, no

Table 1. Demographic data and postoperative Hgb values of study patients.

	Resurfaced 30 patients		Not resurfaced 39 patients		p
	n	Mean±SD	n	Mean±SD	
Age		66.77±6.393		67.33±6.276	0.713
Gender					0.345
Female	21		23		
Male	9		16		
BMI (kg/m^2)	31.53		31.20		0.701
Side					0.387
Right	13		21		
Left	17		18		
Pre-op Hgb		13.24±0.79		13.50±0.82	0.195
Pre-op Hct		39.63±2.29		40.34±2.44	0.220
TBL (mL)		4891.18±585.96		4935.95±462.08	0.728
Post-op day 1 Hgb (g/dl)		11.93±0.76		12.06±0.81	0.499
Post-op day 2 Hgb (g/dl)		10.53±0.77		10.65±0.89	0.561
Post-op day 3 Hgb (g/dl)		9.04±0.78		9.16±0.89	0.561

Hgb: hemoglobin; SD: standard deviation; BMI: body mass index; Hct: hematocrit value; TBL: total blood volume.

Table 2. Comparison of groups in terms of bleeding-related parameters and transfusion amount.

Bleeding parameters	Resurfaced 30 patients	Not resurfaced 39 patients	
	Mean±SD	Mean±SD	p
Postoperative drain volume (mL)	443.00±128.952	474.10±104.974	0.273
Hidden blood loss (mL)	569.405±159.421	584.338±160.918	0.702
Total blood loss (mL)	716.665±161.851	744.704±163.000	0.480
Comparison of groups according to transfusion amount			
Transfusion (U)			**0.881**
1	10	9	
2	3	2	
3–4	0	0	

SD: standard deviation.

significant effect of patellar resurface surgery on bleeding was demonstrated[6]. However, in this study, it was stated that there was no difference in bleeding by evaluating only the Hct levels of the patients, whereas the methods calculated in the evaluation of bleeding were not used in the current literature[5,16,17]. In another study comparing patients with and without patellar resurfacing, only the difference in intraoperative bleeding was examined in terms of bleeding, and it was stated that there was no difference[12]. However, this information is not useful for many surgeons who use tourniquets during the operation, as in our clinic. Another study, which not only focusing on patellar resurfacing but also investigating the effect of many factors on bleeding, has stated that patellar resurfacing increases the amount of bleeding, but not the amount of transfusion[13].

Another important finding of our study is that there was no significant difference in the amount of blood transfused between the groups with and without patellar resurfacing. Expected TBL in patients who had undergone total joint arthroplasty ranges between 590 and 1,800 mL[18]. This situation should be taken into account when planning patellar resurfacing in elderly patients undergoing TKA and having various comorbidities[16]. There may also be medical conditions where blood transfusion may be contraindicated or patients who refuse blood transfusion for religious reasons, such as Jehovah's witnesses, or patients who cannot be transfused[6,19]. In such cases, if the surgeon prefers the patellar component, they should provide sufficient evidence to the patients that it will not increase bleeding and require additional transfusion. However, there are very limited studies on this subject in the current literature, and the results of the studies are contradictory. Therefore, we think that the results of our study will be beneficial for surgeons considering patellar resurfacing in patients who cannot receive blood transfusion.

In our study, we evaluated the relationship between postoperative drainage volume and HBL or TBL. A positive correlation was found between postoperative drainage volume and TBL. The reason for this positive correlation may be that TBL plays a major role in postoperative drainage volume. However, we did not find a significant correlation between postoperative drainage volume and HBL in our study. In a study investigating the effect of TXA on bleeding in patients undergoing TKA, a positive correlation between HBL and postoperative drainage volume was found, the finding inconsistent with our study[5]. In contrast, while TXA was used in only some of the patients in the mentioned study, TXA was used in all patients in our study.

The main limitation of our study is that it is retrospective and single centered. Moreover, the postoperative drainage volumes of the patients were obtained from the data in the patient file recorded by the clinical nurse on duty. Another limitation may be that the same person did not measure the postoperative drainage volumes. However, the homogeneity of the demographic data of the groups compared and the application of standard surgical procedures by a single orthopedic surgeon to the patients can be ranked among the strengths of our study.

CONCLUSION

Patellar component application in patients who underwent TKA does not change the blood loss of the patients.

AUTHORS' CONTRIBUTIONS

SA: Conceptualization, Data curation, Formal Analysis, Writing – original draft. **DC:** Data curation, Writing – review & editing. **SK**: Formal Analysis, Writing – original draft. **ZO**: Data curation, Writing – review & editing. **HO**: Writing – review & editing. **OB:** Writing – review & editing.

REFERENCES

1. Grosso MJ, Trofa DP, Danoff JR, Hickernell TR, Murtaugh T, Lakra A, et al. Tranexamic acid increases early perioperative functional outcomes after total knee arthroplasty. Arthroplast Today. 2017;4(1):74-7. https://doi.org/10.1016/j.artd.2017.05.009
2. Kornuijt A, de Kort GJL, Das D, Lenssen AF, van der Weegen W. Recovery of knee range of motion after total knee arthroplasty in the first postoperative weeks: poor recovery can be detected early. Musculoskelet Surg. 2019;103(3):289-97. https://doi.org/10.1007/s12306-019-00588-0
3. Search data of blood loss. PubMed [Internet]. Available from: https://pubmed.ncbi.nlm.nih.gov/?term=blood+loss
4. Cankaya D, Dasar U, Satilmis AB, Basaran SH, Akkaya M, Bozkurt M. The combined use of oral and topical tranexamic acid is a safe, efficient and low-cost method in reducing blood loss and transfusion rates in total knee arthroplasty. J Orthop Surg (Hong Kong). 2017;25(1):2309499016684725. https://doi.org/10.1177/2309499016684725
5. Turan S, Bingöl O. Is tranexamic acid effective on hidden blood loss in patients during total knee arthroplasty? Jt Dis Relat Surg. 2020;31(3):488-93. https://doi.org/10.5606/ehc.2020.78024
6. Girdler SJ, Glezos CD. Does patella resurfacing affect postoperative blood loss in patients undergoing total knee replacement? Tech Orthop. 2020;35(2):134-6. https://doi.org/10.1097/BTO.0000000000000328
7. He JY, Jiang LS, Dai LY. Is patellar resurfacing superior than nonresurfacing in total knee arthroplasty? A meta-analysis of randomized trials. Knee. 2011;18(3):137-44. https://doi.org/10.1016/j.knee.2010.04.004
8. Maney AJ, Koh CK, Frampton CM, Young SW. Usually, selectively, or rarely resurfacing the patella during primary total knee arthroplasty: determining the best strategy. J Bone Joint Surg Am. 2019;101(5):412-20. https://doi.org/10.2106/JBJS.18.00389
9. Fraser JF, Spangehl MJ. International rates of patellar resurfacing in primary total knee arthroplasty, 2004–2014. J Arthroplasty. 2017;32(1):83-6. https://doi.org/10.1016/j.arth.2016.06.010
10. Putman S, Boureau F, Girard J, Migaud H, Pasquier G. Patellar complications after total knee arthroplasty. Orthop Traumatol Surg Res. 2019;105(1S):S43-51. https://doi.org/10.1016/j.otsr.2018.04.028
11. Healy WL, Wasilewski SA, Takei R, Oberlander M. Patellofemoral complications following total knee arthroplasty. Correlation with implant design and patient risk factors. J Arthroplasty. 1995;10(2):197-201. https://doi.org/10.1016/s0883-5403(05)80127-5
12. Jia C, Ni M, Fu J, Li X, Li X, Chai W, et al. A comparative study on effectiveness of patellar resurfacing against non-resurfacing in total knee arthroplasty. Zhongguo Xiu Fu Chong Jian Wai Ke Za Zhi. 2018;32(4):394-9. https://doi.org/10.7507/1002-1892.201708128
13. Saengjumrut P, Suwanjutah T, Ingkutanonta P, Sopakhayang W, Chaluay S, Benchasiriluck P, et al. Factors related to blood loss in total knee arthroplasty. J Southeast Asian Med Res. 2018;2(2):85-91. https://doi.org/10.55374/jseamed.v2i2.13
14. Nadler SB, Hidalgo JH, Bloch T. Prediction of blood volume in normal human adults. Surgery. 1962;51(2):224-32. PMID: 21936146
15. Gross JB. Estimating allowable blood loss: corrected for dilution. Anesthesiology. 1983;58(3):277-80. https://doi.org/10.1097/00000542-198303000-00016
16. Sehat KR, Evans R, Newman JH. How much blood is really lost in total knee arthroplasty?. Correct blood loss management should take hidden loss into account. Knee. 2000;7(3):151-5. https://doi.org/10.1016/s0968-0160(00)00047-8
17. Hu Y, Li Q, Wei BG, Zhang XS, Torsha TT, Xiao J, et al. Blood loss of total knee arthroplasty in osteoarthritis: an analysis of influential factors. J Orthop Surg Res. 2018;13(1):325. https://doi.org/10.1186/s13018-018-1038-0
18. Dong Q, Zhang Y, Sun X, Hu F. The effectiveness and safety of aminocaproic acid for reducing blood loss in total knee and hip arthroplasty: a meta-analysis. Int J Surg. 2018;52:156-63. https://doi.org/10.1016/j.ijsu.2018.02.035
19. Issa K, Banerjee S, Rifai A, Kapadia BH, Harwin SF, McInerney VK, et al. Blood management strategies in primary and revision total knee arthroplasty for Jehovah's Witness patients. J Knee Surg. 2013;26(6):401-4. https://doi.org/10.1055/s-0033-1353994

ORIGINAL ARTICLE

https://doi.org/10.1590/1806-9282.20220516

Association of 25-hydroxyvitamin D with hematological profile and anthropometry in patients with glioma

Saman Shahid[1]*, Muhammad Anwar Chaudary[2]

SUMMARY

OBJECTIVE: Gliomas are immune system suppressive tumors, and the role of vitamin D is pivotal in the immune system. This study aimed to observe if there is any significant association between the serum levels of 25-hydroxyvitamin D with hematological indices and anthropometric measurements.
METHODS: A total of 75 glioma patients were included, and the information was collected on gender, age group, area, socioeconomic status, intake of vitamin D and calcium in food and supplements, skin color, sunlight exposure, body mass index, and muscle strength. A nonparametric Kendall's tau-b correlation test was performed to find a correlation between 25-hydroxyvitamin D levels and blood counts, body mass index, and muscle strength.
RESULTS: The majority of patients (72%) were having low lymphocytes followed by high granulocytes and high white blood cells. The majority were having low levels of both 25-hydroxyvitamin D (84%) and calcium (73%). Patients were mainly from urban areas, and the majority belonged to middle-class families having sedentary lifestyles. The majority of patients were not taking vitamin D supplements. An insufficient amount of sunlight exposure was found in most of them. The majority of the patients were although had normal weight but weak muscle strength (74.6%). An insignificant correlation was found between 25-hydroxyvitamin D levels with the hematological indices or anthropometric measurements in brain tumor patients.
CONCLUSION: Vitamin D is a powerful immune modulator, and there is a great need for sufficient amounts of sunlight exposure and vitamin D-enriched diets to prevent cancer.
KEYWORDS: Glioma. Hydroxycholecalciferols. Lymphocytes. Body Mass Index. Muscle strength.

INTRODUCTION

Gliomas are immune suppressing tumors of the nervous system originating in the glial tissue of the brain generally notorious for carrying a poor prognosis and shorter survival. Vitamins may have a role in the etiopathogenesis of central nervous system (CNS) cancers[1]. The anti-cancer activity occurs through the vitamin D receptor signaling mediated by 1,25-dihydroxyvitamin D[2]. We conducted an epidemiological study to find the prevalence of vitamin D and calcium deficiencies in glioma patients. Vitamin D is a neurosteroid, and it regulates the production of neurotrophic factors, which are responsible for the differentiation and maturation of neurons. Moreover, vitamin D is also a neuroprotective agent as it stimulates phagocytosis of the amyloid-beta peptides and hence attenuates amyloid accumulation in the brain[1,2]. Garland et al.[3] suggested that the levels of calcifediol in a range of 40–60 ng/mL had reduced the risk of breast cancer by 25% and colonic cancer by 27%. Maintaining proper body weight and regular physical activity plays favorably. Notably, 30–50% of all cancers are preventable by healthy dietary intake and lifestyle modification. A higher attained height and excessive body mass index (BMI) is related to a higher risk of gliomas[4].

Hypovitaminosis is associated with decreased muscle strength, and its supplementation in the elderly has been known to increase muscle strength and help with gait[5]. A sedentary lifestyle resulted in a significant decrease in vitamin D levels in the body[6]. A higher BMI had also been related to the increased risk of gliomas[7]. Vitamin D modulates the adaptive immune system so are the leukocytes as immune cells, which participate in innate or adaptive immune systems. Therefore, we wanted to discover if there is any association between the altered levels of 25-hydroxyvitamin D [25(OH)D] and the hematological profile. BMI and muscle strengths are known to be impacted by decreased levels of calcifediol. We conducted a correlation between 25(OH)D levels and anthropometric measurements. There is not much literature available on such association. Some studies have reported the correlation between the grades of glioma and the counts of infiltrating and circulating neutrophils.

[1]National University of Computer and Emerging Sciences, Department of Sciences and Humanities – Lahore, Pakistan.
[2]Punjab Institute of Neurosciences, Department of Neurosurgery – Lahore, Pakistan.
*Corresponding author: drshahidsaman@gmail.com
Conflicts of interest: the authors declare there is no conflicts of interest. Funding: none.
Received on July 14, 2022. Accepted on July 29, 2022.

METHODS

Study design, setting, and patients: This cross-sectional epidemiological study was conducted from January to December 2019 and included 75 histologically confirmed glioma patients from the neurosurgical departments of Punjab Institute of Neurosciences (PINS), Lahore Pakistan, before surgery. Informed consent was taken from all patients for the data collection.

Inclusion/exclusion criteria: All consecutive histologically confirmed glioma patients aged between 25 and 70 years were included before surgery. The patients were not undergoing any chemotherapy or radiotherapy at the time of data collection. We did not include the metastasis cases. Patients with endocrinal abnormalities, previous operation, bone disease, and kidney or liver diseases were excluded. Patients on anti-tuberculous drugs, diuretics, anti-epileptics, bisphosphonates, hypnotics and opioids, chloroquine, and corticosteroids were also excluded.

Background and clinical information: The clinical information was collected through a self-designed proforma. The muscle strength was measured from an electronic, handy dynamometer (model CE-EH101). The dynamometer scale was to categorize muscle strength into normal, weak, or strong categories. A complete blood count (CBC) test was conducted in PINS Biochemistry Laboratory with "Sysmex Hematology Analyzer & Systems" through an automated hematology system. The serum 25(OH)D and calcium levels were conducted from the laboratory of PINS with the "I Chroma II Immune Assay Analyzer" through the kit method. The following normal ranges were considered for the blood counts: white blood cells (WBC): $5–10\times10^{9}$/L; red blood cells (RBC): $4–5\times10^{12}$/L; mean cell volume (MCV): $76–96\times10^{12}$/L; hematocrit (HCT): 36–50%; mean cell hemoglobin concentration (MCHC): 30–35 g/dL; mean corpuscular hemoglobin (MCH): 27–32 pg; lymphocytes (LYM): 25–40%; monocytes (MO): 3–7%; platelet (PLT): $150–400\times10^{9}$/L; and hemoglobin (HGB): 12–20 g/dL. Serum 25(OH)D levels were measured in ng/mL, and the normal range considered was 30–100. Serum calcium levels were measured in mg/dL with the normal range of 8.5–10.5.

Statistical analyses: A nonparametric Kendall's tau-b correlation analysis was performed to find out if any significant association exists between 25(OH)D levels versus blood counts, BMI (underweight, normal weight, overweight, and obese), and muscle strength (weak, normal, and strong).

RESULTS

Demographics: There were 40 (53.3%) male and 35 (46.6%) female patients. The mean age of the patients was 41 years. In all, 20 (26.6%) patients belonged to the age group 25–40 years, 35 (46.6%) patients in 41–55 years, and 20 (26.6%) patients were in 56–70 years. Notably, 10 (13.3%) patients were from rural areas, 50 (66.6%) were from urban, and 15 (20%) were from suburban areas of Lahore. In total, 540 (55.5%) patients belonged to the middle class, 20 (26.66%) patients were poor, and 15 (20%) were from upper-class families.

Histopathology: The following glioma types were reported: astrocytoma (grades II/III), glioblastoma (GBM) (grade IV), ependymoma (grade III), and oligodendroglioma (grade III). Out of 75 patients, there were 22 (29.3%) cases of astrocytoma, 21 (28%) cases of GBM, 17 (22.6%) cases of ependymoma, and 15 (20%) cases of oligodendroglioma.

Vitamin D and calcium intake: Out of 75 patients, the majority (80%) did not take any vitamin D or calcium supplements. A total of 30 (40%) patients have darker skin tone, while 45 (60%) have a light skin tone. Notably, 54% of patients were having a good and regular intake of milk, ghee, fruits, vegetables, yogurt, cheese, and butter; 20% of patients also included the intake of fish with the food; and 26% of patients did not have a regular intake of all these foods.

Around 75% of patients were having exposure to sunlight in summers of up to 15 min only. Up to 25% of patients were having summer sunlight exposure of 30–40 min. In wintertime, around 75% of patients were having sunlight exposure of up to 30 min, whereas 25% were having exposure of 30–90 min.

BMI, muscle strength, and bone health: Table 1 shows the assessments. The majority of patients (51%) were having normal

Table 1. Glioma patients (n=75).

Parameters	Classes	n (%)
BMI	Underweight	8 (10.6)
	Normal weight	38 (50.6)
	Overweight	17 (22.6)
	Obese	12 (16)
Muscle strength	Weak	56 (74.6)
	Normal	16 (21.3)
	Strong	3 (4)
History of bone fracture	Yes	10 (13.3)
	No	65 (86.6)
Lifestyle	Moderately active	30 (40)
	Sedentary lifestyle	45 (60)
Vitamin D/calcium supplements	Yes	15 (20)
	No	60 (80)
25-Hydroxyvitamin D (ng/mL)	Normal levels	12 (16)
	Low levels	63 (84)
Calcium (mg/dL)	Normal levels	20 (26.6)
	Low levels	55 (73)
Skin color	Dark	30 (40)
	Light	45 (60)

weight (normal BMI), whereas 16% were obese. The majority (74.6%) of patients were having weak muscle strength. The majority (87%) of patients did not encounter any bone fracture. Most of the patients (60%) were having a sedentary lifestyle.

Laboratory findings: The majority of patients were having low levels (mean: 14 ng/mL) of serum 25(OH)D (84%) and calcium levels (73%; mean: 7 mg/dL) (Table 1). The majority patients were having low (mean: 13.233) LYM levels (72%), followed by high (mean: 85.164) granulocytes (GR) (59%) and high (mean: 14.57×10^{9}) WBCs (59%) and low (mean: 24.14) MCH and low (10.4) HGB (45%). Notably, 23% were having low (mean: 2) MO, 17% were having high (6.123×10^{12}) RBC and low MCHC (mean: 27.6), and 11% were having high (453×10^{9}) PLT. RBC (67%), MCV (74.6%), HCT (64%), MCHC (69%), MCH (48%), PLT (86%), and HGB (56%) were the most often reported normal values in glioma patients. Also, the normal values of WBC, LYM, MO, and GR were reported between 24 and 37% (see details in Table 2).

Kendall's Tau-b correlation analyses: Kendall's tau-b correlation analysis was conducted between dependent hematological variables' levels (normal/low/high) and independent variables' levels (normal/low/high) of serum 25(OH)D levels. Kendall's tau-b correlation analysis was also conducted to see the correlations between ordinal dependent variables: BMI (underweight/normal weight/overweight/obese) and muscle strength (weak/normal/strong) and independent variables' levels (normal/low/high) of serum 25(OH)D. No statistically significant correlation was found. The detail of the correlations is mentioned in Table 3.

DISCUSSION

Vitamin D metabolites cross the blood-brain barrier, and its receptors are dispersed throughout the brain, examining its role in glioma formation is not implausible[8]. The function of blood vitamin D levels and hematopoietic markers in this

Table 2. Complete blood count profile.

Parameters	Normal range	Glioma patients (n=75)		
		Mean of normal values (n*, PP%**)	Mean of high values (n*, PP%**)	Mean of low values (n*, PP%**)
WBC ($\times10^{9}$/L)	5.00–10.00	8.214	14.57	4.9
		(28, 37.33%)	(44, 58.67%)	(3, 4%)
RBC ($\times10^{12}$/L)	4.00–5.50	4.707	6.123	3.816
		(50, 66.67%)	(13, 17.33%)	(12, 16%)
MCV (fL)	76.0–96.0	82.575	99.567	72.875
		(56, 74.67%)	(3, 4%)	(16, 21.33%)
HCT (%)	36.0–50.0	40.58		32.994
		(48, 64%)	–	(27, 36%)
MCHC (g/dL)	30.00–35.00	33.167	37.65	27.685
		(52, 69.33%)	(10, 13.33%)	(13, 17.33%)
MCH (pg)	27.0–32.0	28.636	32.2	24.144
		(36, 48%)	(5, 6.67%)	(34, 45.33%)
LYM (%)	25.0–40.0	29.722	43.2	13.233
		(18, 24%)	(3, 4%)	(54, 72%)
MO (%)	3.0–7.0	4.917	10.229	2.065
		(23, 30.67%)	(35, 46.67%)	(17, 22.67%)
GR (%)	50.0–75.0	65.4	85.164	22.853
		(22, 29.33%)	(44, 58.67%)	(9, 12%)
PLT ($\times10^{9}$/L)	150–400	274.554	453.5	118
		(65, 86.67%)	(2, 2.67%)	(8, 10.67%)
HGB (g/dL)	12.0–20.0	13.629		10.497
		(42, 56%)	–	(33, 44%)

*n=number of patients. **PP%=percentage prevalence.

Table 3. Correlation between serum 25-hydroxyvitamin D levels and blood counts, body mass index, and muscle strength.

Dependent variables	25-Hydroxyvitamin D levels (normal/low/high)	
	Kendall's tau-b coefficient	p-value
WBC	0.117	0.308
RBC	-0.006	0.959
MCV	0.104	0.362
HCT	-0.134	0.250
MCHC	0.022	0.844
MCH	0.101	0.372
LYM	-0.163	0.154
MO	-0.068	0.536
GR	0.210	0.061
PLT	0.062	0.589
HGB	-0.086	0.459
BMI	0.124	0.258
Muscle strength	-0.035	0.757

setting is debatable and requires a bigger cohort of patient data. Furthermore, the net effect of elevated vitamin D levels above the typical threshold on hematopoiesis is not clearly understood. According to certain studies, there is even a detrimental relationship between hematological parameters and increasing levels of vitamin D[9]. The current study sought to determine whether there is a link between blood counts and aberrant levels of calcifediol in glioma patients prior to surgery. We wanted to affirm these correlations, as some studies reported such results. There could also be links between altered levels of vitamin D with blood counts, or the deficiency of vitamin D can impact blood counts, but in the present data, we did not find any statistically significant correlations. Weak and insignificant results are reported because most of the patients (48–86%) reported normal RBC, MCV, HCT, MCHC, MCH, PLT, and HGB. Some more altered values were found in WBC, MO, and GR, but not greater than 58%. However, the LYMs were depressed in 72% of glioma patients. However, BMI and muscle strengths can be impacted by altered levels of calcifediol. Therefore, we were interested to know whether BMI and muscle strength are interrelated to the low levels of both calcifediol. Half of the patients had a normal range of BMI. We did not report any significant variations in BMI or muscle strength from altered levels of calcifediol. The majority of our patients with GBM were having low levels of serum 25(OH) D (84%) and calcium (73%).

Under normal homeostatic settings, leukocytes remain in the cerebrospinal fluid (CSF) and blood arteries and do not penetrate brain tissue. The only immune cells found in the CNS are macrophages or microglia. For a long time, neutrophils were assumed to have protumoral functions. In many malignancies, the presence of neutrophils and high NLR (neutrophil-to-lymphocyte ratio) is associated with a poor prognosis[10]. In gliomas, the severity of the disease correlates with the counts of infiltrating and circulating neutrophils. This indicates a prognostic and possible protumoral role for these leukocytes. One research identified a significant connection between key hematological measures and vitamin D levels in patients (with restrictive inclusion/exclusion criteria), but with no significant confounders, such as chronic illnesses or disorders that may affect hematological parameters[9]. However, we did not find any significant association between serum 25(OH)D levels with blood indices. On the contrary, other studies have shown that neutrophils orchestrate anti-tumor responses and directly kill tumor cells[11]. GBMs are heavily infiltrated with MO, which are derived from circulation and not from some local transformation. Patients with brain tumors had reported a decreased macrophage-to-lymphocyte ratio. This was attributed to a reduced MO count as the cell-mediated immunity gets suppressed[12]. A significant prognostic indicator reported was the altered HGB level before radiotherapy in cancer patients[13]. Cure et al.[14] reported a strong association between a low vitamin D level and a high mean platelet volume (MPV). Increased PLT indices and deficiency of vitamin D are known to be associated with a higher risk of metabolic syndromes and cardiovascular disease as well[15]. Regarding the relationship between vitamin D and anemia, 25(OH)D and 1,25-dihydroxyvitamin D are found to be linked with low HGB during stages of chronic kidney disease (CKD)[16].

We did not find any statistically significant link between serum 25(OH)D levels with anthropometric measures in our glioma patients. However, few studies reported that obesity was strongly associated and reported with lower levels of vitamin D[17]. BMI and vitamin D levels are inversely proportional as reported by Delle Monache et al.[18]. A significant correlation exists between deficiency of vitamin D and increased risk of bone fractures and poor muscle strength in elders[19]. Vitamin D supplementation is associated with a better prognosis in GBMs. Studies that explain a relationship between the vitamin D receptor protein and the outcome of gliomas are still lacking. In French adults in an urban setting, lack of sunlight exposure and relatively low dietary intake of vitamin D require attention owing to the prevalence of vitamin D deficiency in that community[20]. Klement et al.[21] suggested that low vitamin

D in cancer patients can be enhanced with proper exposure to the sunlight and intake of supplements. They investigated the levels of calcifediol with blood counts and some anthropometric measurements. A strong negative correlation is found between 25(OH)D with leukocytes and C-reactive protein (CRP). A recent study by Disney-Hogg et al.[22] explored the association between dietary factors of vitamin D, immunity, and obesity. However, they did not find any significant link of risk of glioma development with obesity, BMI, type 2 diabetes mellitus, and lipids. Vitamin D deficiency and the reduction of telomere length have also been investigated in some research. Mixed results are observed; therefore, further investigation is recommended. For example, Zigmont et al.[8] found no overall effect of serum 25(OH)D concentration on glioma risk. Mazidi et al.[23] supported a positive correlation of calcifediol with telomere length. Julin et al.[24] reported that age and BMI were inversely associated with telomere length. However, neither 25(OH)D nor 1,25-dihydroxyvitamin D was found to be linked with telomere length[25].

Women showed a stronger linear association between vitamin D and moderate-to-severe physical activity in the highest tertile of activity[26]. A higher BMI had also been related to the increased risk of gliomas[7]. In this study, we gathered information on calcifediol through information on the intake of vitamin D and calcium in foods/supplements, skin color, sunlight exposure, BMI, muscle strength, history of bone fracture, and lifestyle. Vitamin D modulates the adaptive immune system, so are the leukocytes as immune cells, which participate in innate or adaptive immune systems. Therefore, we wanted to discover if there is any association between the altered levels of 25(OH)D and the hematological profile. BMI and muscle strengths are known to be impacted by decreased levels of calcifediol. Therefore, we also included a correlation between 25(OH)D levels and anthropometric measurements (i.e., BMI and muscle strength). There is no much literature available on such association. Some studies have reported the correlation between the grades of glioma and the counts of infiltrating and circulating neutrophils. A decrease in HGB levels, a relative increase in PLT counts, and a reduction in MO counts have also been seen in brain tumors[12]. Moreover, decreased MPV and increased RBC distribution width both are associated with brain tumors[27].

CONCLUSION AND RECOMMENDATIONS

There could be links between altered levels of vitamin D with blood counts, and with anthropometry (BMI and muscle strength), but in the present data, we did not find any statistically significant correlations. Since most of the patients (48–86%) reported normal blood counts, around half patients reported altered WBC, MO, and GR. However, the most disturbed parameter was the LYM (72%). Also, half of the patients had a normal range of BMI. The correlations can also depend on the type of cancer included. We reported data on brain cancer. The majority of glioma patients had low 25(OH)D and calcium levels. The patients usually did not use vitamin D or calcium supplements. As a result, we highly advise patients with brain tumors to take vitamin D supplements. Larger investigations are needed to investigate the possible involvement of vitamin D in glioma patients in conjunction with the other immune busters. Clinical trials to determine optimal dosages are required before they may be used as a supplement in cancer patients. As vitamin D is a powerful immune modulator, there is a great need for sufficient amounts of sunlight exposure and vitamin D-enriched diets as low-cost and cost-effective cancer prevention methods.

ETHICAL CONSIDERATIONS

The study conformed to institutional ethical standards.

AUTHORS' CONTRIBUTIONS

SS: Conceptualization, Formal analysis, Investigation, Methodology, Project administration, Software, Supervision, Validation, Visualization, Writing – original draft. **MAC:** Data curation, Resources, Validation, Visualization, Writing – review & editing.

REFERENCES

1. Yue Y, Creed JH, Cote DJ, Stampfer MJ, Wang M, Midttun Ø, et al. Pre-diagnostic circulating concentrations of fat-soluble vitamins and risk of glioma in three cohort studies. Sci Rep. 2021;11(1):9318. https://doi.org/10.1038/s41598-021-88485-0
2. Holick MF. Vitamin D is not as toxic as was once thought: a historical and an up-to-date perspective. Mayo Clin Proc. 2015;90(5):561-4. https://doi.org/10.1016/j.mayocp.2015.03.015
3. Garland CF, French CB, Baggerly LL, Heaney RP. Vitamin D supplement doses and serum 25-hydroxyvitamin D in the range associated with cancer prevention. Anticancer Res. 2011;31(2):607-11. PMID: 21378345
4. Kyritsis AP, Bondy ML, Levin VA. Modulation of glioma risk and progression by dietary nutrients and antiinflammatory agents. Nutr Cancer. 2011;63(2):174-84. https://doi.org/10.1080/01635581.2011.523807

5. Halfon M, Phan O, Teta D. Vitamin D: a review on its effects on muscle strength, the risk of fall, and frailty. BioMed Res Int. 2015;2015:95324. https://doi.org/10.1155/2015/953241
6. Solis-Urra P, Cristi-Montero C, Romero-Parra J, Zavala-Crichton JP, Saez-Lara MJ, Plaza-Diaz J. Passive commuting and higher sedentary time is associated with vitamin D deficiency in adult and older women: results from Chilean National Health Survey 2016–2017. Nutrients. 2019;11(2):300. https://doi.org/10.3390/nu11020300
7. Bielecka J, Markiewicz-Żukowska R. The influence of nutritional and lifestyle factors on glioma incidence. Nutrients. 2020;12(6):1812. https://doi.org/10.3390/nu12061812
8. Zigmont V, Garrett A, Peng J, Seweryn M, Rempala GA, Harris R, et al. Association between prediagnostic serum 25-hydroxyvitamin D concentration and glioma. Nutr Cancer. 2015;67(7):1120-30. https://doi.org/10.1080/01635581.2015.1073757
9. Olmuşçelik O, Sevindik ÖG. Correlation between serum vitamin D level and dichotomous distribution of hematological parameters in a cohort of 12709 patients. Turk J Med Sci. 2020;50(8):1941-50. https://doi.org/10.3906/sag-2008-124
10. Shen M, Hu P, Donskov F, Wang G, Liu Q, Du J. Tumor-associated neutrophils as a new prognostic factor in cancer: a systematic review and meta-analysis. PLoS One. 2014;9(6):e98259. https://doi.org/10.1371/journal.pone.0098259
11. Massara M, Persico P, Bonavita O, Mollica Poeta V, Locati M, Simonelli M, et al. Neutrophils in gliomas. Front Immunol. 2017;8:1349. https://doi.org/10.3389/fimmu.2017.01349
12. Subeikshanan V, Dutt A, Basu D, Tejus MN, Maurya VP, Madhugiri VS. A prospective comparative clinical study of peripheral blood counts and indices in patients with primary brain tumors. J Postgrad Med. 2016;62(2):86-90. https://doi.org/10.4103/0022-3859.180551
13. Odrazka K, Petera J, Kohlova T, Dolezel M, Vaculikova M, Zouhar M, et al. Prognostic impact of hemoglobin level prior to radiotherapy on survival in patients with glioblastoma. Strahlenther Onkol. 2003;179(9):615-9. https://doi.org/10.1007/s00066-003-1097-x
14. Cumhur Cure M, Cure E, Yuce S, Yazici T, Karakoyun I, Efe H. Mean platelet volume and vitamin D level. Ann Lab Med. 2014;34(2):98-103. https://doi.org/10.3343/alm.2014.34.2.98
15. Park D, Kwon H, Oh SW, Joh HK, Hwang SS, Park JH, et al. Is vitamin D an independent risk factor of nonalcoholic fatty liver disease? A cross-sectional study of the healthy population. J Korean Med Sci. 2017;32(1):95-101. https://doi.org/10.3346/jkms.2017.32.1.95
16. Boronat M, Santana A, Bosch E, Lorenzo D, Riano M, Garcia-Canton C. Relationship between anemia and serum concentrations of calcium and phosphorus in advanced non-dialysis-dependent chronic kidney disease. Nephron. 2017;135(2):97-104. https://doi.org/10.1159/000450892
17. Orces C. The association between body mass index and vitamin D supplement use among adults in the United States. Cureus. 2019;11(9):e5721. https://doi.org/10.7759/cureus.5721
18. Delle Monache S, Di Fulvio P, Iannetti E, Valerii L, Capone L, Nespoli MG, et al. Body mass index represents a good predictor of vitamin D status in women independently from age. Clin Nutr. 2019;38(2):829-34. https://doi.org/10.1016/j.clnu.2018.02.024
19. Visser M, Deeg DJ, Lips P. Low vitamin D and high parathyroid hormone levels as determinants of loss of muscle strength and muscle mass (sarcopenia): the Longitudinal Aging Study Amsterdam. J Clin Endocrinol Metab. 2003;88(12):5766-72. https://doi.org/10.1210/jc.2003-030604
20. Chapuy MC, Preziosi P, Maamer M, Arnaud S, Galan P, Hercberg S, et al. Prevalence of vitamin D insufficiency in an adult normal population. Osteoporos Int. 1997;7(5):439-43. https://doi.org/10.1007/s001980050030
21. Klement RJ, Koebrunner PS, Krage K, Sweeney RA. Low vitamin D status in a cancer patient population from Franconia, Germany. Complement Med Res. 2020;14:1-7. https://doi.org/10.1159/000511993
22. Disney-Hogg L, Sud A, Law PJ, Cornish AJ, Kinnersley B, Ostrom QT, et al. Influence of obesity-related risk factors in the aetiology of glioma. Br J Cancer. 2018;118(7):1020-7. https://doi.org/10.1038/s41416-018-0009-x
23. Mazidi M, Michos ED, Banach M. The association of telomere length and serum 25-hydroxyvitamin D levels in US adults: the National Health and Nutrition Examination Survey. Arch Med Sci. 2017;13(1):61-5. https://doi.org/10.5114/aoms.2017.64714
24. Julin B, Shui IM, Prescott J, Giovannucci EL, De Vivo I. Plasma vitamin D biomarkers and leukocyte telomere length in men. Eur J Nutr. 2017;56(2):501-8. https://doi.org/10.1007/s00394-015-1095-7
25. Richards JB, Valdes AM, Gardner JP, Paximadas D, Kimura M, Nessa A, et al. Higher serum vitamin D concentrations are associated with longer leukocyte telomere length in women. Am J Clin Nutr. 2007;86(5):1420-5. https://doi.org/10.1093/ajcn/86.5.1420
26. Hibler EA, Sardo Molmenti CL, Dai Q, Kohler LN, Warren Anderson S, Jurutka PW, et al. Physical activity, sedentary behavior, and vitamin D metabolites. Bone. 2016;83:248-55. https://doi.org/10.1016/j.bone.2015.11.016
27. Dagistan Y, Dagistan E, Citisli V. Evaluation of simple blood counts as inflammation markers for brain tumor patients. Neurol Neurochir Pol. 2016;50(4):231-5. https://doi.org/10.1016/j.pjnns.2016.03.002

ORIGINAL ARTICLE

https://doi.org/10.1590/1806-9282.220220564

Analysis of risk factors of abdominal wound dehiscence after radical cystectomy

Serdar Kalemci[1]*, Kasim Emre Ergun[1], Fuat Kizilay[1], Bugra Yildiz[1], Adnan Simsir[1]

SUMMARY

OBJECTIVE: Wound dehiscence is associated with high morbidity and mortality. This study aimed to analyze the risk factors and comorbidities in the patients undergoing radical cystectomy with early postoperative wound dehiscence.

METHODS: In all, 539 patients with bladder cancer who underwent radical cystectomy and urinary diversion at a single center between January 2008 and January 2022 were included in the study. The data related to the demographics, medical history, and perioperative clinical features were reviewed. Univariate and multivariate regression analysis was performed to identify risk factors for wound dehiscence.

RESULTS: The mean age of the patients was 64.2 years (22–91). The mean body mass index was 26.4 kg/m^2 (18.7–35.4). Wound dehiscence was observed in 43 (7.9%) of 539 patients. The patients with wound dehiscence had significantly higher mean BMI (27.8 vs. 26.3, p=0.006), ASA scores (p=0.002), history of chronic obstructive pulmonary disease (30.2 vs. 14.3%, p=0.006), diabetes mellitus (44.2 vs. 17.9%, p=0.003), previous abdominal surgery (18.6 vs. 7.7%, p=0.014), and postoperative ileus (58.1 vs. 16.9%, p=0.006). In the multivariable regression model, diabetes mellitus (odds ratio [OR] 4.9, 95%CI 2.3–10.1; p<0.001), postoperative ileus (OR 8.1, 95%CI 4.1–16.5; p<0.001), and chronic obstructive pulmonary disease (OR 2.6, 95%CI 1.2–5.7; p=0.013) were independent predictors of abdominal wound dehiscence following radical cystectomy.

CONCLUSION: Diabetes mellitus, chronic obstructive pulmonary disease, and postoperative ileus were strongly associated with abdominal wound dehiscence following radical cystectomy. Both potential preventive and therapeutic interventions may decrease the risk of wound dehiscence.

KEYWORDS: Urinary bladder neoplasms. Postoperative complications. Surgical wound dehiscence. Cystectomy. Risk factors.

INTRODUCTION

Bladder cancer is the second most common urological malignancy, with urothelial carcinoma accounting for approximately 90% of all primary bladder tumors[1]. The worldwide incidence rate is 9.5 for men and 2.4 for women (per 100,000 person-years)[2]. At the time of diagnosis, 70–75% of patients have a disease localized to the mucosa or submucosa, while 25–30% of patients have a muscle-invasive tumor[3]. Radical cystectomy is the gold standard treatment option for muscle-invasive and high-risk non-muscle-invasive bladder cancer unresponsive to intravesical therapy. Radical cystectomy may lead to serious complications, particularly in the perioperative period. Although radical cystectomy can be performed with minimally invasive methods such as laparoscopic and robot-assisted laparoscopic methods, open radical cystectomy is still the most common treatment method[4,5].

Open radical cystectomy surgery is performed through an abdominal midline incision. An abdominal wall surgical incision is created by cutting through all layers of the abdominal wall. The incidence of abdominal wound dehiscence after open radical cystectomy ranges between 3.5 and 9%[6,7]. Abdominal wound dehiscence is a severe postoperative complication of abdominal surgeries with high morbidity and mortality rates. Despite technological advancement in materials, by constantly improving surgical techniques and precautionary measures, wound dehiscence continues to occur. Moreover, evisceration may occur as a result of abdominal wound dehiscence, requiring immediate surgical treatment. Wound dehiscence can lead to an increase in treatment costs, hospitalization, and re-intervention/readmission rates[8-10]. Several retrospective studies have been conducted to investigate the risk factors for this complication, but the results are contradictory[6,11]. This study aimed to analyze the predictors of the wound dehiscence of the abdominal wall in patients undergoing open radical cystectomy and urinary diversion.

METHODS

A single-center, retrospective study was conducted. We reviewed the electronic data and records of the patients with bladder

[1]Ege University, Faculty of Medicine, Department of Urology – Izmir, Turkey.
*Corresponding author: serdarkalemci@gmail.com
Conflicts of interest: the authors declare there is no conflicts of interest. Funding: none.
Received on July 31, 2022. Accepted on August 03, 2022.

cancer who underwent radical cystectomy and urinary diversion between January 2008 and January 2022 in our department. The patients were divided into two groups based on the presence of abdominal wound dehiscence. The data related to the demographics, medical history, and perioperative clinical features were reviewed. Diabetes mellitus (DM), chronic obstructive pulmonary disease (COPD), and hypertension (HT) were defined as comorbidities and were recorded. Patients smoking cigarettes in the year before admission for surgery were considered smokers. Postoperative ileus (POI) was defined as the insertion of a nasogastric tube for nausea, abdominal distension, vomiting, or failure to tolerate a solid diet in the postoperative period. The American Society of Anesthesiologists (ASA) scores were evaluated by the anesthesiologists.

All radical cystectomy and urinary diversion surgeries were performed with a midline incision. Radical cystectomy included the bladder, seminal vesicles, and prostate in men and the bladder, uterus, both ovaries, and the anterior vaginal wall in women. Pelvic lymphadenectomy was performed in all cases, with the upper limit of lymphadenectomy extending to the common iliac vessels. Abdominal fascial closure was performed in all patients by or under the supervision of experienced urologists. Synthetic absorbable 0 polydioxanone monofilament sutures with running technique and mass closure method were used for all fascial closures. Abdominal dehiscence was defined as a partial or total separation of wound edges after the operation with or without intact fascia.

Statistical analysis

Data were analyzed using SPSS version 20.0 for Windows (SPSS Inc., Chicago, IL, USA). Determination of statistically significant factors was made by univariate and multivariate analysis. Statistical analyses were carried out using an unpaired t-test and the Mann-Whitney U test for univariate analysis. The main analysis of the study was multivariable analysis. Logistic regression analysis was used to estimate the association between categorical variables and postoperative wound dehiscence, and multivariate analysis using linear regression was used for the continuous variables. For each correlation, the odds ratio (OR) with a 95% confidence interval was calculated and reported. A $p<0.05$ was considered statistically significant.

RESULTS

Overall, 539 patients who underwent radical cystectomy and urinary diversion were identified. In descriptive analyses, 492 (91.3%) were male and 47 (8.7%) were female. The mean age of the patients was 64.2 years (range 22–91 years). The mean body mass index (BMI) was 26.4 kg/m^2 (range 18.7–35.4 kg/m^2). Patients with and without wound dehiscence were compared for demographic data, comorbidities, and perioperative outcomes, as reported in Table 1. Urinary diversion included

Table 1. Patient characteristics.

Characteristics	Wound dehiscence (–) (n=496)	Wound dehiscence (+) (n=43)	p-value
Age (years)	64.2±9.3	65.3±8.9	0.429
BMI (kg/m^2)	26.3±3.4	27.8±2.3	0.006
Gender, n (%)			
Male	456 (91.9)	36 (83.7)	0.067
Female	40 (8.1)	7 (16.3)	
ASA score, n (%)			
ASA 1	167(33.7)	4 (9.3)	0.022
ASA 2	305 (61.5)	34 (79.1)	
ASA 3	24 (4.8)	5 (11.6)	
Diversion type, n (%)			
Ileal conduit	437 (88.1)	37 (86)	0.225
Studer neobladder	25 (5)	5 (11.6)	
Ureterocutaneostomy	33 (6.9)	1 (2.6)	
Hypertension, n (%)			
Yes	102 (20.6)	7 (16.3)	0.507
No	394 (79.4)	36 (83.7)	
Diabetes mellitus, n (%)			
Yes	89 (17.9)	19 (44.2)	0.003
No	407 (82.1)	24 (55.8)	
COPD, n (%)			
Yes	71 (14.3)	13 (30.2)	0.006
No	425 (85.7)	30 (69.8)	
POI, n (%)			
Yes	84 (16.9)	25 (58.1)	0.001
No	412 (83.1)	18 (41.9)	
Previous surgery, n (%)			
Yes	38 (7.7)	8 (18.6)	0.122
No	458 (92.3)	35 (81.4)	
Status of smoking, n (%)			
Yes	188 (37.9)	14 (32.6)	0.487
No	308 (62.1)	29 (67.4)	
Operative time (min)	336±41.4	339±40.6	0.731
Length of hospital stay (days)	15.4±3.7	25.6±3.1	0.001

BMI: body mass index; ASA: American Society of Anesthesiologists; COPD: chronic obstructive pulmonary disease; POI: postoperative ileus.

ileal conduit in 474 (87.9%), ileal neobladder in 31 (5.7%), and ureterocutaneostomy in 34 (6.3%) patients. The mean operation time was 337 min (range 210–450 min).

Wound dehiscence was observed in 43 (7.9%) of 539 patients. The median day of diagnosis of wound dehiscence was 7.4 days (range 5–10 days) after the operation. Notably, 14 (32.5%) patients underwent a surgical revision for abdominal evisceration. The mean length of hospital stay was significantly longer in patients with wound dehiscence (25.6±3.1 days vs. 15.4±3.7 days, p<0.001).

The patients in the wound dehiscence group had higher mean BMI (27.8 vs. 26.3 kg/m^2, p=0.006) and ASA score (p=0.002). History of COPD (30.2 vs. 14.3%, p=0.006), DM (44.2 vs. 17.9%, p=0.003), previous abdominal surgery (18.6 vs. 7.7%, p=0.014), and POI (58.1 vs. 16.9%, p=0.006) were also higher in this group. There was no difference between the two groups in terms of the history of HT, duration of operation, type of urinary diversion, and status of smoking. In the multivariable regression model, DM (OR 4.9, 95%CI 2.3–10.1; p<0.001), POI (OR 8.1, 95%CI 4.1–16.5; p<0.001), and COPD (OR 2.6, 95%CI 1.2–5.7; p=0.013) were independent predictors of abdominal wound dehiscence following radical cystectomy (Table 2).

DISCUSSION

Although the use of minimally invasive techniques such as laparoscopic and robot-assisted laparoscopic radical cystectomy has been increased in the past two decades, open radical cystectomy is still the gold standard treatment for muscle-invasive and high-risk non-muscle-invasive bladder cancer unresponsive to intravesical therapy. Radical cystectomy is a complicated procedure with a high rate of risk and significant morbidity. Abdominal wound dehiscence is a rare but laborious postoperative complication after radical cystectomy. Our study indicated the importance of prognostic factors in abdominal wound dehiscence. The major finding of our study was that POI and comorbidities such as DM and COPD were the independent prognostic factors associated with abdominal wound dehiscence.

Table 2. Risk-adjusted analysis of predictors of wound dehiscence after radical cystectomy.

Variables	Odds ratio	95% confidence interval	p-value
DM	4.9	2.3–10.1	<0.001
COPD	2.6	1.2–5.7	0.013
POI	8.1	4.1–16.5	<0.001
Previous surgery	1.9	0.7–4.9	0.172

Dehiscence is the partial or complete separation of previously approximated wound margins caused by a failure of adequate wound healing. The basis of wound dehiscence is similar to the causes of inadequate wound healing and includes infection, increased abdominal pressure, DM, smoking, and obesity[12,13]. We found that POI is also an important predictive factor in the etiology of wound dehiscence since it increases intra-abdominal pressure in the postoperative period. We found the incidence of wound dehiscence following radical cystectomy to be 7.8%, which was similar to that found by the previous studies[7,11].

Obesity increases the risk of wound dehiscence. The association between obesity and wound healing has long been determined in the literature[14]. We found that patients with a higher BMI have the highest rates of wound dehiscence. Prior to surgery, the patient's nutrition intake should be optimized to reduce the risk of wound dehiscence. These patients may benefit from dietary supplementation with vitamins and zinc[14]. DM-related microvascular dysfunction may impair regular blood flow, resulting in poor wound perfusion. Hyperglycemia also raises the risk of wound infection, which slows the healing process[15]. In our study, we found that DM was a predictor of wound dehiscence. Preoperative blood glucose control and postoperative blood glucose level monitoring appear to be effective in preventing wound complications. Moreover, it is well established that older patients are at greater risk of complications after radical cystectomy[16]. However, a large series of radical cystectomies showed that patients' age did not predict postoperative wound complications[6,11]. Age was not found to have a significant effect on our cohort. This finding may be explained by the fact that patients undergoing radical cystectomy are mostly within the same decade of age. Furthermore, a recent predictive model emphasized the five-factor model (i.e., male gender, infection, COPD, smoking, and overweight) for estimation of the incidence of wound dehiscence risk following radical cystectomy[17].

In our study, the risk of wound dehiscence increased in patients with COPD, which was consistent with the previous studies[6]. Wound healing may be impaired in patients with COPD since they have low oxygen levels and are usually long-term smokers[18]. Moreover, patients with COPD have a high risk of postoperative atelectasis and pneumonia, which may cause intense cough[19]. This intense cough in the postoperative period causes an increase in intra-abdominal pressure, which may lead to wound dehiscence. In the treatment of these patients, regional anesthesia should be used whenever possible since it provides both postoperative lung rehabilitation and pain management[20]. Similar to COPD, smoking can lead to both impaired wound healing and pulmonary complications

in the postoperative period. To prevent complications due to intense cough in the postoperative period, quitting smoking for 4–6 weeks before the operation reduces postoperative pulmonary complications[21].

The type of abdominal closure may play an important role in wound complications. In our experience, we use slowly absorbable monofilament (polydioxanone) sutures with continuous technique and mass closure method for abdominal wall closure after laparotomy. In a Cochrane review of 55 randomized trials (19,174 patients), no evidence was found that suture absorption (absorbable vs. nonabsorbable sutures, or slow vs. fast absorbable sutures), closure method (mass vs. layered), or closure technique (continuous vs. interrupted) resulted in any difference in the risk of wound complications[22]. However, only about one-half of the included trials (26) enrolled patients who underwent midline incisions exclusively. Preventive strategies such as negative pressure wound therapy and prophylactic retention sutures in patients undergoing radical cystectomy seem feasible[23,24].

The incidence/definition of POI after radical cystectomy is highly variable, and the incidence of POI ranges from 1.5 to 23.5%[25]. POI is characterized by abdominal distention and bloating, nausea, vomiting, and delayed passage of flatus and defecation. Increased intra-abdominal pressure due to prolonged POI causes more strain on the wound margins, causing the sutures to injure the muscles and fascia. The choice of anesthesia and postoperative analgesia method also affects the development of prolonged POI. It has been shown that patients with epidural catheters have been found to have reduced recovery time to return to normal gastrointestinal function[26]. Moreover, patients who receive alvimopan (a selective peripherally acting mu-opioid receptor antagonist) after radical cystectomy had quicker bowel recovery[27].

The study has certain limitations, the most important being its retrospective nature. Considering the small number of patients with these risk factors, another limitation is the lack of information about hypoproteinemia, preoperative steroid use, and wound infection, which are shown to be risk factors for wound dehiscence. Another limitation is that although the same closure technique is used in each patient, this procedure may be performed by different surgeons.

CONCLUSION

Wound dehiscence is a severe complication with a low incidence but significant morbidity, and it increases treatment costs and length of hospital stay. In the literature, there is a lack of evidence about prognostic factors for abdominal wound dehiscence in patients undergoing radical cystectomy. This study adds new data about the predictors of wound dehiscence risk after radical cystectomy. We identified POI and comorbidities such as DM and COPD as independent risk factors for abdominal wound dehiscence following radical cystectomy. Preoperative identification of these risk factors and taking necessary precautions may help prevent this challenging complication after radical cystectomy.

AUTHORS' CONTRIBUTION

SK: Conceptualization, Data curation, Formal Analysis, Investigation, Methodology, Project administration, Writing – original draft, Writing – review & editing. **KEE:** Formal Analysis, Investigation, Writing – original draft. **FK:** Formal Analysis, Investigation, Resources. **BY:** Data curation, Project administration, Supervision. **AS:** Project administration, Supervision.

REFERENCES

1. Burger M, Catto JW, Dalbagni G, Grossman HB, Herr H, Karakiewicz P, et al. Epidemiology and risk factors of urothelial bladder cancer. Eur Urol. 2013;63(2):234-41. https://doi.org/10.1016/j.eururo.2012.07.033
2. Ferlay J, Steliarova-Foucher E, Lortet-Tieulent J, Rosso S, Coebergh JW, Comber H, et al. Cancer incidence and mortality patterns in Europe: estimates for 40 countries in 2012. Eur J Cancer. 2013;49(6):1374-403. https://doi.org/10.1016/j.ejca.2012.12.027
3. Compérat E, Larré S, Roupret M, Neuzillet Y, Pignot G, Quintens H, et al. Clinicopathological characteristics of urothelial bladder cancer in patients less than 40 years old. Virchows Arch. 2015;466(5):589-94. https://doi.org/10.1007/s00428-015-1739-2
4. Gill IS, Cacciamani GE. The changing face of urologic oncologic surgery from 2000–2018 (63 141 patients) - impact of robotics. Eur Urol Suppl. 2019;18(1):e656-7. https://doi.org/10.1016/S1569-9056(19)30485-3
5. Jong IJ. Jaarverslag cystectomieregistratie NVU 2017. Tijdschr Urol. 2019;9:56-67. https://doi.org/10.1007/s13629-018-0241-4
6. Meyer CP, Rios Diaz AJ, Dalela D, Hanske J, Pucheril D, Schmid M, et al. Wound dehiscence in a sample of 1 776 cystectomies: identification of predictors and implications for outcomes. BJU Int. 2016;117(6B):E95-101. https://doi.org/10.1111/bju.13213
7. Novotny V, Hakenberg OW, Wiessner D, Heberling U, Litz RJ, Oehlschlaeger S, et al. Perioperative complications of radical cystectomy in a contemporary series. Eur Urol. 2007;51(2):397-401. https://doi.org/10.1016/j.eururo.2006.06.014
8. van Ramshorst GH, Nieuwenhuizen J, Hop WC, Arends P, Boom J, Jeekel J, et al. Abdominal wound dehiscence in adults: development and validation of a risk model. World J Surg. 2010;34(1):20-7. https://doi.org/10.1007/s00268-009-0277-y
9. Zoucas E, Lydrup ML. Hospital costs associated with surgical morbidity after elective colorectal procedures: a retrospective observational cohort study in 530 patients. Patient Saf Surg. 2014;8(1):2. https://doi.org/10.1186/1754-9493-8-2

10. Rosen AK, Loveland S, Shin M, Shwartz M, Hanchate A, Chen Q, et al. Examining the impact of the AHRQ Patient Safety Indicators (PSIs) on the Veterans Health Administration: the case of readmissions. Med Care. 2013;51(1):37-44. https://doi.org/10.1097/MLR.0b013e318270c0f7
11. Mazzone E, Preisser F, Nazzani S, Tian Z, Zaffuto E, Gallina A, et al. The effect of age and comorbidities on early postoperative complications after radical cystectomy: a contemporary population-based analysis. J Geriatr Oncol. 2019;10(4):623-31. https://doi.org/10.1016/j.jgo.2019.04.011
12. Pavlidis TE, Galatianos IN, Papaziogas BT, Lazaridis CN, Atmatzidis KS, Makris JG et al. Complete dehiscence of the abdominal wound and incriminating factors. Eur J Surg. 2001;167(5):351-4. https://doi.org/10.1080/110241501750215221
13. Aksamija G, Mulabdic A, Rasic I, Aksamija L. Evaluation of risk factors of surgical wound dehiscence in adults after laparotomy. Med Arch. 2016;70(5):369-72. https://doi.org/10.5455/medarh.2016.70.369-372
14. Pierpont YN, Dinh TP, Salas RE, Johnson EL, Wright TG, Robson MC, et al. Obesity and surgical wound healing: a current review. ISRN Obes. 2014;2014:638936. https://doi.org/10.1155/2014/638936
15. Black E, Vibe-Petersen J, Jorgensen LN, Madsen SM, Agren MS, Holstein PE, et al. Decrease of collagen deposition in wound repair in type 1 diabetes independent of glycemic control. Arch Surg. 2003;138(1):34-40. https://doi.org/10.1001/archsurg.138.1.34
16. Novotny V, Zastrow S, Koch R, Wirth MP. Radical cystectomy in patients over 70 years of age: impact of comorbidity on perioperative morbidity and mortality. World J Urol. 2012;30(6):769-76. https://doi.org/10.1007/s00345-011-0782-0
17. Nasrallah AA, Mansour M, Abou Heidar NF, Ayoub C, Najdi JA, Tamim H, et al. Risk factors for wound dehiscence following radical cystectomy: a prediction model. Ther Adv Urol. 2021;13:17562872211060570. https://doi.org 10.1177/17562872211060570
18. Sørensen LT. Wound healing and infection in surgery. The clinical impact of smoking and smoking cessation: a systematic review and meta-analysis. Arch Surg. 2012;147(4):373-83. https://doi.org/10.1001/archsurg.2012.5
19. Wong DH, Weber EC, Schell MJ, Wong AB, Anderson CT, Barker SJ. Factors associated with postoperative pulmonary complications in patients with severe chronic obstructive pulmonary disease. Anesth Analg. 1995;80(2):276-84. https://doi.org/10.1097/00000539-199502000-00013
20. Maddali MM. Chronic obstructive lung disease: Perioperative management. Middle East J Anesthesiol. 2008;19(6):1219-39. PMID: 18942241
21. Nakagawa M, Tanaka H, Tsukuma H, Kishi Y. Relationship between the duration of the preoperative smoke-free period and the incidence of postoperative pulmonary complications after pulmonary surgery. Chest. 2001;120(3):705-10. https://doi.org/10.1378/chest.120.3.705
22. Patel SV, Paskar DD, Nelson RL, Vedula SS, Steele SR. Closure methods for laparotomy incisions for preventing incisional hernias and other wound complications. Cochrane Database Syst Rev. 2017;11(11):CD005661. https://doi.org/10.1002/14651858.CD005661.pub2
23. Khorgami Z, Shoar S, Laghaie B, Aminian A, Hosseini Araghi N, Soroush A. Prophylactic retention sutures in midline laparotomy in high-risk patients for wound dehiscence: a randomized controlled trial. J Surg Res. 2013;180(2):238-43. https://doi.org/10.1016/j.jss.2012.05.012
24. Joice GA, Tema G, Semerjian A, Gupta M, Bell M, Walker J, et al. Evaluation of incisional negative pressure wound therapy in the prevention of surgical site occurrences after radical cystectomy: a new addition to enhanced recovery after surgery protocol. Eur Urol Focus. 2020;6(4):698-703. https://doi.org/10.1016/j.euf.2019.09.016
25. Ramirez JA, McIntosh AG, Strehlow R, Lawrence VA, Parekh DJ, Svatek RS. Definition, incidence, risk factors, and prevention of paralytic ileus following radical cystectomy: a systematic review. Eur Urol. 2013;64(4):588-97. https://doi.org/10.1016/j.eururo.2012.11.051
26. Guay J, Nishimori M, Kopp S. Epidural local anaesthetics versus opioid-based analgesic regimens for postoperative gastrointestinal paralysis, vomiting and pain after abdominal surgery. Cochrane Database Syst Rev. 2016;7(7):CD001893. https://doi.org/10.1002/14651858.CD001893.pub2
27. Lee CT, Chang SS, Kamat AM, Amiel G, Beard TL, Fergany A, et al. Alvimopan accelerates gastrointestinal recovery after radical cystectomy: a multicenter randomized placebo-controlled trial. Eur Urol. 2014;66(2):265-72. https://doi.org/10.1016/j.eururo.2014.02.036

ORIGINAL ARTICLE

https://doi.org/10.1590/1806-9282.20220654

Investigation of allele frequencies of polymorphic variants in genes that are related to polycystic ovary syndrome

Abdulkadir Rabiu Adam[1], Burcu Ozbakir[2,3], Ali Cenk Ozay[2,3], Pinar Tulay[1,3*]

SUMMARY

OBJECTIVE: Polycystic ovary syndrome is a hormonal disorder that normally affects women of reproductive age in the range of 18–44 years. This study aimed to investigate the allelic frequencies of two polymorphisms, *IRS rs18012781* and *INSR rs1799817*, which are suspected to be involved in polycystic ovary syndrome.

METHODS: The samples were obtained from the patients admitted to the Near East University Hospital, Department of Gynecology and Obstetrics. The samples were divided into two groups: control and polycystic ovary syndrome groups. Blood samples were collected from 55 women in the control group and 65 samples from the patient group. DNA from whole blood was obtained. The allelic frequencies of single-nucleotide polymorphisms were determined using real-time PCR. Results were presented as the heterozygous and homozygous state of the single-nucleotide polymorphisms.

RESULTS: There were no significant differences in the allelic frequencies of the single-nucleotide polymorphisms between the patient and control groups. Further statistical analysis investigating the *INSR* Tm using the Mann-Whitney U test value revealed that there was no difference in the homozygous and heterozygous state of *INSR rs1799817*. The result of this study showed that there was no statistically significant difference between the allelic frequencies of *IRS1 rs1801278* and *INSR rs1799817* between the patient and control groups.

CONCLUSION: These single-nucleotide polymorphisms do not seem to modify the risk of polycystic ovary syndrome, and they cannot be used as a marker in clinical circumstances to evaluate the possible occurrence of polycystic ovary syndrome.

KEYWORDS: Polymorphism, genetic. Polycystic ovary syndrome. Insulin resistance. Genetic testing.

INTRODUCTION

Polycystic ovary syndrome (PCOS) is one of the underdiagnosed and underrated medical conditions that affect women around the world. PCOS is a heterogeneous condition that causes intense endocrine and reproductive malfunction. It commonly affects women of reproductive age in the range of 18–44 years. The gross effects of this condition can lead to hormonal complexities, such as dysfunctional menstrual cycles that may lead to infertility, obesity, hirsutism, and acne. The diagnosis of PCOS is performed following the Rotterdam Criteria and the Androgen Excess Society Criteria[1]. Furthermore, PCOS is associated with metabolic abnormalities as well as obesity[2,3]. However, management of this syndrome varies based on observable symptoms. PCOS is usually not diagnosed unless the patient encounters other related medical challenges, such as alopecia, hirsutism, androgenic acne, or infertility[4].

PCOS is shown to be clustered in families. Numerous studies are carried out to identify the ultimate etiology and the genetic background of PCOS[5]. However, the molecular regulation of this disease is not well understood. All the genes that function in oogenesis and ovulation may have a role in the development of PCOS. Some of these genes are the luteinizing hormone/choriogonadotropin receptor (*LHCGR*), estrogen receptor (*ER*), and androgen receptor (*AR*). In addition to these genes involved in gametogenesis, genes involved in insulin homeostasis, such as insulin receptor substrate 1 (*IRS1*) and insulin receptor (*INSR*), contribute to the pathogenesis of PCOS[6]. Furthermore, recent studies revealed that single-nucleotide polymorphisms (SNPs) may be important for evaluating PCOS susceptibility. Therefore, this study aimed to investigate the allelic frequencies of SNPs within genes associated with PCOS.

METHODS

Sample collection

Ethical approval was granted by the Institution Review Board of Near East University (YDU/2019/67-784). The samples

[1]Yakın Doğu Üniversitesi, Faculty of Medicine, Department of Medical Genetics – Nicosia, Cyprus.
[2]Yakın Doğu Üniversitesi, Faculty of Medicine, Department of Obstetrics and Gynecology – Nicosia, Cyprus.
[3]Yakın Doğu Üniversitesi, DESAM Research Institute – Nicosia, Cyprus.
*Corresponding author: pinar.tulay@neu.edu.tr
Conflicts of interest: the authors declare there is no conflicts of interest. Funding: none.
Received on July 28, 2022. Accepted on July 31, 2022.

required for this study were obtained from patients of Near East University Hospital, Department of Obstetrics and Gynecology. Informed consent was obtained from each patient. Clinical information of the patient was collected, and body mass indexes were reported. The samples to be studied were divided into two groups: the control group consisting of normal ovulation and non-obese women, and the patient group involving non-obese patients with PCOS. Blood samples were collected from 55 women in the control group and from 65 women included in the patient group. DNA from whole blood was obtained. The allelic frequencies of SNPs in two genes associated with PCOS were determined using real-time PCR.

DNA extraction from blood samples

DNA from each sample was extracted using an Invitrogen pure link genomic DNA mini kit (Invitrogen, USA) following the manufacturer's protocol. The concentration of the DNA was measured using NanoDrop (Thermo Scientific, Pittsburg, USA) at a wavelength of 260 nm (OD_{260}). The purity and quality were evaluated by the 230/260 ratio.

PCR amplification

Real-time PCR was conducted in order to identify the allelic frequencies at the particular SNP sites of the polymorphic genes, *IRS1* and *INSR*, which are associated with PCOS. Primer sequences are listed in Table 1. The reaction mixture consisted of 5 µl of master mix (LightCycler 480 SYBR Green, Roche), 0.8 µl of both forward and reverse primer (Table 1, final concentration of 0.25 µM), 0.6 µl of $MgCl_2$, and 0.8 µl of H_2O were included in the reaction mixture. A volume of 2 µl of the extracted DNA was added to each reaction. All the PCRs were set up in a laminar flow hood in order to avoid contamination. The PCR condition is shown in Table 2. The allelic frequencies of the two SNPs within two genes were analyzed using the high-resolution melting (HRM) method, and the thermal cycler software was used to obtain the cycle of threshold (Ct) and melting temperature (Tm) values.

Statistical analysis

Statistical packages for the social sciences (SPSS version 10, Chicago, IL, USA) were used in this study. Descriptive statistics and an independent sample test of the Mann-Whitney U test were performed. The results were considered statistically significant if $p \leq 0.05$.

RESULTS

This study was designed to investigate the allelic frequencies for the polymorphic variant genes that are associated with PCOS. A total number of 120 blood samples were collected. Of these, 65 were diagnosed with PCOS and 55 were included in the control group, who did not present any signs of PCOS. The average age was 20 years and the average body mass index for all the patients and the control group was 17. The PCOS patients were diagnosed by correcting their hormonal levels as well as by vaginal ultrasonography.

For each amplification, the cycle of threshold (Ct) was recorded. Ct indicates the total amount of cycle required for the fluorescent signal to cross the threshold. Likewise, for each amplification, melting temperature (Tm) values were recorded. Tm represents the melting temperature when the DNA is 50% double-stranded and 50% single-stranded. In HRM analysis, following PCR amplification, the amplicons produced are subjected to a gradual melting analysis. This enables the emission of fluorescence that is detected by real-time PCR equipment. These melt curves have different shapes due to the differences in the Tm values.

In this study, a total of 79.3% of the patients were shown to be homozygous for *IRS1 rs1801278*, respectively (Figure 1, Tables 3 and 4). There was no significant

Table 1. Details of primers used.

Primer name	Sequence (forward primer)	Sequence (reverse primer)
IRS1 rs1801278	GGAAGAGACTGGCACTGAGG	CTGACGGGGACAACTCATCT
INSR rs1799817	GGTGAAGACGGTCAACGAGT	AGAAAGGGAAGGGTCAGGAA

Table 2. PCR cycling conditions used in the amplification of *IRS* and *INSR* sites.

PCR conditions	Denaturation	Annealing	Extension	HRM
Temperature/time	95 for 10 min	95 for 10 s	72 for 25 s	95 for 1 h
				40 for 1 h
				65 for 1 s
				97 for 1 s
Cycle	1	40		

Figure 1. (A) PCR-HRM image showing melting curve analysis of the PCR products of the homozygote samples for IRS1 rs1801278. (B) PCR-HRM image showing melting curve analysis of the PCR products of the homozygote samples for different alleles of IRS1 rs1801278.

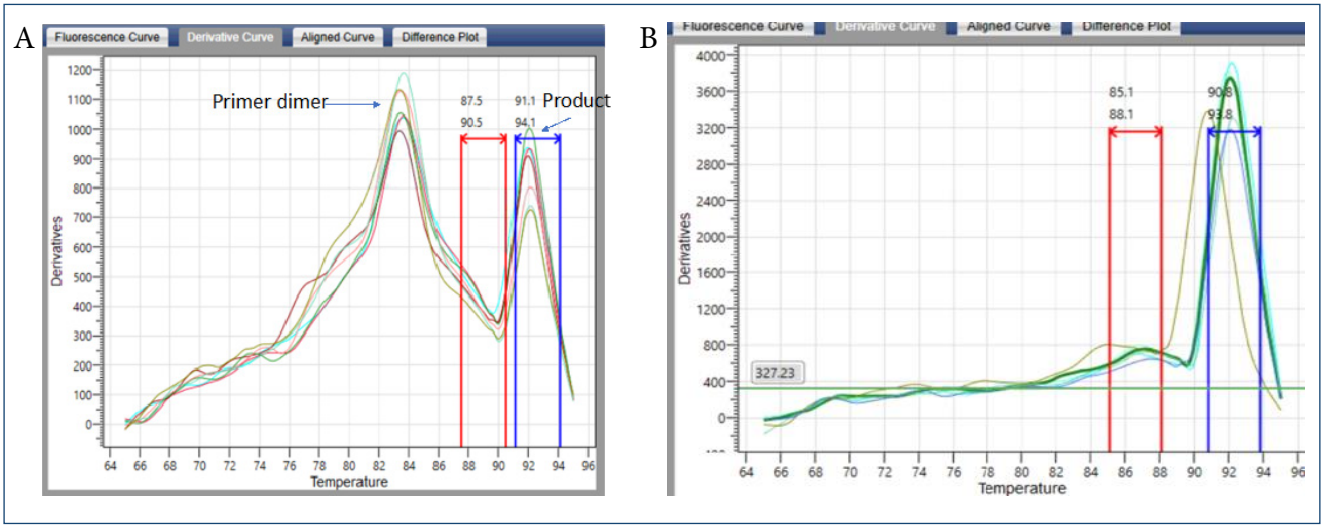

Table 3. Heterozygosity status with the Ct and Tm values for *IRS1 rs1801278* and *INSR rs1799817* in polycystic ovary syndrome patients.

Patients code	IRS1 Ct	IRS1 Tm	Heterozygosity	INSR Ct	INSR Tm	Heterozygosity
1	27.13	91.5	Homozygous	23.7	85.8	Homozygous
2	25.22	91.4	Homozygous	23.04	86.2	Homozygous
3	25.7	92.1	Homozygous	25.8	86	Homozygous
4	30.98	78.9	Homozygous	27.2	86	Homozygous
5	31.37	78	Homozygous	27.8	87.4	Homozygous
6	24.99	91.4	Homozygous	26.1	84.6	Homozygous
7	29.44	83.6	Homozygous	29.94	87.36	homozygous
8	28.22	83.3	Homozygous	36.7	86.3	Heterozygous
9	22.8	91.2	Heterozygous	22.5	85.7	Homozygous
10	32.75	92	Homozygous	28.9	86.7	Homozygous
11	29.7	78.7	Homozygous	24.26	86.4	Homozygous
12	25.85	91.8	Homozygous	23.1	86.1	Homozygous
13	29.33	91.2	Homozygous	23.1	85.4	Homozygous
14	25.48	91.3	Homozygous	23.49	85.8	Homozygous
15	31.31	76.5	Homozygous	22.75	86.1	Homozygous
16	28.02	91	Heterozygous	23.4	86	Homozygous
17	22.27	92.3	Heterozygous	23.58	85.9	Homozygous
18	31.99	77.9	Homozygous	22.1	90.1	heterozygous
19	30.29	79	Homozygous	26.3	85.8	Homozygous
20	23.93	91.6	Homozygous	24.2	86.5	Homozygous
21	30.52	78.1	Homozygous	24.05	86.1	Homozygous
22	22.2	92.19	Heterozygous	23.6	85.7	Homozygous
23	30.47	79.1	Homozygous	23.36	86.1	Homozygous
24	29.36	78.9	Homozygous	23.7	85.9	Homozygous

Continue...

Table 3. Continuation.

Patients code	IRS1 Ct	IRS1 Tm	Heterozygosity	INSR Ct	INSR Tm	Heterozygosity
25	26.5	92.02	Homozygous	22.4	85.6	Homozygous
26	No result	No result	No result	35.4	86.4	Homozygous
27	31.96	78.4	Homozygous	24.77	85.6	Homozygous
28	29.85	79.1	Homozygous	23.35	86.1	Homozygous
29	No result	No result	No result	22.3	86	Homozygous
30	No result	No result	No result	28.1	86.2	Homozygous
31	29.48	78.5	Homozygous	27.7	85.9	Homozygous
32	31.8	78.7	Homozygous	27.5	86	Homozygous
33	No result	No result	No result	23.5	86	Homozygous
34	30.91	78.5	Homozygous	26.6	85.7	Homozygous
35	29.65	91.7	Homozygous	26.9	86.2	Homozygous
36	32.07	78.4	Homozygous	26.7	86.5	Homozygous
37	31.99	85.62	Homozygous	23	86.3	Homozygous
38	31.68	86.04	Homozygous	25.8	87.3	Homozygous
39	30.42	91.6	Homozygous	25.77	87.1	Homozygous
40	24.47	83.6	Homozygous	23	85.9	Homozygous
41	No result	No result	No result	24.1	85.7	Homozygous
42	27.2	91.74	Homozygous	22.63	85.7	Homozygous
43	25.85	91.6	Homozygous	23.5	85.8	Homozygous
44	25.15	91.5	Homozygous	23	86	Homozygous
45	No result	No result	No result	23.7	86.6	Homozygous
46	25.85	90.7	Heterozygous	23	84.9	Homozygous
47	27.4	91.6	Homozygous	24.3	84.6	Homozygous
48	31.77	82	Homozygous	29.34	87.1	Homozygous
49	23.88	91	Homozygous	23.3	84.9	Homozygous
50	24.15	91.9	Heterozygous	24.1	84.8	Homozygous
51	26.35	91.6	Homozygous	28.89	87.1	Homozygous
52	24.04	83.8	Homozygous	23.15	86	Homozygous
53	25.7	91.6	Homozygous	26.41	61.3	Homozygous
54	25.98	91.5	Homozygous	25.36	61.7	Homozygous
55	25.83	91.6	Homozygous	27.72	61.5	Homozygous
56	26.6	91.1	Homozygous	22.8	85.9	Homozygous
57	25.65	92.1	Homozygous	23.4	85.9	Homozygous
58	26.36	92.2	Homozygous	22.9	85.9	Homozygous

difference between the homozygote and heterozygote status of *IRS1* rs1801278 when the patient group was compared with the control group. Furthermore, the heterozygosity of *INSR* rs1799817 did not show any significant difference between the patient group and the control group (p=0.059, Tables 3 and 4).

DISCUSSION

PCOS is one of the most common endocrine disorders affecting women of reproductive age. PCOS is one of the leading causes of infertility. Genetic and environmental factors tend to influence the complexity of PCOS (Figure 2). A number of studies have shown that genes and proteins are overexpressed

Table 4. Heterozygosity status with the Ct and Tm values for *IRS1 rs1801278* and *INSR rs1799817* in control group.

Patients code	IRS1 Ct	IRS1 Tm	Genetic conditions	INSR Ct	INSR Tm	Genetic conditions
1	No result	No result	No result	23.5	87.5	Homozygous
2	27.72	83.8	Homozygous	24.5	85.4	Homozygous
3	29.94	82.6	Homozygous	22.7	86.3	Homozygous
4	30.74	78.6	Homozygous	23.2	85.9	Homozygous
5	31.1	78.4	Homozygous	24	90.94	Heterozygous
6	25.88	92.1	Homozygous	29.29	87.23	Homozygous
7	26.5	92.26	Homozygous	23.2	85.9	Homozygous
8	32.27	78.5	Homozygous	24.1	85.9	Homozygous
9	27.3	91.47	Homozygous	22.83	85.8	Homozygous
10	27.2	92	Homozygous	23.01	85.9	Homozygous
11	26.09	92	Homozygous	33.15	87.3	Homozygous
12	26.21	91.4	Homozygous	28.76	87	Homozygous
13	30.35	82.38	Homozygous	27.1	87.56	Homozygous
14	25.92	91.6	Homozygous	25.69	62.8	Heterozygous
15	21.91	91.4	Homozygous	25	84.8	Homozygous
16	24.4	91.7	Homozygous	24.7	85	Homozygous
17	25.3	92.4	Homozygous	24.9	84.5	Homozygous
18	24.5	92.2	Homozygous	24.1	85.6	Homozygous
19	24.86	91.9	Homozygous	22.4	85.7	Homozygous
20	35.17	77.9	Homozygous	23	84.8	Homozygous
21	24.67	91.4	Homozygous	25	84.7	Homozygous
22	23.42	91.3	Homozygous	23.3	84.7	Homozygous
23	25.92	91.4	Homozygous	23.9	84.2	Homozygous
24	28.74	91.6	Homozygous	23.2	85	Homozygous
25	26.01	91.7	Homozygous	25.91	62.54	Homozygous
26	25.02	91.8	Homozygous	25.36	63.9	Heterozygous
27	25.11	99.9	Homozygous	26.7	63	Homozygous
28	25.38	91.6	Homozygous	24.95	62.9	Heterozygous
29	26.8	91.7	Homozygous	26.41	63.3	Homozygous
30	29.35	83.2	Homozygous	24.96	85.6	Homozygous
31	30.33	83.2	Homozygous	27.88	87.56	Homozygous
32	20.99	87.6	Heterozygous	29.41	86.84	Homozygous
33	No result	No result	No result	29.5	87.36	Homozygous
34	30.13	83.9	Heterozygous			Homozygous
35	26.8	91.8	Homozygous	28.59	87.3	Homozygous
36	25.85	91.8	Homozygous	31.16	87.2	Homozygous
37	25.46	91.6	Homozygous	26.47	86.9	Homozygous
38	22.55	91.7	Heterozygous	23.61	62.6	Homozygous
39	26.8	91.4	Homozygous	28.17	86.9	Homozygous
40	25.63	91.5	Homozygous	29.22	86.7	Homozygous
41	No result	No result	No result	No result	No result	No result
42	25.55	91.6	Homozygous	29.06	87.1	Homozygous
43	30.63	82.8	Homozygous	28.7	87.62	Homozygous
44	29.51	82.8	Homozygous	23.6	87.2	Heterozygous
45	21.49	84.1	Homozygous	22.99	86	Homozygous
46	29.96	83.3	Homozygous	23.27	86.1	Homozygous
47	22.97	83.9	Homozygous	22.32	85.8	Homozygous

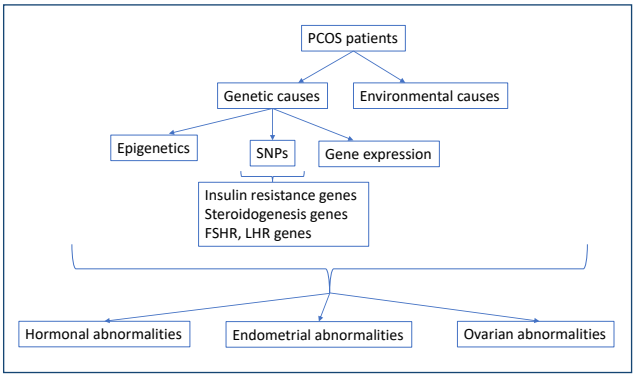

Figure 2. Flowchart diagram of causes of polycystic ovary syndrome.

or underexpressed in samples from PCOS patients. One of the examples of these is the androgen receptors that have been shown to be overexpressed in the endometrial samples obtained from PCOS patients. Furthermore, MKI67, BCL2/BAX, and FASLG/FAS were overexpressed in endometrium samples of PCOS patients. Moreover, these expression patterns were positively correlated with the levels of fasting insulin and negatively correlated with the levels of DHEA-S. Thus, endometrial homeostasis is associated with the levels of fasting insulin and DHEA-S that can also be correlated with the expression of the mentioned proteins[7]. Studies have shown that PCOS patients have high resistance to insulin. Insulin receptor genes, such as *IRS1* and *INSR*, are among the key genes that can be associated with the pathogenesis of PCOS. *IRS1* and *INSR* polymorphisms have tendencies to participate in problems with insulin signaling[8]. In this study, we aimed to investigate the heterozygosity status of two SNPs within *IRS1* and *INSR* genes that may have an increased risk of PCOS.

In this study, the homozygosity and heterozygosity status of the SNPs within *IRS1* and *INSR* genes were analyzed using Tm. The statistical differences were investigated using the Mann-Whitney U test. The results of this study showed that the heterozygosity and homozygosity status of *INSR* showed no significant difference between the control and patient groups. Similarly, another study reported no significant differences between the SNPs investigated within the *IRS1* and *INSR* genes in 48 Iranian women diagnosed with PCOS and 52 women in the control group. Furthermore, the same research group reported no association of *IRS1* polymorphism in PCOS patients and controls in Spain[9]. Similarly, genome-wide association studies have failed to show the link between the polymorphism of *IRS1* and PCOS in Han Chinese population[10]. Moreover, further studies reported no association between SNPs within *INS*, *INSR*, *IRS1*, *IRS2*, *PPAR-G*, and *CAPN10* genes and PCOS[11].

In contrast, one study reported significantly different frequencies of *IRS1* Gly972Arg polymorphism in PCOS and the control subjects in Turkish population[12]. Furthermore, another study was conducted to determine the frequency of polymorphism for the *IRS1* at codon 972 in women with PCOS in South Italy, consisting of 65 women with PCOS and 27 age-matched healthy women. They reported that there was a significant difference in the frequencies of Gly972Arg present in PCOS patients compared to controls. Furthermore, Tang et al. performed a comprehensive meta-analysis consisting of more than 4,000 subjects and reported that the AA/GA genotype of *IRS1* rs1801278 increased the susceptibility of PCOS when compared to the homozygote GG genotype. Similarly, a meta-analysis by Ruan et al. reported that the presence of the A allele significantly increased the risk of PCOS. They further recorded no significant association observed in the *IRS2* Gly1057Asp polymorphism[13].

Further studies also investigated the genotypes of *INSR* rs1799817 in relation to susceptibility of PCOS in Saudi Arabia, reporting that the homozygous allele was significantly higher compared to the control group[14]. Similarly, Chen et al.[15] also reported a significant difference in *INSR* rs1799817 genotypes in nonobese patients with PCOS compared to the controls.

CONCLUSION

Allelic frequencies of genes *IRS1* rs1801278 and *INSR* rs1799817 involved in PCOS recorded no significant difference in the study population. One of the limitations of this study was the small sample size. It is a possibility that, with the increased number of PCOS patients and control group, the heterozygosity status may have shown significant differences. Furthermore, we were able to only analyze a small number of polymorphisms. It would have been ideal to have a genome-wide investigation using next-generation sequencing (NGS) techniques. However, the results of this study are crucial to associate the insulin-related genetic polymorphisms with the PCOS patients. Furthermore, one of the most important strengths of this study was the statistical analysis techniques used. The results of this study form the basis of future studies, especially in newly developed countries where newer technologies such as NGS are out of reach.

AUTHORS' CONTRIBUTIONS

ARA: Data curation, Formal Analysis, Investigation, Methodology, Software, Validation, Visualization, Writing – original draft, Writing – review & editing. BO:

Conceptualization, Data curation, Formal Analysis, Resources, Software, Validation, Visualization, Writing – review & editing. **ACO:** Conceptualization, Data curation, Formal Analysis, Resources, Software, Validation, Visualization, Writing – review & editing. **PT:** Conceptualization, Data curation, Formal Analysis, Funding acquisition, Investigation, Methodology, Resources, Software, Supervision, Validation, Visualization, Writing – original draft, Writing – review & editing.

REFERENCES

1. Bani Mohammad M, Majdi Seghinsara A. Polycystic ovary syndrome (PCOS), diagnostic criteria, and AMH. Asian Pac J Cancer Prev. 2017;18(1):17-21. https://doi.org/10.22034/APJCP.2017.18.1.17
2. Maffazioli GDN, Lopes CP, Heinrich-Oliveira V, Lobo RA, Hayashida SAY, Soares JM Jr, et al. Prevalence of metabolic disturbances among women with polycystic ovary syndrome in different regions of Brazil. Int J Gynaecol Obstet. 2020;151(13):383-91. https://doi.org/10.1002/ijgo.13374
3. Neves LPP, Marcondes RR, Maffazioli GN, Simões RS, Maciel GAR, Soares JM Jr, et al. Nutritional and dietary aspects in polycystic ovary syndrome: insights into the biology of nutritional interventions. Gynecol Endocrinol. 2020;36(12):1047-50. https://doi.org/10.1080/09513590.2020.1822797
4. Sonthalia S, Agrawal M, Sehgal VN. Topical ciclopirox olamine 1%: revisiting a unique antifungal. Indian Dermatol Online J. 2017;10(4):481-5. https://doi.org/10.4103/idoj.IDOJ_29_19
5. Khan MJ, Ullah A, Basit S. Genetic basis of polycystic ovary syndrome (PCOS): current perspectives. Appl Clin Genet. 2019;12:249-60. https://doi.org/10.2147/TACG.S200341
6. Crespo RP, Bachega TASS, Mendonça BB, Gomes LG. An update of genetic basis of PCOS pathogenesis. Arch Endocrinol Metab. 2018;62(3):352-61. https://doi.org/10.20945/2359-3997000000049
7. Giordano LA, Giordano MV, Célia Teixeira Gomes R, Dos Santos Simões R, Baracat MCP, Giordano MG, et al. Effects of clinical and metabolic variables and hormones on the expression of immune protein biomarkers in the endometrium of women with polycystic ovary syndrome and normal-cycling controls. Gynecol Endocrinol. 2022;38(6):508-15. https://doi.org/10.1080/09513590.2022.2061454
8. Thangavelu M, Godla UR, Paul Solomon FD, Maddaly R. Single-nucleotide polymorphism of INS, INSR, IRS1, IRS2, PPAR-G and CAPN10 genes in the pathogenesis of polycystic ovary syndrome. J Genet. 2017;96(1):87-96. https://doi.org/10.1007/s12041-017-0749-z
9. Rashidi B, Azizy L, Najmeddin F, Azizi E. Prevalence of the insulin receptor substrate-1(IRS-1) Gly972Arg and the insulin receptor substrate-2(IRS-2) Gly1057Asp polymorphisms in PCOS patients and non-diabetic healthy women. J Assist Reprod Genet. 2012;29(2):195-201. https://doi.org/10.1007/s10815-011-9693-7
10. Galusha AM. Improvement of symptoms in patients with polycystic ovarian syndrome by vitamin d and calcium supplementation. 2013. School of Physician Assistant Studies. Paper 461.
11. Thangavelu M, Godla UR, Godi S, Paul SFD, Maddaly R. A case-controlled comparative hospital-based study on the clinical, biochemical, hormonal, and gynecological parameters in polycystic ovary syndrome. Indian J Pharm Sci. 2017;79(4):608-16. https://doi.org/10.4172/pharmaceutical-sciences.1000269
12. Dilek S, Ertunc D, Tok EC, Erdal EM, Aktas A. Association of Gly972Arg variant of insulin receptor substrate-1 with metabolic features in women with polycystic ovary syndrome. Fertil Steril. 2005;84(2):407-12. https://doi.org/10.1016/j.fertnstert.2005.01.133
13. Ruan Y, Ma J, Xie X. Association of IRS-1 and IRS-2 genes polymorphisms with polycystic ovary syndrome: a meta-analysis. Endocr J. 2012;59(7):601-09. https://doi.org/10.1507/endocrj.ej11-0387
14. Daghestani MH. Rs1799817 in INSR associates with susceptibility to polycystic ovary syndrome. J Med Biochem. 2019;39(2):149-59. https://doi.org/10.2478/jomb-2019-0023
15. Chen ZJ, Shi YH, Zhao YR, Li Y, Tang R, Zhao LX, et al. Correlation between single nucleotide polymorphism of insulin receptor gene with polycystic ovary syndrome. Zhonghua Fu Chan Ke Za Zhi. 2004;39(9):582-5. PMID: 15498182

ORIGINAL ARTICLE

https://doi.org/10.1590/1806-9282.20220662

Fatigue and primary sarcopenia in geriatric patients

Veysel Suzan[1*], Bahar Bektan Kanat[1], Hakan Yavuzer[1]

SUMMARY

OBJECTIVE: This study aimed to investigate the frequency of fatigue in geriatric patients with primary sarcopenia and to evaluate the relationship between fatigue and symptoms such as depression and sleepiness.

METHODS: This case-control study was conducted between December 2020 and August 2021 in the geriatrics outpatient clinic of Istanbul University-Cerrahpasa. The European Working Group on Sarcopenia in Older People 2 criteria were considered for the diagnosis of sarcopenia. Demographic data, accompanying chronic diseases, comprehensive geriatric assessments, and laboratory values of the patients were noted. Scales used to assess fatigue in all participants include Fatigue Assessment Scale, Fatigue Severity Scale, and Fatigue Impact Scale and associated symptoms include Geriatric Depression Scale and Epworth Sleepiness Scale.

RESULTS: The mean (standard deviation) age was 75.3 (7.1) for 51 primary sarcopenia (38 female) patients and 73.5 (5.8) for 51 control (37 female) patients. There was no significant difference between the two groups in terms of gender and age (p=0.822, p=0.171). The prevalence of hypertension was higher, and the level of education was lower in the sarcopenic group than in the nonsarcopenic group (p=0.017, p=0.013). Fatigue Assessment Scale, Fatigue Severity Scale, Fatigue Impact Scale total, Fatigue Impact Scale cognitive, Fatigue Impact Scale physical, and Fatigue Impact Scale social questionnaire scores were significantly higher in the sarcopenic group (all p<0.001). The Geriatric Depression Scale score was statistically higher in the sarcopenic group; however, there was no significant difference in the Epworth Sleepiness Scale score between the two groups (p=0.014, p=0.072). Multivariate analysis was performed on education level, hypertension, fatigue questionnaires, and Geriatric Depression Scale, which were found to be significant in the univariate logistic regression analysis. In the multivariate logistic regression analysis, only the Fatigue Impact Scale total was determined to be associated with sarcopenia [odds ratio 1.161, 95% confidence interval (1.084–1.242)].

CONCLUSION: In primary sarcopenia, there is mental and social fatigue as well as physical fatigue. Therefore, the prevention and treatment of sarcopenia in geriatric patients is important.

KEYWORDS: Sarcopenia. Fatigue. Depression. Sleepiness.

INTRODUCTION

With advancing age, various degrees of loss in body functions occur. Muscle loss in the elderly is one of the most important natural processes. The third decade for muscle mass was accepted as the turning point, and 27 years was indicated as the threshold at which skeletal mass began to be negatively correlated with age among both men and women[1]. The European Working Group on Sarcopenia in Older People (EWGSOP) updated the 2010 sarcopenia definition in 2019. According to the decisions taken in EWGSOP2, the primary parameter of sarcopenia is low muscle strength. Sarcopenia is probable when low muscle strength is detected. By adding "low muscle mass" to this, the diagnosis of "sarcopenia" is made[2]. Sarcopenia can cause an increase in the risk of falls and fractures due to falls, deterioration in activities of daily living, movement disorders, increased hospitalization, decreased quality of life, and even death. As can be seen, sarcopenia is associated with many adverse conditions in the elderly and can be considered a marker of frailty[3,4].

Fatigue can be defined as "an overwhelming, debilitating, and persistent feeling of burnout that reduces the person's ability to perform activities of daily living, including working effectively and performing customary family and social duties"[5]. The 50% concordance in idiopathic chronic fatigue in monozygotic twins suggests that both genetic and environmental factors are important in the pathogenesis[6]. Fatigue is common, with a rate of approximately 20% in the general population[7]. Researchers have investigated the relationship between fatigue and many diseases and revealed that this rate increases up to 50% in cancer, chronic infections, autoimmune, and neurological diseases in which the immune system is affected[8]. The geriatric population is at higher risk of fatigue due to both physiological changes and comorbid conditions.

This study aimed to investigate the frequency of fatigue in geriatric patients with primary sarcopenia and to evaluate the relationship between fatigue and symptoms such as depression and sleepiness in these patients.

[1]İstanbul Üniversitesi-Cerrahpaşa, Cerrahpaşa Tıp Fakültesi, Department of Internal Medicine, Division of Geriatric Medicine – İstanbul, Turkey.
*Corresponding author: veysel.suzan@hotmail.com

Conflicts of interest: the authors declare there is no conflicts of interest. Funding: none.
Received on July 26, 2022. Accepted on August 01, 2022.

METHOD

This prospective, case-control study was conducted between December 2020 and August 2021 in the geriatrics outpatient clinic of Istanbul University-Cerrahpasa, Cerrahpasa Medical Faculty. The Ethics Committee of the Cerrahpasa Medical Faculty approved the study protocol (09.09.2020-117341) and written informed consent for study participation was obtained from all participants.

Study population and setting

A total of 102 patients, 51 patients with primary sarcopenia and 51 controls, who applied to our geriatrics outpatient clinic, were included in this study. Demographic data, accompanying chronic diseases, and laboratory values of the patients were noted. In addition, comprehensive geriatric evaluations of the patients were performed.

Patients with probable secondary sarcopenia (being bedbound, advanced organ failure, malignancy, malnutrition, HIV infection, rheumatoid arthritis, malabsorption, and steroid use) and active infection were excluded from the study. Dementia was excluded as it may make it difficult to cooperate to the questionnaires. Due to the effect of depression on fatigue, patients who were already diagnosed with depression or who were diagnosed with depression during our clinical evaluation were not included in the study.

Sarcopenia diagnosis

The EWGSOP2 criteria were considered for the diagnosis of sarcopenia and cutoff values[2]. For the diagnosis of sarcopenia, a handgrip strength test is performed initially. If low muscle strength is detected, it is considered "probable sarcopenia." Afterward, muscle mass is measured, and in case of low muscle mass, it is considered "sarcopenia." If low muscle strength and slowed walking speed are added to muscle mass, it is defined as "severe sarcopenia." For a positive handgrip strength test, the cutoff value was accepted as 27 kg for men and 16 kg for women. Bioelectrical impedance analyzer device (Tanita Body Composition Analyzer® TBF-300 model, Tanita Co., Tokyo, Japan) was used to measure skeletal muscle mass index (SMMI) in kg/m^2 after 12 h of fasting and its cutoff value was <7.0 kg/m^2 in males and <5.5 kg/m^2 in females. The cutoff value of the gait speed was accepted as ≤0.8 m/s[2].

Fatigue Questionnaires and Geriatric Assessment

Fatigue Severity Scale (FSS): It is a nine-item questionnaire. By evaluating the last week's process, the participant is asked nine questions. As an answer, the participant is asked to give a score between 1 and 7 for each item: 1 signifies strong discord, and 7 signifies strong harmony. The total score is divided by 9, and if it is ≥, the participant is considered to have fatigue. The FSS was developed by Krupp et al. and the Turkish validation was performed by Gencay-Can and Can[9,10].

Fatigue Impact Scale (FIS): It determines the physical, cognitive, and social effects of fatigue in the last month. It consists of 40 questions in total: cognitive effects are evaluated with 10 questions, social effects are evaluated with 10 questions, and psychosocial effects are evaluated with 20 questions. Each question is read to the participants and asked to give the most suitable value between 0 (no problem) and 3 (very big problem). Each field is evaluated separately. The FIS was first developed by Fisk et al. in 1994, and its Turkish validation was done by Armutlu et al.[11,12].

Fatigue Assessment Scale (FAS): FAS, consisting of a total of 10 questions, 5 of which are about physical fatigue and 5 about mental fatigue, was designed by De Vries et al.[13]. Each option is read to the participants and asked to answer each question on a scale of 1–5, with 1 indicating never and 5 always. The total score ranges from 10 to 50. A score between 22 and 50 indicates fatigue.

Epworth Sleepiness Scale (ESS): This scale consists of eight questions developed to determine daytime sleepiness[14]. A Turkish validity and reliability study was also conducted[15]. Considering the last month, the probability of napping is questioned in a total of eight different daily situations. Each condition is read to the patient individually and asked to give a value between 0 (I never sleep) and 3 (I probably sleep). The value given to each state is summed up numerically, the maximum score is 24, and the higher score indicates more daytime sleepiness. Value of >10 is considered abnormally increased daytime sleepiness.

Geriatric Depression Scale (GDS): It was developed by Yesavage et al.[16]. The Turkish validation of the short form of the GDS was performed by Durmaz et al.[17]. The participant is asked 15 questions to be answered as yes or no. The numerical value given to each question is summed up; a maximum of 15 points can be obtained, and the higher the scale score, the higher the depressive state. Value of ≥5 is considered increased depressive mood.

Mini-Mental State Examination (MMSE): The MMSE used to screen for cognitive disorders was designed by Folstein et al.[18]. Turkish validation of the MMSE was performed by Güngen et al.[19]. In the MMSE, the participant is asked to answer questions about orientation, recording memory, attention-calculation, recall, and language. It is evaluated out of a total of 30 points. Score of <24 points is considered decreased cognitive function.

Mini Nutritional Assessment (MNA): This test was developed in the 1990s and is approved for use in hospitals, clinics, and nursing homes in the geriatric population aged 65 years and above. In the first part of the MNA form, there are six questions evaluating food consumption, weight loss, mobility, stress or acute illness, the presence of neuropsychological problems, and body mass index. In the second part of the MNA form, questions about dietary habits, medical history, drug use, and subjective evaluation of health are asked, and anthropometric measurements are recorded. The highest score is 30; score of ≤17 points is considered malnutrition[20].

Statistical analysis

Pearson's chi-square test and Fisher's exact test were used to compare categorical variables. The Student's t-test was used to compare numerical variables. Spearman's correlation analysis was used to evaluate the relationship between sarcopenia, fatigue questionnaires, and comprehensive geriatric assessment tests. In the study, FAS, FSS, FIS total, GDS, hypertension, and level of education were analyzed first with the univariate logistic regression (LR) method and then variables that were found to be significant were analyzed with the stepwise multivariate LR method. The results were evaluated at 95% confidence interval and p<0.05 significance level. The IBM SPSS-20 (Statistical Package for Social Sciences, Chicago, IL, USA) package program was used for statistical analysis.

RESULTS

Of the 51 patients with sarcopenia, 38 were female and the mean (standard deviation) age was 75.3 (7.1) years, while in the control group with 51 patients, 37 were female and the mean (standard deviation) age was 73.5 (5.8) years. There was no significant difference between the two groups in terms of gender and age (p=0.822, p=0.171). When compared in terms of education level, the rate of being a high school graduate was statistically significantly lower in the sarcopenia group (p=0.013). Of the chronic diseases, only hypertension was seen statistically significantly more frequent in sarcopenic patients than in non-sarcopenic patients (p=0.017). When the laboratory levels were examined, no significant difference was found between the two groups in terms of hemoglobin, TSH, hemoglobin A1c, and 25-hydroxyvitamin D levels (p=0.061, p=0.906, p=0.133, and p=0.113, respectively). Details of patients' demographic data and chronic diseases are given in Table 1.

The FAS, FSS, FIS total, FIS cognitive, FIS physical, and FIS social questionnaire scores were statistically significantly higher in the sarcopenic group (all p<0.001). When we accept that >22 points have fatigue according to the FAS questionnaire, 44 patients in the sarcopenia group and 26 patients in the control group had fatigue (p<0.001). Considering ≥4 points having fatigue according to the FSS questionnaire, 32 patients in the sarcopenia group and 12 patients in the control group had fatigue (p<0.001). While the GDS score was statistically higher in the sarcopenic group, there was

Table 1. Demographic data and chronic diseases of patients.

	With sarcopenia	Without sarcopenia	p-value
Number of patients	51	51	
Gender (female/male)	38/13	37/14	0.822
Age*	75.3 (7.1)	73.5 (5.8)	0.171
Education (elementary/high school)	46/5	36/15	**0.013**
Body mass index*	28.2 (5.2)	28.7 (4.8)	0.604
Hypertension	47 (92%)	38 (74%)	**0.017**
Diabetes mellitus	20 (39%)	16 (31%)	0.407
Heart failure	5 (9%)	1 (2%)	0.205
Osteoporosis	8 (16%)	4 (8%)	0.219
Hypothyroidism	9 (18%)	9 (18%)	1.000
Asthma	3 (6%)	2 (4%)	0.647
Hyperlipidemia	8 (16%)	13 (25%)	0.221
Chronic obstructive pulmonary disease	5 (10%)	5 (10%)	0.184
Chronic kidney disease	4 (8%)	4 (8%)	1.000
Benign prostatic hyperplasia	7 (14%)	3 (6%)	0.183

Data are shown as mean (standard deviation). Statistically significant p-values are indicated as bold.

no significant difference in the ESS score between the two groups (p=0.014 and p=0.072). Muscle strength, muscle mass, and walking speed were lower in the sarcopenia group (all p<0.001). The details of the comprehensive geriatric evaluation and fatigue questionnaire results of the sarcopenia and control group are given in Table 2. Fatigue survey results of the sarcopenia group and control group are shown in Figure 1. GDS and ESS results of the sarcopenia group and control group are shown in Figure 2.

The FAS, FSS, FIS total, GDS, hypertension, and education level were statistically significant in univariate LR analysis (p<0.001, p<0.001, p<0.001, p=0.017, p<0.001, and p=0.017, respectively). In the multivariate LR analysis performed on these parameters, which were significant in the univariate analysis, only the FIS total was significant [odds ratio (OR) 1.161, 95% confidence interval (CI) 1.084–1.242]. Details of the regression analysis are given in Table 3.

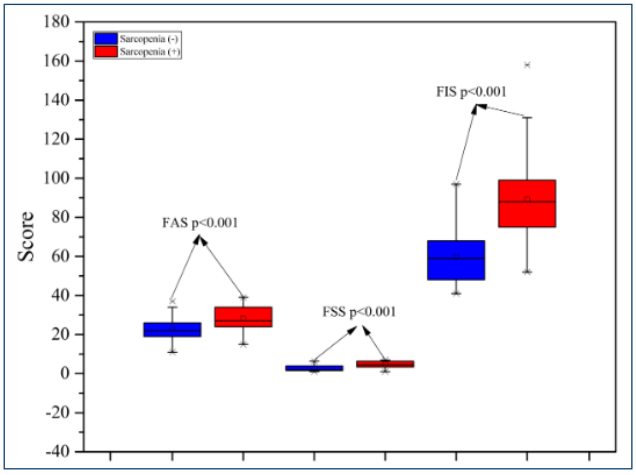

Figure 1. Fatigue survey results of sarcopenia and control groups.

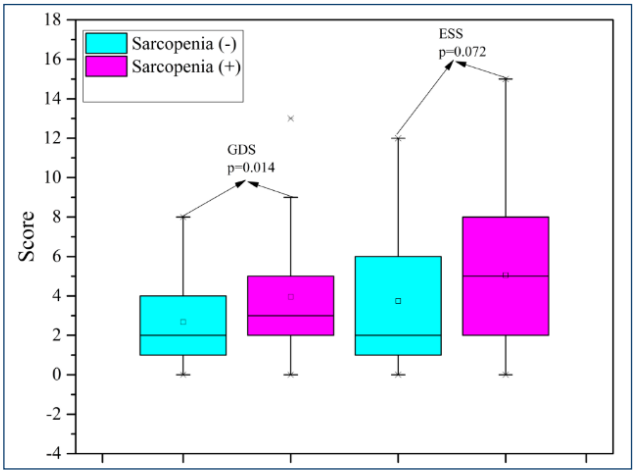

Figure 2. Geriatric Depression Scale and Epworth Sleepiness Scale results of sarcopenia and control groups.

DISCUSSION

To the best of our knowledge, this is the first study to evaluate the relationship between primary sarcopenia and fatigue, sleepiness, and depression. Diabetes mellitus, hypothyroidism, chronic heart failure, chronic obstructive pulmonary disease, vitamin D deficiency, or anemia can be counted as some of the secondary causes of fatigue. In this study, the fact that there was no difference between the two groups in terms of these diseases or conditions enabled us to rule out other causes of fatigue other than sarcopenia. Thus, we were able to evaluate sarcopenia as the primary cause of fatigue.

Table 2. Comprehensive geriatric evaluation and fatigue questionnaire results of patients.

	With sarcopenia (n=51)	Without sarcopenia (n=51)	p-value
Mini-Mental State Examination	27.0 (1.8)	27.6 (1.3)	0.076
Mini Nutritional Assessment	24.6 (2.9)	26.0 (2.8)	**0.017**
SARC-F	4.0 (2.3)	1.5 (1.5)	**<0.001**
Grip strength (kg)	15.6 (4.8)	24.9 (8.2)	**<0.001**
Skeletal muscle mass index (kg/m^2)	6.1 (0.5)	6.7 (0.7)	**<0.001**
Gait speed (m/s)	0.7 (0.2)	0.9 80.3)	**<0.001**
Fatigue Assessment Scale	28.2 (6.6)	23.1 85.6)	**<0.001**
Fatigue Severity Scale	4.5 (1.7)	2.9 (1.6)	**<0.001**
Fatigue Impact Scale total	89.1 (21.6)	59.8 (13.8)	**<0.001**
FIS cognitive	20.0 (5.7)	14.3 (4.4)	**<0.001**
FIS physical	24.8 (6.5)	16.1 (5.4)	**<0.001**
FIS social	59.8 (13.8)	44.3 (13.2)	**<0.001**
Epworth Sleepiness Scale	5.0 (3.9)	3.7 (3.3)	0.072
Geriatric Depression Scale	3.9 (2.7)	2.6 (2.4)	**0.014**

SMMI: skeletal muscle mass index. Data are shown as mean (standard deviation). Statistically significant p-values are indicated as bold.

Table 3. Univariate and stepwise multivariate logistic regression analysis for factors associated with sarcopenia.

	Univariate LR		Multivariate LR	
	Odds ratio (95%CI)	p-value	Odds ratio (95%CI)	p-value
Fatigue Assessment Scale	1.143 (1.064–1.229)	**<0.001**	1.001 (0.873–1.147)	0.989
Fatigue Severity Scale	1.713 (1.334–2.200)	**<0.001**	0.689 (0.392–1.208)	0.193
Fatigue Impact Scale total	1.111 (1.068–1.157)	**<0.001**	1.161 (1.084–1.242)	**<0.001**
Geriatric Depression Scale	1.218 (1.035–1.434)	**0.017**	0.807 (0.603–1.080)	0.150
Hypertension	4.020 (1.211–13.339)	**<0.001**	1.826 (0.395–8.435)	0.441
Education	0.261 (0.087–0.785)	**0.017**	0.596 (0.107–3.327)	0.556

LR: logistic regression; CI: confidence interval. Statistically significant p-values are indicated as bold.

This study revealed that the incidence of sarcopenia decreased as the level of education increased. In fact, this result is not surprising since educated individuals pay more attention to a balanced diet and physical activities, do not delay hospital visits, and try to apply physician recommendations more carefully. Although we excluded malnutrition as the cause of secondary sarcopenia when designing the study, the MNA scores were found to be significantly lower in the sarcopenic group. This may be because the sarcopenic group might be taking foods with less protein content.

Vlietstra et al. applied the fatigue scales to 157 patients with osteoarthritis or rheumatoid arthritis, divided the patients into groups with and without sarcopenia, and found no significant difference between the groups in terms of fatigue[21]. In a study evaluating the relationship between sarcopenia and its components and fatigue, no significant relationship was found between sarcopenia and fatigue. However, a significant relationship was found between decreased hand grip strength and walking speed and fatigue[22]. In our study, however, in addition to hand grip strength and walking speed, which are the components of sarcopenia, there was also a significant relationship between sarcopenia and fatigue. The fact that the FIS total was significant in the multivariate regression analysis of our study may be due to the elaboration of fatigue as a result of the 40 questions in the FIS total.

In the literature, inflammatory immune response and pro-inflammatory cytokine levels have been associated with fatigue in various diseases[23]. Since sarcopenia is an inflammatory condition, pro-inflammatory cytokines involved in the pathogenesis of sarcopenia may cause fatigue[24].

The limitations of our study are that it is a case-control study and the number of study participants is low.

CONCLUSION

Fatigue is a condition with an increased frequency in sarcopenia. FIS total, FAS, and FSS fatigue scores were higher in the sarcopenic group, indicating that mental and social fatigue are present in addition to physical fatigue in sarcopenia. For this reason, protein-rich diet, adequate vitamin D intake, and physical exercise are of great importance in order to prevent sarcopenia and subsequent fatigue in geriatric patients. The biggest contribution we have made to the literature with this study is presenting the sarcopenia-fatigue relationship comprehensively by the simultaneous application of all FAS, FIS (cognitive, social, and physical), and FSS fatigue questionnaires and evaluating their relationship with ESS and GDS.

STATEMENT OF ETHICS

The study was approved by the ethics committee of Istanbul University-Cerrahpasa, Cerrahpasa Medical Faculty (09.09.2020-117341).

AUTHORS' CONTRIBUTIONS

VS: Conceptualization, Formal Analysis, Investigation, Methodology. **BBK:** Data curation, Investigation, Writing – original draft. **HY:** Methodology, Supervision, Writing – review & editing.

REFERENCES

1. Silva AM, Shen W, Heo M, Gallagher D, Wang Z, Sardinha LB, et al. Ethnicity-related skeletal muscle differences across the lifespan. Am J Hum Biol. 2010;22(1):76-82. https://doi.org/10.1002/ajhb.20956

2. 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(1):16-31. https://doi.org/10.1093/ageing/afy169

3. Hao R, Guo H. Anorexia, undernutrition, weight loss, sarcopenia, and cachexia of aging. Eur Rev Aging Phys Act. 2012;9(2):119-27. https://doi.org/10.1007/s11556-012-0103-7
4. Daly RM, Iuliano S, Fyfe JJ, Scott D, Kirk B, Thompson MQ, et al. Screening, diagnosis and management of sarcopenia and frailty in hospitalized older adults: recommendations from the Australian and New Zealand Society for Sarcopenia and Frailty Research (ANZSSFR) Expert Working Group. J Nutr Health Aging. 2022;26(6):637-51. https://doi.org/10.1007/s12603-022-1801-0
5. Riley WT, Rothrock N, Bruce B, Christodolou C, Cook K, Hahn EA, et al. Patient-reported outcomes measurement information system (PROMIS) domain names and definitions revisions: further evaluation of content validity in IRT-derived item banks. Qual Life Res. 2010;19(9):1311-21. https://doi.org/10.1007/s11136-010-9694-5
6. Buchwald D, Herrell R, Ashton S, Belcourt M, Schmaling K, Sullivan P, et al. A twin study of chronic fatigue. Psychosom Med. 2001;63(6):936-43. https://doi.org/10.1097/00006842-200111000-00012
7. Akkan Suzan A, Kahraman Koytak P, Uluc K, Tanridag T. Physical and mental fatigue in myasthenia gravis and its correlation with other symptoms. Acta Neurol Belg. 2022;122(4):915-23. https://doi.org/10.1007/s13760-022-01919-y
8. Kroenke K, Stump T, Clark DO, Callahan CM, McDonald CJ. Symptoms in hospitalized patients: outcome and satisfaction with care. Am J Med. 1999;107(5):425-31. https://doi.org/10.1016/s0002-9343(99)00268-5
9. Krupp LB, LaRocca NG, Muir-Nash J, Steinberg AD. The fatigue severity scale. Application to patients with multiple sclerosis and systemic lupus erythematosus. Arch Neurol. 1989;46(10):1121-3. https://doi.org/10.1001/archneur.1989.00520460115022
10. Gencay-Can A, Can SS. Validation of the Turkish version of the fatigue severity scale in patients with fibromyalgia. Rheumatol Int. 2012;32(1):27-31. https://doi.org/10.1007/s00296-010-1558-3
11. Fisk JD, Ritvo PG, Ross L, Haase DA, Marrie TJ, Schlech WF. Measuring the functional impact of fatigue: initial validation of the fatigue impact scale. Clin Infect Dis. 1994;18(Suppl 1):S79-83. https://doi.org/10.1093/clinids/18.supplement_1.s79
12. Armutlu K, Keser I, Korkmaz N, Akbiyik DI, Sümbüloğlu V, Güney Z, et al. Psychometric study of Turkish version of Fatigue Impact Scale in multiple sclerosis patients. J Neurol Sci. 2007;255(1-2):64-8. https://doi.org/10.1016/j.jns.2007.01.073
13. De Vries J, Michielsen H, Van Heck GL, Drent M. Measuring fatigue in sarcoidosis: the Fatigue Assessment Scale (FAS). Br J Health Psychol. 2004;9(Pt 3):279-91. https://doi.org/10.1348/1359107041557048
14. Johns MW. A new method for measuring daytime sleepiness: the Epworth sleepiness scale. Sleep. 1991;14(6):540-5. https://doi.org/10.1093/sleep/14.6.540
15. Izci B, Ardic S, Firat H, Sahin A, Altinors M, Karacan I. Reliability and validity studies of the Turkish version of the Epworth Sleepiness Scale. Sleep Breath. 2008;12(2):161-8. https://doi.org/10.1007/s11325-007-0145-7
16. Yesavage JA, Brink TL, Rose TL, Lum O, Huang V, Adey M, et al. Development and validation of a geriatric depression screening scale: a preliminary report. J Psychiatr Res. 1982;17(1):37-49. https://doi.org/10.1016/0022-3956(82)90033-4
17. Durmaz B, Soysal P, Ellidokuz H, Isik AT. Validity and reliability of geriatric depression scale-15 (short form) in Turkish older adults. North Clin Istanb. 2018;5(3):216-20. https://doi.org/10.14744/nci.2017.85047
18. Folstein MF, Folstein SE, McHugh PR. "Mini-mental state". A practical method for grading the cognitive state of patients for the clinician. J Psychiatr Res. 1975;12(3):189-98. https://doi.org/10.1016/0022-3956(75)90026-6
19. Güngen C, Ertan T, Eker E, Yaşar R, Engin F. Reliability and validity of the standardized Mini Mental State Examination in the diagnosis of mild dementia in Turkish population. Turk Psikiyatri Derg. 2002;13(4):273-81. PMID: 12794644
20. Vellas B, Guigoz Y, Garry PJ, Nourhashemi F, Bennahum D, Lauque S, et al. The Mini Nutritional Assessment (MNA) and its use in grading the nutritional state of elderly patients. Nutrition. 1999;15:116-22. https://doi.org/10.1016/s0899-9007(98)00171-3
21. Vlietstra L, Stebbings S, Meredith-Jones K, Abbott JH, Treharne GJ, Waters DL. Sarcopenia in osteoarthritis and rheumatoid arthritis: the association with self-reported fatigue, physical function and obesity. PLoS One. 2019;14(6):e0217462. https://doi.org/10.1371/journal.pone.0217462
22. Patino-Hernandez D, David-Pardo DG, Borda MG, Pérez-Zepeda MU, Cano-Gutiérrez C. Association of fatigue with sarcopenia and its elements: a secondary analysis of SABE-Bogotá. Gerontol Geriatr Med. 2017;3:2333721417703734. https://doi.org/10.1177/2333721417703734
23. Lee CH, Giuliani F. The role of inflammation in depression and fatigue. Front Immunol. 2019;10:1696. https://doi.org/10.3389/fimmu.2019.01696
24. Bian AL, Hu HY, Rong YD, Wang J, Wang JX, Zhou XZ. A study on relationship between elderly sarcopenia and inflammatory factors IL-6 and TNF-α. Eur J Med Res. 2017;22(1):25. https://doi.org/10.1186/s40001-017-0266-9

ORIGINAL ARTICLE

https://doi.org/10.1590/1806-9282.20220676

Association between ventricular premature contraction burden and ventricular repolarization duration

Nihat Söylemez[1], Belma Yaman[2*]

SUMMARY

OBJECTIVE: Premature ventricular contraction is generally known as benign in the absence of structural heart disease; however, premature ventricular contraction-induced left ventricular systolic dysfunction or ventricular arrhythmias are defined in some cases. Ventricular repolarization duration differs between myocardial cells, which causes myocardial electrical heterogeneity and is thought to be responsible for ventricular arrhythmias. In our study, we aimed to evaluate the association of ventricular repolarization parameters including Tp-Te interval, Tp-Te/QT ratio, and QRS-T angle with premature ventricular contraction frequency in patients with premature ventricular contraction burden.

METHODS: A total of 80 subjects who were admitted to our cardiology department and underwent 24-h electrocardiography Holter monitoring were included. Patients were divided into two groups: group 1 is defined as premature ventricular contraction burden that had frequent premature ventricular contraction ≥1% in 24-h Holter monitoring, and group 2 is defined as rare premature ventricular contraction <1% in 24-h Holter monitoring.

RESULTS: Tp-Te interval and Tp-Te/QT ratio are statistically significantly prolonged in the premature ventricular contraction burden group than in the control group (85.3±13.9 vs. 65.7±11.9, p<0.001; 0.19±0.03 vs. 0.15±0.02, p<0.001, respectively). QRS-T angle was statistically significantly abnormal in the premature ventricular contraction burden group (p=0.024).

CONCLUSION: Increased Tp-Te interval and widened QRS-T angle are associated with ventricular arrhythmias and might be used for the prediction of premature ventricular contraction burden in patients with premature ventricular contraction in electrocardiography in the absence of 24-h Holter monitoring.

KEYWORDS: Arrhythmias, cardiac. Ventricular premature complexes. Tachycardia, ventricular.

INTRODUCTION

Premature ventricular contraction (PVC) can be detected in structurally normal hearts with a prevalence of 1–4% in the general population[1]. A previous study found the prevalence of PVC as 40–75% in healthy populations by 24–48 h electrocardiography (ECG) Holter monitoring[2]. PVC is generally known as benign in the absence of structural heart disease; however, PVC induces deterioration of the left ventricular systolic functions in some cases. Also, frequent PVC might worsen the existing cardiomyopathies. There is no consensus in the literature about the cutoff amount of PVC, which has a high risk for cardiomyopathy or ventricular arrhythmias[3,4].

Myocardial cells are divided into three groups: epicardium, midmyocardium, and endocardium cells, which have different durations of action potentials. The action potential of the epicardium is shorter than the endocardium. The midmyocardium has the longest action potential[5]. As a result of these different action potential durations, heterogeneity of electrical conduction occurs in the myocardium. Transmural dispersion of heterogeneous electrical activity is shown as a responsible mechanism of arrhythmogenesis[6]. T_{peak} to T_{end} (Tp-Te) interval is the indicator of transmural dispersion of repolarization. Previous studies showed that a prolonged Tp-Te interval is associated with a high risk of ventricular tachycardia (VT)[7]. A previous study evaluated the Tp-Te interval during ventricular pacing in an electrophysiological study and showed that the Tp-Te interval is prolonged by ventricular premature beats[8]. In recent years, the Tp-Te/QT ratio has been used as a more sensitive marker than the Tp-Te interval for the assessment of transmural dispersion of repolarization[9]. The Tp-Te/QT ratio is superior to the Tp-Te interval due to its independence from heart rate[10]. Previous studies showed that increased Tp-Te/QT ratio is associated with an increased risk of VT in Brugada syndrome, short QT, and long syndromes[11,12].

In recent years, the QRS-T angle has gained importance for the prediction of cardiac poor prognosis. QRS-T angle is an ECG parameter and is defined as the difference between ventricular depolarization and repolarization. Previous studies showed that widened QRS-T angle increased arrhythmia-associated mortality in patients with ischemic cardiomyopathy[13].

[1]Mersin City Training and Research Hospital, Department of Cardiology – Mersin, Turkey.
[2]Yakın Doğu Üniversitesi, Faculty of Medicine, Department of Cardiology – Nicosia, Cyprus.
*Corresponding author: belmayaman@yahoo.com
Conflicts of interest: the authors declare there is no conflicts of interest. Funding: none.
Received on July 17, 2022. Accepted on August 03, 2022.

In our study, we aimed to evaluate the association of ECG parameters including Tp-Te interval, corrected QT (QTc), Tp-Te/QT ratio, and QRS-T angle with PVC frequency in patients who underwent 24-h ECG Holter monitoring.

METHODS

A total of 80 subjects who were admitted to our cardiology department with palpitation, syncope, dyspnea, or any other cardiac complaint and underwent 24-h ECG Holter monitoring between January 2018 and October 2019 were included. A 24-h ECG Holter monitoring was performed on all patients, irrespective of having PVC on baseline ECG, and analyzed by the same operator. Patients were divided into two groups: group 1 was defined as PVC burden, which had frequent PVC≥1% in 24-h Holter monitoring, and group 2 was defined as rare PVC<1% in 24-h Holter monitoring. Patients with low ejection fraction, structural heart disease, moderate-to-severe degree heart valve disease, coronary artery disease with the sign of ischemia, thyroid disorders, and anemia were excluded from the study. The patient's medical history and medications were questioned.

A 12-lead ECG was performed at a speed of 25 mm/s. V5 derivation was chosen for the analysis of Tp-Te, QT, and Tp-Te/QT measurements in all patients. Tp-Te ratio was calculated from the baseline ECG as the interval of the peak to the end of the T wave. QT interval was defined as the duration from the beginning of the QRS complex to the end of the T wave. The QTc interval was calculated according to the patient's heart rate with Bazett's formula. Tp-Te interval is divided by the QTc interval for the measurement of the Tp-Te/QT ratio. The frontal QRS-T angle is calculated as the difference between the QRS axis and the T-wave axis. According to previous studies, we chose the normal range of QRS-T angle as -39 to 71°[14]. Patients were divided into two groups according to QRS-T angle: the normal group (QRS-T angle is between -39 and 71°) and the abnormal group (QRS-T angle is out of this range). The single operator analyzed the ECG parameters.

A 2D echocardiography was performed on all patients for the detection of any heart valve disease or structural heart disease. The ejection fraction (EF) was measured by the modified Simpson method.

The study was approved by the local Ethical Committee.

Statistical analysis

Statistical analysis was performed using the SPSS (version 20.0, SPSS Inc., Chicago, IL, USA) software package. Continuous variables were expressed as the mean±standard deviation (mean±SD), and categorical variables were expressed as a percentage (%). The Kolmogorov-Smirnov test was used to evaluate the distribution of variables. The Student's t-test was used to evaluate continuous variables showing normal distribution, and the Mann-Whitney U test was used to evaluate variables that did not show normal distribution. For categorical variables, the chi-square test was used. Multivariable logistic regression using the enter method was used to assess independent predictors for regression. A $p<0.05$ was considered statistically significant.

RESULTS

A total of 37 patients had PVC burden (PVC≥1%) and 43 patients had rare PVC<1% in 24-h ECG Holter monitoring. The mean age of the study population was 49.4±14.6, and 50% of them were male. In total, 20% of them had a history of coronary artery disease, and 41.3% of them were taking antiarrhythmic treatment (81.8% of them are beta-blockers). Baseline characteristics of the study population are shown in Table 1.

Demographic features regarding diabetes mellitus (DM), hypertension (HT), smoking status, coronary artery disease, and EF were similar between the two groups (Table 2). Patients with PVC burden were significantly older than the other group (53±17.5 vs. 46.2±11, p=0.046). Tp-Te interval, Tp-Te/QT, and Tp-Te/QTc interval were statistically significantly prolonged in patients with frequent PVC than control group (86.6±13.3 vs. 65.4±12.8, p<0.001; 0.22±0.04 vs. 0.15±0.03, p<0.001; 0.2±0.03 vs. 0.15±0.03, p<0.001, respectively). QT and QTc intervals were similar between the two groups (387±29.3 vs. 375.4±32.8, p=0.098; 428.5±29.2 vs. 429.1±23.5, p=0.928,

Table 1. Demographic features.

	Mean±SD
Age	49.4±14.6
Male (%)	40 (50)
DM (%)	7 (8.8)
HT (%)	18 (22.5)
Smoking (%)	21 (26.3)
CAD (%)	16 (20)
Antiarrhythmic medication	33 (41.3)
PVC>1%	37 (46.3)
Nonsustained VT	4 (5)
EF (%)	60.3±2.3
Number/percentage of PVC	5268.2±9384.7/4.9±8.6

DM: diabetes mellitus; HT: hypertension; CAD: coronary artery disease; PVC: premature ventricular contraction; VT: ventricular tachycardia; EF: ejection fraction.

respectively). QRS-T angle was statistically significantly wider in the group with PVC burden (p=0.024). A comparison of ECG parameters between the two groups is shown in Table 2.

Pearson's correlation analysis showed a significant correlation between Tp-Te and PVC frequency. Also, Tp-Te/QT and Tp-Te/QTc ratios were significantly correlated with PVC frequency. The correlation of ECG parameters with PVC frequency is shown in Table 3. Multivariate analysis of ECG parameters showed that Tp-Te interval and QRS-T angle are the independent predictors of an excessive amount of PVC in 24-h ECG Holter monitoring (p<0.001 and p=0.04, respectively).

Table 2. Comparison of the basic demographic features and electrocardiography parameters.

Parameters	Group 1 (PVC>1%) (n=37)	Group 2 (PVC≤1%) (n=43)	p-value
Age (year)	53±17.5	46.2±11	**0.046**
Male, n (%)	22 (59.5)	18 (41.9)	0.178
HT (%)	9 (24.3)	9 (20.9)	0.792
DM (%)	3 (8.1)	4 (9.3)	1.0
Smoking (%)	10 (27)	11 (25.6)	1.0
CAD (%)	8 (21.6)	8 (18.6)	0.785
Nonsustained VT	3 (8.1)	1 (2.3)	0.253
EF (%)	60.4±2	60.2±2.6	0.673
HR (beat/min)	75.5±15.3	79.9±15.8	0.213
Tp-Te interval	86.6±13.3	65.4±12.8	**<0.001**
QT interval	387±29.3	375.4±32.8	0.098
QTc interval	428.5±29.2	429.1±23.5	0.928
Tp-Te/QT	0.22±0.04	0.15±0.03	**<0.001**
Tp-Te/QTc	0.2±0.03	0.15±0.03	**<0.001**
Abnormal QRS-T angle (%)	11 (29.7)	4 (9.3)	**0.024**

PVC: premature ventricular contraction; HT: hypertension; DM: diabetes mellitus; CAD: coronary artery disease; VT: ventricular tachycardia; EF: ejection fraction; HR: heart rate. Bold value indicates the significance of p<0.05.

Table 3. Correlation of electrocardiography parameters with premature ventricular contraction frequency.

	PVC (n)		PVC (%)	
	r	P	R	p
Heart beat/24 h	0.070	0.535	-0.008	0.945
Tp-Te interval	**0.372**	**0.001**	**0.384**	**<0.001**
QT interval	0.77	0.495	0.108	0.341
QTc interval	0.163	0.148	0.158	0.161
Tp-Te/QT ratio	**0.323**	**0.003**	**0.323**	**0.003**
Tp-Te/QTc ratio	**0.311**	**0.005**	**0.326**	**0.003**

PVC: premature ventricular contraction. Bold value indicates the significance of p<0.05.

DISCUSSION

The main finding of our study is the increased Tp-Te interval, Tp-Te/QT, Tp-Te/QTc ratio, and abnormal QRS-T angle in patients with frequent PVC in 24-h ECG Holter monitoring. As compared to QTc interval and heart rate, there was no statistically significant difference between the groups. The Tp-Te interval and abnormal QRS-T angle are the independent predictors of an excessive amount of PVC in 24-h ECG Holter monitoring.

The myocardium has three types of cells: epicardium cells, midmyocardium cells, and endocardium cells, which have different action potential durations[15]. Midmyocardium cells have the longest action potential duration. Different action potential durations are thought to be responsible for ventricular arrhythmias. QT, QTc, Tp-Te interval, and Tp-Te/QT ratio are the indicators of transmural dispersion of ventricular repolarisation[9]. A previous study showed that ventricular extra stimuli increase QTc interval, which may indicate the increased action potential duration in midmyocardium cells during the electrophysiological study[8]. It is shown that PVC causes increased transmural dispersion of repolarization as a result of increased midmyocardium action potential duration in patients with long QT syndrome[16]. In our study, the QTc interval was not different between the PVC burden and the rare PVC group. Several studies showed that an increased Tp-Te interval and Tp-Te/QTc ratio are linked with ventricular arrhythmias in Brugada syndrome, long QT syndrome, and hypertrophic cardiomyopathy[11,12]. Nugraheni et al.[17] showed that the Tp-Te/QT ratio is associated with an increased risk of VT in patients with idiopathic outflow tract PVC. Comparably with previous studies, we found an association between Tp-Te, Tp-Te/QT, and PVC burden. The relationship between ventricular repolarization parameters and sudden cardiac death has been known for many years[18]. However, there are controversial findings about the association between coronary artery severity and ventricular repolarization parameters. Bektaş et al.[19] evaluated 172 participants with coronary artery disease and found that Tp-Te and Tp-Te/QTc were higher in the group that had high Syntax score levels. On the contrary, Cosgun et al.[20] found that Tp-Te and Tp-Te/QTc are similar between high and low Syntax score groups.

QRS-T angle is defined as the angle between the QRS axis and T-wave axis[13,14]. Widened QRS-T angle predicts abnormal depolarization and repolarization, in situations with abnormal electrical activation including ischemia, bundle branch block, and left ventricular hypertrophy[21]. There is a limitation in the use of spatial QRS-T angle in clinical practice as a result of difficulties in the calculation. Frontal QRS-T angle is more

widely used than spatial QRS-T angle because of its availability in most ECG devices, so it is easily evaluated by most clinicians[22]. In our study, we defined an abnormal QRS-T angle as being out of the range of -39 to 71º, in the light of findings in previous studies[14]. We found that an abnormally widened QRS-T angle is significantly associated with PVC burden in 24-h ECG Holter monitoring.

Most of the PVCs are considered benign and not associated with ventricular arrhythmias in the absence of structural heart disease[23]. PVC frequency is important to predict ventricular arrhythmias. Multiple Risk Factor Intervention Trial showed that more than one PVC in 2-min ECG is associated with increased sudden cardiac death 7.5-year follow-up[24]. Although asymptomatic PVC is known as a benign arrhythmia, it may induce premature ventricular complex-induced cardiomyopathy. As asymptomatic patients are unaware of their conditions and arrhythmias, they have a higher risk of prolonged exposure to frequent PVC, which might be progressed to cardiomyopathy[25]. Ventricular repolarization parameters can be used to predict the PVC burden for high-risk patients. However, patients with detected PVC in ECG should be advised to undergo 24-h Holter monitoring for the assessment of PVC frequency, morphology, and distribution pattern in a day.

CONCLUSION

Increased Tp-Te interval and abnormal QRS-T angle might be used for the prediction of high PVC burden risk from baseline ECG in patients with PVC in ECG in the absence of 24-h Holter monitoring.

ACKNOWLEDGMENTS

We thank the physicians and participants involved in this study.

AUTHORS' CONTRIBUTIONS

NS: Conceptualization, Data curation, Formal Analysis, Supervision, Validation, Writing – review & editing. **BY:** Conceptualization, Data curation, Formal Analysis, Investigation, Methodology, Visualization, Writing – original draft.

REFERENCES

1. Kennedy HL, Whitlock JA, Sprague MK, Kennedy LJ, Buckingham TA, Goldberg RJ. Long-term follow-up of asymptomatic healthy subjects with frequent and complex ventricular ectopy. N Engl J Med. 1985;312(4):193-7. https://doi.org/10.1056/NEJM198501243120401
2. Sobotka PA, Mayer JH, Bauernfeind RA, Kanakis C Jr, Rosen KM. Arrhythmias were documented by 24-hour continuous ambulatory electrocardiographic monitoring in young women without apparent heart disease. Am Heart J. 1981;101(6):753-9. https://doi.org/10.1016/0002-8703(81)90611-6
3. El Kadri M, Yokokawa M, Labounty T, Mueller G, Crawford T, Good E, et al. Effect of ablation of frequent premature ventricular complexes on left ventricular function in patients with nonischemic cardiomyopathy. Heart Rhythm. 2015;12(4):706-13. https://doi.org/10.1016/j.hrthm.2014.12.017
4. Mountantonakis SE, Frankel DS, Gerstenfeld EP, Dixit S, Lin D, Hutchinson MD, et al. Reversal of outflow tract ventricular premature depolarization-induced cardiomyopathy with ablation: effect of residual arrhythmia burden and preexisting cardiomyopathy on outcome. Heart Rhythm. 2011;8(10):1608-14. https://doi.org/10.1016/j.hrthm.2011.04.026
5. Antzelevitch C, Sicouri S, Litovsky SH, Lukas A, Krishnan SC, Di Diego JM, et al. Heterogeneity within the ventricular wall. Electrophysiology and pharmacology of epicardial, endocardial, and M cells. Circ Res. 1991;69(6):1427-49. https://doi.org/10.1161/01.res.69.6.1427
6. Antzelevitch C, Sicouri S. Clinical relevance of cardiac arrhythmias generated by afterdepolarizations. Role of M cells in the generation of U waves, triggered activity and torsade de pointes. J Am Coll Cardiol. 1994;23(1):259-77. https://doi.org/10.1016/0735-1097(94)90529-0
7. Antzelevitch C, Shimizu W, Yan GX, Sicouri S. Cellular basis for QT dispersion. J Electrocardiol. 1998;30(Suppl):168-75. https://doi.org/10.1016/s0022-0736(98)80070-8
8. Wolk R, Stec S, Kulakowski P. Extrasystolic beats affect transmural electrical dispersion during programmed electrical stimulation. Eur J Clin Invest. 2001;31(4):293-301. https://doi.org/10.1046/j.1365-2362.2001.00817.x
9. Gupta P, Patel C, Patel H, Narayanaswamy S, Malhotra B, Green JT, et al. T(p-e)/QT ratio as an index of arrhythmogenesis. J Electrocardiol. 2008;41(6):567-74. https://doi.org/10.1016/j.jelectrocard.2008.07.016
10. Barbhaiya C, Po JR, Hanon S, Schweitzer P. Tpeak - Tend and Tpeak - Tend /QT ratio as markers of ventricular arrhythmia risk in cardiac resynchronization therapy patients. Pacing Clin Electrophysiol. 2013;36(1):103-8. https://doi.org/10.1111/pace.12031
11. Yamaguchi M, Shimizu M, Ino H, Terai H, Uchiyama K, Oe K, et al. T wave peak-to-end interval and QT dispersion in acquired long QT syndrome: a new index for arrhythmogenicity. Clin Sci (Lond). 2003;105(6):671-6. https://doi.org/10.1042/CS20030010
12. Shimizu M, Ino H, Okeie K, Yamaguchi M, Nagata M, Hayashi K, et al. T-peak to T-end interval may be a better predictor of high-risk patients with hypertrophic cardiomyopathy associated with a cardiac troponin I mutation than QT dispersion. Clin Cardiol. 2002;25(7):335-9. https://doi.org/10.1002/clc.4950250706

13. Pavri BB, Hillis MB, Subacius H, Brumberg GE, Schaechter A, Levine JH, et al. Defibrillators in Nonischemic Cardiomyopathy Treatment Evaluation (DEFINITE) Investigators. Prognostic value and temporal behavior of the planar QRS-T angle in patients with nonischemic cardiomyopathy. Circulation. 2008;117(25):3181-6. https://doi.org/10.1161/CIRCULATIONAHA.107.733451

14. Macfarlane PW, Lawrie TDV (eds). Comprehensive electrocardiology. Oxford: Pergamon Press; 1989. p.1459.

15. Kardys I, Kors JA, van der Meer IM, Hofman A, van der Kuip DA, Witteman JC. Spatial QRS-T angle predicts cardiac death in a general population. Eur Heart J. 2003;24(14):1357-64. https://doi.org/10.1016/s0195-668x(03)00203-3

16. Yan GX, Antzelevitch C. Cellular basis for the normal T wave and the electrocardiographic manifestations of the long-QT syndrome. Circulation. 1998;98(18):1928-36. https://doi.org/10.1161/01.cir.98.18.1928

17. Rautaharju PM, Kooperberg C, Larson JC, LaCroix A. Electrocardiographic abnormalities that predict coronary heart disease events and mortality in postmenopausal women: the Women's Health Initiative. Circulation. 2006;113(4):473-80. https://doi.org/10.1161/CIRCULATIONAHA.104.496091

18. Panikkath R, Reinier K, Uy-Evanado A, Teodorescu C, Hattenhauer J, Mariani R, et al. Prolonged Tpeak-to-tend interval on the resting ECG is associated with increased risk of sudden cardiac death. Circ Arrhythm Electrophysiol. 2011;4(4):441-7. https://doi.org/10.1161/CIRCEP.110.960658

19. Bektaş O. The association between coronary artery disease severity and Tp-e interval, Tp-e/qt ratio parameters including fragmented Qrs. Am J Cardiol. 2018;121(8):e54. https://doi.org/10.1016/j.amjcard.2018.03.146

20. Cosgun M, Erdal E, Guneş Y, Sincer I, Mansıroğlu A. Evaluation of electrocardiographic ventricular repolarization parameters in stable coronary artery disease. Exp Biomed Res. 2021;4(2):141-7. https://doi.org/10.30714/j-ebr.2021267977

21. Nugraheni AP, Arso IA, Maharani E. Association of Tp-Te/QT ratio with ventricular tachycardia in patients with idiopathic outflow tract ventricular premature contraction. Cardiol Res. 2018;9(4):215-23. https://doi.org/10.14740/cr735w

22. Castro Hevia J, Antzelevitch C, Tornés Bárzaga F, Dorantes Sánchez M, Dorticós Balea F, Zayas Molina R, et al. Tpeak-Tend and Tpeak-Tend dispersion as risk factors for ventricular tachycardia/ventricular fibrillation in patients with the Brugada syndrome. J Am Coll Cardiol. 2006;47:1828-34. https://doi.org/10.1016/j.jacc.2005.12.049

23. Gaita F, Giustetto C, Di Donna P, Richiardi E, Libero L, Brusin MC, et al. Long-tern follow-up of right ventricular monomorphic extrasystoles. J Am Coll Cardiol. 2001;38(2):364-70. https://doi.org/10.1016/s0735-1097(01)01403-6

24. Abdalla IS, Prineas RJ, Neaton JD, Jacobs DR Jr, Crow RS. Relation between ventricular premature complexes and sudden cardiac death in apparently healthy men. Am J Cardiol. 1987;60(13):1036-42. https://doi.org/10.1016/0002-9149(87)90348-1

25. Wang Y, Eltit JM, Kaszala K, Tan A, Jiang M, Zhang M, et al. Cellular mechanism of premature ventricular contraction-induced cardiomyopathy. Heart Rhythm. 2014;11(11):2064-72. https://doi.org/10.1016/j.hrthm.2014.07.022

ORIGINAL ARTICLE

https://doi.org/10.1590/1806-9282.20220737

Effects of sodium-glucose cotransporter-2 inhibitors on nutritional status in heart failure with reduced ejection fraction

Kadem Arslan[1*], Emre Yılmaz[2], Ercan Aydın[3]

SUMMARY

OBJECTIVE: This study aimed to evaluate the effects of sodium-glucose cotransporter-2 inhibitors on nutritional status in patients with heart failure with reduced ejection fraction.

METHODS: The sodium-glucose cotransporter-2 inhibitor treatment was initiated in 153 patients with heart failure with reduced ejection fraction who were symptomatic despite optimal medical treatment and were followed up for 6 months. The Minnesota Living With Heart Failure Questionnaire scores, New York Heart Association functional class, NT-pro-BNP levels, and nutritional index scores of the patients were evaluated before sodium-glucose cotransporter-2 inhibitor treatment and at the 6-month follow-up. The nutritional status of the patients was evaluated with the COntrolling NUTritional Status score, Geriatric Nutritional Risk Index, and Prognostic Nutritional Index.

RESULTS: After sodium-glucose cotransporter-2 inhibitor treatment, significant changes were observed in the mean scores of the three different nutritional indexes: COntrolling NUTritional Status (before: 2.76±2.43 vs. after: 1.12±1.23, p<0.001), Geriatric Nutritional Risk Index (before: 98.2±9.63 vs. after: 104.4±5.83, p<0.001), and Prognostic Nutritional Index (before: 37.9±4.63 vs. after: 42.9±3.83, p<0.001) scores. A significant decrease in the number of patients with malnutrition was observed according to the COntrolling NUTritional Status (before: 46.4% vs. after: 9.7%, p<0.001), Geriatric Nutritional Risk Index (before: 41.8% vs. after: 18.9%, p=0.006), and Prognostic Nutritional Index (before: 36.6% vs. after: 13.7%, p=0.007) scores. A significant functional improvement was observed in patients after sodium-glucose cotransporter-2 treatment: Minnesota Living With Heart Failure Questionnaire scores (before: 39.2±7.2 vs. after: 20.4±7.4, p<0.001), NT-pro-BNP levels (before: 2989±681 vs. after: 1236±760, p<0.001), and New York Heart Association class (before: class II-III: 95.5%; class IV: 4.5% vs. after: class II-III: 78%; class IV: 0%, p<0.001).

CONCLUSION: In patients with heart failure with reduced ejection fraction who are symptomatic despite optimal medical treatment, the addition of an sodium-glucose cotransporter-2 inhibitor to treatment can significantly improve both the nutritional and functional statuses.

KEYWORDS: Heart failure. Malnutrition. Nutrition assessment. Sodium-glucose transporter 2 inhibitors.

INTRODUCTION

Heart failure (HF) is a chronic inflammatory syndrome with typical symptoms and signs, which reduces the quality of life and increases the risk of mortality and morbidity[1]. HF can lead to malnutrition by causing inadequate nutrient intake and malabsorption due to intestinal edema and anorexia and an increased resting metabolic rate secondary to the high energy needs of the heart[2]. Malnutrition can lead to poor prognosis in patients with HF by leading to fluid retention, inflammation, and increased neurohormonal activity due to hypoproteinemia[3].

The Dapagliflozin in Patients with Heart Failure and Reduced Ejection Fraction (DAPA-HF) and Empagliflozin Outcome Trial in Patients With Chronic Heart Failure With Reduced Ejection Fraction (EMPEROR-Reduced) trials showed that sodium-glucose cotransporter-2 (SGLT-2) inhibitor treatment improves the quality of life and HF symptoms in patients with heart failure with reduced ejection fraction (HFrEF) who describe symptoms in the New York Heart Association (NYHA) class II-IV categories despite optimal medical treatment[4,5]. We can conclude that the symptomatic and functional improvement with SGLT-2 inhibitor treatment in patients with HFrEF does not occur only with diuresis, but SGLT-2 inhibitors can improve the nutritional status of patients.

PATIENTS AND METHODS

Patients

This prospective study included patients with the diagnosis of HFrEF. The study's inclusion criteria were as follows: (1) the presence of left ventricular ejection fraction (LVEF) of less than 40%, (2) having an NYHA functional class II–IV despite optimal

[1]Sancaktepe Şehit Prof. Dr. İlhan Varank Training and Research Hospital, Department of Internal Medicine – İstanbul, Turkey.
[2]Giresun University, Medical School, Department of Cardiology – Giresun, Turkey.
[3]Trabzon Kanuni Training and Research Hospital, Department of Cardiology – Trabzon, Turkey.
*Corresponding author: kademarslan@hotmail.com
Conflicts of interest: the authors declare there is no conflicts of interest. Funding: none.
Received on July 16, 2022. Accepted on July 25, 2022.

medical treatment, (3) having an SGLT-2 inhibitor drug added to the treatment and used regularly for at least 6 months, (4) attendance at the 6-month follow-up and attendance at least two of the three follow-up visits. The study's exclusion criteria were as follows: In the past 6 months, before and during the study's follow-up (1) undergone cardiac pacemaker, implantable cardioverter-defibrillator (ICD) implantation or cardiac resynchronization therapy (CRT), (2) undergone coronary artery bypass graft surgery, (3) undergone surgical or percutaneous intervention for heart valve disease, (4) undergone percutaneous coronary intervention for acute coronary syndrome, (5) having an inflammatory and infectious disease under follow-up or treatment, (6) having a malignancy, and (7) having advanced liver and kidney failure (glomerular filtration rate <30 mL/min/1.73 m^2).

Optimal medical treatment: The fact that the patients were symptomatic despite optimal medical treatment was expressed after applying the maximum doses of the maximum number of optimal medical treatment drug groups that they could tolerate[1].

Patient follow-ups and data records were made prospectively in the cardiology outpatient clinic. Patients who were initiated SGLT-2 inhibitor treatment were invited to follow-ups at the first, third, and sixth months to monitor treatment adherence. Demographic characteristics of the patients, blood test results, systolic and diastolic blood pressures, heart rates, body weight, and height measurements were recorded at the follow-up visits. At each follow-up visit, nutritional index scores and body mass index (BMI) values of patients were calculated, blood samples were taken to test serum albumin and NT-pro-BNP levels, and NYHA functional classification and Minnesota Living with Heart Failure Questionnaire (MLWHFQ) were repeated.

Nutritional indexes

The nutritional status of all patients was assessed using three scoring systems: (1) Geriatric Nutritional Risk Index (GNRI), (2) COntrolling NUTritional Status (CONUT), and (3) Prognostic Nutritional Index (PNI). The GNRI scores were calculated as follows: 1489xserum albumin (g/L)+41.7x[weight (kg)/ideal body weight][6]. Ideal body weight (IBW) was calculated using the formula: 22x(height in meters)^2[2,7]. The GNRI scores were evaluated as follows: <82 points: severe, 82–91 points: moderate, 92–98 points: mild malnutrition, and >98 points: normal. The CONUT score was calculated by the previously described formula based on serum albumin level, total lymphocyte count, and total cholesterol level[8]. The CONUT scores were evaluated as follows: 0–1 points: normal, 2–4 points: mild, 5–8 points: moderate, and 9–12 points: severe malnutrition. The PNI score was calculated by the formula: 10xserum albumin (g/dL)+0.005xtotal lymphocyte count (µl)[9]. The PNI scores were evaluated as follows: >38 points: normal, 35–38 points: mild, and <35 points: severe malnutrition. In our study, patients with normal nutritional status and patients with malnutrition were evaluated mutually in the subgroup analyses. Patients were considered malnourished if GNRI score <98, CONUT score ≥2, and PNI score <38.

Ethical standards

For this study, written consent was obtained from the patients, and approval was obtained from the local ethics committee with the decision number 2022/046. This study was performed in accordance with the 1964 Declaration of Helsinki.

Statistical analysis

The IBM Statistical Package for Social Sciences, version 20 for Windows (Chicago, IL, USA) was used for statistical analyses. The compatibility of the parameters with the normal distribution was evaluated using the Kolmogorov-Smirnov test and the normality using the Shapiro-Wilk test. Normally distributed data were presented as the mean±standard deviation (SD) and non-normally distributed data were presented as the median with 25–75%. The categorical variables were expressed as percentages. The Student's t-test and Mann-Whitney U test were used to compare the differences in variables between the groups. The chi-square test was used to analyze categorical variables. The McNemar test and sample t-test were performed according to the normality of malnutrition using three scoring systems before and after the SGLT-2 inhibitor treatment. Pearson's and Spearman's correlation tests were used to evaluate the correlation between the variables. A $p \leq 0.05$ was considered significant for all statistical analyses.

RESULTS

A total of 153 patients with HFrEF were included in the study. The mean follow-up period of the patients was 245±22 days. Demographic, clinical, and laboratory characteristics of the patients are presented in Table 1. The mean age of the patients was 62.4±10.6 years, and 35 (22.8%) patients were female. In 58.8% of the patients, the cause of HF was ischemic heart disease.

Serum albumin levels were found to be increased significantly after treatment (before: 4.1±0.5 vs. after: 4.9±0.67, p=0.022). NT-pro-BNP levels were found to be decreased significantly after treatment (before: 2989±681 pg/mL vs. after: 1236±760 pg/mL, p<0.001) (Table 1).

According to the NYHA functional classification, 64 (42%) patients were grouped under class II, 82 (53.5%) patients were

Table 1. Demographic characteristics, clinical and laboratory parameters, and nutritional index scores of the study population (baseline and after treatment).

Parameter	Baseline (n=153)		
Age (years)	62.4±10.6		
Gender: female, n (%)	35 (22.8)		
Ischemic heart failure, n (%)	90 (58.8)		
Hypertension, n (%)	98 (64.1)		
Diabetes mellitus, n (%)	50 (32.6)		
Coronary artery disease, n (%)	104 (67.9)		
Dyslipidemia (n/%)	77 (50.3)		
COPD (n/%)	35 (22.8)		
Atrial fibrillation	34 (22.2)		
LVEF, n (%)	27.5±4.7		
β-Blocker use, n (%)	143 (93.4)		
ACE inhibitor use, n (%)	80 (52.2)		
Sacubitril use, n (%)	71 (46.4)		
Spironolactone use, n (%)	98 (64.1)		
Statin use, n (%)	30 (19.6)		
Ivabradine use, n (%)	56 (36.6)		
Diuretic use, n (%)	142 (92.8)		
Digoxin use, n (%)	26 (16.9)		
	Baseline	**After treatment**	**p-value**
SBP (mmHg)	126.3±24	124.9±22	0.456
DBP (mmHg)	68.4±13	66.3±12	0.518
Sodium (mmol/L)	137.8±4.6	138.6±4.4	0.356
Potassium (mmol/L)	4.4 (3.2–5.8)	4.5 (3.3–5.8)	0.408
Hematocrit (%)	38.5±4.6	39.2±4.8	0.486
Lymphocyte (10^9/L)	1.82±0.39	1.88±0.32	0.398
eGFR, mL/min/1.73 m^2	66.8±15.4	68.2±14.2	0.246
Total cholesterol (mg/dL)	172.46±12.66	174.38±14.06	0.286
LDL (mg/dL)	108.82 (52.4–140.6)	109.64 (56.8–148.5)	0.308
CRP	4.9 (2.4–12.6)	4.5 (3.1–10.4)	0.382
Heart rate	74.1±4.8	73.8±4.4	0.412
HbA1c (%)	6.9±1.4	6.7±1.2	0.422
BMI (kg/m^2)	27.9±5.2	27.7±4.7	0.620
Weight (kg)	75.6±13	76.1±14	0.668
Albumin (g/dL)	4.1±0.5	4.9±0.6	0.022
NT-pro-BNP, pg/mL	2989±681	1236±760	<0.001
NYHA class, n (%)			<0.001
I	0	34 (22)	
II	64 (42)	88 (58)	
III	82 (53.5)	31 (20)	
IV	7 (4.5)	0	
MLWHFQ score	39.2±7.2	20.4±7.4	<0.001
CONUT score	2.76±2.4	1.12±1.2	<0.001
CONUT ≥2, n (%)	71 (46.4)	14 (9.7)	<0.001
GNRI score	98.2±9.6	104.4±5.8	<0.001
GNRI <98, n (%)	64 (41.8)	29 (18.9)	0.006
PNI score	37.9±4.6	42.9±3.8	<0.001
PNI <38, n (%)	56 (36.6)	21 (13.7)	0.007

Numerical variables with normally distributed data were presented as the mean±standard deviation (SD), numerical variables without normally distributed data were presented as the median (25th and 75th percentages), and categorical variables were presented as percentages. COPD: chronic obstructive pulmonary disease; LVEF: left ventricular ejection fraction; ACE: angiotensin-converting enzyme; SBP: systolic blood pressure; DBP: diastolic blood pressure; GFR: glomerular filtration rate; LDL: low-density lipoprotein; CRP: C-reactive protein; BMI: body mass index; NT-pro-BNP: N-terminal-pro B-type natriuretic peptide, NYHA: New York Heart Association; MLWHFQ: Minnesota Living with Heart Failure Questionnaire; CONUT: COntrolling NUTritional status; GNRI: Geriatric Nutritional Risk Index; PNI: Prognostic Nutritional Index.

grouped under class III, and 7 (4.5%) patients were grouped under class IV before SGLT-2 treatment. Significant symptomatic and functional improvement was observed in patients after SGLT-2 inhibitor treatment. After treatment, the rate of patients in NYHA class III decreased to 20%, the rate of patients in NYHA class II-III decreased to 78%, and there were no patients in the NYHA class IV category (p<0001). The mean MLWHFQ score was found to be decreased significantly after treatment (before: 39.2±7.2 vs. after: 20.4±7.4, p<0.001) (Table 1). We found that MLWHFQ score, NT-pro-BNP level, and NYHA classification were significantly correlated with each other (Table 2).

We found that there was a significant improvement in the mean index scores we used for nutritional status assessment after SGLT-2 inhibitor treatment compared to before treatment (CONUT—before: 2.76±2.43 vs. after: 1.12±1.23, p<0.001; GNRI—before: 98.2±9.63 vs. after: 104.4±5.83, p<0.001; PNI—before: 37.9±4.63 vs. after: 42.9±3.83, p<0.001). The distribution of patients with malnutrition was determined according to the nutritional indexes as follows: CONUT ≥2 [before, n (%): 71 (46.4%) vs. after, n (%): 14 (9.7%)]; GNRI <98 [before, n (%): 64 (41.8%) vs. after, n (%): 29 (18.9%)], and PNI <38 [before, n (%): 56 (36.6%) vs. after, n (%): 21 (13.7%)]. The rate of patients with malnutrition was found to be decreased significantly after SGLT-2 inhibitor treatment (p: <0.001, 0.006, 0.007, respectively) (Figure 1). We found that the nutritional index scores were significantly correlated with

Table 2. Correlation analyses of Minnesota Living with Heart Failure Questionnaire score, NT-pro-BNP level, and New York Heart Association class with nutritional index scores of patients.

Variables	MLWHFQ score	NT-pro-BNP level	NYHA class	CONUT score	GNRI score	PNI score
MLWHFQ score		r: 0.230	r: 0.454	r: 0.302	r: -0.364	r: -0.392
		p: 0.028	p<0.001	p: 0.004	p<0.001	p<0.001
NT-pro-BNP level	r: 0.230		r: 0.278	r: 0.320	r: -0.339	r: -0.388
	p: 0.028		p: 0.006	p: 0.001	p<0.001	p<0.001
NYHA class	r: 0.454	r: 0.278		r: 0.288	r: -0.310	r: -0.354
	p<0.001	p: 0.006		p: 0.007	p: 0.001	p<0.001
CONUT score	r: 0.302	r: 0.320	r: 0.288		r: -0.402	r: - 0.388
	p: 0.004	p: 0.001	p: 0.007		p<0.001	p<0.001
GNRI score	r: -0.364	r: -0.339	r: -0.310	r: -0.402		r: 0.672
	p<0.001	p<0.001	p: 0.001	p<0.001		p<0.001
PNI score	r: -0.392	r: -0.388	r: -0.354	r: - 0.388	r: 0.672	
	p<0.001	p<0.001	p<0.001	p<0.001	p<0.001	

MLWHFQ: Minnesota Living with Heart Failure Questionnaire; BNP: B-type natriuretic peptide; NYHA: New York Heart Association; CONUT: COntrolling NUTritional status; GNRI: Geriatric Nutritional Risk Index; PNI: Prognostic Nutritional Index.

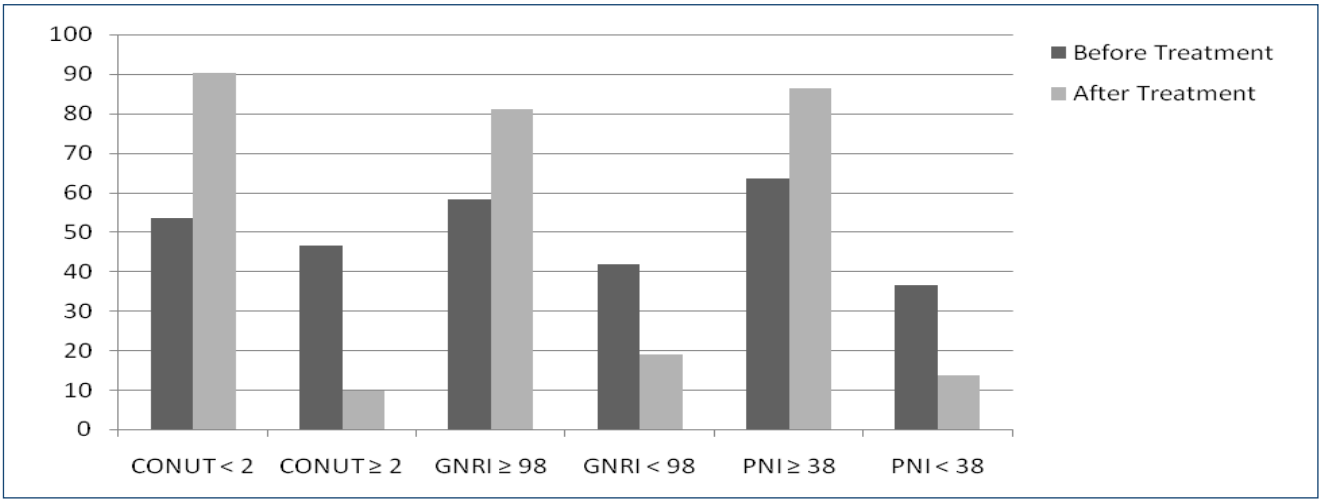

Figure 1. Changes in nutritional index scores of patients before and after sodium-glucose cotransporter-2 inhibitor treatment. CONUT: COntrolling NUTritional Status; GNRI: Geriatric Nutritional Risk Index; PNI: Prognostic Nutritional Index.

each other (CONUT vs. GNRI: r=-0.402, p<0.001; CONUT vs. PNI: r=-0.388, p<0.001; GNRI vs. PNI: r=0.672, p<0.001). It was determined that the same 31 (20.2%) patients were in the malnutrition group in three different nutritional index scoring systems (Table 2).

The functional assessment scores and parameters were found to be significantly correlated with the nutritional index scores: (1) MLWHFQ scores were positively correlated with CONUT score (r=0.302) and negatively correlated with GNRI (r=-0.364) and PNI (r=-0.392) scores (p: 0.004, <0.001, <0.001, respectively); (2) NT-pro-BNP levels were positively correlated with CONUT scores (r=0.320) and negatively correlated with GNRI (r=-0.339) and PNI (r=-0.388) scores (p: 0.001, <0.001, <0.001, respectively); (3) NYHA classification was positively correlated with the CONUT score (r=0.288) and negatively correlated with the GNRI (r=-0.310) and PNI (r=-0.354) scores (p: 0.007, 0.001, <0.001, respectively) (Table 2).

DISCUSSION

To the best of our knowledge, this study is the first to show that SGLT-2 inhibitor treatment may be associated with the improvement of nutritional status in patients with HFrEF. SGLT-2 inhibitors are recommended in current guidelines as drugs that improve symptoms and quality of life in patients with HF who are symptomatic despite optimal medical treatment[1]. SGLT-2 inhibitors are a relatively new drug class, and new clinical studies are required to show additional benefits in patients with HF. We conducted this study based on the hypothesis that while SGLT-2 inhibitors provide symptomatic and functional improvement in patients with HFrEF, they also improve the nutritional status of the patients. There are not enough data in the literature to support our hypothesis. For this purpose, we examined the nutritional and functional statuses of patients with HFrEF receiving SGLT-2 inhibitor treatment and investigated the effects of SGLT-2 inhibitors on nutritional status.

In our study, it was observed that the index scores (CONUT, GNRI, and PNI) that we used for nutritional status assessment showed a significant change after SGLT-2 treatment and that the number of patients with malnutrition decreased significantly. In addition, the functional assessment scores and parameters were found to be significantly correlated with nutritional index scores. However, the mechanisms by which SGLT-2 inhibitors may improve nutritional status are not clear. SGLT-2 inhibitors can be thought to regress the congestion in the hepatic and splanchnic areas with their diuretic effects and thus reduce intestinal edema and malabsorption, which is one of the important causes of malnutrition in patients with HF[10-12]. In addition, some studies have shown that SGLT-2 inhibitors reduce the release of pro-inflammatory cytokines[13]. By this mechanism, SGLT-2 inhibitors can reduce anorexia and malnutrition caused by cytokines. Also, in this study, there was a significant increase in serum albumin levels, one of the parameters used in the calculation of nutritional index scores, after SGLT-2 treatment. It is already known as a result of extensive studies that SGLT-2 inhibitors reduce albuminuria and proteinuria[11,14]. In addition, a relative increase in serum albumin levels due to decreased venous volume as a result of the diuretic effect of SGLT-2 inhibitor treatment may also be considered.

After SGLT-2 inhibitor treatment, we observed improvement in the parameters that we used to evaluate the functional status and treatment response of patients with HFrEF. The MLWHFQ scores and NYHA class categories of patients changed significantly, and the NT-pro-BNP levels decreased significantly. Also, these parameters were significantly correlated with each other. Similarly, lower NT-pro-BNP levels were found after SGLT-2 inhibitor treatment in other studies involving patients with HF[15,16]. In some studies, improvement in exercise capacity, quality of life, and NYHA class were observed in patients with symptomatic HF after SGLT-2 inhibitor treatment[16,17]. SGLT-2 inhibitors increase urinary glucose excretion together with sodium excretion. Fluid excretion increases with osmotic diuresis and natriuresis. Thus, SGLT-2 inhibitors, like a diuretic drug, cause a decrease in extravascular and intravascular volume, resulting in a decrease in blood pressure and body weight. As a result of these mechanisms, they may contribute to functional and symptomatic improvements in patients with HFrEF.

CONCLUSION

In patients with HFrEF who are symptomatic despite optimal medical treatment, the addition of an SGLT-2 inhibitor to treatment can significantly improve both nutritional status and functional capacity. SGLT-2 inhibitors were shown to provide significant improvement in malnutrition when patients with HFrEF are screened for malnutrition using three scoring systems (CONUT, GNRI, and PNI) and followed up after treatment. SGLT-2 inhibitors can assist symptomatic treatment of patients with HFrEF, improve malnutrition, prolong patient survival, and improve quality of life.

AUTHORS' CONTRIBUTIONS

KA: Conceptualization, Data curation, Formal Analysis, Investigation, Methodology, Project administration, Software, Supervision, Validation, Visualization, Writing – review & editing. **EY**: Conceptualization, Visualization, Data curation, Investigation, Methodology, Supervision, Validation. **EA**: Visualization, Data curation, Investigation, Writing – review & editing. All authors read and approved the final version of the manuscript.

REFERENCES

1. McDonagh TA, Metra M, Adamo M, Gardner RS, Baumbach A, Böhm M. 2021 ESC Guidelines for the diagnosis and treatment of acute and chronic heart failure. Eur Heart J. 2021;42(36):3599-726. https://doi.org/10.1093/eurheartj/ehab368
2. Poehlman ET, Scheffers J, Gottlieb SS, Fisher ML, Vaitekevicius P. Increased resting metabolic rate in patients with congestive heart failure. Ann Intern Med. 1994;121(11):860-2. https://doi.org/10.7326/0003-4819-121-11-199412010-00006
3. Lin H, Zhang H, Lin Z, Li X, Kong X, Sun G. Review of nutritional screening and assessment tools and clinical outcomes in heart failure. Heart Fail Rev. 2016;21(5):549-65. https://doi.org/10.1007/s10741-016-9540-0
4. McMurray JJV, Solomon SD, Inzucchi SE, Køber L, Kosiborod MN, Martinez FA, et al. Dapagliflozin in patients with heart failure and reduced ejection fraction. N Engl J Med. 2019;381(21):1995-2008. https://doi.org/10.1056/NEJMoa191130
5. Packer M, Anker SD, Butler J, Filippatos G, Pocock SJ, Carson P, et al. Cardiovascular and renal outcomes with empagliflozin in heart failure. N Engl J Med. 2020;383(15):1413-24. https://doi.org/10.1056/NEJMoa2022190
6. Bouillanne O, Morineau G, Dupont C, Coulombel I, Vincent JP, Nicolis I, et al. Geriatric nutritional risk index: a new index for evaluating at-risk elderly medical patients. Am J Clin Nutr. 2005;82(4):777-83. https://doi.org/10.1093/ajcn/82.4.777
7. Cereda E, Pedrolli C. The Geriatric Nutritional Risk Index. Curr Opin Clin Nutr Metab Care. 2009;12(1):1-7. https://doi.org/10.1097/MCO.0b013e3283186f59
8. Ignacio de Ulíbarri J, González-Madroño A, de Villar NG, González P, González B, Mancha A, et al. CONUT: a tool for controlling nutritional status. First validation in a hospital population. Nutr Hosp. 2005;20(1):38-45. PMID: 15762418
9. Li D, Yuan X, Liu J, Li C, Li W. Prognostic value of prognostic nutritional index in lung cancer: a meta-analysis. J Thorac Dis. 2018;10(9):5298-307. https://doi.org/10.21037/jtd.2018.08.51
10. Valentova M, von Haehling S, Bauditz J, Doehner W, Ebner N, Bekfani T, et al. Intestinal congestion and right ventricular dysfunction: a link with appetite loss, inflammation, and cachexia in chronic heart failure. Eur Heart J. 2016;37(21):1684-91. https://doi.org/10.1093/eurheartj/ehw008
11. Sandek A, Bauditz J, Swidsinski A, Buhner S, Weber-Eibel J, von Haehling S, et al. Altered intestinal function in patients with chronic heart failure. J Am Coll Cardiol. 2007;50(16):1561-9. https://doi.org/10.1016/j.jacc.2007.07.016
12. Kalantar-Zadeh K, Anker SD, Horwich TB, Fonarow GC. Nutritional and anti-inflammatory interventions in chronic heart failure. Am J Cardiol. 2008;101(11A):S89-103. https://doi.org/10.1016/j.amjcard.2008.03.007
13. Gembardt F, Bartaun C, Jarzebska N, Mayoux E, Todorov VT, Hohenstein B, et al. The SGLT2 inhibitor empagliflozin ameliorates early features of diabetic nephropathy in BTBR ob/ob type 2 diabetic mice with and without hypertension. Am J Physiol Renal Physiol. 2014;307(3):F317-25. https://doi.org/10.1152/ajprenal.00145.2014
14. Terami N, Ogawa D, Tachibana H, Hatanaka T, Wada J, Nakatsuka A, et al. Long-term treatment with the sodium glucose cotransporter 2 inhibitor, dapagliflozin, ameliorates glucose homeostasis and diabetic nephropathy in db/db mice. PLoS One. 2014;9(6):e100777. https://doi.org/10.1371/journal.pone.010077
15. Nassif ME, Windsor SL, Tang F, Khariton Y, Husain M, Inzucchi SE, et al. Dapagliflozin effects on biomarkers, symptoms, and functional status in patients with heart failure with reduced ejection fraction: the DEFINE-HF trial. Circulation. 2019;140(18):1463-76. https://doi.org/10.1161/CIRCULATIONAHA.119.042929
16. Tanaka A, Toyoda S, Imai T, Shiina K, Tomiyama H, Matsuzawa Y, et al. Effect of canagliflozin on N-terminal pro-brain natriuretic peptide in patients with type 2 diabetes and chronic heart failure according to baseline use of glucose-lowering agents. Cardiovasc Diabetol. 2021;20(1):175. https://doi.org/10.1186/s12933-021-01369-5
17. Núñez J, Palau P, Domínguez E, Mollar A, Núñez E, Ramón JM, et al. Early effects of empagliflozin on exercise tolerance in patients with heart failure: a pilot study. Clin Cardiol. 2018;41(4):476-80. https://doi.org/10.1002/clc.22899

ORIGINAL ARTICLE

https://doi.org/10.1590/1806-9282.20220809

Perinatal outcomes of prenatal diagnosis of congenital pulmonary airway malformation: an experience

Liliam Cristine Rolo[1], Giovana Domingues Ribeiro[1], João Victor Jacomele Caldas[1], Luiza Graça Coutinho[1], Thalita Diógenes Muniz[1], Edward Araujo Júnior[1*]

SUMMARY

OBJECTIVE: This study aimed to assess the perinatal outcomes of pregnancies with a prenatal diagnosis of congenital cystic adenomatoid malformation.

METHODS: We conducted a retrospective cohort study based on information contained in the medical records of pregnant women whose fetuses had been prenatally diagnosed with congenital cystic adenomatoid malformation by ultrasonography.

RESULTS: Sample analysis was based on 21 singleton pregnancies with confirmed isolated fetal congenital cystic adenomatoid malformations. The mean maternal±standard deviation age was 28±7.7 years. Types I, II, and III congenital cystic adenomatoid malformation were detected in 19% (4/21), 52.4% (11/21), and 28.6% (6/21), respectively. All fetuses presented with unilateral congenital cystic adenomatoid malformation (21/21) without associated anomalies, and 52.3% (11/21) were in the right lung. In total, 33.3% (7/21) of fetuses presented a "congenital cystic adenomatoid malformation volume ratio" >1.6 and were managed with maternal betamethasone administration. The mean gestational age at the time of steroid administration was 28.5±0.9 weeks, with a reduction in the lesion dimensions of 9.5% (2/21) (Types I and III of congenital cystic adenomatoid malformation). The mean gestational age at delivery was 38.7±2.4 weeks, and a cesarean section was performed in 76.2% (16/21) cases. Postsurgical resection was necessary for 23.8% (5/21) of the patients, and 4.7% (1/21) of them died because of respiratory complications after surgery. Pulmonary hypoplasia occurred in 9.5% (2/21) of the patients, and 4.7% (1/21) of them died because of respiratory insufficiency. The survival rate was 90.5% (19/21), and 57.2% (12/21) remained asymptomatic.

CONCLUSION: Despite the isolated prenatal diagnosis of congenital cystic adenomatoid malformation, which showed good survival, congenital cystic adenomatoid malformation is associated with significant perinatal morbidity. Maternal betamethasone administration did not significantly reduce fetal lung lesion dimensions.

KEYWORDS: Prenatal diagnosis. Cystic adenomatoid malformation of lung, congenital. Ultrasonography. Perinatal mortality.

INTRODUCTION

Congenital cystic adenomatoid malformation (CCAM) is a multicystic mass of pulmonary tissue, with an incidence of approximately 1:25,000 to 1:35,000[1]. This may represent a failure in the developmental phase of terminal bronchiolar structures, which occurs between the fifth and sixth weeks of gestation during the pseudo-glandular phase of the lung[2,3]. CCAM is somewhat more common in male fetuses and can even occur in any lung lobe, being unilobar in 80–95% of cases and bilateral in less than 2%[4]. The CCAM communicates with the tracheobronchial tree, although this route can be irregular and tortuous. In general, CCAM shows normal pulmonary vascularization, although anomalous vascularization has been reported[5].

Due to routine fetal anomaly scanning and advances in antenatal ultrasonography, CCAM has been increasingly diagnosed[6]. Thus, it is possible to evaluate the lesion type and size, as well as the presence of mediastinal shift, fetal hydrops, or massive fluid retention. Three main types can be identified by ultrasonography: Types I and II as cystic, fluid-filled masses and Type III as a solid mass[5]. The natural history of CCAMs involves intrauterine growth until 28 weeks of gestation, at which growth plateaus or even regresses[7]. Ultrasound findings are important to predict the prognosis and management of CCAM since the presence of larger cysts and/or fetal hydrops are considered high risk and are frequently associated with a poorer prognosis[8,9]. In this situation, antenatal betamethasone is the first-line therapy, while open fetal surgical resection and/or an additional course of steroids are used as alternative treatment options[8-10].

In this report, we evaluated the perinatal outcomes of pregnancies with prenatal diagnoses of CCAM.

[1]Universidade Federal de São Paulo, Escola Paulista de Medicina, Department of Obstetrics – 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 August 09, 2022. Accepted on August 17, 2022.

METHODS

We conducted a retrospective cohort study based on information from medical records of pregnant women whose fetuses had been prenatally diagnosed by ultrasonography with CCAM at the Department of Obstetrics, Paulista School of Medicine, Federal University of São Paulo (EPM-UNIFESP), between November 2013 and July 2017. This study was approved by the Research Ethics Committee of UNIFESP (file: CAE 29171319.4.0000.5505).

Inclusion criteria were (1) singleton pregnancy with a live fetus and (2) CCAM lesion diagnosed by ultrasound at our institution (with or without maternal administration of prenatal corticosteroids). Exclusion criteria were (1) the presence of other congenital malformations, (2) intrauterine fetal death, and (3) unavailable data from the postnatal evaluation.

To perform this study, the following variables were evaluated: maternal age, number of pregnancies and deliveries, gestational age at birth, number of ultrasound examinations during the prenatal period, classification of CCAM according to Stocker et al.[4], the use of antenatal betamethasone, birth weight, type of delivery, gender of the neonates, Apgar scores at the first and fifth minutes in the neonatal intensive care unit, type and localization of the CCAMs, postnatal complications, and hospitalization in childhood.

The data were collected using an Excel 2007 spreadsheet (Microsoft Corp., Redmond, WA, USA). For statistical analysis, continuous variables were presented as mean and standard deviation (SD), and data were compared using the unpaired Student's t-test. Categorical variables were expressed as numbers and percentages and analyzed for comparisons using the Pearson's chi-square test.

RESULTS

During the study period, 27 pregnancies with fetal CCAM were examined. Six cases were excluded: one twin pregnancy, two presenting with other malformations, and three lost to follow-up. Therefore, our statistical analysis was based on 21 singleton pregnancies with confirmed isolated fetal CCAM diagnosed between 22 and 32 weeks of gestation (Table 1). The mean maternal±SD age was 28±7.8 years, with a range of 18–44 years. The mean of previous deliveries±SD was 1±1.3, with a range of 0–4. According to the classification by Stocker et al.[4], 19.0% (4/21) were Type I, 52.4% (11/21) were Type II, and 28.6% (6/21) were Type III. The mean of ultrasound examinations±SD was 4.1±1.4, with a range of 2.0–6.0. The mean gestational age at the last ultrasound examination±SD was 36.2±1.8 weeks, with a range of 32.1–39.4 weeks, and the mean CCAM volume±SD was 10.7±15.1 cm^3, with a range of 0–57.3 cm^3. The last ultrasound examination did not identify lesions in 5 (23.8%) cases (Table 1).

All CCAMs were unilateral (21/21) without associated anomalies, and 52.3% (11/21) were in the right lung. Of the fetuses, 33.3% (7/21) presented signs of increased risk for fetal hydrops or lesions with "CCAM volume ratio" (CVR) [length (cm)×height (cm)×width (cm)×0.52/head circumference (cm)] >1.6 after lesion growth plateau (28 weeks of gestation). For this reason, these fetuses were managed with prenatal steroids (a single course of betamethasone, 12 mg intramuscularly, two doses, and 24 h apart), but the prenatal intervention was not needed. The mean gestational age at the time of steroid administration±SD was 28.5±0.9 weeks, with a range of 28.0–30.1 weeks. Subsequently, the fetal lung lesions exhibited a 9.5% (2/21) reduction in dimensions (Types I and III CCAM). The fetal lung lesion increased in 14.3% (3/21) of the cases (all were Type III CCAM) and 9.5% (2/21) remained the same size (Figure 1).

Table 1. Clinical data of congenital cystic adenomatoid malformation.

Characteristics	Mean (standard deviation)
Maternal age (years)	28 (7.8)
Number of pregnancies	2 (1.5)
Parity	1 (1.3)
Body mass index (kg/m^2)	29.1 (3.9)
Ultrasound examinations	4.1 (1.4)
Gestational age at last scan (weeks)	36.2 (1.8)
CCAM volume (cm^3)	10.7 (15.1)
Gestational age at delivery (weeks)	38.7 (2.4)
Birth weight (g)	3158.1 (658.0)
Apgar scores at the first minute	7.8 (1.8)
Apgar scores at the fifth minute	8.7 (1.1)
Total (n)	21
Percentage (%)	
Delivery	
Cesarean section	76.2
Vaginal	23.8
Gender	
Male	52.4
Female	47.6
Side affected	
Right lung	52.3
Left lung	47.7
Total (%)	100

Cesarean section was performed in 76.2% (16/21) of the cases, and 23.8% (5/21) were vaginal deliveries. The mean gestational age at delivery±SD was 38.7±2.4 weeks, with a range of 31–41 weeks. In 90.5% (19/21) of the cases, delivery occurred at >37 weeks and 57.1% (12/21) at >39 weeks. The mean birth weight±SD was 3158.1±658.0 g, with a range of 1705.0–4795.0 g (Table 1). The mean Apgar scores±SD at the first and fifth minutes were 7.8±1.8 and 8.7±1.1, respectively, with 81.0% of them being >9. In terms of gender, 52.4% (11/21) were male and 47.6% (10/21) were female (Table 1).

Postsurgical resection was necessary for 23.8% (5/21) of the patients, and 4.7% (1/21) died because of respiratory complications after surgical resection. Recurrent pneumonia occurred in 9.5% (2/21) of the patients. Pulmonary hypoplasia occurred in 9.5% (2/21) of the patients, and 4.7% (1/21) of the patients died because of respiratory insufficiency. The survival rate was 90.5% (19/21), and 57.2% (12/21) of the patients remained asymptomatic. A total of 33.4% (7/21) received betamethasone as a maternal therapeutic option during the prenatal period, and 24.6% (6/21) survived (Table 2).

DISCUSSION

CCAM is a malformation originating from abnormal airway development, wherein the terminal bronchioles proliferate abnormally at the beginning of embryonic development, generating intraparenchymal cysts of varying sizes[11,12]. Many congenital abnormalities can be identified and managed owing to advances in prenatal diagnostics and sonographic improvements. According to the literature, the antenatal diagnosis rate can reach 85%[11], and the majority of lung cysts can be detected with routine ultrasounds during the 18–20 weeks of gestation[8]. However, in our study, all cases of CCAM were diagnosed after 20 weeks of gestation. Fetal magnetic resonance imaging is not demonstrably better than ultrasound for the evaluation of this pathology[13].

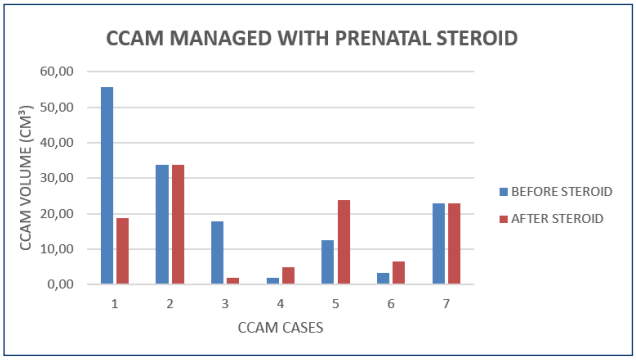

Figure 1. Congenital cystic adenomatoid malformation volume before (blue bar) after (red bar) steroid administration. Cases according to Stocker et al.'s[4] classification: Type I: 4, 5, and 6; Type II: 1 and 2; Type III: 3 and 7.

According to the Stocker et al.'s[4] classification, CCAM can be subdivided into three types. Type I has a good prognosis, is present in about 50% of cases, and consists of single or multiple cysts of larger dimensions (usually >2.0 cm), filled with air or fluid. They appear to communicate with the normal lung parenchyma and may be surrounded by smaller cysts. Type II lesions occur in approximately 40% of cases and consist of numerous small cysts (<2.0 cm) mixed with areas of increased echogenicity on ultrasound. The prognosis depends on the severity of the lesion and its association with other fetal malformations. There is a strong association between congenital anomalies and Type II CCAM, the main ones being genitourinary, such as renal dysgenesis or agenesis, and cardiac, such as tetralogy of Fallot and truncus arteriosus; others include diaphragmatic hernia and musculoskeletal anomalies. Type III is a solid mass that contains very small cysts (<5.0 mm)[4].

We observed that in ultrasound examinations, Type II was the main type of CCAM, corresponding to 52.4% of the cases, which disagrees with the findings of Mehta et al.[2], wherein Type I was more common. All cases were unilateral, localized, and not accompanied by other malformations. CCAMs usually grow until 28 weeks of gestation when it reaches a plateau and may regress in size. However, in some cases, the lesion can grow rapidly, causing the mediastinal shift, polyhydramnios, nonimmune fetal hydrops, and even fetal death[7].

Ultrasound evaluation should be performed weekly to assess the CCAM volume, and CVR may identify early signs

Table 2. Perinatal outcomes following prenatal diagnosis of congenital cystic adenomatoid malformation using or not maternal steroid administration.

Maternal therapeutic	Asymptomatic	Perinatal outcomes of CCAM			Total
		Neonatal resection	Pulmonary hypoplasia	Recurrent pneumonia	
With betamethasone	3 (14.3%)	3 (14.3%)	1* (4.7%)	0 (0%)	7 (33.4%)
Without betamethasone	9 (42.9%)	2 (9.5%)	1 (4.7%)	2 (9.5%)	14 (66.6%)
Total	12 (57.2%)	5** (23.8%)	2 (9.5%)	2 (9.5%)	21 (100.0%)

*One death after surgery by respiratory complications. **One death by respiratory insufficiency.

of fetal hydrops. Crombleholme et al.[14] showed that CVR >1.6 proved to be a good predictor of fetal hydrops and perinatal mortality. If there are any dominant cysts, even with a CVR <1.6, there is a risk of acute cyst growth and development of fetal hydrops. A thoracoamniotic shunt may be considered if signs of fetal decompensation at <32 weeks' gestation are identified[15]. Microcystic lesions increase the risk of fetal hydrops, pulmonary hypoplasia, and polyhydramnios[16].

Although the mechanism is unknown, the maternal use of corticosteroids has been performed in pregnancies with CCAM in an attempt to reduce the size of the lesion and reverse fetal hydrops. Curran et al.[17] evaluated the effect of prenatal use of a single cycle of steroids in patients with predominantly microcystic lesions and/or a CVR >1.6. Lesion reduction was observed in 61% of the cases, and fetal hydrops was resolved in 78%. The neonatal survival rate is approximately 85%. In this study, 33.3% of the fetuses showed signs of increased risk of fetal hydrops/lesions, had a CVR >1.6, and their mothers received corticosteroid therapy with betamethasone while pregnant. Post-therapy, almost 50% of the fetuses had no progression/increase of CCAM, although most cases were Type II, and none required prenatal intervention.

It is important to emphasize the limitation of this study in defending the use of corticosteroids as therapy, which was not proven, because of the small sample size. However, as it is a rare disease, it may encourage the development of more representative multicenter studies.

CONCLUSION

Despite the isolated prenatal diagnosis of CCAM that showed good survival, CCAM is associated with significant perinatal morbidity. Maternal betamethasone administration did not significantly reduce fetal lung lesion dimensions. More studies are needed to determine whether or not to encourage steroid therapy in an attempt to reduce the size of the lesion and reverse fetal hydrops.

AUTHORS' CONTRIBUTIONS

LCR: Conceptualization, Formal Analysis, Project administration, Visualization. **GDR:** Data curation, Visualization. **TDM:** Investigation, Validation, Visualization. **LGC:** Data curation, Investigation, Methodology. **EAJ:** Supervision, Visualization, Writing – review & editing. **JVJC:** Visualization, Writing – original draft.

REFERENCES

1. Gautam MS, Naren Satya SM, Prathyusha IS, Reddy KHC, Mayilvaganan KR, Raidu D. An atypical presentation of congenital pulmonary airway malformation (CPAM): a rare case with antenatal ultrasound findings and review of literature. Pol J Radiol. 2017;82:299-303. https://doi.org/10.12659/PJR.901447
2. Mehta AA, Viswanathan N, Vasudevan AK, Paulose R, Abraham M. Congenital cystic adenomatoid malformation: a tertiary care hospital experience. J Clin Diagn Res. 2016;10(11):SC01-4. https://doi.org/10.7860/JCDR/2016/19205.8775
3. Miller JA, Corteville JE, Langer JC. Congenital cystic adenomatoid malformation in the fetus: natural history and predictors of outcome. J Pediatr Surg. 1996;31(6):805-8. https://doi.org/10.1016/s0022-3468(96)90138-4
4. Stocker JT, Madewell JE, Drake RM. Congenital cystic adenomatoid malformation of the lung. Human Pathol. 1977;8(2):155-71. https://doi.org/10.1016/S0046-8177(77)80078-6
5. Rashad F, Grisoni E, Gaglione S. Aberrant arterial supply in congenital cystic adenomatoid malformation of the lung. J Pediatr Surg. 1988;23(11):1007-8. https://doi.org/10.1016/s0022-3468(88)80007-1
6. Nicolaides KH, Blott M, Greenough A. Chronic drainage of fetal pulmonary cyst. Lancet. 1987;1(8533):618. https://doi.org/10.1016/s0140-6736(87)90248-0
7. Cavoretto P, Molina F, Poggi S, Davenport M, Nicolaides KH. Prenatal diagnosis and outcome of echogenic fetal lung lesions. Ultrasound Obstet Gynecol. 2008;32(6):769-83. https://doi.org/10.1002/uog.6218
8. Fan D, Wu S, Wang R, Huang Y, Fu Y, Ai W, et al. Successfully treated congenital cystic adenomatoid malformation by open fetal surgery: a care-compliant case report of a 5-year follow-up and review of the literature. Medicine (Baltimore). 2017;96(2):e5865. https://doi.org/10.1097/MD.0000000000005865
9. Derderian SC, Coleman AM, Jeanty C, Lim FY, Shaaban AM, Farrell JA, et al. Favorable outcomes in high-risk congenital pulmonary airway malformations treated with multiple courses of maternal betamethasone. J Pediatr Surg. 2015;50(4):515-8. https://doi.org/10.1016/j.jpedsurg.2014.08.019
10. Peranteau WH, Wilson RD, Liechty KW, Johnson MP, Bebbington MW, Hedrick HL, et al. Effect of maternal betamethasone administration on prenatal congenital cystic adenomatoid malformation growth and fetal survival. Fetal Diagn Ther. 2007;22(5):365-71. https://doi.org/10.1159/000103298
11. Leblanc C, Baron M, Desselas E, Phan MH, Rybak A, Thouvenin G, et al. Congenital pulmonary airway malformations: state-of-the-art review for pediatrician's use. Eur J Pediatr. 2017;176(12):1559-71. https://doi.org/10.1007/s00431-017-3032-7
12. Shamas AG, Bohara K. Congenital cystic adenomatoid malformation of the lung (CCAM), a retrospective clinical audit and literature review in a tertiary centre in Scotland over a period of 14 years. J Obstet Gynaecol. 2017;37(1):19-24. https://doi.org/10.1080/01443615.2016.1196480
13. Lezmi G, Hadchouel A, Khen-Dunlop N, Vibhushan S, Benachi A, Delacourt C. [Congenital cystic adenomatoid malformations of

the lung: diagnosis, treatment, pathophysiological hypothesis]. Rev Pneumol Clin. 2013;69(4):190-7. https://doi.org/10.1016/j.pneumo.2013.06.001

14. Crombleholme TM, Coleman B, Hedrick H, Liechty K, Howell L, Flake AW, et al. Cystic adenomatoid malformation volume ratio predicts outcome in prenatally diagnosed cystic adenomatoid malformation of the lung. J Pediatr Surg. 2002;37(3):331-8. https://doi.org/10.1053/jpsu.2002.30832
15. Viggiano MB, Naves do Amaral W, Peres Fonseca PS, Hamú ZC, Damasceno de Castro J, Pulcinelli F. Prenatal catheter placement for fetal cystic adenomatoid pulmonary malformation: a case report. Fetal Diagn Ther. 2006;21(2):194-7. https://doi.org/10.1159/000089302
16. Adzick NS, Harrison MR, Glick PL, Golbus MS, Anderson RL, Mahony BS, et al. Fetal cystic adenomatoid malformation: prenatal diagnosis and natural history. J Pediatr Surg. 1985;20(5):483-8. https://doi.org/10.1016/s0022-3468(85)80470-x
17. Curran PF, Jelin EB, Rand L, Hirose S, Feldstein VA, Goldstein RB, et al. Prenatal steroids for microcystic congenital cystic adenomatoid malformations. J Pediatr Surg. 2010;45(1):145-50. https://doi.org/10.1016/j.jpedsurg.2009.10.025

ORIGINAL ARTICLE

https://doi.org/10.1590/1806-9282.20220812

The prognostic impact of tumor necrosis in non-muscle invasive bladder cancer

Meftun Culpan[1*], Ayberk Iplikci[1], Gozde Kir[2], Gozde Ecem Cecikoglu[2], Gokhan Atis[1], Asif Yildirim[1]

SUMMARY

OBJECTIVE: We aimed to investigate the impact of tumor necrosis in non-muscle invasive bladder cancer on patients' recurrence and progression rates and survival outcomes.

METHODS: This study was conducted retrospectively in a single tertiary center in Turkey. Medical records of patients who underwent transurethral resection of the bladder tumor between January 2016 and January 2021 were reviewed. Patients with pTa and pT1 non-muscle invasive bladder cancer who had undergone complete resection were included in our study. All pathological specimens were reevaluated for the presence of tumor necrosis.

RESULTS: A total of 287 patients (244 males and 43 females) were included in our study. Of them, 33 (11.5%) patients had tumor necrosis. The rates of multiple and large tumors (>3 cm) were higher in patients with tumor necrosis (p=0.002 and p<0.001, respectively). Tumor necrosis was associated with higher rates of pT1 diseases (p<0.001), high-grade tumors (p<0.001), and the presence of lymphovascular invasion (p=0.007). The mean recurrence-free survival of patients with tumor necrosis was 42.3 (4.6) months, and the recurrence-free survival of patients without tumor necrosis was 43.5 (1.8) months (p=0.720). The mean progression-free survival of patients with tumor necrosis was 43.1 (4.6) months, and the progression-free survival of patients without tumor necrosis was 58.4 (0.9) months. In log-rank analysis, there was a statistically significant difference between patients with and without tumor necrosis in terms of progression-free survival (p<0.001).

CONCLUSION: In this study, we demonstrated that patients with non-muscle invasive bladder cancer and tumor necrosis in pathological specimens have shorter progression-free survival and more adverse pathological features.

KEYWORDS: Urinary bladder neoplasms. Necrosis. Prognosis. Disease progression. Recurrence.

INTRODUCTION

Bladder cancer is the fourth most frequent malignancy in men and the eighth leading cause of cancer death[1]. Localized bladder cancers are classified according to muscle invasion status, and muscle-invasive bladder cancers (MIBCs) require more aggressive treatments such as radical cystectomy and urinary diversion. Despite more favorable oncological outcomes, non-muscle invasive bladder cancers (NMIBC) have up to 40% progression rates after transurethral resection of bladder tumor (TUR-BT) at 5 years[2]. Several predictive factors for progression were identified, such as age, the number of tumors, tumor size, T stage, concomitant carcinoma in situ (CIS), and histological grade[3].

Several studies reported that tumor necrosis had adverse oncological outcomes in some malignant epithelial tumors such as breast, kidney, or lung[4-6]. In 2010, Zigeuner et al. investigated the oncological impact of tumor necrosis in patients with upper urinary tract urothelial carcinoma (UTUC) and concluded that tumor necrosis is significantly associated with adverse pathological features, disease recurrence, and survival[7]. To date, few studies have investigated the oncological effect of tumor necrosis in bladder cancer. Therefore, the clinical significance of tumor necrosis in NMIBC remains an issue that should be investigated.

Accurately forecasting the clinical outcomes of patients with NMIBC is critical to providing counseling and making decisions about adjuvant intravesical therapies, possible early cystectomy, and follow-up appointments. Tumor necrosis is a potentially relevant prognostic factor that has gotten less attention thus far. To the best of our knowledge, only one study has investigated the clinical significance of tumor necrosis in TUR-BT specimens. This previous study demonstrated that tumor necrosis in TUR-BT specimens without muscle invasion was a significant predictor of upstaging at subsequent radical cystectomy[8].

[1]Istanbul Medeniyet University, Faculty of Medicine, Department of Urology – İstanbul, Turkey.
[2]Istanbul Medeniyet University, Faculty of Medicine, Department of Pathology – İstanbul, Turkey.
*Corresponding author: mculpan@gmail.com

Conflicts of interest: the authors declare there is no conflicts of interest. Funding: none.
Received on July 21, 2022. Accepted on August 01, 2022.

In this study, we aimed to investigate the impact of tumor necrosis in NMIBC on patients' recurrence and progression rates and survival outcomes.

METHODS

This study was conducted retrospectively in a single tertiary center in Turkey after receiving approval from the institutional review board (decision no.: 2021/0720, date: January 12, 2022). The medical records of patients who underwent TUR-BT for bladder cancer between January 2016 and January 2021 were reviewed retrospectively. Patients with pTa and pT1 NMIBC who had undergone complete resection were included in our study. Patients with incomplete resection (n=36), MIBC at second TUR (n=5), early cystectomy (within 6 months) (n=37), concomitant UTUC (n=2), and without at least 6 months of follow-up (n=43) were excluded from the study. Patients' demographics such as age, gender, and clinical tumor characteristics such as recurrence status, tumor number, and size were noted.

All patients had undergone a complete initial TUR-BT, and an experienced uropathologist performed pathological examinations. All TUR-BT procedures were performed with standard techniques and a monopolar or bipolar cauterization system. The en bloc resection technique was not used. The pathological T stage was determined according to the 2017 tumor, node, and metastasis classification of urinary bladder cancer. The World Health Organization 2004/2016 histological grading system was used to determine the histological grade. Concurrent carcinoma in situ (CIS), variant histology, and lymphovascular invasion were recorded. All pathological specimens were reevaluated by the same experienced uropathologist to determine the presence of tumor necrosis. The occurrence of microscopic granular necrosis without inflammation or fibrosis was evaluated as tumor necrosis. Tumor necrosis was characterized by well-defined necrotic foci being sharply demarcated from adjacent viable tumors. A constant feature was the loss of architecture, resulting in an amorphous necrotic mass containing granular nuclear and cytoplasmic debris without an associated neutrophilic infiltrate. These foci were often microscopic, but many ranged up to several millimeters or larger[9].

After initial TUR-BT and pathological examinations, patients with pT1 tumors underwent a second TUR-BT. Afterward, all patients with high-grade or pT1 tumors were recommended to receive adjuvant intravesical Bacillus Calmette-Guerin (BCG) treatment. Adjuvant intravesical mitomycin C (MMC) treatment was recommended for patients with intermediate-risk NMIBC according to the European Urological Association (EAU) guidelines. Postoperative single-dose MMC was administered to patients with tumors who appeared to be low risk. Patients with low-risk NMIBC confirmed by the pathology report were followed without any further adjuvant intravesical therapy. Cystoscopy and urine cytology were used for patients' follow-ups, and the schedule was determined according to risk stratification and EAU guidelines. High- and intermediate-risk patients underwent cystoscopy every 3 months for the first 2 years, every 6 months for the subsequent 3 years, and every year after 5 years. Patients with low-risk diseases underwent follow-up cystoscopies 3 and 12 months after the initial TUR-BT and then yearly for 5 years. Tumor recurrence was defined as the detection of pathologically confirmed urothelial carcinoma, and progression was defined as the detection of pT2 urothelial carcinoma at tumor recurrence during patients' follow-up.

Statistical analysis

Statistical Package for the Social Sciences version 26.0 (SPSS Inc., IBM, NY, USA) was used to perform statistical analyses. Evaluation of distributions was performed with the Kolmogorov-Smirnov and Shapiro-Wilk tests. Descriptive statistics (frequency, percentage, mean, standard deviation, median, etc.) were used to evaluate the data. Pearson's chi-square and Fisher's exact tests were used to analyze categorical variables. Cox regression analyses were used to determine the predictive factors for recurrence and progression. Cumulative survival rates were analyzed using the Kaplan-Meier method, and the significance of differences in the survival rates was analyzed using the log-rank test. A $p<0.05$ was accepted for statistical significance.

RESULTS

After the exclusions, a total of 287 patients, 244 (85%) males and 43 females (15%), were included in our study. The mean (SD) age was 66.2 (10.3) years, and 93 (32.4%) of the patients had recurrent NMIBC. Patients' clinicopathologic characteristics are presented in Table 1. A total of 33 (11.5%) patients had tumor necrosis. Patients' clinical and pathological characteristics were compared between the two groups with or without tumor necrosis. The rates of multiple and large tumors (>3 cm) were higher in patients with tumor necrosis ($p=0.002$ and $p<0.001$, respectively). Tumor necrosis was associated with higher rates of pT1 diseases ($p<0.001$), high-grade tumors ($p<0.001$), and the presence of lymphovascular invasion (LVI) ($p=0.007$) (Table 1).

During the mean (SD) 27.9 (13.6) months of follow-up, 85 (29.6%) patients had tumor recurrence and 23 (8%) patients had tumor progression. Tumor necrosis was significantly associated with tumor progression ($p=0.001$), but not with tumor recurrence ($p=0.927$). In multivariate Cox regression analysis,

Table 1. Patients' clinicopathologic variables and comparisons according to presence of tumor necrosis.

	Total	Necrosis (-)	Necrosis (+)	p-value
Age				
≤70 years	187 (65.2%)	168 (66.1%)	19 (57.6%)	0.331[a]
>70 years	100 (34.8%)	86 (33.9%)	14 (42.4%)	
Sex				
Female	43 (15.0%)	38 (15.0%)	5 (15.2%)	1.000[b]
Male	244 (85.0%)	216 (85.0%)	28 (84.8%)	
Recurrence status				
Primary	194 (67.6%)	170 (66.9%)	24 (72.7%)	0.503[a]
Recurrent	93 (32.4%)	84 (33.1%)	9 (27.3%)	
Tumor number				
Single	144 (50.2%)	136 (53.5%)	8 (24.2%)	**0.002[a]**
Multiple	143 (49.8%)	118 (46.5%)	25 (75.8%)	
Tumor size				
≤3 cm	171 (59.6%)	164 (64.6%)	7 (21.2%)	**<0.001[a]**
>3 cm	116 (40.4%)	90 (35.4%)	26 (78.8%)	
T stage				
pTa	209 (72.8%)	204 (80.3%)	5 (15.2%)	**<0.001[a]**
pT1	78 (27.2%)	50 (19.7%)	28 (84.8%)	
Tumor grade				
Low	135 (47.0%)	135 (53.1%)	0 (0.0%)	**<0.001[a]**
High	152 (53.0%)	119 (46.9%)	33 (100.0%)	
Concurrent CIS				
No	265 (92.3%)	237 (93.3%)	28 (84.4%)	0.153[b]
Yes	22 (7.7%)	17 (6.7%)	5 (15.2%)	
Variant histology				
No	273 (95.1%)	243 (95.7%)	30 (90.9%)	0.209[b]
Yes	14 (4.9%)	11 (4.3%)	3 (9.1%)	
Lymphovascular invasion				
Negative	270 (94.1%)	243 (95.7%)	27 (81.8%)	**0.007[b]**
Positive	17 (5.9%)	11 (4.3%)	6 (18.2%)	
Single-dose intravesical chemotherapy				
No	223 (77.7%)	192 (75.6%)	31 (93.9%)	**0.017[a]**
Yes	64 (22.3%)	62 (24.4%)	2 (6.1%)	
Adjuvant treatment				
None	99 (34.5%)	93 (36.6%)	6 (18.2%)	**0.000[a]**
Mitomycin	58 (20.2%)	57 (22.4%)	1 (3.0%)	
BCG	130 (45.3%)	104 (40.9%)	26 (78.8%)	
Recurrence				
No	202 (70.4%)	179 (70.5%)	23 (69.7%)	0.927[a]
Yes	85 (29.6%)	75 (29.5%)	10 (30.3%)	
Progression				
No	264 (92.0%)	240 (94.5%)	24 (72.7%)	**<0.001[b]**
Yes	23 (8.0%)	14 (5.5%)	9 (27.3%)	

[a]Pearson's chi-square. [b]Fisher's exact test. BCG: Bacillus Calmette-Guerin; CIS: carcinoma in situ. Bold indicates statistically significant value.

T stage (pT1 vs. pTa) (HR: 2.479, 95%CI 1.362–4.513, p=0.003) and adjuvant BCG treatment (HR: 0.343, 95%CI 0.193–0.609, p<0.001) were significant predictive factors for tumor recurrence. However, the only significant predictive factor for progression was the T stage (pT1 vs. pTa) (HR: 18.494, 95%CI 3.153–108.476) in multivariate analysis (Table 2).

In Kaplan-Meier analyses, the overall mean (SD) estimated recurrence-free survival (RFS) was 43.7 (1.7) months. The RFS of patients with tumor necrosis was 42.3 (4.6) months, and the RFS of patients without tumor necrosis was 43.5 (1.8) months. RFS was similar between the two groups (p=0.720) (Figure 1). The progression-free survival (PFS) was 57.0 (1.0) months in the overall population. The PFS of patients with tumor necrosis was 43.1 (4.6) months, and the PFS of patients without tumor necrosis was 58.4 (0.9) months. In log-rank analysis, patients with tumor necrosis exhibited a considerably shorter PFS than those without (p<0.001) (Figure 1).

DISCUSSION

Tumor necrosis is a pathophysiological manifestation of ischemia and hypoxia-induced by inadequate neovascularization, which is seen in rapidly growing tumors[10]. Ischemia or reduced oxygen causes the hypoxia-inducible factor (HIF) transcription factor to stabilize and activate, causing gene transcription to stimulate angiogenesis and restore oxygen and nutritional balance[11]. Hypoxia and HIF regulate the transcription of genes encoding processes like angiogenesis, invasion, and apoptosis. Some previous studies demonstrated that HIF-1 alpha overexpression was significantly correlated with worse prognosis in urothelial bladder cancer or upper urinary tract cancer[12,13].

The potential prognostic significance of tumor necrosis in urothelial cancers was investigated by Langner et al. in 2006. They included 268 patients with UTUC in this study and reported that 133 (42.2%) patients had tumor necrosis. In this

Table 2. Univariate and multivariate Cox regression analysis for recurrence and progression.

	Recurrence				Progression			
	Univariate		Multivariate		Univariate		Multivariate	
	HR (95%CI)	p-value	HR (95%CI)	p-value	HR (95%CI)	p-value	HR (95%CI)	p-value
Age (>70 vs. ≤70*) (years)	1.048 (0.668–1.644)	0.839	–	–	1.362 (0.587–3.156)	0.472	–	–
Sex (male vs. female*)	0.787 (0.450–1.377)	0.402	–	–	1.264 (0.375–4.266)	0.706	–	–
Recurrence status (recurrent vs. primary*)	2.009 (1.306–3.089)	<0.001	–	–	1.710 (0.749–3.908)	0.203	–	–
Tumor number (multiple vs. single*)	1.651 (1.071–2.545)	0.023	–	–	2.100 (0.889–4.960)	0.091	–	–
Tumor size (>3 cm vs. ≤3 cm*)	1.518 (0.990–2.326)	0.055	–	–	2.562 (1.107–5.932)	0.028	–	–
T stage (pT1 vs. pTa*)	1.554 (0.991–2.436)	0.055	2.479 (1.362–4.513)	0.003	22.988 (6.699–78.886)	<0.001	18.494 (3.153–108.476)	<0.001
Tumor grade (high vs. low*)	1.037 (0.677–1.587)	0.869	–	–	10.625 (2.487–45.387)	<0.001	–	–
Concurrent CIS (yes vs. no*)	1.411 (0.680–2.925)	0.355	–	–	3.100 (1.045–9.192)	0.041	–	–
Variant histology (yes vs. no*)	0.477 (0.110–1.819)	0.261	–	–	1.006 (0.135–7.485)	0.995	–	–
Lymphovascular invasion (yes vs. no*)	0.608 (0.192–1.925)	0.397	–	–	1.773 (0.414–7.597)	0.440	–	–
Tumor necrosis (yes vs. no*)	1.127 (0.581–2.184)	0.724	–	–	5.828 (2.513–13.515)	<0.001	–	–
Single-dose intravesical chemotherapy (yes vs. no*)	0.604 (0.379–0.962)	0.034	–	–	0.968 (0.358–2.616)	0.949	–	–
Adjuvant treatment		0.123		<0.001		0.150		
Mitomycin vs. none*	1.114 (0.646–1.921)	0.697	1.052 (0.599–1.847)	0.860	0.206 (0.026–1.646)	0.136		
BCG vs. none*	0.660 (0.404–1.079)	0.098	0.343 (0.193–0.609)	<0.001	1.439 (0.602–3.441)	0.413	–	–

*Reference.

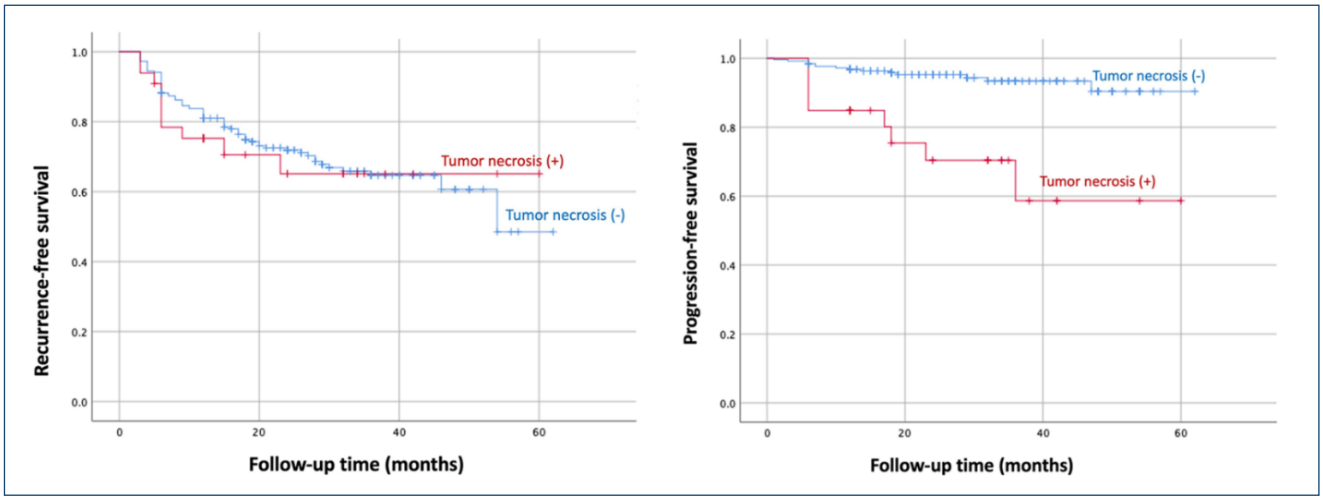

Figure 1. Kaplan-Meier survival curves for recurrence-free survival and progression-free survival.

study, the authors stated that higher tumor stage (p<0.001) and grade (p<0.001) were significantly associated with tumor necrosis. In addition to these findings, extensive tumor necrosis was an independent predictor of worse metastasis-free survival[14]. After this study, several studies were conducted to investigate the prognostic influence of tumor necrosis in UTUC. In summary, these studies reported that tumor necrosis was an independent prognostic variable of disease-specific survival, metastasis-free survival, and overall survival[15-19].

Only a limited number of papers in the literature investigate the prognostic effect of tumor necrosis in urothelial bladder cancer. In 2007, Ord et al. investigated the prognostic significance of hypoxia and necrosis in radical cystectomy specimens. They reported that the prevalence of tumor necrosis increased with a higher T stage. Tumor necrosis was an independent prognostic factor of cancer-specific survival (CSS) besides the T stage[20]. Then, Soave et al. conducted a study investigating the impact of tumor diameter and necrosis on disease recurrence and CSS. They included 517 patients who had undergone radical cystectomy and reported that tumor necrosis was present in 30.2% of the patients. This study demonstrated that tumor necrosis was significantly associated with adverse tumor features such as higher T stage and grade, lymph node invasion, positive surgical margin, and lymphovascular invasion[21]. Finally, Hodgson et al. also examined patients who had undergone radical cystectomy in their study and found that the presence of tumor necrosis was associated with a poor prognosis[22].

Our study has some limitations. First, patients' clinical and follow-up variables were noted retrospectively. However, despite the retrospective design, we reevaluated the pathological specimens for tumor necrosis. Second, this study was a single-center study with a limited number of patients. We could not evaluate CSS because of the small number of events (cancer-related death). Despite these limitations, to the best of our knowledge, no other study in English-written literature has investigated the prognostic impact of tumor necrosis in NMIBC. The only study that studied NMIBC pathological specimens included patients who had undergone early cystectomy, unlike ours[8]. In our study, we excluded patients with early cystectomy (within the first 6 months after initial TUR-BT).

CONCLUSION

This study demonstrated that patients with NMIBC and tumor necrosis in pathological specimens have shorter PFS and more adverse pathological features. Our results support that the presence of tumor necrosis should be reported regularly to help better understand patients' prognoses. Prospective and multicenter studies are required for more robust evidence-based recommendations.

ETHICAL APPROVAL

The protocol for this research has been approved by a suitably constituted ethics committee of the institution, and it conforms to the provisions of the Declaration of Helsinki. Committee of Istanbul Medeniyet University, approval no.: 2021/0720.

AUTHORS' CONTRIBUTIONS

MC: Conceptualization (lead), Formal Analysis (lead), Investigation (equal), Methodology (equal), Project administration (lead), Resources (equal), Writing – original draft (lead). **AI:** Data curation (equal), Investigation (equal), Methodology (equal), Resources (equal). **GK:** Data curation (equal), Investigation (equal), Methodology (equal), Resources (equal). **GEC:** Data curation (equal), Investigation (equal), Methodology (equal), Resources (equal). **GA:** Data curation (equal), Investigation (equal), Methodology (equal), Resources (equal), Supervision (equal). **AY:** Data curation (equal), Investigation (equal), Methodology (equal), Resources (equal), Supervision (equal), Writing – review & editing (lead).

REFERENCES

1. Siegel RL, Miller KD, Fuchs HE, Jemal A. Cancer statistics, 2022. CA Cancer J Clin. 2022;72(1):7-33. https://doi.org/10.3322/caac.21708
2. Babjuk M, Burger M, Capoun O, Cohen D, Compérat EM, Dominguez Escrig JL, et al. European Association of Urology Guidelines on non-muscle-invasive bladder cancer (Ta, T1, and carcinoma in situ). Eur Urol. 2022;81(1):75-94. https://doi.org/10.1016/j.eururo.2021.08.010
3. Sylvester RJ, Rodríguez O, Hernández V, Turturica D, Bauerová L, Bruins HM, et al. European Association of Urology (EAU) prognostic factor risk groups for non-muscle-invasive bladder cancer (NMIBC) incorporating the WHO 2004/2016 and WHO 1973 classification systems for grade: an update from the EAU NMIBC Guidelines Panel. Eur Urol. 2021;79(4):480-8. https://doi.org/10.1016/j.eururo.2020.12.033
4. Leek RD, Landers RJ, Harris AL, Lewis CE. Necrosis correlates with high vascular density and focal macrophage infiltration in invasive carcinoma of the breast. Br J Cancer. 1999;79(5-6):991-5. https://doi.org/10.1038/sj.bjc.6690158
5. Lam JS, Shvarts O, Said JW, Pantuck AJ, Seligson DB, Aldridge ME, et al. Clinicopathologic and molecular correlations of necrosis in the primary tumor of patients with renal cell carcinoma. Cancer. 2005;103(12):2517-25. https://doi.org/10.1002/cncr.21127
6. Swinson DE, Jones JL, Richardson D, Cox G, Edwards JG, O'Byrne KJ. Tumour necrosis is an independent prognostic marker in non-small cell lung cancer: correlation with biological variables. Lung Cancer. 2002;37(3):235-40.https://doi.org/10.1016/s0169-5002(02)00172-1
7. Zigeuner R, Shariat SF, Margulis V, Karakiewicz PI, Roscigno M, Weizer A, et al. Tumour necrosis is an indicator of aggressive biology in patients with urothelial carcinoma of the upper urinary tract. Eur Urol. 2010;57(4):575-81. https://doi.org/10.1016/j.eururo.2009.11.035
8. Kir GG, Girgin RBB, Soylemez Söylemez TT, Melemez MKK, Topal CSS, Turan T, et al. Assessment of transurethral resection of the bladder specimens with pT1 high-grade urothelial carcinoma for the predictor features of muscularis propria invasion on radical cystectomy specimens. Ann Diagn Pathol. 2018;37:25-9. https://doi.org/10.1016/j.anndiagpath.2018.09.003
9. Samaratunga H, Delahunt B, Srigley JR, Berney DM, Cheng L, Evans A, et al. Granular necrosis: a distinctive form of cell death in malignant tumours. Pathology. 2020;52(5):507-14. https://doi.org/10.1016/j.pathol.2020.06.002
10. Dang CV, Semenza GL. Oncogenic alterations of metabolism. Trends Biochem Sci. 1999;24(2):68-72. https://doi.org/10.1016/s0968-0004(98)01344-9
11. Maragoudakis ME. Angiogenesis in health and disease. Gen Pharmacol. 2000;35(5):225-6. https://doi.org/ 10.1016/s0306-3623(01)00111-2
12. Ke HL, Wei YC, Yang SF, Li CC, Wu DC, Huang CH, et al. Overexpression of hypoxia-inducible factor-1α predicts an unfavorable outcome in urothelial carcinoma of the upper urinary tract. Int J Urol. 2008;15(3):200-5. https://doi.org/10.1111/j.1442-2042.2007.01978.x
13. Theodoropoulos VE, Lazaris ACh, Sofras F, Gerzelis I, Tsoukala V, Ghikonti I, et al. Hypoxia-inducible factor 1α expression correlates with angiogenesis and unfavorable prognosis in bladder cancer. Eur Urol. 2004;46(2):200-8. https://doi.org/10.1016/j.eururo.2004.04.008
14. Langner C, Hutterer G, Chromecki T, Leibl S, Rehak P, Zigeuner R. Tumor necrosis as prognostic indicator in transitional cell carcinoma of the upper urinary tract. J Urol. 2006;176(3):910-3. https://doi.org/10.1016/j.juro.2006.04.019
15. Lee SE, Hong SK, Han BK, Yu JH, Han JH, Jeong SJ, et al. Prognostic significance of tumor necrosis in primary transitional cell carcinoma of upper urinary tract. Jpn J Clin Oncol. 2007;37(1):49-55. https://doi.org/10.1093/jjco/hyl123
16. Simone G, Papalia R, Loreto A, Leonardo C, Sentinelli S, Gallucci M. Independent prognostic value of tumour diameter and tumour necrosis in upper urinary tract urothelial carcinoma. BJU Int. 2009;103(8):1052-7. https://doi.org/10.1111/j.1464-410X.2008.08134.x
17. Zhang XK, Zhang ZL, Yang P, Cai MY, Hu WM, Yun JP, et al. Tumor necrosis predicts poor clinical outcomes in patients with node-negative upper urinary tract urothelial carcinoma. Jpn J Clin Oncol. 2015;45(11):1069-75. https://doi.org/10.1093/jjco/hyv127
18. Ekmekçi S, Küçük Ü, Dere Y, Çakır E, Sayar HC, Ergani B, et al. 8-armed octopus: evaluation of clinicopathologic prognostic factors of urothelial carcinoma of the upper urinary system. Turk J Med Sci. 2019;49(1):153-61. https://doi.org/10.3906/sag-1805-51
19. Lin KC, Jan HC, Hu CY, Ou YC, Kao YL, Yang WH, et al. Tumor necrosis with adjunction of preoperative monocyte-to-lymphocyte ratio as a new risk stratification marker can independently predict poor outcomes in upper tract urothelial carcinoma. J Clin Med. 2021;10(13):2983. https://doi.org/10.3390/jcm10132983
20. Ord JJ, Agrawal S, Thamboo TP, Roberts I, Campo L, Turley H, et al. An investigation into the prognostic significance of necrosis and hypoxia in high grade and invasive bladder cancer. J Urol. 2007;178(2):677-82. https://doi.org/10.1016/j.juro.2007.03.112
21. Soave A, John LM, Dahlem R, Minner S, Engel O, Schmidt S, et al. The impact of tumor diameter and tumor necrosis on oncologic outcomes in patients with urothelial carcinoma of the bladder treated with radical cystectomy. Urology. 2015;86(1):92-8. https://doi.org/10.1016/j.urology.2015.03.036
22. Hodgson A, Xu B, Satkunasivam R, Downes MR. Tumour front inflammation and necrosis are independent prognostic predictors in high-grade urothelial carcinoma of the bladder. J Clin Pathol. 2018;71(2):154-60. https://doi.org/10.1136/jclinpath-2017-204562

ORIGINAL ARTICLE

https://doi.org/10.1590/1806-9282.20220904

Impact of ICU bed availability on ovarian cancer surgical hospitalization rates during the first wave of the coronavirus disease 2019 pandemic

Vinicius Cesar Moterani[1,2*], Nino Jose Wilson Moterani Junior[1,2], Franklin Fernandes Pimentel[1], Francisco Jose Candido dos Reis[1]

SUMMARY

OBJECTIVES: The coronavirus disease 2019 pandemic, which began in 2020, disrupted healthcare services. Reports of changes in surgical activities coincide with the outbreak period. We aimed to identify if changes could be determined in hospitalization rates of ovarian cancer patients from 2016 to 2020, comparing pre-pandemic and pandemic levels.

METHODS: Aggregated data were obtained from the State of São Paulo Secretary of Health regarding ovarian cancer clinical and surgical hospitalization, both Coronavirus disease-specific ICU and infirmary bed occupation rates, average social distancing rates, coronavirus disease 2019 incidence, mortality, and lethality rates. We performed the joinpoint analysis to verify if there were changes regarding hospitalization rates during this period. We also calculated hospitalization rate ratios and tested if they were correlated with pandemic-related variables.

RESULTS: Hospitalization rates in the state fell, coinciding with the pandemic. Surgical hospitalization rate ratios were inversely correlated with Coronavirus disease-specific ICU bed occupation rates during the third trimester of 2020, with a Pearson's correlation coefficient of -0.50 (95%CI -0.78 to -0.05, p=0.03).

CONCLUSION: These results demonstrate the impact of the coronavirus disease 2019 pandemic on the treatment of conditions that compete for the same healthcare resources.

KEYWORDS: Intensive care units. Ovarian neoplasms. COVID-19. Hospitalization.

INTRODUCTION

Coronavirus disease 2019 (COVID-19) was declared a global pandemic by the World Health Organization (WHO) on March 11, 2020[1]. In Brazil, the first case was registered on February 26, 2020, in São Paulo. By March 20, 2020, Brazil's Ministry of Health recognized COVID-19 community transmission in country[2]. Spatiotemporal analysis indicated the disease spread quickly in the country for multiple reasons, including disparities in health resources[3].

The pandemic's impact is far more significant than COVID-19's incidence and mortality rates. The population's healthcare-seeking behavior and service provision have changed since the outbreak began[4]. These changes have been demonstrated even among conditions such as acute myocardial infarction[5] and cerebrovascular events[6], reducing hospitalization rates compared to pre-pandemic levels.

Regarding specifically surgical activity, initial reports indicated a decrease in the number of elective surgeries following the pandemic's start[7,8]. As the pandemic progressed, the following reports stated a reduction in surgery incidence, followed by an increase in surgery rates and waiting times[9]. As for oncological surgery, in Finland, oncological surgery did not see changes during the outbreak compared to pre-pandemic levels, which might reflect healthcare service reorganization toward prioritizing oncological surgeries[10].

In ovarian cancer, surgery plays a significant role in staging and treating both initial and advanced diseases. Several patients will necessitate platinum-based chemotherapy to improve recurrence-free and overall survival[11].

In this study, we aimed to assess the clinical and surgical hospitalization rates for ovarian cancer in the state of São Paulo before and during the pandemic, and whether there is any correlation between these data and pandemic-related variables.

[1]Universidade de São Paulo, Faculdade de Medicina de Ribeirão Preto, Department of Gynaecology and Obstetrics – Ribeirão Preto (SP), Brazil.
[2]Faculdade de Medicina de Marília, Department of Obstetrics and Gynaecology – Marília (SP), Brazil.
*Corresponding author: vmoterani@hotmail.com

Conflicts of interest: the authors declare there is no conflicts of interest. Funding: This project was funded by the Coordenação de Aperfeiçoamento de Pessoal de Nível Superior (CAPES) – Programa CAPES EPIDEMIAS (grant number 88887.506852/2020-00). FJCR (grant number 310262/2021-6) was funded by the Conselho Nacional de Desenvolvimento Científico e Tecnológico (CNPq).
Received on June 30, 2022. Accepted on August 01, 2022.

METHODS

This study is an ecological analysis. Our main hypothesis was whether there was any change in the rate of hospital admissions for ovarian cancer during the first wave of the COVID-19 pandemic, and if possible, changes were correlated with variables associated with the COVID-19 outbreak progression in the state. This research encompasses 19 trimesters, from the first trimester of 2016 to the third trimester of 2020. The first trimester of 2020 is considered the beginning of the pandemic.

Data regarding hospital admissions for ovarian cancer were publicly available on the São Paulo State Secretary of Health website. It contained the total number of clinical and surgical hospital admissions per trimester having the primary diagnosis of ovarian cancer, both at the state level and by one of 17 numbered state subdivisions known as the Regional Departments of Health (RDH). This information is aggregated from the Authorization for Hospital Admission (AHA) documents. The inclusion criteria were the primary *International Disease Code* (*ICD*) be C56 and the main procedure being either clinical or surgical treatment.

We obtained from Brazil's Ministry of Health the female population and the total population. We obtained from the National Supplementary Health Agency the female population who had private medical insurance. We calculated the exclusively public-insured female population from these data.

We performed an age-adjusted joinpoint regression analysis for clinical, surgical, and overall ovarian cancer hospitalization rates during the study period using the Joinpoint Trend Analysis software. The population was exclusively public-insured women. We used the WHO standard population in this analysis. We identified the last trimester before the pandemic in which there was a change in the hospitalization rates and calculated average pre-pandemic hospitalization rates. We calculated an average from the whole pre-pandemic period when the above method was not possible.

We calculated the hospitalization rate ratio (HRR) by comparing each trimester during the COVID-19 pandemic and the baseline period before the pandemic, utilizing the exact Poisson test. We also calculated the COVID-19-specific ICU and infirmary bed occupation percentage, COVID-19 incidence and mortality rate, and the social distancing average percentage in both state and RDH populations per trimester using publicly available data obtained from the State of São Paulo government. Data for ICU and bed availability were not available before May 19, 2020. We used Pearson's correlation tests to assess if there was any correlation between HRR in a given trimester and pandemic-related variables.

We compared expected and observed hospitalizations. Expected hospitalizations were obtained by applying the quarterly percentual change, which was identified in the last trimester before the pandemic began, calculated in the joinpoint regression, and applied these to the observed hospitalizations identified in the last trimester before the pandemic.

We also calculated the proportion of the state's female population exclusively public-insured during the same period and performed a Pearson's correlation test.

Data manipulation and statistical analysis were conducted using the RStudio software, version 1.4.1717 (2021-05-24).

Temporal series analysis was performed as a joinpoint regression using the Joinpoint Trend Analysis software, version 4.9.0.0. We allowed from zero up to five joinpoints. We used the minimal number of two observ ations from a joinpoint to either end of the data and between two joinpoints.

The study followed the Declaration of Helsinki. According to Resolution 510/2016 of the National Health Council of Brazil, studies that use publicly available data without patient identification do not require approval from an ethics committee.

RESULTS

A total of 12,856 hospital admissions were analyzed during the study period. Of these, 6,597 were classified as surgical, and 6,259 were identified as clinical. Overall hospitalization rates for ovarian cancer declined during the pandemic period, reversing the previous upward trend. Among all RDH which demonstrated changes in their tendencies, none presented an increase during the COVID-19 outbreak period. Clinical hospitalizations demonstrated a continuous decline during the study. Surgical hospitalizations showed a downward trend during the pandemic, and none of the RDH showed an increase during the outbreak.

Surgical HRR displayed an inverse correlation with COVID-specific ICU bed occupation rates during the third trimester of 2020. We identified a Pearson's correlation coefficient of −-0.50 (95%CI −-0.78 to −-0.05, p=0.03). This is represented in Figure 1. Overall clinical and surgical HRR did not display a correlation with any of the other studied variables in each trimester.

Regarding the third trimester of 2020, Table 1 displays the calculated HRR for each RDH and the state and the values of pandemic-related variables.

Overall hospitalizations showed a 15% decrease compared to expected values. These results can be found in Table 2.

The proportion of exclusively public-insured women in the state has demonstrated an increase in the study. The Pearson's correlation coefficient is 0.95 (95%CI 0.88–0.98, p<0.001).

DISCUSSION

We found a decrease in the hospitalization rates for ovarian cancer in the public health system during the pandemic and an inverse correlation between HRR and COVID-specific ICU bed occupation rates among RDH during the third quarter of 2020. This supports our primary hypothesis that the pandemic impacted ovarian cancer care in the state of São Paulo. It suggests ICU bed availability could have limited ovarian cancer surgical activity.

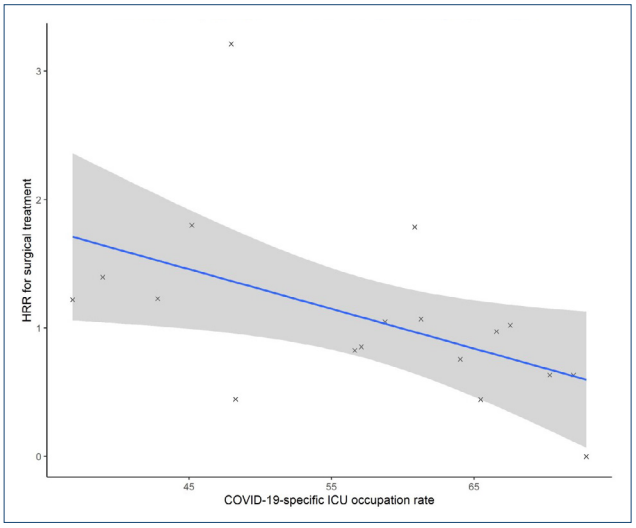

Figure 1. Relationship between hospitalization rate ratio for ovarian cancer treatment and the ICU occupation rate in the state of São Paulo in the third trimester of 2020.

This study has several strengths. It includes a large number of hospitalizations during a significant period. It is also based on AHA records, which are mandatory in the public health system. Furthermore, our pandemic-related variables encompassed different pathways that could correlate to healthcare disruption.

Limitations are inherent to retrospective and ecological analysis. Hospitalization could not be classified further than "clinical" or "surgical" treatment. COVID-specific bed occupations, both infirmary and ICU data, were absent for the first trimester and partially available for the second trimester of 2020. However, these do not seem to invalidate the conclusions presented above.

Similar research regarding surgical activity during the COVID-19 pandemic shows convergence and divergence points. A decrease in surgery incidence has been reported during restrictive periods in Finland, followed by an increase compared to the reference years, as an attempt to address the accumulated elective surgery backlog[9]. Another Finnish

Table 1. Hospitalization rate ratio for each type of hospitalization and pandemic-related variables in the third trimester of 2020.

RDH	Overall HRR	Surgical HRR	Clinical HRR	COVID-19 Incidence	COVID-19 mortality	COVID-19 Lethality	Average social distancing rate	Infirmary bed occupation rate	ICU occupation rate
State	0.86	0.85	0.88	104.56	3.96	3.78	42.48	42.57	57.09
1	0.91	0.83	0.99	10.42	0.35	3.35	43.1	43.53	56.63
2	1.09	0.45	1.38	55.12	1.61	2.91	40.07	32.72	48.26
3	1.32	1.4	1.24	303.33	11.96	3.94	43.12	32.69	38.94
4	0.98	1.22	0.72	24.46	0.71	2.91	44.21	30.84	36.83
5	0.92	0.97	0.67	63.94	1.13	1.76	42.54	28.43	66.57
6	0.46	0.44	0.5	86.16	2.18	2.53	39.71	37.34	65.46
7	0.86	0.76	0.92	13.31	0.31	2.32	40.26	46.21	64.04
8	0	0	0	61.67	0.65	1.05	42.09	33.19	72.87
9	1.14	1.8	0.54	13.28	0.33	2.49	39.41	26.45	45.2
10	0.81	1.07	0.59	1824.61	79.53	4.36	39.92	44.88	61.28
11	1.18	1.02	1.3	168.55	4.39	2.6	36.24	55.41	67.54
12	0.88	1.23	0	370.34	6.77	1.83	40.9	42.89	42.8
13	0.76	0.63	0.81	138.13	4.1	2.97	44.17	57.94	71.97
14	2.31	3.21	1.73	29.66	0.81	2.73	45.95	24.29	47.96
15	0.91	0.63	1.01	136.4	3.71	2.72	40.63	50.7	70.31
16	1.9	1.79	2.13	16.9	0.49	2.92	40.39	36.25	60.84
17	0.85	1.05	0.67	68.86	1.71	2.48	44.53	38.42	58.75

Table 2. Difference between observed and expected ovarian cancer hospitalizations in the state of São Paulo during the first three trimesters of the coronavirus disease 2019 pandemic and pre-pandemic levels.

RDH	Fourth trimester of 2019	First trimester of 2020	Second trimester of 2020	Third trimester of 2020	Pre-pandemic trimestral percentual change rate	Expected value for first trimester of 2020	Expected value for second trimester of 2020	Expected value for third trimester of 2020	Difference between observed and expected hospitalizations in first trimester of 2020	Difference between observed and expected hospitalizations in second trimester of 2020	Difference between observed and expected hospitalizations in third trimester of 2020	Sum of the difference between observed and expected hospitalizations during the pandemic period	Relationship between observed and expected hospitalizations
State	750	745	615	617	1.63	762.23	774.65	787.28	−17.23	−159.65	−170.28	−347.15	0.85
1	312	328	290	267	1.42	316.43	320.92	325.48	11.57	−30.92	−58.48	−77.83	0.92
2	2	6	4	8	−2.64	1.95	1.9	1.85	4.05	2.1	6.15	12.31	3.16
3	19	11	9	20	0.19	19.04	19.07	19.11	−8.04	−10.07	0.89	−17.22	0.7
4	15	13	17	17	−1.24	14.81	14.63	14.45	−1.81	2.37	2.55	3.11	1.07
5	69	51	42	44	8.81	75.08	81.69	88.89	−24.08	−39.69	−44.89	−108.66	0.56
6	73	68	39	36	−2.9	70.88	68.83	66.83	−2.88	−29.83	−30.83	−63.54	0.69
7	58	73	60	46	−0.21	57.88	57.76	57.64	15.12	2.24	−11.64	5.73	1.03
8	3	8	4	0	1.63	3.05	3.1	3.15	4.95	0.9	−3.15	2.7	1.29
9	9	9	5	12	0.88	9.08	9.16	9.24	−0.08	−4.16	2.76	−1.48	0.95
10	13	17	11	13	1.13	13.15	13.3	13.45	3.85	−2.3	−0.45	1.11	1.03
11	19	17	7	11	3.82	19.73	20.48	21.26	−2.73	−13.48	−10.26	−26.47	0.57
12	4	4	1	4	−5.8	3.77	3.55	3.34	0.23	−2.55	0.66	−1.66	0.84
13	21	29	22	28	−15.78	17.69	14.9	12.54	11.31	7.1	15.46	33.87	1.75
14	11	13	6	11	1.63	11.18	11.36	11.55	1.82	−5.36	−0.55	−4.09	0.88
15	46	38	46	31	−11.66	40.64	35.9	31.71	−2.64	10.1	−0.71	6.75	1.06
16	26	22	25	29	3.92	27.02	28.08	29.18	−5.02	−3.08	−0.18	−8.28	0.9
17	50	38	27	40	−2.32	48.84	47.71	46.6	−10.84	−20.71	−6.6	−38.15	0.73

study did not identify decreases in the oncologic surgery rate, suggesting prioritization of these cases[10]. Similarly, an Italian study did not identify any decreases in oncological surgical activity during the pandemic[12]. These divergences might be attributable to the fact that these studies included several different oncological conditions, each of which could behave differently.

In Austria, a study reported a decrease of 49% in diagnosing new ovarian cancers during the first 2 months of the pandemic[13]. Notably, the study cites a maximum ICU occupation rate of 26%. In France, one report identified a 13% decrease in gynecological oncology cases in an unicenter study[14]. Another French study reported that 32.7% of patients with ovarian cancer had their surgeries postponed or suspended[15]. These results highlight the importance of further research to better comprehend the role of restrictive measures, ICU occupation rate, and different healthcare systems in ovarian cancer care during the pandemic.

Some studies tried to determine more accurately possible correlations and causes for changes in surgical activity during the pandemic. A Japanese case series of patients with confirmed or suspected gynecological malignancies suggests COVID-19 overdiagnosis might have played a role in treatment delay[16]. Another research from India identified longer waiting times from diagnosis to the start of treatment among epithelial ovarian cancer patients, and travel restrictions during lockdown might have acted as a factor limiting treatment[17].

Our data suggest ICU beds could be a bottleneck for ovarian cancer treatment during the pandemic. It is possible that these so-called "COVID-specific ICU beds" were established using previously existing ICU structures. Thus, both conditions compete for the same resources. We cannot exclude other factors that could be associated with higher ICU occupation and surgical activity decreases, such as sedative drug and personal protective equipment shortage and prioritization. Available data do not allow us to discuss how patient referral and exam availability might have impacted these results; however, the absence of correlation with other COVID-19-related variables is a possible indicator that different pathways might not have contributed to the surgical activity decline.

Cancer treatment centralization has been the subject of research[18]. Evidence indicates that ovarian cancer patients benefit from surgical treatment being performed in high-volume hospitals[19]. In São Paulo, ovarian cancer has demonstrated high rates of centralization[20]. Disruptions to healthcare services challenge this centralized model since patient treatment could be impacted if resources in a region become suddenly unavailable.

Exploratory analysis indicates a higher proportion of patients being exclusively dependent on public healthcare insurance. Thus, we do not expect a high proportion of these treatments might have happened in private healthcare services.

CONCLUSION

Ovarian cancer hospitalization rates in São Paulo decreased by 15% during the pandemic, when comparing expected and observed hospitalizations. Among different RDH, a lower HRR was determined among regions with higher COVID-specific ICU bed occupation. These findings indicate a possible delay in treatment, which could impact disease curability. They also point to ICU bed availability as a possible limiting factor for ovarian cancer surgical activity during the first wave of the COVID-19 pandemic. Additional studies are required to better understand which resources act as treatment bottlenecks and to better direct investments in similar future scenarios.

AUTHORS' CONTRIBUTIONS

VCM: Conceptualization, Data curation, Formal Analysis, Investigation, Methodology, Validation, Visualization, Writing – original draft, Writing – review and editing. **FJCR:** Conceptualization, Formal Analysis, Funding acquisition, Methodology, Project administration, Supervision, Writing – review and editing. **FFP:** Methodology, Validation, Writing – review and editing. **NJWMJ:** Methodology, Validation, Writing – review and editing.

REFERENCES

1. Cucinotta D, Vanelli M. WHO declares COVID-19 a pandemic. Acta BioMed. 2020;91(1):157-60. https://doi.org/10.23750/abm.v91i1.9397
2. Croda J, Oliveira WK, Frutuoso RL, Mandetta LH, Baia-da-Silva DC, Brito-Sousa JD, et al. COVID-19 in Brazil: advantages of a socialized unified health system and preparation to contain cases. Rev Soc Bras Med Trop. 2020;53:e20200167. https://doi.org/10.1590/0037-8682-0167-2020
3. Castro MC, Kim S, Barberia L, Ribeiro AF, Gurzenda S, Ribeiro KB, et al. Spatiotemporal pattern of COVID-19 spread in Brazil. Science. 2021;372(6544):821-6. https://doi.org/10.1126/science.abh1558
4. Sutherland K, Chessman J, Zhao J, Sara G, Shetty A, Smith S, et al. Impact of COVID-19 on healthcare activity in NSW, Australia. Public Health Res Pract. 2020;30(4):3042030. https://doi.org/10.17061/phrp3042030
5. Solomon MD, McNulty EJ, Rana JS, Leong TK, Lee C, Sung SH, et al. The COVID-19 pandemic and the incidence of acute

myocardial infarction. N Engl J Med. 2020;383(7):691-3. https://doi.org/10.1056/NEJMc2015630

6. Sacco S, Ricci S, Ornello R, Eusebi P, Petraglia L, Toni D, et al. Reduced admissions for cerebrovascular events during COVID-19 outbreak in Italy. Stroke. 2020;51(12):3746-50. https://doi.org/10.1161/STROKEAHA.120.031293
7. Zanus G, Romano M, Santoro GA, Rossi S, Grossi U. Impact of COVID-19 on urgent surgical activity. Br J Surg. 2020;107(10):e414. https://doi.org/10.1002/bjs.11856
8. Farid Y, Schettino M, Kapila AK, Hamdi M, Cuylits N, Wauthy P, et al. Decrease in surgical activity in the COVID-19 pandemic: an economic crisis. Br J Surg. 2020;107(9):e300. https://doi.org/10.1002/bjs.11738
9. Uimonen M, Kuitunen I, Paloneva J, Launonen AP, Ponkilainen V, Mattila VM. The impact of the COVID-19 pandemic on waiting times for elective surgery patients: a multicenter study. PLoS One. 2021;16(7):e0253875. https://doi.org/10.1371/journal.pone.0253875
10. Kuitunen I, Ponkilainen VT, Uimonen MM, Paloneva J, Launonen AP, Mattila VM. Postponing elective surgery due to COVID-19 did not decrease the oncological surgery rate in Finland. Br J Surg. 2021;108(5):e191-3. https://doi.org/10.1093/bjs/znab046
11. Burges A, Schmalfeldt B. Ovarian cancer. Dtsch aerzteblatt Online. Published online September 23, 2011. https://doi.org/10.3238/arztebl.2011.0635
12. Vissio E, Falco EC, Collemi G, Borella F, Papotti M, Scarmozzino A, et al. Impact of COVID-19 lockdown measures on oncological surgical activity: analysis of the surgical pathology caseload of a tertiary referral hospital in Northwestern Italy. J Surg Oncol. 2021;123(1):24-31. https://doi.org/10.1002/jso.26256
13. Tsibulak I, Reiser E, Bogner G, Petru E, Hell-Teutsch J, Reinthaller A, et al. Decrease in gynecological cancer diagnoses during the COVID-19 pandemic: an Austrian perspective. Int J Gynecol Cancer. 2020;30(11):1667-71. https://doi.org/10.1136/ijgc-2020-001975
14. Piketty J, Carbonnel M, Murtada R, Revaux A, Asmar J, Favre-Inhofer A, et al. Collateral damage of COVID-19 pandemic: the impact on a gynecologic surgery department. J Gynecol Obstet Hum Reprod. 2021;51(1):102255. https://doi.org/10.1016/j.jogoh.2021.102255
15. Jouen T, Gauthier T, Azais H, Bendifallah S, Chauvet P, Fernandez H, et al. The impact of the COVID-19 coronavirus pandemic on the surgical management of gynecological cancers: analysis of the multicenter database of the French SCGP and the FRANCOGYN group. J Gynecol Obstet Hum Reprod. 2021;50(8):102133. https://doi.org/10.1016/j.jogoh.2021.102133
16. Nogami Y, Kobayashi Y, Tsuji K, Yokota M, Nishio H, Nakamura M, et al. Impact of the COVID-19 epidemic at a high-volume facility in gynecological oncology in Tokyo, Japan: a single-center experience. J Ovarian Res. 2020;13(1):105. https://doi.org/10.1186/s13048-020-00711-x
17. Goenka L, Anandaradje A, Nakka T, Kayal S, Dubashi B, Chaturvedula L, et al. The "collateral damage" of the war on COVID-19: impact of the pandemic on the care of epithelial ovarian cancer. Med Oncol. 2021;38(11):137. https://doi.org/10.1007/s12032-021-01588-6
18. Jolly K, Parry J, Rouse A, Stevens A. Volumes of cancer surgery for breast, colorectal and ovarian cancer 1992–97: is there evidence of increasing sub-specialization by surgeons? Br J Cancer. 2001;84(10):1308-13. https://doi.org/10.1054/bjoc.2001.1794
19. Bristow R, Chang J, Ziogas A, Anton-Culver H. NCCN treatment guidelines for ovarian cancer: a population-based validation study of structural and process quality measures. Gynecol Oncol. 2013;130(1):e18. https://doi.org/10.1016/j.ygyno.2013.04.104
20. Moterani VC, Tiezzi DG, Andrade JM, Candido dos Reis FJ. Analysis of the relationship between hospital characteristics and survival in ovarian cancer: a historical cohort. J Surg Oncol. 2020;122(38):1802-7. https://doi.org/10.1002/jso.26186

REVIEW ARTICLE

https://doi.org/10.1590/1806-9282.20220583

Comparison of continuous loop diuretic versus bolus injection regimens in patients with heart failure: a comprehensive meta-analysis of the literature

Faysal Şaylık[1*], Tufan Cinar[2]

INTRODUCTION

Heart failure (HF) is a challenging clinical syndrome and the leading cause of morbidity and mortality worldwide[1]. In decompensated HF patients, diuretic administration is a crucial and first-line therapeutic option for reducing fluid overload by diuresis[1]. Optimizing the loop diuretic dose is essential to produce a high proportion of loop diuretic transport in the proximal renal tubule, enabling it to optimally function on a Na^+-K^+-2Cl cotransporter on the luminal surface of the thick ascending limb of the loop of Henle[2]. Theoretically, continuous infusion of a loop diuretic may be preferable to intermittent bolus injection treatment in terms of length of hospital stay, weight loss, and urine output[3]. Possible underlying reasons may include that continuous infusion of a loop diuretic may ensure better urine output and less neurohormonal stimulation due to the constant delivery rate of the loop diuretics to the tubule, resulting in less alteration in intravascular volume and fewer occurrences of adverse side effects[3]. Despite the fact that most randomized controlled trials (RCTs) supported a continuous infusion in regard to diuretic efficiency, there is no convincing evidence in the present literature to indicate that continuous infusion of a loop diuretic is preferable to bolus injection treatment or vice versa[1,4]. As a result, we intended to perform a meta-analysis of RCTs that evaluated these two treatment options in HF patients.

METHODS

Data collection

We followed the recommended reporting items for systematic reviews and meta-analyses guidelines to report our results. Since the investigation was a meta-analysis, neither ethics committee approval nor patient informed consent was needed. First, we reviewed PubMed, Scopus, Google Scholar, and Cochrane libraries for relevant studies utilizing keywords such as "randomized controlled," "heart failure," "diuretic," and "continuous," "bolus," and "comparison." When all abstracts were reviewed, 39 studies remained out of 395 prospective investigations. Following an examination of the entire texts of the remaining articles, 21 studies were removed because they were duplicated and irrelevant, included meta-analyses, or had inaccurate results. Finally, the remaining 18 papers were subjected to our meta-analysis (Table 1).

Study evaluation

Two authors thoroughly reviewed the studies' applicability and bias probability. The studies were selected based on the following criteria: (1) prospective, randomized studies comparing intravenous (IV) continuous infusion of a loop diuretic to IV bolus injection of diuretics treatment in decompensated HF patients; (2) studies with at least in-hospital follow-up duration; (3) studies with the clinical outcomes, such as urine sodium excretion, weight loss, urine output, length of hospital stay, serum creatinine change, estimated glomerular filtration (eGFR) change, and mortality; and (4) only furosemide treatment was used as the main diuretic regimen. Due to the possibility of selection bias, studies with a retrospective or observational design were not included in this meta-analysis. Finally, our meta-analysis excluded papers in which the effect size and standard error could not be calculated. All studies were evaluated using a modified Jadad scale with respect to study quality[5]. To assess the risk of bias, we used the Rob2 risk of bias tool as advised in the Cochrane Handbook for Systematic Reviews of Interventions (Supplementary 1)[6].

[1]Van Training and Research Hospital, Department of Cardiology – Van, Turkey.
[2]Sultan II. Abdulhamid Han Training and Research Hospital, Department of Cardiology – İstanbul, Turkey.
*Corresponding author: faysalsaylik@gmail.com
Conflicts of interest: the authors declare there is no conflicts of interest. Funding: none.
Received on July 02, 2022. Accepted on July 08, 2022.

Table 1. Characteristics of studies in the meta-analysis.

Study	Year	Country	Age	Patient population	Dose of diuretics	Duration of interventions (day)	Study design	Total sample size	Bolus group sample size	Continuous group sample size	End-points	Modified Jadad Scale
Makhoul et al[7].	1997	Israel	NA	NA	Bolus: 324 (110.8) mg tid, continuous: 329 (186.7) mg/24 h	24 h	RCT	20	10	10	Urine output	5
Allen et al.[8]	2010	USA	59.5 (14.9)	LVEF: 35 (19%), NYHA II-IV	Bolus: 162 (48) mg bid, continuous: 162 (52) mg/24 h	48 h	RCT	41	21	20	Change in creatinine, urine output, weight loss, length of hospital stay	6
Thomson et al.[9]	2010	USA	53.5 (23.2)	LVEF: 26.3 (13.6%), NYHA III-IV	Bolus: 172 (97) mg, continuous: 197 (148) mg/24 h	100 h	RCT	56	30	26	Change in creatinine, urine output, weight loss, length of hospital stay	6
Felker et al.[10]	2011	USA	66 (13.6)	LVEF: 35 (18%)	Bolus: 162 (52) mg bid, continuous: 162 (48) mg/24 h	72 h	RCT	308	156	152	Change in creatinine, urine output, weight loss, length of hospital stay, mortality	8
Palazzuoli et al.[11]	2015	Italy	71.9 (7.5)	LVEF: 35 (9%)	Bolus: 160 (80) mg, continuous: 170 (70)	112 h	RCT	58	28	30	Change in creatinine, urine output, weight loss, length of hospital stay, mortality	6
Llorens et al.[12]	2014	Spain	82 (9)	LVEF: <35 in 50% patients, NYHA I-IV	Bolus: 80 mg qid, continuous: 240 mg/10 h	24 h	RCT	73	37	36	Change in creatinine, urine output	6.5
Shah et al.[13]	2014	India	59.3 (7.5)	LVEF: 33% (SD not available)	Bolus: 100 mg bid, continuous: 100 mg/24 h	48 h	RCT	60	30	30	Change in creatinine, urine output	5.5
Yayla et al.[14]	2015	Turkey	68.4 (11.7)	LVEF: 42.9 (13.1)	Bolus: 160 mg bid, continuous: 160 mg/24 h	48 h	RCT	29	14	15	Change in creatinine, urine output, weight loss, length of hospital stay	8
Aaser et al.[15]	1997	Norway	54 (3)	LVEF: 24 (5)	Bolus: 145 (80) mg bid, continuous: 145 (80) mg/24 h	24 h	RCT	8	4	4	Urine output, sodium excretion	3
Dormans et al.[16]	1996	Netherlands	71 (11)	LVEF: NA	Bolus: 690 mg (250–2,000) bid, continuous: 690 (250–2000)/8 h	24 h	RCT	40	20	20	Urine output, sodium excretion	4
Shree et al.[17]	2020	India	66 (11.5)	LVEF: <40%, NYHA II-IV	Bolus: 120 mg tid, continuous: 2–3 mg/h	48 h	RCT	56	28	28	Urine output, length of hospital stay	4
Sager et al.[18]	2020	Sweden	82.4 (3.1)	LVEF: NA, NYHA III-IV	Bolus: 20–100 mg, Continuous: 100–500 mg/4–10 h	NA	RCT	40	20	20	Weight loss, change in creatinine, mortality	4
Zheng et al.[3]	2021	China	66.4 (8.2)	LVEF: 57.4 (11), NYHA III-IV	Bolus: 200 mg, Continuous: 160 mg	72 h	RCT	81	39	42	Change in creatinine, urine output, weight loss, length of hospital stay, mortality	7
Lahav et al.[19]	1992	Israel	74.1 (SD not available)	NYHA III-IV	Bolus: 90–120 mg tid, 60–80 mg/24 h	48 h	RCT	18	9	9	Urine output, sodium excretion	4
Malkiwodeyar et al.[20]	2017	India	55.9 (SD not available)	LVEF: 33.3%	Bolus: 100 mg tid, continuous: 100 mg	24 h	RCT	50	25	25	Change in creatinine, urine output, weight loss, length of hospital stay, mortality	6
Ragab et al.[21]	2018	Egypt	NA	NYHA III-IV	Bolus: 120 mg tid, continuous: 5 mg/h	24 h	RCT	40	20	20	Weight loss, mortality	5
Wang et al.[22]	2016	China	NA	NA	Bolus: 188 (64) mg, continuous: 197 (59) mg	52 h	RCT	70	35	35	Weight loss, length of hospital stay	5
Sharma et al.[23]	2018	USA	65.3 (11.6)	HFpEF	Bolus: 80 mg bid, continuous: 80 mg/24 h	72 h	RCT	42	19	23	Urine output, weight loss, length of hospital stay, mortality	7.5
Frea et al.[24]	2020	Italy	60.9 (11.9)	LVEF: <30%	Bolus: 120/240 mg bid, continuous: 120/240 mg 24 h	72 h	RCT	80	40	40	Urine output, weight loss	7

NA: non-applicable; RCT: randomized controlled trial; LVEF: left-ventricular ejection fraction; NYHA: New York Heart Association Functional Classification; bid: twice a day; tid: three times a day; qid: four times a day.

Clinical end points

The major end points evaluated in this meta-analysis were urine sodium excretion, weight loss, urine output, length of hospital stay, serum creatinine change, eGFR change, and mortality.

Statistical analysis

This meta-analysis was carried out using the R software version 3.6.3 (R statistical software, Institute for Statistics and Mathematics, Vienna, Austria). For analyses of pooled risk ratio and standardized mean difference (SMD) with 95% confidence intervals, a "meta" package containing "metabin" and "metacont" was utilized. The Higgins I^2 and Cochran's Q tests were used to analyze study heterogeneity. In the case of moderate to high heterogeneity (I^2>25%), the random-effect model was used to predict a pooled effect size, while the fixed-effect model was utilized in the case of low heterogeneity (I^2<25%). To determine publication bias, Egger's regression test was chosen. A funnel plot was also utilized to detect any potential publication bias among publications. To identify the likelihood of the underlying source of between-study heterogeneity, outlier and influential analyses were conducted. After the outlier or influential study was eliminated, the pooled effect size was recalculated. A p-value of 0.05 was used to determine statistical significance (two-tailed tests).

RESULTS

The meta-analysis examined 18 RCTs[3,7-24] with a total of 1,178 individuals (Table 1). The continuous infusion group (CG) had higher urine output than the bolus injection group (BG) (SMD=0.78 [0.11; 1.44], p<0.01) (Figure 1). The Eggers regression test was statistically meaningful for the pooled effect size for urine output (p<0.05), and I^2 was calculated as 87%, implying publication bias. A funnel plot revealed that the studies by "Dormans et al." and "Zheng et al." might have publication bias. Furthermore, these studies were also identified as outliers and influential articles. As a result, we eliminated these papers and repeated the pooled effect size for urine output. The overall heterogeneity dropped to 0%, and the CG still had higher urine output than the BG (SMD=0.40 [0.20; 0.61], p<0.01). In the subgroup analysis of urine output, the difference was significant between groups for 24-h urine output (p<0.01), whereas it was not significant between compared groups for 72 h (p=0.21). The CG actually had higher weight loss than the BG (SMD=0.39 [0.13; 0.65], p<0.01) (Figure 1). For weight loss, the study by "Zheng et al." was detected as might to be an outlier study and to have publication bias. So, the random-effect model was recalculated after removing this study, and the CG had still higher weight loss than the BG (SMD=0.24 [0.14; 0.34], p<0.01). The CG excreted more sodium than the BG (SMD=0.61 [-0.73; 1.94], p<0.01) (Figure 1). However, there was high heterogeneity between studies regarding the results for sodium excretion. As the study by "Zheng et al." was suspected to have high bias according to the Rob2 bias assessment, we removed this study from the pooled effect for urinary sodium excretion, which indicated a nonsignificant difference between groups (p=0.29). Finally, there were no significant differences in terms of in-hospital duration, variations in serum creatinine, eGFR rates, and mortality rates between groups (Figure 2).

DISCUSSION

This meta-analysis showed that HF patients who received a continuous diuretic regimen had higher urine output and weight loss compared to a bolus regimen. There was no change between groups in terms of hospital stay, change in serum creatinine, eGFR, and mortality. The issue of sodium excretion should be examined in future meta-analyses with more recent studies.

The main therapy goal for congestive HF is fluid removal, resulting in decreased congestion and reduced afterload. This objective would enhance hemodynamics and improve HF symptoms, as well as prevent rehospitalizations and mortality[25]. Loop diuretics, especially furosemide, are mainly used for this purpose via inhibiting salt and chloride reabsorption by acting on the Na^+-K^+-2Cl cotransporter in the thick ascending limb of the Henle loop[4]. The use of loop diuretics was recommended with a class IC indication in the recent guideline[1]. However, the decision of using continuous versus bolus diuretic therapy has been left to the physician's discretion. Bolus therapy has the advantage of convenience of preparation and administration compared to continuous therapy. Unfortunately, it might not be able to achieve sufficient concentration to block sodium reabsorption[26].

The comparison of continuous diuretic therapy with a bolus regimen has been evaluated in RCTs and meta-analyses. This meta-analysis was more comprehensive than previous ones by including 17 RCTs. Amer et al. reported similar findings with this report that the continuous group had higher urine output and weight loss with no difference in the duration of hospital stay[27]. However, they had a higher heterogeneity due to the study populations of RCTs included in their meta-analysis. Chan et al. found significant differences between groups with respect to urine output and weight loss, which was in accordance with our study[28]. Kuriyama et al. showed significant differences between the continuous and bolus regimens

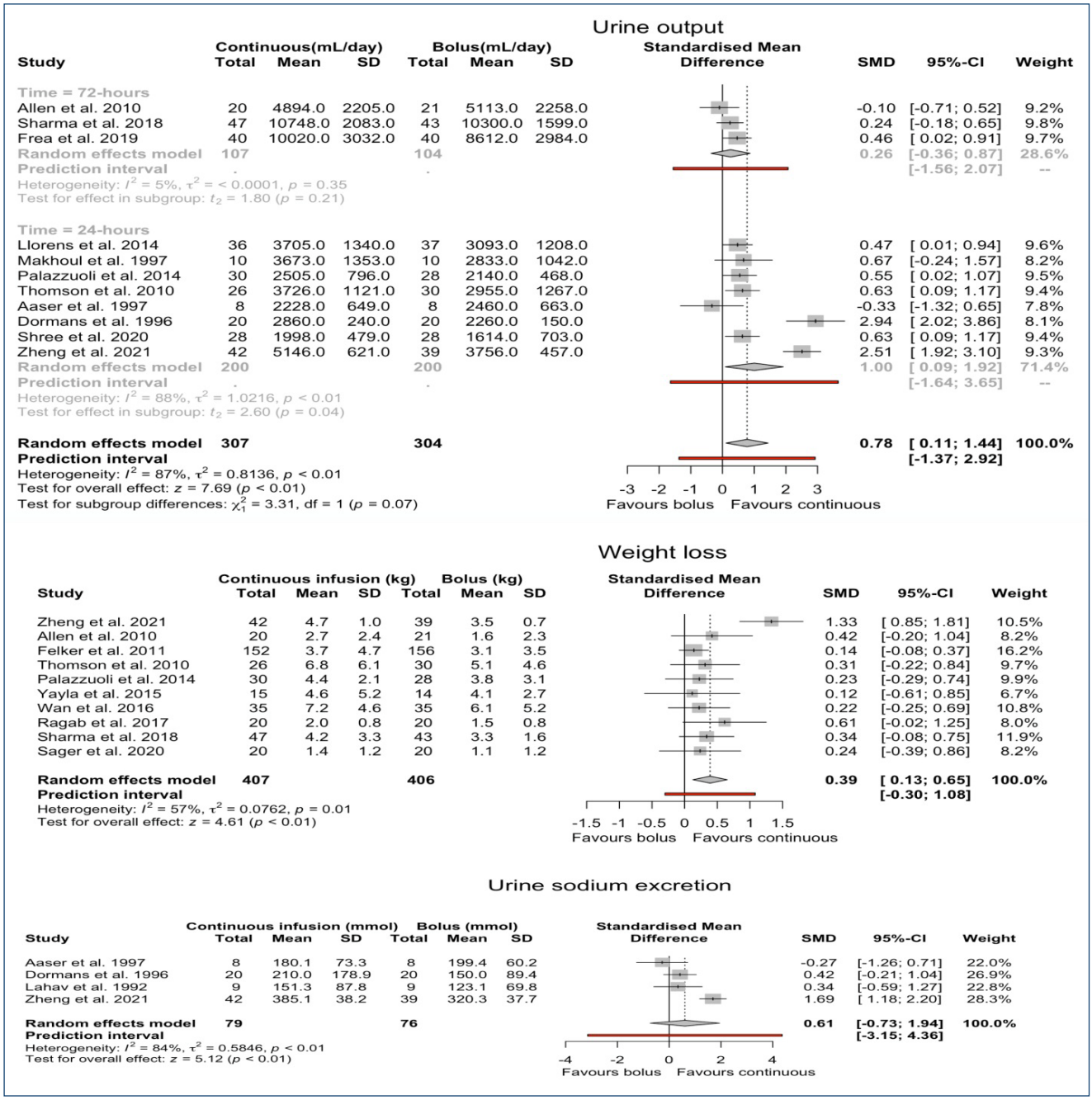

Figure 1. Forest plots of urine output, weight loss, and urine sodium excretion.

for urine output and weight loss but not for mortality, with similar findings reported in the current meta-analysis[29]. In a recent review, Shastri et al. did not find a difference between treatment regimens regarding mortality, length of hospital stay, and weight loss[30]. Compared to our study, fewer studies and sample size seem to have led to these results. Finally, Wu et al. conducted a meta-analysis and could not find a difference between continuous and bolus therapy groups[4]. The fact that some of the studies in the meta-analysis used torasemide instead of furosemide in the treatment and some of them were examined in all intensive care patients may also have contributed to these results. We included only studies that consisted of HF patients and used furosemide as a therapeutic agent in our meta-analysis.

There was high heterogeneity between studies in our meta-analysis. Most of them had an acceptable quality as

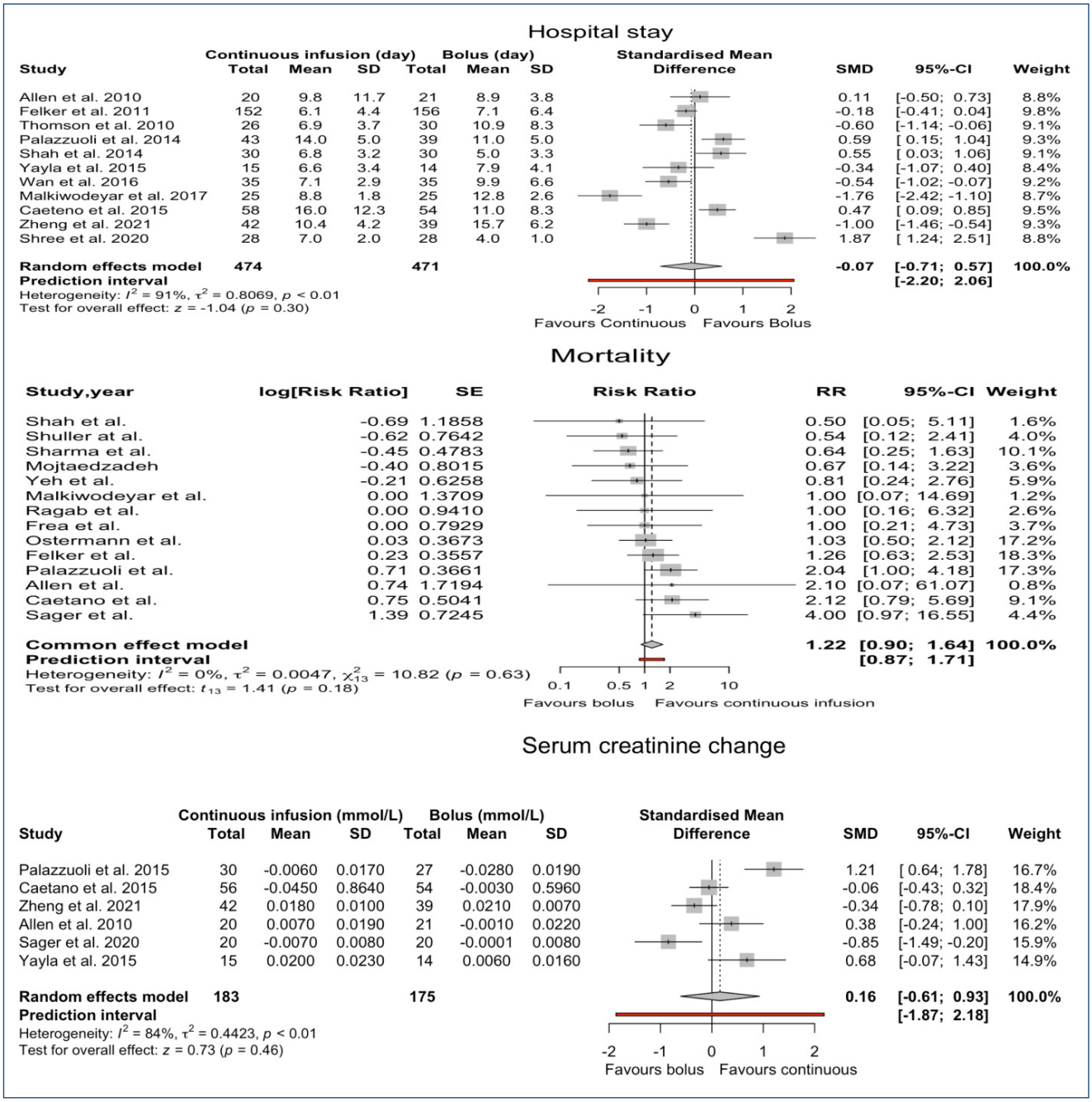

Figure 2. Forest plots of urine hospital stay, mortality, and serum creatinine change.

evaluated using the modified Jadad scale. Four studies were more likely to have a bias as assessed with Rob2[3,7,12,17]. Blinding is an important factor for avoiding bias in RCTs. Only 7 of 18 RCTs were designed in blinded study design[10-12,14,23,24], in which 3 of them reported blinding methods[14,23,24]. Another contributing factor that led to high heterogeneity in our meta-analysis might be the lack of a wash-out period in RCTs with a cross-over design[9,15,16,19]. Additionally, most studies in this meta-analysis did not explain which statistical analyses were used to detect differences between groups in detail, for accounting loss follow-up, missing data, or analyses were conducted on an intention-to-treat versus per-protocol basis in the presence of nonadherence. It has been suggested that, on a per-protocol basis, the groups should be balanced with and adjusted for nonadherence[31]. Finally, furosemide was used in all RCTs as a diuretic agent, but the differences between the

diuretic doses for both regimens of studies might have contributed to the existence of heterogeneity.

Limitations

This review had some limitations due to variances in basal characteristics of populations, various diuretic doses, and administration schedules, and using a concomitant medication, which were all the typical limitations of RCTs. Although the rate of mortality did not differ between compared groups, the mortality was calculated based on the risk ratio. So, it should be better to adjust for covariates and time. Unfortunately, none of the studies presented an adjusted hazard ratio for in-hospital mortality. Further meta-analyses with more RCTs might provide more information for the decision to use a continuous versus bolus diuretic regimen in HF patients.

CONCLUSION

The continuous diuretic infusion had a higher diuretic effect and weight loss than the bolus diuretic regimen, without affecting serum creatinine, eGFR, and mortality in HF patients.

AUTHORS' CONTRIBUTIONS

FŞ: Conceptualization, Data curation, Formal Analysis, Investigation, Methodology, Software, Supervision, Validation, Visualization, Writing – original draft, Writing – review & editing. **TC:** Conceptualization, Data curation, Formal Analysis, Investigation, Methodology, Software, Supervision, Validation, Visualization, Writing – original draft, Writing – review & editing.

REFERENCES

1. McDonagh TA, Metra M, Adamo M, Gardner RS, Baumbach A, Böhm M, et al. 2021 ESC Guidelines for the diagnosis and treatment of acute and chronic heart failure. Eur Heart J. 2021;42(36):3599-726. https://doi.org/10.1093/eurheartj/ehab368
2. Verbrugge FH, Mullens W, Tang WH. Management of cardio-renal syndrome and diuretic resistance. Curr Treat Options Cardiovasc Med. 2016;18(12):11. https://doi.org/10.1007/s11936-015-0436-4
3. Zheng Z, Jiang X, Chen J, He D, Xie X, Lu Y. Continuous versus intermittent use of furosemide in patients with heart failure and moderate chronic renal dysfunction. ESC Heart Fail. 2021;8(3):2070-8. https://doi.org/10.1002/ehf2.13286
4. Wu MY, Chang NC, Su CL, Hsu YH, Chen TW, Lin YF, et al. Loop diuretic strategies in patients with acute decompensated heart failure: a meta-analysis of randomized controlled trials. J Crit Care. 2014;29(1):2-9. https://doi.org/10.1016/j.jcrc.2013.10.009
5. Jadad AR, Moore RA, Carroll D, Jenkinson C, Reynolds DJ, Gavaghan DJ, et al. Assessing the quality of reports of randomized clinical trials: is blinding necessary? Control Clin Trials. 1996;17(1):1-12. https://doi.org/10.1016/0197-2456(95)00134-4.
6. McGuinness LA, Higgins JPT. Risk-of-bias VISualization (robvis): an R package and Shiny web app for visualizing risk-of-bias assessments. Res Synth Methods. 2020;12(1):55-61. https://doi.org/10.1002/jrsm.1411
7. Makhoul N, Riad T, Friedstrom S, Zveibil FR. Frusemide in pulmonary oedema: continuous versus intermittent. Clin Intensive Care. 1997;8(6):273-6. https://doi.org/10.3109/tcic.8.6.273.276
8. Allen LA, Turer AT, DeWald T, Stough WG, Cotter G, O'Connor CM. Continuous versus bolus dosing of furosemide for patients hospitalized for heart failure. Am J Cardiol. 2010;105(12):1794-7. https://doi.org/10.1016/j.amjcard.2010.01.355
9. Thomson MR, Nappi JM, Dunn SP, Hollis IB, Rodgers JE, Van Bakel AB. Continuous versus intermittent infusion of furosemide in acute decompensated heart failure. J Card Fail. 2010;16(3):188-93. https://doi.org/10.1016/j.cardfail.2009.11.005
10. Felker GM, Lee KL, Bull DA, Redfield MM, Stevenson LW, Goldsmith SR, et al. Diuretic strategies in patients with acute decompensated heart failure. N Engl J Med. 2011;364(9):797-805. https://doi.org/10.1056/NEJMoa1005419
11. Palazzuoli A, Pellegrini M, Ruocco G, Martini G, Franci B, Campagna MS, et al. Continuous versus bolus intermittent loop diuretic infusion in acutely decompensated heart failure: a prospective randomized trial. Crit Care. 2014;18(3):R134. https://doi.org/10.1186/cc13952
12. Llorens P, Miró Ò, Herrero P, Martín-Sánchez FJ, Jacob J, Valero A, et al. Clinical effects and safety of different strategies for administering intravenous diuretics in acutely decompensated heart failure: a randomised clinical trial. Emerg Med J. 2014;31(9):706-13. https://doi.org/10.1136/emermed-2013-202526
13. Shah RA, Subban V, Lakshmanan A, Narayanan S, Udhayakumaran K, Pakshirajan B, et al. A prospective, randomized study to evaluate the efficacy of various diuretic strategies in acute decompensated heart failure. Indian Heart J. 2014;66(3):309-16. https://doi.org/10.1016/j.ihj.2014.03.006
14. Yayla Ç, Akyel A, Canpolat U, Gayretli Yayla K, Eyiol A, Akboğa MK, et al. Comparison of three diuretic treatment strategies for patients with acute decompensated heart failure. Herz. 2015;40(8):1115-20. https://doi.org/10.1007/s00059-015-4327-y
15. Aaser E, Gullestad L, Tølløfsrud S, Lundberg J, Hall C, Djøseland O, et al. Effect of bolus injection versus continuous infusion of furosemide on diuresis and neurohormonal activation in patients with severe congestive heart failure. Scand J Clin Lab Invest. 1997;57(4):361-7. https://doi.org/10.3109/00365519709099409
16. Dormans TP, van Meyel JJ, Gerlag PG, Tan Y, Russel FG, Smits P. Diuretic efficacy of high dose furosemide in severe heart failure: bolus injection versus continuous infusion. J Am Coll Cardiol. 1996;28(2):376-82. https://doi.org/10.1016/0735-1097(96)00161-1
17. Shree JD, Daniel CJ, Marsh C, Daniel JS, Lavanya S. A study on continuous infusion versus intermittent bolus dosing of furosemide in hospitalized heart failure patients. Res J Pharm Technol. 2021;14(5):2814-8. https://doi.org/10.52711/0974-360X.2021.00496

18. Sager R, Lindstedt I, Edvinsson L, Edvinsson ML. Increased mortality in elderly heart failure patients receiving infusion of furosemide compared to elderly heart failure patients receiving bolus injection. J Geriatr Cardiol. 2020;17(6):359-64. https://doi.org/10.11909/j.issn.1671-5411.2020.06.009
19. Lahav M, Regev A, Ra'anani P, Theodor E. Intermittent administration of furosemide vs continuous infusion preceded by a loading dose for congestive heart failure. Chest. 1992;102(3):725-31. https://doi.org/10.1378/chest.102.3.725
20. Malkiwodeyar PK, Hiregoudar N, Kabade D, Hasabi I. Continuous versus bolus dosing of furosemide in the treatment of patients with acute decompensated heart failure. Sch J Applied Med Sci. 2017;5(9B):3551-6. https://doi.org/10.21276/sjams.2017.5.9.17
21. Ragab D, Taema KM, Farouk W, Saad M. Continuous infusion of furosemide versus intermittent boluses in acute decompensated heart failure: effect on thoracic fluid content. Egypt Heart J. 2018;70(2):65-70. https://doi.org/10.1016/j.ehj.2017.12.005
22. Wang YTB, Xue L. A comparative study of continuous and intermittent administration of furosemide in acute decompensated heart failure. J Clin Med. 2016;3:8154-5.
23. Sharma K, Vaishnav J, Kalathiya R, Hu JR, Miller J, Shah N, et al. Randomized evaluation of heart failure with preserved ejection fraction patients with acute heart failure and dopamine: the ROPA-DOP trial. JACC Heart Fail. 2018;6(10):859-70. https://doi.org/10.1016/j.jchf.2018.04.008
24. Frea S, Pidello S, Volpe A, Canavosio FG, Galluzzo A, Bovolo V, et al. Diuretic treatment in high-risk acute decompensation of advanced chronic heart failure-bolus intermittent vs. continuous infusion of furosemide: a randomized controlled trial. Clin Res Cardiol. 2020;109(4):417-25. https://doi.org/10.1007/s00392-019-01521-y
25. Herzog E, Varley C, Kukin M. Pathway for the management of acute heart failure. Crit Pathw Cardiol. 2005;4(1):37-42. https://doi.org/10.1097/01.hpc.0000154606.55424.fc
26. Brater DC. Diuretic resistance: mechanisms and therapeutic strategies. Cardiology. 1994;84(Suppl. 2):57-67. https://doi.org/10.1159/000176458
27. Amer M, Adomaityte J, Qayyum R. Continuous infusion versus intermittent bolus furosemide in ADHF: an updated meta-analysis of randomized control trials. J Hosp Med. 2012;7(3):270-5. https://doi.org/10.1002/jhm.991
28. Chan JSK, Kot TKM, Ng M, Harky A. Continuous infusion versus intermittent boluses of furosemide in acute heart failure: a systematic review and meta-analysis. J Card Fail. 2020;26(9):786-93. https://doi.org/10.1016/j.cardfail.2019.11.013
29. Kuriyama A, Urushidani S. Continuous versus intermittent administration of furosemide in acute decompensated heart failure: a systematic review and meta-analysis. Heart Fail Rev. 2019;24(1):31-9. https://doi.org/10.1007/s10741-018-9727-7
30. Shastri P, Burmeister C, Tomcho J, Patel M, Elzanaty A, Bhuta S, et al. Continuous infusion versus intermittent bolus furosemide for acute decompensated heart failure: a systematic review and meta-analysis. J Am Coll Cardiol. 2021;77:616. https://doi.org/10.1016/S0735-1097(21)01975-6
31. Hernán MA, Robins JM. Per-protocol analyses of pragmatic trials. N Engl J Med. 2017;377(14):1391-8. https://doi.org/10.1056/NEJMsm1605385

https://doi.org/10.1590/1806-9282.20220283ERRATUM

In the manuscript "Relationship between contrast-induced nephropathy and long-term mortality after percutaneous coronary intervention in patients with chronic coronary total occlusion", DOI: 10.1590/1806-9282.20220283, published in the Rev Assoc Med Bras. 2022;68(8):1078-1083, on page 1078, the Results section of Summary:

Where it reads:

RESULTS: Mean age of patients with incidence of contrast-induced nephropathy was 66.7±11.8, and 23.8% of them were comprised by female. We found a significantly higher mortality in long-term follow-up in the patient group with contrast-induced nephropathy (42.9 vs. 57.1%, p=<0.001). According to Kaplan-Meier analysis performed additionally, survival during follow-up was significantly shorter in this group and, in logistic regression analysis, it was an independent predictor of mortality (OR 11.78; 95%CI 3.38–40.9).

It should read:

RESULTS: Mean age of patients with incidence of contrast-induced nephropathy was 66.7±11.8, and 23.8% of them were comprised by female. We found a significantly higher mortality in long-term follow-up in the patient group with contrast-induced nephropathy (42.9 vs. 57.1%, p≤0.001). According to Kaplan-Meier analysis performed additionally, survival during follow-up was significantly shorter in this group and, in logistic regression analysis, it was an independent predictor of mortality (OR 3.02; 95%CI 1.41–6.45, p=0.004).