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

RAMB

Journal of The Brazilian Medical Association

Volume 68, Number 5
May, 2022

AMB
Associação Médica Brasileira

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ISSN 0104-4230
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RAMB - REVISTA DA ASSOCIAÇÃO MÉDICA BRASILEIRA
(JOURNAL OF THE BRAZILIAN MEDICAL ASSOCIATION)

Editors-in-Chief: Renato Delásio 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.
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Publication norms are available on the website www.ramb.org.br

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

Editorial Production

https://doi.org/10.1590/1806-9282.20220154

Association between human papillomavirus and urothelial carcinoma of the bladder

Mehmet Sarier[1,2*]

Human papillomavirus (HPV) is the most common sexually transmitted viral pathogen in the world and poses a serious global socioeconomic burden due to its oncogenic nature. HPV is responsible for one of the most common virus-associated cancers worldwide, accounting for approximately 8% of all malignancies[1]. HPV causes low-grade, benign lesions such as condyloma acuminata in the anogenital region and is also strongly associated with cervical, anal, vulvo-vaginal, and penile carcinomas[2]. Although they are in close proximity anatomically, it has long been debated whether urothelial carcinoma of the bladder (UCB) is associated with HPV. The main hypothesis regarding the relationship between HPV and UCB is that HPV shows epithelial tropism and, during transmission, one of the first sites where HPV is encountered by the host is the urethral external meatus[3]. The lack of a clear consensus on this relationship until recently can be attributed to limitations related to the methodological differences in previous studies. These factors include small case series, not sampling fresh tissue, and the lack of adequate case-controlled studies[4]. In light of this information, a case-controlled study conducted with fresh tissue samples demonstrated a strong correlation between UCB and HPV infection (odds ratio: 4.24, 95% confidence interval 1.63–12.34)[5]. Once this relationship is established, the next question is about the prognostic value of HPV in UCB. HPV positivity has been shown to be a favorable prognostic factor in cervical, anal, and head and neck cancers[6]. In UCB, in contrast, tumor grade is very important in terms of disease progression. However, it seems that there is also no consensus on the relationship between tumor grade and HPV in UCB. Tenti et al.[7] reported that HPV was associated with low-grade tumors, Cai et al.[8] determined that HPV was associated with high-grade tumors, and Sarier et al.[5] observed no significant relationship between tumor grade and HPV.

This may explain the absence of studies investigating the prognostic value of HPV positivity in bladder carcinoma until recently. However, two recent studies sought answers to this question. In their study evaluating the 2-year follow-up results of HPV-positive UCB patients with pTa or PT1 disease, Sarier et al.[9] observed no statistical difference in disease progression compared to HPV-negative patients. However, a noteworthy finding of the study was that HPV-positive patients had a higher tumor recurrence rate during the follow-up period. Moghadam et al.[10], on the other hand, reported significant associations between HPV and both tumor recurrence and tumor stage. In summary, the increasing diagnostic use of nucleic acid amplification tests such as PCR in recent years has further elucidated the relationship between UCB and HPV. The significant relationship between HPV and tumor recurrence may guide future research to determine the prognostic value of HPV in UCB.

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[1]Istinye University, Department of Urology – Istanbul, Turkey.
[2]Medical Park Hospitals Group, Department of Urology – Antalya, Turkey.
*Corresponding author: drsarier@gmail.com

Conflicts of interest: the authors declare there is no conflicts of interest. Funding: none.
Received on February 04, 2022. Accepted on February 08, 2022.

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https://doi.org/10.1590/1806-9282.2022D685

Antibiotics in the prophylaxis of COVID or in the treatment of mild COVID

Alexandre Naime Barbosa[1], Antonio Silvinato[2], Hélio Bacha[3], Idevaldo Floriano[4], Suzana Tanni[5], Wanderley Bernardo[2,6*]

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.

Guideline conclusion: April, 2021

Societies: Associação Médica Brasileira, Sociedade Brasileira de Infectologia and Sociedade Brasileira de Pneumologia e Tisiologia.

Group AMB: Wanderley Marques Bernardo

CLINICAL QUESTION

In patients at risk or diagnosed with mild COVID-19, does the prophylactic use of antibiotics reduce the occurrence of infection (PCR positive), hospitalization, and mechanical ventilation or mortality, and does it not increase the risk of adverse events?

METHOD

Eligibility criteria for the studies to be included

PICO

Patient: risk of COVID or mild COVID confirmed by PCR

Intervention: antibiotics (not associated)

Comparison: no antibiotic or placebo

Outcome: infection (PCR+), hospitalization (ward or intensive care unit [ICU]), mechanical ventilation, mortality, and adverse events

Study design

Phase 3 randomized controlled trials (RCTs) and Phase 3 RCT systematic reviews meeting PICO

No limits on time consulted, language or full text availability.

Bases consulted with the respective strategies

Medline and EMBASE

#1 = COVID OR COV OR CORONAVIRUS OR SARS

#2 = (Anti-Bacterial Agents OR Antibacterial Agents OR Antibacterial Agent OR Anti-Bacterial Agent OR Anti Bacterial Agent OR Anti-Bacterial OR Anti Bacterial OR Bacteriocidal Agent OR Bacteriocide OR Bacteriocides OR Antibiotics OR Antibiotic)

#3 = #1 AND #2

#4 = #3 AND Random*

Clinical trials

COVID AND Antibiotics

Extracted data

Data on authorship, year of publication, description of patients, interventions (antibiotics and comparison), outcomes, and follow-up time will be extracted from the works.

Risk of bias and quality of evidence

The risk of bias will be assessed using the items in Rob 2[1], plus other fundamental elements, and expressed as very serious, serious, or not serious. The quality of evidence will be extrapolated from the risk of bias obtained from the study(s) (if there is no meta-analysis) using the GRADE[2] terminology in very

[1]Universidade Estadual Paulista, Faculdade de Medicina de Botucatu, Departamento de Infectologia – Botucatu (SP), Brazil.
[2]Associação Médica Brasileira, Medicina Baseada em Evidências – São Paulo (SP), Brazil.
[3]Hospital Israelita Albert Einstein – São Paulo (SP), Brazil.
[4]Cooperativa Baixa Mogiana, Medicina Baseada em Evidências – Mogi Guaçu (SP), Brazil.
[5]Universidade Estadual Paulista, Faculdade de Medicina de Botucatu, Departamento de Clínica Médica, Disciplina de Pneumologia – Botucatu (SP), Brazil.
[6]Universidade de São Paulo, Faculdade de Medicina – São Paulo (SP), Brazil.
*Corresponding author: wmbernardo@usp.br

Conflicts of interest: the authors declare there is no conflicts of interest. Funding: none.
Received on March 10, 2022. Accepted on March 11, 2022.

low, low, and high and through the GRADEpro[2] software (if there is a meta-analysis) into very low, low, moderate, and high.

Analysis and synthesis of outcomes

The outcomes, when categorical, will be expressed by group (antibiotics and comparison) and through the number of events and the calculated risk (%) for each group (dividing the number of events by the total number of patients in each group). If the difference in risk (DR) between the groups is significant (95% confidence interval), it will be expressed accompanied by the 95% confidence Interval (95%CI) and the Number Needed to Treat (NNT) or to Produce Harm (NNH). If there is more than one study included with common outcomes, they will be aggregated through meta-analysis using the RevMan 5.4 software[3].

RESULTS

At the sources of scientific information, 288, 317, and 301 studies were recovered in Medline, Embase and Clinical trials, respectively. By eliminating duplicates and meeting the eligibility criteria, six studies were selected so that their full texts could be accessed, from which four works[4-7] were excluded (exclusion reasons in Table 1 worksheet – inclusion/exclusion reasons). Therefore, there are currently two randomized trials available to support this assessment, meeting the eligibility criteria adopted[8, 9]. It was not possible to aggregate the results of the two studies selected through meta-analysis because the primary outcomes analyzed were different, in addition to differences in the populations studied, in the form of the intervention and in the comparisons.

The Azithromycin for COVID-19 Trial study, Investigating Outpatients Nationwide (ACTION) was a 2:1 randomized clinical trial that evaluated the efficacy of a single 1.2 g oral dose of azithromycin compared to placebo on self-reported COVID-19 symptoms among outpatients[8].

Participants were eligible for the study if they had a documented positive SARS-CoV-2 test result (nucleic acid or antigen amplification) within 7 days prior to enrollment[8].

Participants were randomized in a 2:1 ratio to azithromycin or matching placebo. Randomization was unrestricted (no blocking or stratification), and the sequence was generated by the study's unmasked data team using a computer-generated pseudo-random number generator[8].

To facilitate allocation masking and concealment, letters were randomly assigned (e.g., A, B, and C; six letters total) to each study treatment (azithromycin or placebo). Study medication vial labeling was identical with the exception of the treatment letter to allow for masking of investigators, study staff, and participants. After randomization, participants received a single oral dose of 1.2 g of azithromycin suspension or matching placebo by overnight mail. The placebo was specifically formulated to combine with azithromycin. Allocation was concealed by not revealing the letter randomly assigned to the participant until enrollment and baseline assessments were completed[8].

Prespecified primary end point was the self-reported absence of symptoms of COVID-19 on day 14. The prespecified secondary end points included adverse events on day 3, hospitalization and/or death on day 21, emergency department and/or use of urgent care on day 21, household members who were diagnosed with or developed symptoms of COVID-19 on day 21, and patient-reported COVID-19 symptoms on day 21 (including fever, cough, diarrhea, abdominal pain, anosmia, conjunctivitis, pain sore throat, shortness of breath, myalgia, fatigue, dizziness, and an open "other" category). Participants completed online surveys on days 3, 7, 14, and 21 after enrollment to assess results[8].

A total of 263 participants were enrolled, of which 171 were randomized to azithromycin and 92 to placebo, with 76% completing the study visit on day 14 (77% in the azithromycin group and 76% in the placebo group)[8].

Table 1. Antibiotics COVID prophylaxis or treatment of mild COVID.

PMID	First author	Journal/book	Publication year	DOI	Included/excluded (reasons)
33676597	PRINCIPLE Trial Collaborative Group	*Lancet*	2021	10.1016/S0140-6736(21)00461-X	Excluded (trial phase ii)
32853672	Sekhavati E	*Int J Antimicrob Agents*	2020	10.1016/j.ijantimicag.2020.106143	Excluded hospitalized
32706953	Cavalcanti AB	*N Engl J Med*	2020	10.1056/NEJMoa2019014	Excluded association
32205204	Gautret P	*Int J Antimicrob Agents*	2020	10.1016/j.ijantimicag.2020.105949	Excluded association
34269813	Oldenburg CE	*JAMA*	2021	10.1001/jama.2021.11517	Included
34252378	Hinks TSC	*Lancet Respir Med*	2021	10.1016/S2213-2600(21)00263-0	Included

	Absence of symptoms Number/total (%) Azithromycin	Placebo	Difference in prevalence % (95%CI)
All participants	66/131 (50)	35/70 (50)	0 (–14 to 15)
Asymptomatic	9/10 (90)	3/4 (75)	15 (–46 to 76)
Symptomatic	57/120 (48)	32/66 (48)	–1 (–17 to 15)

On day 3, more participants reported gastrointestinal adverse events in the azithromycin group compared to placebo, including diarrhea (azithromycin: 41%; placebo: 17%), abdominal pain (azithromycin: 17%; placebo: 1%), and nausea (azithromycin: 22%; placebo: 10%). There were no significant differences in self-reported specific COVID-19 symptoms reported at day 14. No serious adverse events were reported and there were no deaths in any of the study groups. Among the participants followed up to day 21, five reported being hospitalized, all in the azithromycin group. Emergency/urgent care visits in the azithromycin group were significantly higher than in the placebo group (azithromycin: 14%; placebo: 3%; difference, 12%; 95%CI 3%–20%; p=0.01)[8].

ATOMIC 2 was a prospective, open-label, two-arm, randomized superiority study of standard care and azithromycin compared to standard care alone[9].

Eligible participants were adults aged at least 18 years assessed at an acute care hospital with a clinical diagnosis of highly probable or confirmed COVID-19 infection made by the clinical staff, with onset of symptoms within the last 14 days and assessed by the attending physician and clinical staff as appropriate for initial outpatient (i.e., outpatient) management[9].

Patients were randomly assigned (1:1) to azithromycin plus standard care or standard care alone using an automated web-based service, with a minimization algorithm to ensure balanced allocation between treatment groups, stratified by center, sex, and attendance of hypertension and diabetes. To ensure the unpredictability of treatment allocation, the first 30 participants were randomly assigned by simple randomization and the minimization algorithm included a probabilistic element (participants had an 80% chance of being allocated to treatment, which minimized imbalance between groups). Patients, investigators, and health care professionals were not masked to study drug assignment[9].

Patients in the azithromycin group received 500 mg of azithromycin once daily orally plus standard care for 14 days, and those in the control group received standard care as per local guidelines[9].

The primary end point was the proportion of participants with hospital admission or death from any cause within 28 days of randomization. Secondary outcomes were the proportion of participants admitted to hospital with respiratory failure requiring noninvasive mechanical ventilation (level 2) or invasive mechanical ventilation (level 3) or death from any cause within 28 days of randomization[9].

Of the 295 participants, 147 were randomly assigned to azithromycin plus standard care and 148 were randomly assigned to standard care alone. Of the 295 patients, 3 withdrew consent after randomization; thus, data on the primary outcome were available from 292 participants[9].

Mortality from all causes	1/145 (1%)	1/147 (1%)
Hospitalization or death (ITT)	15/145 (10%)	17/147(12%)
Level 2 or 3 ventilation or death	2/145 (1%)	2/147 (1%)

Risk of bias

The risk of bias in both included studies is high, giving consequently a low quality of evidence to the results (Table 2).

SUMMARY OF THE EVIDENCE (CONCLUSION)

The evidence based on RCTs available at the moment does not support the indication of prophylactic antibiotic therapy or specific therapy for patients with mild COVID-19, because when compared with conventional treatment or placebo, there are no differences in the presence of symptoms, hospitalization rates, mortality, or the need for ventilation. In addition,

Table 2. Risk of bias.

First author	Year	Randomization	Blind allocation	Double blind	Outcome researcher blind	Lost	Prognostic characteristics	Appropriate outcomes	Intention to treat analysis	Sample size calculation	Early interruption
Oldenburg CE	2021										
Hinks TSC	2021										
LEGENDA		High risk			Not informed			Low risk			

the group of intervention had more adverse effects and a low quality of evidence.

AUTHORS' CONTRIBUTIONS

ANB: study concept and design, critical review and approval of the final version. **AS:** data collection, statistical analyses and interpretation of data, drafting of the manuscript. **HB:** study concept and design. **IF:** data collection, statistical analyses and interpretation of data, drafting of the manuscript. **ST:** study concept and design, data collection, statistical analyses and interpretation of data, drafting of the manuscript, critical review and approval of the final version. **WB:** study concept and design, data collection, statistical analyses and interpretation of data, drafting of the manuscript, critical review and approval of the final version.

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https://doi.org/10.1590/1806-9282.20211142

Disability and pain in capoeira practitioners

Zhongguo Ren[1*], Aihua Shu[1], Feng Zhou[1]

Dear Editor,

We were very pleased to read the article entitled "Disability and pain in capoeira practitioners" by Jorge William de Sá Campos[1] and his colleagues. In this article, the authors revealed that the knees, lower back, and wrists/hands were the regions of the body with the highest reports of pain and disability. However, some issues have been noted from our point of views.

Most studies used nonprobability sampling across a wide variety of settings, which may introduce selection bias. Therefore, one limitation of this study is that selection bias is not avoided. Where does sample come from? General demographic characteristics of participants are not explained in this study. Another limitation is a small sample size and possible sample biases.

In this study, the practice of fighting, martial art, or combat sport were excluded; thus, it is unclear that disability of the knees, lower back, and wrists/hands is also common among participants who take the practice of fighting, martial art, or combat sport. The reliability and validity of pain questionnaire was not offered in this study. In additional, details of the quality control process should be reported in the "Methods" section.

AUTHORS' CONTRIBUTIONS

ZR: Data curation, Formal Analysis, Writing – original draft.
AS: Data curation, Formal Analysis, Writing – original draft.
FZ: Conceptualization, Writing – review & editing.

REFERENCE

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):1692-95. https://doi.org/10.1590/1806-9282.20210740

[1]Peoples Hospital of China Three Gorges University, Department of Anesthesiology – Hubei, China.
*Corresponding author: rongrongdoctor@126.com
Conflicts of interest: the authors declare there is no conflicts of interest. Funding: none.
Received on November 09, 2021. Accepted on February 01, 2022.

https://doi.org/10.1590/1806-9282.20220099

Comment on:"Metabolic syndrome in adolescents and antioxidant nutrient intake: a cross-sectional study"

Bo Zhu[1], Lianping He[1*]

Dear Editor,

We are very lucky enough to read the article entitled "Metabolic syndrome in adolescents and antioxidant nutrient intake: a cross-sectional study," written by Batista et al.[1]. This valuable study found no association between metabolic syndrome (MS) and the tertiles of the intake of antioxidant nutrients, while lower intakes of vitamins A and E are associated with risks of MS-related substrates, such as triglycerides and glucose. Although the findings of the study have explained part of the problem, we believe, from our point of view, that this article still deserves further discussion.

We suggested the authors to provide the family diet spectrum of the sample because the family dietary habit and levels for intake of vitamins from food were discrepant. In controlling for confounding factors, the authors controlled only for education of the mother. However, education for the father and other family members should also be described in detail. Furthermore, detailed procedures of height, weight, and waist circumference measurement should be described in the "Methods" section. It is also suggested to specify the time of blood pressure measurement, as blood pressure varies with time.

Another concern of this study was that the diagnostic criteria w ere unclear; generally, diastolic blood pressure 90 mmHg or higher and/or systolic blood pressure 130 mmHg or higher are considered hypertension. We also suggest the authors to describe the diagnostic criteria for MS. The authors investigated the association between MS and antioxidant intake in adolescents; however, the definition of adolescents in this article was not accurate enough, because the World Health Organization defines adolescents as those aging between 10 and 19 years.

DATA AVAILABILITY

The data sets generated and analyzed during this study are available from the corresponding author on reasonable request.

ACKNOWLEDGMENTS

We thank International Science Editing (http://www.internationalscienceediting.com) for editing this manuscript.

AUTHORS' CONTRIBUTIONS

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

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[1]Taizhou University, School of Medicine – Taizhou, China.
*Corresponding author: lianpinghe@tzc.edu.cn

Conflicts of interest: the authors declare there is no conflicts of interest.
Funding: The study was supported by curriculum reform project of Taizhou University in 2021 (grant no. xkg2021087).
Received on January 24, 2022. Accepted on February 27, 2022.

ORIGINAL ARTICLE

https://doi.org/10.1590/1806-9282.20210896

Wheelchair basketball improves the treatment of urinary tract infection in people with motor disabilities: a clinical trial

Ramirie N. Cavalcante[1], Adeliana C. S. Santos[1,2], Rosilene Andrade Silva Rodrigues[1,3], Amanda Colichio Bini Napoleão[7], Sikiru O. Balogun[3,4], Benedito R. M. de Andrade[1], Carlos A. Fett[3,5], Arturo A. Z. Zavala[6], Karuppusamy Arunachalam[5], Ruberlei G. de Oliveira[1,3,7*]

SUMMARY

OBJECTIVE: Few studies on physical medicine and rehabilitation analyze the benefit of wheelchair basketball in people with motor disabilities. Given these, this study aimed to investigate the effect of the intervention of wheelchair basketball on urinary tract infection in people with motor disabilities.

METHODS: A 12-month experimental *follow-up* was conducted in a single-center study. A total of 48 male individuals aged 18–55 years were allocated to the control group and experimental group. The experimental group practiced wheelchair basketball for 2 h, twice a week. Intra- and intergroup comparisons were made pre- and post-interventions over urinary tract infection.

RESULTS: There was a significant improvement in urinary tract infection and urine culture in pre- and post-intervention antibiograms, respectively. Moreover, the intergroup comparison presented a decrease in infection caused by *Klebsiella pneumoniae*, as well as an increase in the time variability of partially activated thromboplastin, average corpuscular hemoglobin, and hemoglobin and platelets. In the GE, there was an increase in hemoglobin and hematocrit and a decrease in glycated hemoglobin. On the intragroup comparison, there was a reduction of triiodothyronine, $\%HbA1_C$, interleukin-6 pre-intervention, and C-reactive protein post-intervention.

CONCLUSIONS: There was a decrease in urinary tract infection and improvement in biochemical, immunological, and microbiological biomarkers evaluated with physical exercise practice by wheelchair basketball, as well as by multiprofessional *follow-up* and health guidance.

KEYWORDS: C-reactive protein. *Klebsiella pneumoniae*. Interleukin-6. *Escherichia coli*. Sports medicine. Quality of life.

INTRODUCTION

There are several types of people in a wheelchair with motor disabilities (PWD-M)[1], featuring the spinal cord injury (SCI) and presenting typical neurological symptoms, such as neurogenic intestine and bladder[2]. PWD-M are constantly affected by urinary tract infection (UTI) due to the incomplete bladder emptying and incorrect usage of relief probes, which are potential triggers for cystitis, urethritis, and pyelonephritis, leading to increased inflammation of biomarkers (i.e., IL-6, C-reactive protein, and leukocytes) and increased complications of kidney dysfunction (urea and creatinine) such as chronic kidney disease[3].

Few studies on physical medicine and rehabilitation have analyzed the benefits of wheelchair basketball (WB) in PWD-M on the prevalence of UTI[4-6]. because it is asymptomatic and has limited complaints in the early stages of the infection[7,8].

Therefore, there is a knowledge gap in the understanding of functional limitations in PWD-M engaged in high-performance

[1]Universidade Federal de Mato Grosso, Programa de Pós-Graduação em Educação Física – Cuiabá (MT), Brazil.
[2]Chinese Academy of Sciences, Kunming Institute of Botany, Key Laboratory of Economic Plants and Biotechnology, Yunnan Key Laboratory for Wild Plant Resources – Kunming, China.
[3]Universidade Federal de Mato Grosso, Faculdade de Medicina, Programa de Pós-Graduação em Ciências da Saúde – Cuiabá (MT), Brazil.
[4]Universidade Federal da Grande Dourados, Faculdade de Ciências da Saúde, Programa de Pós-Graduação em Ciências da Saúde – Dourados (MS), Brazil.
[5]Universidade Federal de Mato Grosso, Programa de Pós-Graduação em Propriedade Intelectual e Transferência de Tecnologia para a Inovação – Cuiabá (MT), Brazil.
[6]Faculdade de Economia da Universidade Federal de Mato Grosso – Cuiabá (MT), Brazil.
[7]Hospital Universitário Júlio Muller (HUJM), Programa de Pós-Graduação em Ciências Aplicadas à Atenção Hospitalar – Cuiabá (MT), Brazil.
*Corresponding author: ruberlei_godinho@hotmail.com

Conflicts of interest: the authors declare there is no conflicts of interest. Funding: This study was financially supported by the Programa Pesquisa para o SUS: gestão compartilhada em saúde (PPSUS) – Edital nº 003/2017 da Fundação de Amparo à Pesquisa e Inovação do Estado de Mato Grosso (FAPEMAT), em parceria com o Ministério da Saúde (MS), por meio do Departamento de Ciência e Tecnologia da Secretaria de Ciência, Tecnologia e Insumos Estratégicos (Decit/SCTIE/MS), com o Conselho Nacional de Desenvolvimento Científico e Tecnológico (CNPq) e com a Secretaria de Estado da Saúde de Mato Grosso (SES). RGO was recipient of National Post-Doctoral Fellowship (CAPES/PNPD).
Received on February 09, 2022. Accepted on February 09, 2022.

exercise associated with kidney function[7]. In this sense, data regarding the accessibility of complete examinations, as well as health services, and clinical trial research with a long-term *follow-up* of intervention with WB in PWD-M are scarce in the literature[8].

In view of these, this clinical trial aimed to investigate the effect of the 12-month intervention of WB on the inflammatory, immunological, microbiological, and biochemical parameters, as well as the effect on UTI in PWD-M.

METHODS

Study design

This is a 12-month experimental *follow-up* study with intervention of WB training. It is outlined by randomized clinical essay strategy, allocated in two arms, following standardization from Consolidated Standards of Reporting Trials (CONSORT, 2010) (Figure 1).

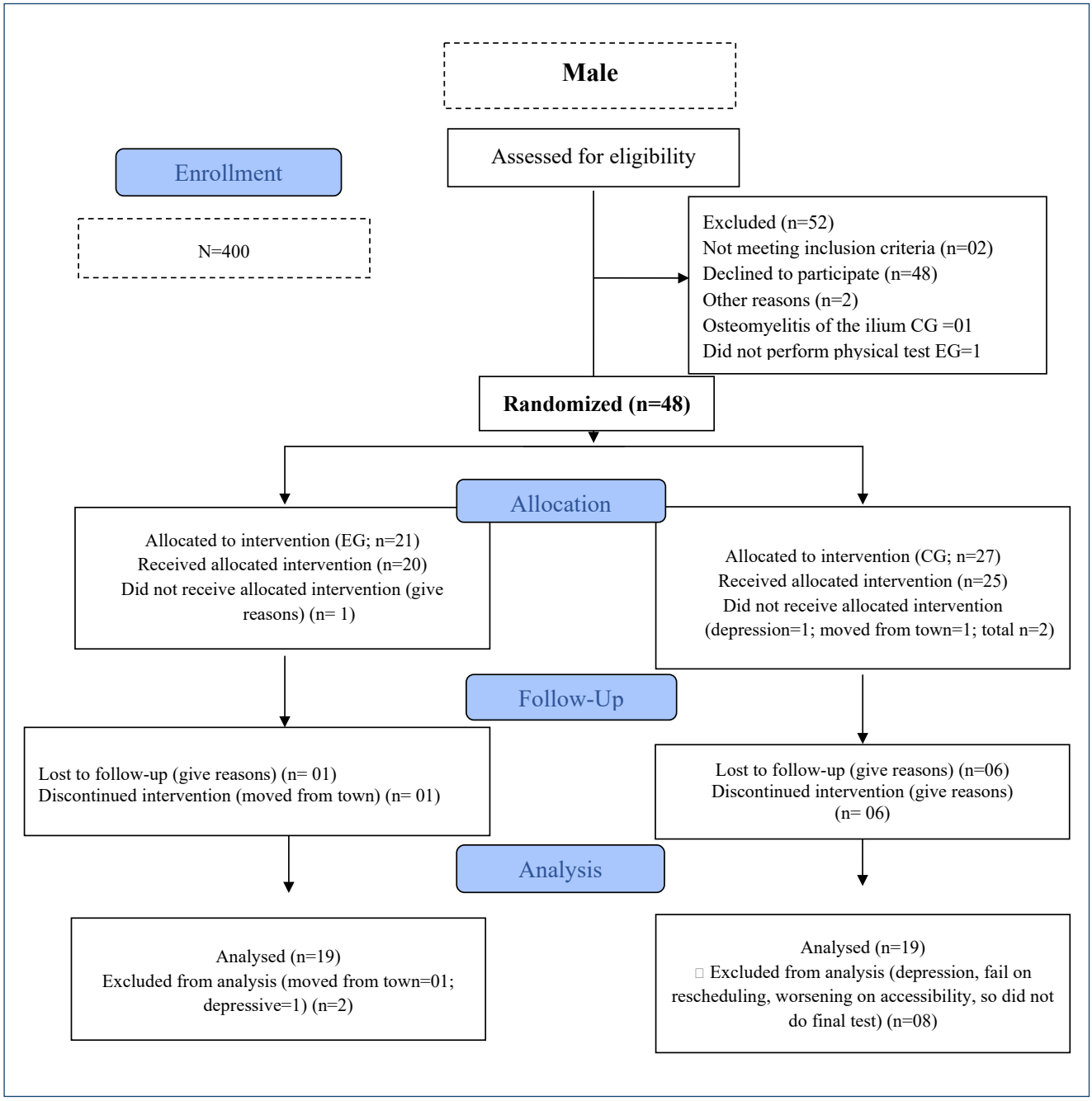

Figure 1. Standardization from Consolidated Standards of Reporting Trials (CONSORT, 2010).

Participants, criteria of selection, exclusion criteria, and randomization

A total of 48 male individuals, aged 18–55 years, were divided into the control group (CG; n=21) and experimental group (EG; n=27).

People with motor disabilities who signed the free informed consent form were presorted and then recruited through subscription supplied by Physically PWD Association and State Health Secretary.

People with motor disabilities who refused to give blood and urine samples examination, those not participated in the WB intervention, absence or affinity with the sport, severe scoliosis, advanced cancer, usage of amphetamines, and those who gave up the research were excluded from the study.

Later, a simple-random raffle of 100 male PWD-M was made, for possible losses and withdrawals. Out of this raffle, 50 participants were selected for EG and CG in accordance with the International Wheelchair Basketball Federation (IWBF).

Clinic trial registration: All participants signed the consent form (TCLE in Portuguese) according to resolutions 466/12 from National Health Council (CNS) approved by the Research Ethics Committee CEP-HUJM: CAAE: 56973516.3.000.5541 and Brazilian Clinical Trials Registry (ReBEC) number: RBR-9w7vxd (https://ensaiosclinicos.gov.br/rg/RBR-9w7vxd) and WHO UTN U1111-1204-1907 (https://apps.who.int/utn/utnvalid.aspx).

Intervention

By following general rules for the sports practice, the EG performed WB training twice a week, with approximately 2 h of training involving physical and tactical conditioning techniques. The study was performed between 2018 and 2019. The WB training was performed in the Gymnasium of Sports and Leisure Adjunct Secretary with support from the Hospital and the University staff.

Assessment

The biochemical tests were performed using an automated biochemical device, VITROS Fusion 5.1 model, *System of Ortho-Clinical Diagnostics* from Johnson & Johnson® (Barcelona, CA, USA). For hematological analysis, a complete hemogram test was performed, using the device from MINDRAY© of Bio-Medical Electronics (Shenzhen, China).

The urinalysis was performed by simple reading of biochemical values in the Uriscan pro BioSys+ Kovalent© (Niterói, RJ, Brazil) device, and then through centrifugation and analysis. In the second sample, the urine was cultured in a CPS culture medium plate, and in the case of positive urine culture samples, the antibiograms were processed in a VITEK Compact 2 device, BIOMERIEU© (Niterói, RJ, Brazil). T3, T4, and TSH levels, serum concentrations of vitamins D and B12, and MDA and IL-6 levels were evaluated.

Efficacy measures

The primary outcome was to estimate the UTI prevalence by sedimentoscopy analyses of abnormal elements (SAE) on moment's pre- and post-intragroup intervention with drugs prescription according to the medical records of urine and blood markers. As a secondary outcome, the objectives were the quantification of biomarkers on moment's pre- (baseline) and post-intragroup and intergroup interventions.

Safety measures

Adverse events to health were monitored during the research by a multiprofessional team. Monitoring of the participant was adopted, with field journal, standardized form for anamnesis, which included sociodemographic data, lifestyle and health background, usage of medication or illicit drugs, anthropometry, functional physical tests, and complementary examinations. During WB training, blood pressure, pulse oximeter, and frequency counters were assessed.

Sample size

The sample calculation used the following formula:

$$n = \frac{z^2 p(1-p)N}{E^2(N-1)+z^2 p(1-p)} = \frac{1{,}96^2 \times 0.5 \times 0.5 \times 320}{0{,}1^2 \times 319 + 1.96^2 \times 0.5 \times 0.5} = 74 \quad \text{n}\approx 74 \text{ PWD} \quad (1)$$

Statistical analysis

Sample distribution analysis was made with the Shapiro-Wilk test, and comparison on moments pre- and post-interventions was carried out with t-test, paired or not paired, with significance level at $p<0.05$ and 95% confidence interval. Analysis was done with the intent of treating (ITT) for UTI with physical exercise (PE) compared to WB effect versus CG without WB effect.

RESULTS

Of the participants included (n=100), allocated, and randomized by stratification and initial sample pairing, EG began and concluded the study, due to one participant not having accomplished the first part of laboratory exams requested. Next, the CG initiated the study but concluded with withdrawal and participants who did not perform laboratory examinations PWD-M were analyzed (Table 1).

Table 1. Descriptive characteristic of sample of males with physical disability allocated to the trial arms in the clinical study performed between 2018 and 2019, Cuiabá, Mato Grosso, Brazil.

Variables	n	%
Age (completed years) M±DP (35±8.8) Minimum and maximum=(20–54)	48	100
Etiology		
TRM-spinal injury	28	58.3
Child Poliomyelitis	11	22.9
Plegia fracture of lower member (MI)	02	4.2
TRM-TCE (cranium encephalic trauma)	02	4.2
Amputee, bifid spine, HTLV, transverse myelitis, Suzuki syndrome	05	10.4
Disability time		
2–5 years	16	33.3
6–10 years	15	31.3
11–15 years	01	2.1
Above 20 years	16	33.3
Neurogenic bladder (self-report)		
Yes	32	66.7
No	16	33.3
Pressure ulcer		
Yes	10	20.8
No	38	79.2
UTI (self-report)		
Yes	04	8.3
No	44	91.7
Usage of vesicle probe		
Yes	25	52.1
No	23	47.9
Usage of diapers		
Yes	13	27.1
No	35	72.9
UTI (EAS) biochemical		
Did not do tests	06	12.5
Yes (reference over 5 leukocytes/field)	19	39.6
No	23	47.9
Social security		
Receives nothing (Zero income per capita)	05	10.4
Active worker	06	12.5
Disease aid BPC	14	29.5
Disease aid by work accident	03	6.3
Accident aid (private insurance, DPVAT)	04	8.4
Retirement by accident	16	33.3

HTLV=human T-lymphotropic virus; UTI=urinary tract infection; BPC=continued delivery benefit; DPVAT=Danos Pessoais por Veículos Automotores Terrestres (Brazilian public insurance).

The SAE urinalysis test was found positive in 30% pre-intervention in EG and 75% in CG. On the post-intervention moment, SAE was observed only with a reduction of 19% in the EG, while in the CG, it was 57.90%. In the urine culture test, only *Escherichia coli* was observed in the pre- and post-interventions in EG. In contrast, in the CG pre- and post-intervention moments, these bacteria as well as *Klebsiella pneumonia* (20%) and other strains were observed. There was a reduction of UTI (p=0.004) in the EG compared to the CG. On intergroup comparison, there was an improvement (p=0.011) in the UTI. In addition, on the intergroup comparison, UTI caused by *K. pneumoniae* was found in the CG (p=0.027) (Table 2).

In the pre-intervention intragroup analysis of the EG, there was an increase in mean corpuscular hemoglobin (MCH) (p=0.032), hemoglobin (Hb) (p=0.01), hematocrit (Ht) (p=0.005), and activated partial thromboplastin time (APTT) (p=0.008). In the pre-intervention intergroup comparison, there were higher values in MCH (p=0.032) and mean corpuscular hemoglobin concentration (MCHC) (p=0.021), as well as APTT (p=0.046). However, there was a decrease in platelets (p=0.022). In addition, there was decrease in the prothrombin of EG (p=0.02) (Table 2).

In the EG, the $\%HbA1_C$ (p<0.001) as well as IL-6 (p=0.044) were reduced, and there was an increase in creatinine (p=0.008), when compared at baseline and after intervention. In the CG, a decrease in the values of $\%HBA1_C$ (p=0.026), T3 (p=0.010), and IL-6 (p=0.006) was observed in the intra-group comparison. In the inter-group comparison, there was a reduction in C-reactive protein (CRP) (p=0.035) (Table 2).

DISCUSSION

This clinical study analyzed the effects of a 12-month structured WB. There was a prevalence of *E. coli* in the UTI of participants. Furthermore, the intergroup comparison showed *K. pneumoniae* survived in the CG, but not in the EG, implying that the PWD-M was protected due to the effect of a 12-month exercise of intervention of WB[9].

Poor hygiene during self-catheterization and relief probing, which must be done at least four to five times daily in PWD-M, is linked to the recurrence of UTI. Given the importance, research participants did not know they had UTIs, the incidence of the infection was said to be lower in the initial interview, or in the self-report. The habit of reusing the relief catheter to perform bladder catheterization was also observed by the same token[10].

Physical activity (PA) increased gas exchange through the synthesis and replenishment of red blood cells (RBC) by

Table 2. Characteristics of etiological factors of urinary tract infection and hematological, coagulation, and biochemical parameters in males with motor disability subjected to wheelchair basketball in the clinical trial performed between 2018 and 2019, Cuiabá, Mato Grosso, Brazil.

Variables	Experimental Group (EG)				Control Group (CG)				Intergroup (EG) × (CG)			
	Pre-intervention 2018	Post-intervention 2019	X^2	p-value	Pre-intervention 2018	Post-intervention 2019	X^2	p-value	X^2	p-value	X^2	p-value
Etiology												
Medullary trauma	9 (40.00)	8 (38.10)			15 (68.20)	12 (63.20)						
Poliomyelitis sequels	9 (45.00)	9 (42.90)	0.119	0.942	03 (13.60)	3 (15.80)	0.114	0.994	5.233	0.073	5.233	0.073
Other factors	3 (15.00)	4 (19.00)			04 (18.20)	4 (21.10)						
UTI												
Positive	06 (30.00)	04 (19.00)			15 (75.00)	11 (57.90)						
Negative	14 (70.00)	17 (81.00)	0.666	0.414	05 (25.00)	8 (42.10)	1.283	0.257	8.120	0.004**	6.423	0.011*
Type of bacterial flora (urine culture)												
Escherichia coli	6 (30.00)	4 (19.00)	0.666	0.414	8 (40.00)	4 (21.00)	1.642	0.2	0.440	0.507	0.025	0.874
Klebsiella pneumoniae	0 (0.00)	0 (0.00)			4 (20.00)	4 (21.00)	0.007	0.935	4.444	0.035*	4.912	0.027*
Proteus mirabílis	0 (0.00)	0 (0.00)			1 (5.00)	0 (0.00)	0.975	0.323	1.026	0.311		
Morganella morganii	0 (0.00)	0 (0.00)			1 (5.00)	1 (5.30)	0.001	0.97	1.026	0.311	1.134	0.287
Citrobacter freundii	0 (0.00)	0 (0.00)			0 (0.00)	1 (5.30)	1.080	0.299			1.134	0.287
Flora mista	0 (0.00)	0 (0.00)			1 (5.00)	0 (0.00)	0.975	0.323	1.026	0.311		
Pseudomonas aeruginosa	0 (0.00)	0 (0.00)			0 (0.00)	1 (5.30)	1.080	0.299			1.134	0.287
Red blood cells (millions/mm^3)	19	5.02±0.40	5.11±0.45		0.254	18	4.99±0.49	5.14±0.55		0.126	0.468	0.78

Continue...

Table 2. Continuation.

Variables	Experimental Group (EG)				Control Group (CG)				Intergroup (EG) × (CG)			
	Pre-intervention 2018	Post-intervention 2019	X^2	p-value	Pre-intervention 2018	Post-intervention 2019	X^2	p-value	X^2	p-value	X^2	p-value
Hemoglobin (g/dl)	19	14.44±0.99	14.95 ±1.29		0.01*	18	13.95±1.44	14.52±1.26		0.102	0.068	0.21
Hematocrit (%)	19	43.74±2.89	45,35±3.73		0.005**	18	43.34±3.84	44.16±3.22		0.222	0.239	0.26
MCV (fl)	19	88.43±4,47	88,86±3.96		0.214	18	86.88±5.17	86.76±5.87		0.931	0.156	0.69
MCH (pg)	19	29.22±1.74	28,78 ±3.18		0.446	18	28.05±2.11	28.41±2.22		0.497	0.032*	0.97
MCHC (%)	19	33.03±0,85	32,96±0.77		0.713	18	32.26±1.04	32.66±0.75		0.093	0.021*	0.32
RDW (%)	19	13.67±0.73	13,74±0.639		0.403	18	14.05±1.33	14.47±1.77		0.21	0.369	0.06
Leukocytes (%)	19	6615.2±2064.9	6319,4 ±1779		0.451	18	7363,8±2034.1	6931.1±2122.2		0.402	0.32	0,22
Platelets (mm^3)	19	215,840±44.34	212,379±73752.4		0.792	18	274,500 ±105243.2	250,000±57557.1		0.333	0.022*	0.14
Prothrombin (s)	19	11.28±1.04	11.30±1.17		0.89	17	11.75±0.99	11.42±0.90		0.113	0.223	0,02*
APTT (s)	19	28.07±3.02	32.42±6.59		0.008**	18	30.83±5.40	34.16±5.19		0.082	0.046*	0.30
INR	19	1.01±0.09	1.0±0.11		0.738	17	1.05±0.08	1.55±2.17		0.363	0.206	0.27
Vitamin D3 (ng/ml)	18	32.9±15.84	29.8±11.9		0.263	18	26.84±8.16	24.61±6.98		0.217	0.068	0,08
Vitamin B12 (µmol/L)	18	359.1±111.2	372.0±144.6		0.509	17	447.6±171.8	397.0±141.1		0.219	0.161	0.57
Folic acid (ng/ml)	18	6.41±4.12	6.78±3.39		0.599	18	4.77±±5.76	5.76±2.71		0.11	0.179	0.32
Urea (mg/dl)	18	36.27±16.27	32.77±7.55		0,380	17	33.29±13,43	28.29±8.93		0.19	0.501	0.174
Creatinine (%)	18	0.64±0.17	0.71±0.15		0,008*	17	0.68±0,16	0.65 ±0.16		0.42	0.929	0.158
Sodium (mEq/L)	19	141.7±3.04	141.8±1.60		0,933	18	143.5±3.80	141.4±1.97		0.046	0.109	0.416
Potassium (mEq/L)	19	4.72±1,11	4.50±0.38		0,409	18	4.48±0,37	4.66±0.42		0.169	0.445	0.272

Continue...

Table 2. Continuation.

Variables	Experimental Group (EG)				Control Group (CG)				Intergroup (EG) × (CG)			
	Pre-intervention 2018	Post-intervention 2019	X^2	p-value	Pre-intervention 2018	Post-intervention 2019	X^2	p-value	X^2	p-value	X^2	p-value
Glucose (mg/dl)	19	95.26±29.41	92.84±4,53		0,351	18	92.22±31.96	92.55±29.72		0.905	0.767	0.911
Glycated hemoglobin (%$HBA1_C$)	19	5.47±1.01	5.09±0.67		0,000*	17	5.66 ±1.50	5.28±0.94		0.026*	0.733	0.492
Total cholesterol (mg/dl)	19	165.1±36.03	168.1±38.0		0,481	18	167.5±39.01	178.0±50.08		0.190	0,719	0.405
Triglycerides (mg/dl)	19	148.2±123.2	190.3±215.4		0,181	18	152.2±103.3	150.2±74.92		0.902	0.962	0.474
LDL (mg/dl)	19	87.73±43.89	86.21±37.59		0,753	18	92.05±39.77	107.0±37.95		0.221	0.494	0.102
HDL (mg/dl)	19	41.31 ±15.49	41.84±14.14		0,784	18	39.66±9.03	41.11±9.18		0.430	0.486	0.775
VLDL (mg/dl)	19	20.25±13.95	27.49 ±18.54		0,062	18	24.96±13.28	29.65±14.50		0.256	0.310	0.708
TSH (standardized data)	18	-0.05±0.96	0.045±1.05		0,679	19	0.10±1.06	-0.156±0.90		0.196	0.694	0.948
T3 (standardized data)	17	-0.46±1.10	0.356±1.23		0,059	19	0.34±0.64	-0.23±0.77		0.010*	0.002*	0.142
T4 (standardized data)	18	-0.00±0.85	0.22±1.47		0,611	19	0.07±1.22	-0.22±0.27		0.250	0.875	0.211
C-reactive protein (CRP) (mEq/L)	19	10.91±13.36	7.58±4.96		0,208	16	18.65±15.72	16.79±19.02		0.720	0.143	0.035*
IL-6 (pg/ml)	18	14.97±20.27	4.15±5.71		0,044*	17	26.98±25.38	7.36±10.89		0.006*	0.159	0.136
MDA (µmol/L)	18	2.99±0.57	3.02±0.54		0.823	18	3.21±0.59	2.872±90.79		0.189	0.704	0,715

SAE=sedimentoscopy of abnormal elements; X^2=Pearson's chi-square test, *p<0.05 and **p<0.01; 95% and 99%. Variation set: Student's paired t-test, (average and standard deviation); independent sample t-test=average (minimum and maximum) or Wilcoxon test. Bold indicates *p<0.05; **p<0.01 and confidence interval of 95%. MCV=mean corpuscular volume; MCH=mean corpuscular hemoglobin; MCHC=mean corpuscular hemoglobin concentration; RDW= red cell distribution width; APTT=activated partial thromboplastin time); INR=international normalized ratio; SD=standard deviation.

the bone marrow, as evidenced by improved Ht and Hb values in the EG compared to the CG in hematological tests. In this way, after 12 months of EG intervention, the practice of WB resulted in a positive Ht and Hb outcome[11].

There was an increase in time in the EG in the APTT, a laboratory test that analyses the effectiveness of the intrinsic route to measure the time of fibrin clot formation[12], due to stimulation by prolonged PE, which leads to the improvement of muscle responsiveness to trauma. In the CG, there was an increase in the APTT and platelets at baseline, most likely due to the existing UTI with hematuria issues due to recurrent infections[11,12].

Participants with anemia diagnosed by the Hb, MCH, and MCHC values, dehydration, infection, and coagulation markers, as well as platelet and APTT alterations, had chronic inflammatory and/or infectious processes reported in the baseline clinic[11]. The variable creatinine improved with an increase in the EG, which can be attributed to the care provided and WB that improved kidney function[13]. There is no worldwide consensus estimating kidney function in PWD-M, although they stated that there are limitations as simple approaches based on serum creatinine concentration and glomerular filtration rate generally overestimate creatinine clearance[14]. A 24-h urine collection has been recommended for the monitoring of kidney function in patients with SCI. They also claimed that the serum creatinine level is not sensible on precocious detection of kidney function in SCI patients[15].

$HbA1_C$ was reduced in both EG and CG, but with a greater reduction in the EG, which can be attributed to the practice of PE and multidisciplinary monitoring in both arms of the study[16,17]. In the practice of PE, there is a decrease in % $HbA1_C$ through the mechanism of glucose uptake by skeletal muscle cells through GLUT-4 receptors, as well as by providing cardiometabolic fitness by WB practitioners[18].

IL-6 is an important inflammatory mediator in kidney and inflammatory diseases and was found to be elevated in plasma after the practice of acute PA of high intensity[19]. There was a reduction of intragroup values on pre- and post-interventions on EG and CG. However, no improvement was achieved on intergroup after 12 months of intervention of WB, with both values being above normative parameters of IL-6 according to the normative parameters of PWD-M[19-21].

C-reactive protein is an acute-phase biomarker with low specificity and was the only one biomarker in the intergroup that showed improvement after the WB intervention. Conversely, it was attenuated in the intergroup comparison at post-intervention of the WB intervention. The practice of PE for more than 6 weeks of intervention[20], as well as associated health care contributed positively with a better prognostic adaptation of the anti-inflammatory response and lower UTI rates in PWD[21,22].

Compared with our results, a few PWD studies find difficulty in equalizing participants at baseline and in accessing and transporting participants. Several changes such as locomotion, collection error by PWD-M[23], a lack of hygiene, difficulty in raising awareness on non-reuse of probes on self-catheterism, and insufficient places for the collection were some of the limitations of this study.

CONCLUSIONS

The *follow-up* showed that WB practice reduced UTI as well as improved the prognosis of inflammatory biomarkers in PWD-M. As a result, further training on current recommendations/consensus on the particular management of UTI in people with PWD-M is required. Furthermore, due to the scarcity of evidence-based knowledge, more well-designed research is urgently required.

AUTHORS' CONTRIBUTIONS

RNC: Data curation, Writing – original draft. **ACSS:** Investigation, Visualization. **RASR:** Software, Validation. **ACBN:** Investigation, Data curation, Visualization. **SOB:** Writing – review & editing. **BRMA:** Investigation, Visualization. **CAF:** Investigation, Visualization. **AAZZ:** Investigation, Visualization. **KA:** Writing – review & editing. **RGO:** Conceptualization, Funding acquisition, Methodology, Project administration, Software, Supervision.

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ORIGINAL ARTICLE

https://doi.org/10.1590/1806-9282.20210924

Cochlear implant complications in a low-income area of Brazil

Gabriel Reis Castro[1*], Hágada Cristine Coelho Santiago[2], Rosauro Rodrigues de Aguiar[2], Ana Beatriz Gouveia de Almeida[3], Leonardo Santana Ramos Oliveira[3], Ricardo Queiroz Gurgel[1]

SUMMARY

OBJECTIVE: The primary objective was to analyze and report on the complications that occurred in the cochlear implant surgeries performed at a large philanthropic teaching hospital located in a low-income area of Brazil.

METHODS: A historical cohort study that analyzed surgical records of 432 patients of all age groups and both genders who received unilateral cochlear implant in a tertiary referral center that serves only Brazil's Public Health Care System patients, from February 2009 to December 2017.

RESULTS: A total of 67 (15.5%) complications occurred in the cochlear implant surgeries, with 21 (5.4%) major complications. Minor complications occurred in 50 (12%) cases. The most frequent major complication was receiver-stimulator displacement (four cases). There were three cases of hardware failure. Only one case of meningitis and one case of facial nerve paralysis (grade VI in House-Brackmann scale) were found. Six patients needed to be explanted due to a major complication. The relative risk of major complications in the population aged 60 years and older was 4.41 (1.53–12.72; 95% confidence interval [CI]).

CONCLUSIONS: Elderly patients suffered more complications than younger patients. receiver-stimulator displacement and dizziness were the most frequent complications (major and minor, respectively). The overall complication rates were comparable to those in the literature. Age as an isolated risk factor for complications in cochlear implant surgery is a path to be explored in future observations.

KEYWORDS: Otolaryngology. Cochlear implants. Postoperative complications.

INTRODUCTION

Hearing loss is a frequent public health problem worldwide, and approximately 350,000 Brazilians suffer from severe to profound hearing loss[1]. In such cases, rehabilitation may only be possible with the help of cochlear implant technology.

Cochlear implant surgery can be life-changing for patients, facilitating huge improvements in their social lives, as well as providing academic, professional, and economic gain[1]. However, the procedure is not always complication free and a constant self-assessment of outcome and any complications is necessary.

Complications in cochlear implant surgery are classified into "major" or "minor." Major complications include meningitis, magnet displacement, device failure, skin flap necrosis, implant extrusion, and others. In contrast, minor complications are wound infection that respond to local therapy, dizziness, late and transient facial paralysis, and facial nerve stimulation[2,3].

The overall complication rates in cochlear implant surgeries vary significantly (6–36%) in the literature[4]. The occurrence of surgery-related complications has reduced over the decades as technology and surgery techniques have improved[5]. Fixation techniques have been developed, alongside minimal incisions. The manufacture process of cochlear implant has also been improved to prevent device failure and biocompatibility of the devices has been enhanced. All these increments have promoted a decrease in the incidence rate of postoperative complications[3,5,6].

Brazil's Public Health Care System — also called SUS — guarantees access to a comprehensive audiological rehabilitation program to all citizens since 2005. Indeed, SUS also provides services in the audiological rehabilitation field. Diagnostic and therapeutic procedures, including newborn hearing screening, audiological tests, hearing aids, otolaryngologist appointments, stapes surgeries, and bone implant and cochlear implants, are all covered by Brazil's universal health care system[7].

This study was conducted in a large philanthropic teaching hospital located in a low-income area of Brazil that serves only SUS patients. The primary objective was to analyze and report on the complications that occurred in the cochlear implant surgeries performed at the institution.

[1]Universidade Federal de Sergipe, Programa de Pós-graduação em Gestão, Informação e Tecnologia em pesquisa – Aracaju (SE), Brazil.
[2]Clínica de Otorrinolaringologia do Canela – Salvador (BA), Brazil.
[3]Escola Bahiana de Medicina e Saúde Pública – Salvador (BA), Brazil.
*Corresponding author: gabrielreiscastro@gmail.com
Conflicts of interest: the authors declare there is no conflicts of interest. Funding: none.
Received on December 24, 2021. Accepted on February 01, 2022.

METHODS

A historical cohort study was conducted at the otolaryngology department of a tertiary referral center situated in the Northeast Brazil, where approximately 80 cochlear implant surgeries are performed each year. There are about 15 million inhabitants in the region served by the institution, and the average income of its population is approximately U$D157 per month (Dollar price against Real in October 2020)[8].

The medical records of all patients undergoing cochlear implant surgery were reviewed for any occurrences of complications. The study was approved by the Research Ethics Committee of the Institution (CAAE: 82817318.5.0000.0047) and included patients of all age groups and genders undergoing cochlear implant surgery from February 2009 to December 2017. As a retrospective study, no informed consent form was necessary.

The records of each postoperative review appointment were evaluated for complications, conducted treatments, and outcomes. Data were gathered via electronic form and exported to an Excel spreadsheet. Categorical variables were reported as means of absolute frequency and relative percentage and continuous or discrete variables were reported as median and interquartile range. Fisher's exact hypothesis tests, Pearson's chi-square (association between categorical variables), Shapiro-Wilk (adherence to normal distribution), and Mann-Whitney (differences between medians of continuous/discrete variables not adhering to normal distribution) tests were used. Gross relative risks and their respective 95% confidence intervals were estimated. The final level of significance adopted was 5%, and the software used for analysis was the R Core Team 2020.

RESULTS

The study included 432 patients. All patients received unilateral cochlear implant. There was no statistical difference in complications with respect to gender. In total, 67 (15.5%) complications occurred in the cochlear implant surgeries, with 21 (5.4%) major complications. Minor complications occurred in 50 (12%) cases (Figure 1, Table 1).

The most frequent major complication was receiver-stimulator (RS) displacement (four cases). There were three cases of hardware failure. Only one case of meningitis and one of facial nerve paralysis (grade VI in House-Brackmann Scale) were found.

Six patients needed to be explanted due to major complication. Nine patients who had major complications underwent treatments that resolved the issue. In one case, the patient lost follow-up and four of the patients were still undergoing medical evaluation and their treatment was yet undefined and in progress (Table 2).

Complications were more frequent after 1 year from the procedure. The patients' age was statistically related to the occurrence of complications (Table 3). The relative risk of major

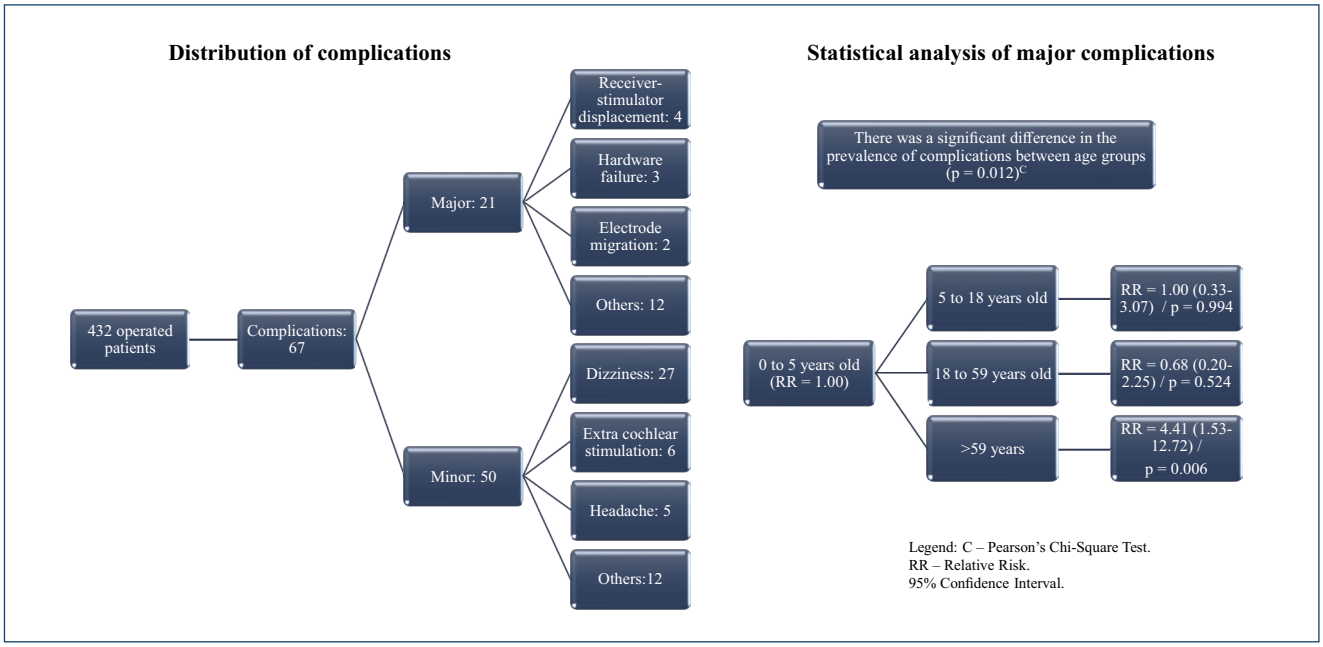

Figure 1. Cochlear implant complications and statistical analysis of major complications.

Table 1. Demographic data and occurrence of complications.

	n	%
Age		
Age group, year		
<2	20	4.6
2–5	132	30.6
5–18	109	25.2
18–59	145	33.6
>59	26	6.0
Gender		
Female	224	51.9
Male	208	48.1
Implant brand		
Advanced bionics (USA)	196	45.4
Med-el (Austria)	211	48.8
Cochlear (Australia)	18	4.2
Oticon (Denmark)	7	1.6
Complication		
Yes	67	15.5
No	365	84.5
MAJOR complication		
Yes	21	5.4
No	365	94.6
MINOR complication		
Yes	50	12.0
No	365	88.0
Time elapsed from surgery to complication		
<30 days	17	25.4
1–3 months	5	7.5
3–12 months	15	22.4
1–5 years	27	40.3
>5 years	3	4.5

n – absolute frequency. % – relative absolute frequency.

complications in the population aged 60 years and older was 4.41 (1.53–12.72; 95%CI), with p-value of 0.006.

Regarding minor complications, 27 patients complained of postoperative dizziness, and 4 patients showed signs of surgical site infection that were resolved with clinical treatment. Adults had more minor complications than children, with a relative risk of 2.43 (18–59 years old) and 3.32 for the group aged 59 years and older (p-value of 0.009 for both groups).

DISCUSSION

All surgeries were performed or supervised by three different attending otologists, using the same surgical technique (mastoidectomy). Despite all particularities, the complication rates were comparable to those reported in the literature, including other teaching hospitals[4,9-11].

Receiver-stimulator displacement occurred in four cases and patients needed procedures to reposition the implant. No head trauma or magnetic resonance imaging (MRI)-induced movement was reported in those cases, which are common in cases of RS displacement[12,13]. It is possible that the migration occurred due to frequently repeated small forces applied to the implanted device[14]. In our surgical technique, a well is drilled into the bone to house the RS, combined with a tight periosteal pocket. No sutures are usually made[15,16].

One patient had three episodes of meningitis and had to be explanted (0.23%). Our patients are routinely vaccinated against *Pneumococci*, *Haemophilus influenzae*, *Neisseria meningitidis,* and *influenza virus*[17]. After 2002, the relation between meningitis and cochlear implants was widely studied by cochlear implant companies and U.S. regulation agencies. It was found that one kind of cochlear implant positioner commonly used was related to a higher risk of meningitis, and, furthermore, that deaf children had also a higher risk than normal hearing individuals[18].

Only a single case of facial paralysis occurred: the first patient operated in our program. No other case of permanent facial paralysis occurred. A facial nerve monitor is routinely used in the surgeries[17].

Six patients needed to be explanted. The number of contralateral implants performed in those cases was not gathered. The occurrence rate of major complications remained under 9% each year during the analyzed period. The highest complication per year rate was seen in 2012 (8.6%), whereas the lowest occurred in 2011 (2.1%). The occurrence rate of minor complications fluctuated from 2.4% in 2015 to 23.3% in 2017. The overall rate for major complications was 5.2%.

Elderly adults suffered significantly more from major complications when compared to other age groups in our study. However, it is not clear whether this occurred due to the presence of comorbidities or if age is a significant risk factor by itself. It is a path to be explored in future observations. Wilkerson et al. reported that no specific comorbidity significantly contributed to the general complication rates in either the older or younger patient population[19].

Surgical site infection was reported in 4 (0.9%) cases and none of them needed surgical treatment. Infection rates range

Table 2. Major complications by patient, their treatment, and outcome.

Age (year)	Major complication	Time from surgery to complication	Treatment	Outcome
3	Cholesteatoma	Over 5 years	Mastoidectomy	Complication resolved
57	Cholesteatoma	Over 5 years	On schedule for re-operation	In progress
12	Electrode array extrusion	9 months	Re-operation	Complication resolved
73	Electrode migration	26 months	Patient lost follow up	Patient lost follow-up
7	Electrode migration	7 months	Re-operation	Complication resolved
80	Electrode misplacement	4 months	Re-operation	Complication resolved
3	Electrode misplacement	15 months	Re-operation	Complication resolved
60	External ear canal erosion and tympanic membrane perforation	11 months	Tympanoplasty	Complication resolved
67	Facial paralysis	Immediate	Re-operation	Facial paralysis HB VI
6	Hardware failure	36 months	Internal component replacement	Complication resolved
4	Hardware failure after head injury	6 months	Internal component replacement	Complication resolved
3	Hardware failure after head injury and poor adaptation	30 months	Explant	Explant
16	Headache	<30 days	Explant	Explant
2	Receiver-stimulator extrusion	16 months	Explant and contralateral implant	Explant
65	Receiver-stimulator displacement	48 months	On schedule for re-operation	In progress
42	Receiver-stimulator displacement	22 months	On schedule for re-operation	In progress
3	Receiver-stimulator displacement	24 months	On schedule for re-operation	In progress
33	Receiver-stimulator displacement	27 months	Re-operation	Complication resolved
5	Meningitis	51 months	Explant	Explant
30	Poor outcome	25 months	Explant	Explant
3	Skin infection after insect sting	27 months	Explant and contralateral implant	Explant

Table 3. Statistical analysis of major complications.

Major complications	Yes	No	p-value	RR (95%CI)	p-value
Age, *Median (IQR)*	12.2 (3.9–58.7)	7 (3.8–32.3)	0.166 [W]		
Age group, year, ***n (%)***					
<2	0 (0) [a,b]	18 (100)	0.012 [C]		
2–5	7 (5.6) [b]	117 (94.4)		1	
5–18	5 (5) [a,b]	96 (95)		1.00 (0.33–3.07)	0.994
18–59	4 (3.3) [b]	116 (96.7)		0.68 (0.20–2.25)	0.524
>59	5 (21.7) [a]	18 (78.3)		4.41 (1.53–12.72)	0.006
Gender, *n (%)*					
Female	12 (6)	187 (94)	0.658 [F]		
Male	9 (4.8)	178 (95.2)			

n – absolute frequency. % – relative absolute frequency. IQR – interquartile range. W – Mann-Whitney test. C – Pearson's chi-square test. F – Fisher's exact test. [a,b] Different subgroups at the 5% level for the Z-test for proportions with Bonferroni correction. RR – relative risk. 95%CI –95% confidence interval.

between 1% and 13% in the literature[20]. Surgical infection rates were significantly higher in the past. This recent reduction is partly due to the evolution in surgical techniques (smaller incisions, for example) and the development of more biocompatible materials used for prostheses[21]. In our surgeries, the surgical wound is closed with absorbable sutures. Ceftriaxone is

used just before the beginning of the surgery and kept for 24 h. Patients are usually discharged on the second day with a sterile dressing and with pain/nausea drugs prescription. The first postoperative appointment is typically 5 days after discharge, when the dressing is removed.

Many patients complained about dizziness (6.25%) and, indeed, Hänsel et al. showed in a meta-analysis that 9.3% of the patients on average suffer from postoperative vertigo after cochlear implant surgery[22].

Cochlear implants are a costly (although cost-effective) rehabilitation tool. Maintaining a publicly funded cochlear implant program in a teaching hospital of a developing country is challenging. Despite all of its qualities, SUS is not a perfect system. Brazil is a huge country with the fifth largest population in the world and profound socioeconomic disparities. Our patients frequently find it difficult to afford transportation and speech therapy, and medical appointments were often missed. A universal health care system is very expensive and, although SUS resources are theoretically guaranteed by the Brazilian Constitution, an imbalance is often seen between the provided funding and the need for resources. In some places, there are extremely long waiting times for treatment and poor housing, for example. Insufficient inputs and low and delayed wages are not uncommon as well.

CONCLUSIONS

Elderly patients suffered significantly more from major complications when compared to other age groups. RS displacement and dizziness were the most frequent complications (major and minor, respectively). The overall complication rates were comparable to those in the literature. Age as an isolated risk factor for complications in cochlear implant surgery is a path to be explored in future observations.

Limitations and strengths

A limitation of the study is that a comparative assessment was not performed between other variables, such as the presence of comorbidities. In the study, specific populations (e.g., patients with Ménière's syndrome, otosclerosis, and chronic otitis media) were part of the whole sample. The impact of those conditions in the occurrence of complications in our analysis could not be assessed.

A strength of the study is its sample size. The total number of patients included allowed the authors to perform a solid statistical analysis, which lead to elaboration of hypothesis to be explored in the future, as stated in the "Conclusion" section.

Also, the study pictured the cochlear implant complications rates in a regional reference center located in a low-income area, which can serve as a parameter for other surveys with similar settings in the future.

AUTHORS' CONTRIBUTIONS

GC: Conceptualization, Data curation, Formal Analysis, Investigation, Methodology, Project administration, Writing –original draft, and Writing –review & editing. **HS**: Conceptualization, Data curation, Formal Analysis, Methodology, and Writing – review & editing. **RA**: Conceptualization, Data curation, Formal Analysis, Methodology, and Writing – review & editing. **ABGA**: Data curation, Formal Analysis, Investigation, Writing – original draft, and Writing – review & editing. **LSRO**: Data curation, Formal Analysis, Investigation, Writing – original draft, and Writing – review & editing. **RG**: Data curation, Formal Analysis, Supervision, and Writing – review & editing.

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ORIGINAL ARTICLE

https://doi.org/10.1590/1806-9282.20211072

Obesity effects on sleep quality with anthropometric and metabolic changes

Müjgan Kaya Tuna[1*], Arzu Cennet Işık[2], Özlem Çakır Madenci[3], Kerem Sami Kaya[4]

SUMMARY

OBJECTIVE: Obesity is one of the etiological factors of sleep disorders (e.g., obstructive sleep apnea and restless leg syndrome). The aim of this study was to determine the effect of obesity on sleep quality by using the Pittsburgh Quality İndex and Berlin Question are and evaluate the association of sleep with anthropometric and metabolic parameters.

METHODS: A total of 76 patients (41 females and 35 males) between the ages of 18 and 70 years with a body mass index >30 kg/m^2 were included in this study. Homeostatic model assessment-insulin resistance, hemoglobin A1c, alanine aminotransferase, aspartate transaminase, total cholesterol, low-density lipoprotein, triglyceride, high-density lipoprotein, and thyroid-stimulating hormone levels were analyzed. Sleep quality was evaluated with the Pittsburgh Sleep Quality Index, Berlin Questionnaire, and the Restless Leg Syndrome Questionnaire.

RESULTS: A significant correlation was observed between Pittsburgh sleep quality index and body mass index, neck circumference, body fat index, muscle mass, hip and waist circumference, hemoglobin A1c, and homeostatic model assessment-insulin resistance (ps<0.005). The Pittsburgh sleep quality index median (2.5–97.5 percentile) value was 8 (2–18.6) in the patient group and 3.5 (0.1–7.9) in the control group (p<0.0001). Body mass index was found to be the predictor on Pittsburgh sleep quality index (R^2=0.162, F=3.726, analysis of variance p=0.008). Notably, 88% (67) and 95% (57) of the poor sleepers were found to be at high risk for obstructive sleep apnea according to Berlin Questionnaire and Pittsburgh Sleep Quality Index, respectively. Also, the frequency of restless leg syndrome was 45% in obese individuals.

CONCLUSIONS: We observed a significant correlation between Pittsburgh sleep quality index and the anthropometric and metabolic parameters. Also, the frequency of obstructive sleep apnea and restless leg syndrome was 88% and 45%, respectively, in obese individuals.

KEYWORDS: Obesity. Obstructive sleep apnea. Restless leg syndrome. Sleep quality. Sleep screening test. Sleep disturbance.

INTRODUCTION

Sleep disorders are common in modern society, and the prevalence of chronic insomnia varies between 6 and 76.3% depending on diagnostic and screening methods used[1]. The prevalence of obesity and sleep disorders is increasing worldwide[2].

The impact of sleep quality on the development of metabolic syndrome was evaluated in several studies[3,4]. Sleep quality affects energy balance through appetite, hypothalamic-pituitary-adrenal axis activity, gut-peptide concentrations, and substrate oxidation[5]. Poor sleep quality enhances positive energy balance through endocrine changes, such as lower leptin and higher ghrelin concentrations, which result in excess food intake and weight gain[6]. Obese patients experience sleeplessness more likely with a reciprocal relationship whereby poor sleep leads to weight gain, which may, in turn, induce more sleep impairment[7,8].

Obstructive sleep apnea (OSA) and restless leg syndrome (RLS) are common sleep disturbances with higher prevalence in obese individuals[2,9]. In OSA, the activity of respiratory tract upper muscle is decreased because of the fat deposits that cause airway narrowing and finally result in hypoxic episodes[9,10]. RLS is composed of sensory symptoms that are accompanied by an irresistible urge to move legs[2,9,11]. The prevalence of RLS in adults was reported as 4–29%[2,12].

To evaluate sleep disorders, the Stanford Sleepiness Scale, Epworth Sleepiness Scale, Pittsburgh Sleep Quality Index (PSQI), Stop-Bang test, Berlin Questionnaire (BQ), and Restless Leg Syndrome (RLS) Questionnaire are used[13,14]. The PSQI is an easy index that provides a standardized measure of sleep quality and discriminates "good" and "poor" sleepers[14].

The aim of this study was to determine the effect of obesity on sleep and the association of sleep with anthropometric and metabolic parameters. The secondary objective was to evaluate the frequency of OSA and RLS in obese individuals.

[1]Lutfi Kırdar Kartal City Hospital, Obesity Department – Istanbul, Turkey.
[2]Lutfi Kırdar Kartal City Hospital, Internal Medicine Department – Istanbul, Turkey.
[3]Kırdar Kartal City Hospital, Biochemistry Department – Istanbul, Turkey.
[4]Sisli Hamidiye Etfal Training and Research Hospital, Otolaryngology Department – Istanbul, Turkey.
*Corresponding author: mjgn-tn@hotmail.com
Conflicts of interest: the authors declare there is no conflicts of interest. Funding: none.
Received on February 09, 2022. Accepted on February 10, 2022.

METHODS

The study was approved by the Ethics Committee of Dr. Lutfi Kırdar Kartal City Hospital (decision number: 2020/514/182/20, dated: July 27, 2020).

The medium effect size (effect size=0.3) was predicted to be statistically significant, and the alpha significance level (0.05) was calculated the sample size as 68 with 80% power. A total of 76 patients (41 females and 35 males; body mass index [BMI] >30 kg/m^2) between the ages of 18 and 70 years who were followed up in the obesity outpatient clinic between July 2020 and February 2021 participated in this study. Notably, 27 volunteers with a BMI <30 kg/m^2 were determined as the control group. Participants were informed about the study and a written consent form was obtained.

Patients using medication for sleep disorders, malignancies, and severe psychiatric disorders were not included in the study.

Body mass index; waist, hip, and neck circumference; soft lean mass (SLM); and percent body fat (PBF) were measured. BMI was calculated as follows: body weight/height^2 (in kg/m^2). Anthropometric measurements were done with Tanita MC-580 body composition analysis (TANITA, MC-580, Japan). Venous blood samples were taken after 8 h of fasting, and glucose, total cholesterol, low-density lipoprotein (LDL), triglyceride, and high-density lipoprotein (HDL) measurements were analyzed with AU 5800 (Beckman Coulter, Brea, CA, USA). Insulin and thyroid-stimulating hormone (TSH) values were analyzed with Unicel DxI 800 (Beckman Coulter). Homeostatic model assessment-insulin resistance (HOMA-IR) was calculated as follows: fasting blood glucose (mg/dL) × insulin (IU/mL) / 405. Finally, PSQI, BQ, and RLS Questionnaire were performed to evaluate sleep quality.

Pittsburgh sleep quality index

Pittsburgh Sleep Quality Index consists of a 19-item questionnaire. Using this index, subjective sleep quality, sleep latency, sleep duration, sleep efficiency, daytime dysfunction, use of medications to sleep, and the presence of sleep disorders are evaluated. Individual with a total PSQI score >5 was considered poor sleeper[15].

Berlin questionnaire

Berlin Questionnaire consists of 11 items with three categories. The first category consists of questions related to snoring and breathing pause during sleep, the second category consists of questions related to daytime sleepiness, fatigue, and drowsiness during driving, and the third category consists of questions about obesity and hypertension. A positive answer to two or more questions from these three categories is considered to be a high risk for OSA[16].

Restless leg syndrome questionnaire

The diagnosis and severity of RLS are determined according to the 2012 IRLSSG criteria[17], including the feeling of restlessness that make ones to move their legs, relaxation when moving, worsening of symptoms during the resting and inactive period, and an increase in the symptoms in the evening and at night. Patients who met these four criteria are considered to be at risk for RLS[7,18].

Statistical analysis

Statistical analysis was performed using the SPSS program (Statistical Package for Social Science, version 11.7; Chicago, IL, USA). The Kolmogorov-Smirnov test was used to determine the distribution of the parameters, and data were expressed as median (2.5–97.5 percentile). The comparison of the group medians was done with the Mann-Whitney U test. Correlations between clinical and anthropometric parameters and the PSQI were determined by Spearman's correlation analysis. Multiple regression analyses were performed, considering PSQI as a dependent variable and BMI, HbA1c, neck circumference, and HOMA-IR as independent variables. Statistical significance for all tests was set at $p<0.05$.

RESULTS

The median (2.5–97.5 percentile) age and BMI values of the patients were 41 (19–69 years) and 40 (30–52) kg/ m^2, respectively.

A significant correlation was observed between PSQI and BMI, body fat index, muscle mass, hip, waist, and neck circumference, HbA1c, and HOMA-IR (Table 1). Poor sleep quality (PSQI>5) was observed in 79% (60) of the obese group and 36% (8) of the control group. Multiple regression analyses showed BMI as the predictor of PSQI (R^2=0.162, F=3.726, analysis of variance [ANOVA] p=0.008) (Table 2). Among the Pittsburgh components, a significant correlation was observed between sleep quality, sleep latency, sleep duration, sleep efficiency, sleep disturbance, and BMI. A significant difference was found between groups with and without RLS in terms of sleep latency and drug use (p=0.044, p=0.019, respectively) (Table 3).

According to BQ, 88% (67) of the patients were found to be at high risk for OSA. Out of 16 patients whose sleep quality was not impaired according to the PSQI, 12 patients were found to be at high risk for OSA by BQ. Notably, 95% (57) of the poor sleepers defined by PSQI also had high risk for OSA and 45% (34) of them had risk for RLS.

Table 1. Partial correlation of Pittsburgh sleep quality index with anthropometric and clinical parameters.

Parameter	r	p
BMI (kg/m²)	0.416	<0.0001
Neck circumference (cm)	0.223	*0.023
Body fat mass %	0.326	*0.009
Waist circumference (cm)	0.339	*0.005
SLM (cm)	0.210	*0.032
Hip circumference (cm)	0.387	*0.001
HOMA-IR	0.275	*0.011
HbA1c (%)	0.214	*0.030
TSH (IU/L)	0.058	0.559
LDL-cholesterol (mg/dL)	0.157	0.113
Triglyceride (mg/dL)	0.157	0.115

*p<0.05 is accepted as significant.

DISCUSSION

Obesity and sleeping disorders may be related to prevalent biological mechanisms, which encourage researchers to investigate the biological basis of these associations[9,12].

Poor sleep quality (PSQI>5) was observed in 79% (60) of the obese group and 36% (8) of the control group. There was a significant correlation between PSQI and BMI, body fat index, muscle mass, hip, waist, and neck circumference, HbA1c, and HOMA-IR values (p<0.005). BMI was found to be the predictor on PSQI (R^2=0.162, F=3.726, ANOVA p=0.008). A significant correlation was observed between BMI and sleep quality, sleep latency, sleep duration, sleep efficiency, and sleep disorder (p<0.005).

Pearson et al. stated that there is an association between sleep problems and comorbid diseases like hypertension, congestive heart failure, anxiety or depression, and obesity, but not with diabetes[19]. Bidulescu et al. reported that cognitive function was impaired with chronic sleep restriction, which also has an impact

Table 2. Multiple regression analyses with Pittsburgh sleep quality index as dependent variable and body mass index, hemoglobin A1c, neck circumference, and homeostatic model assessment-insulin resistance as independent variables

Variables	Unstandardized coefficients		Standardized coefficients	t	p
	B	Std. error	β		
Constant	-1.560	3.539		-0.441	0.661
BMI (kg/m²)	0.089	0.042	0.252	2.149	0.035
Hba1c (%)	0.522	0.353	0.162	1.478	0.143
Neck circumference (cm)	0.057	0.088	0.074	0.648	0.519
HOMA-IR	0.021	0.019	0.115	1.089	0.280

R^2=0.162, F=3.726, ANOVA p=0.008.

Table 3. Comparison of Pittsburgh sleep quality index components in patients with and without restless leg syndrome.

	RLS N=34 (Mean±SD)	Non-RLS N=36 (Mean±SD)	p
Sleep quality	1.500±0.915	1.342±0.802	0.466
Sleep latency	2.843±1.985	1.971±1.484	*0.044
Sleep duration	1.312±0.895	1.228±0.877	0.699
Sleep efficiency	0.500±0.803	0.514±0.950	0.947
Sleep disorder	1.593±0.665	1.400±0.650	0.232
Use of medication	0.500±0.983	0.085±0.284	*0.019
Daytime dysfunction	1.937±2.213	1.371±1.554	0.227
Total score	10.294±4.994	7.833±2.922	*0.013

*p<0.05 is accepted as significant.

on cardiovascular and metabolic disorders[8]. Metabolic disorders may be the result of sleep deprivation, which can also be the reason for increased inflammation and elevated sympathetic tone. Besides, the upward trend of ghrelin and lower trend of leptin result in the subsequent increase of hunger and appetite[20].

Pinto et al. revealed that bariatric surgery caused a significant improvement in the PSQI and BQ, with PSQI decreasing from 6.4±4.7 to 4.1±2.8 and the risk of OSA decreasing from 68.3 to 5% after operation[7].

Obstructive sleep apnea has been observed in 58% of obese individuals and polysomnography is the gold-standard method in diagnosis[21]. Marta et al. defined the sensitivity, specificity, positive predictive value, and negative predictive value of the BQ for OSA as 87.2%, 11.8%, 73.2%, and 25%, respectively[10]. They concluded that BQ was a valuable screening test and patients with high risk for OSA should be directed to polysomnography[10]. In our study, 88% (67) of the obese patients were found to be at high risk for OSA. Likewise, 95% (57) of the poor sleepers had a high risk for OSA.

Several studies found a significant association between obesity and RLS[2,22-24]. In a cross-sectional study with 1,803 adults; an increase of 5 kg/m^2 in BMI was found to be associated with a 31% increased likelihood of having RLS[25]. In our study, 45% (34) of the obese patients also had RLS and 40% (23) of the patients with RLS also had OSA. In addition, patients with RLS had shorter sleep latency and showed more drug use.

Pittsburgh Sleep Quality Index is a valid tool for both clinicians and researchers, but it was not developed for a specific population and might function differently in different populations and settings. Nevertheless, if the sample size is sufficiently large, it will provide a sufficient estimate for sleep quality in the given population[14].

In our study, we defined OSA according to BQ and did not evaluate the polysomnography results of our patients, which may be the limitation of our study.

CONCLUSIONS

We observed a significant correlation between PSQI and the anthropometric and metabolic parameters in obese patients and BMI was the predictor on PSQI. The frequency of OSA and RLS was 88% and 45%, respectively, in obese individuals.

EHICAL APPROVAL

The study was carried at Dr. Lutfi Kırdar Kartal City Hospital in Istanbul.

AUTHORS' CONTRIBUTIONS

MKT: Conceptualization, Data curation, Formal Analysis, Investigation, Resources, Writing – original draft, Writing – review & editing. **ACI**: Project administration. **ÖÇM**: Funding acquisition, Methodology, Supervision, Validation, Writing – review & editing. **KSK**: Software, Visualization, Writing – review & editing.

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ORIGINAL ARTICLE

https://doi.org/10.1590/1806-9282.20211097

A novel predictor in patients with coronary chronic total occlusion: systemic immune-inflammation index: a single-center cross-sectional study

Muhammed Demir[1]*, Mehmet Özbek[1]

SUMMARY

OBJECTIVE: Severe inflammation is reportedly associated with subsequent cardiovascular events, including in patients with coronary artery disease. This study aimed to examine the prognostic value of systemic immune-inflammation index and determine mortality and clinical outcomes in patients with chronic coronary total occlusion.

METHODS: Our study evaluated 366 consecutive coronary total occlusion patients. The clinical end points were all-cause mortality and major adverse cardiovascular events, which include target vessel revascularization, myocardial infarction, and cerebrovascular events during 105 months follow-up.

RESULTS: The study findings showed 59 (16.1%) all-cause death, 22 (6%) target vessel revascularization cases, 32 (8.7%) myocardial infarction cases, and 13 (3.6%) cerebrovascular events cases, with a median follow-up of 49 months (26–74). Multivariate logistic regression analysis showed that systemic immune-inflammation index was not associated with target vessel revascularization, myocardial infarction, and cerebrovascular events. Multivariate Cox regression analysis found systemic immune-inflammation index to be associated with all-cause death. Kaplan-Meier analysis showed a lower survival rate and myocardial infarction-free survival time in patients with higher systemic immune-inflammation index scores.

CONCLUSION: Although systemic immune-inflammation index is a preferable tool for the detection of mortality, it failed to give adverse outcomes. Larger multicenter studies are thus warranted to investigate the effect of systemic immune-inflammation index on clinical outcomes.

KEYWORDS: Inflammation. Inflammation mediators. Coronary artery disease. Prognosis. Atherosclerosis.

INTRODUCTION

Coronary chronic total occlusion (CTO) is defined as occlusion of coronary artery with Thrombolysis in Myocardial Infarction (TIMI) grade 0 flow lasting longer than 3 months in the distal segment of the completely occluded vessel due to atherosclerosis[1]. CTO lesions such as fibrocalcific and thrombotic plaques have been reported in approximately one-third of patients undergoing diagnostic coronary angiography[2].

Coronary chronic total occlusion is associated with poor clinical outcomes, such as ischemia, heart failure, and increased risk of death[3-5]. Moreover, prediction of clinical events in CTO, particularly inflammation, has always been a topic of interest.

In the literature, blood markers have been used to investigate potential complications in patients with CTO[6]. However, an easily measurable marker is still needed in practice for the prediction of clinical events. In addition to routinely used scoring systems, some researchers have used hematological markers for predicting future events as well as comorbidities and risk factors in coronary artery disease (CAD)[7-8].

Systemic immune-inflammation index (SII), which is calculated based on peripheral lymphocyte, neutrophil, and platelet counts, is a recently developed index used for concurrent evaluation of immune and inflammatory responses. SII has been reported to predict adverse cardiovascular events (CVEs) in CAD patients[9]. It has been shown to be a marker for predicting clinical events in patients with acute myocardial infarction (MI)[10]. However, the relationship between SII and clinical outcomes in CTO patients remains unclear. The present study aimed to investigate the prognostic significance of SII as a new inflammatory marker and determine its relationship with cardiovascular clinical outcomes in CTO patients.

METHODS

Study design

This was a single-center, retrospective, and cross-sectional study. All-cause mortality was accepted as the primary end point, while target vessel revascularization (TVR), recurrent

[1]Dicle University, School of Medicine, Department of Cardiology – Diyarbakır, Turkey.
*Corresponding author: drmdemirr@gmail.com
Conflicts of interest: the authors declare there is no conflicts of interest. Funding: none.
Received on October 29, 2021. Accepted on February 11, 2022.

myocardial infarction (MI), and cerebrovascular events (CVEs) were considered secondary end points. Demographic and clinical characteristics including age, gender, follow-up period, clinical outcomes, and relevant laboratory values were retrieved from hospital records.

Subjects

Patients who underwent routine angiography for CAD and were incidentally diagnosed with CTO in our clinic between 2011 and 2020 were included in the study. Patients with hematological diseases, systemic inflammatory diseases, malignancies, chronic kidney diseases, chronic liver diseases, heart failure with ejection fraction (EF) <40%, and acute or chronic infections were excluded from the study (Figure 1A). Each patient or their family was informed about the study criteria, both verbal and nonverbal ways. The study protocol was approved by the Local Ethics Committee, and the study was conducted in accordance with the ethical rules for human experimentation stated in the Declaration of Helsinki (2013).

Protocol

Angiograms and clinical data of patients were retrieved from hospital databases. Angiograms were analyzed by three independent operators experienced in angiography.

Outcomes and follow-up

All-cause mortality was defined as any death recorded from the date of enrollment to the date of the last follow-up visit. Time to TVR was defined as the time from the opening of the target vessel to thrombus or restenosis formation in the vessel. Time to MI was defined as the time to the development of the first MI after the CTO procedure. Time to CVE was defined as the time to the first ischemic or hemorrhagic stroke attack after the CTO procedure.

Additional definitions

Chronic kidney disease (CKD) was defined as an estimated glomerular filtration rate (eGFR) of <60 mL/min/1.73 m^2. Hypertension (HT), dyslipidemia, and diabetes mellitus (DM) were defined according to the 10th Revision Codes of the *International Classification of Diseases*.

Blood samples and inflammatory indexes

Blood samples were analyzed using a hematology analyzer (Abbott Cell-Dyn 3700, IL, USA). SII was calculated using the following formula: neutrophil count × platelet count / lymphocyte counts[11].

Statistical analysis

Data were analyzed using SPSS for Windows version 25.0 (IBM Corp., Armonk, NY, USA). The Kolmogorov-Smirnov test was used to assess the normal distribution of continuous variables. Continuous variables were expressed as mean±standard deviation (SD) or median (interquartile range), and categorical variables were expressed as percentages. Multiple groups were compared using one-way analysis of variance (ANOVA) test or Kruskal-Wallis test, and categorical variables were compared using chi-square test or Fisher's exact test as appropriate. Multivariate logistic regression was performed to examine the association between SII and clinical outcomes. The SII values transformed by the natural logarithm were used in the models due to skewed distributions. A $p<0.05$ was considered statistically significant. Cox regression analysis was performed to identify the predictors of all-cause mortality. Clinical outcomes were assessed by the Kaplan-Meier method.

RESULTS

A total of 366 patients (69.4% male) were enrolled in the study, with a mean age of 62.26±11.09 years. Median follow-up was 49 (26–74) months. Patients were divided into three tertiles based on the SII levels as follows: 340.84±84.65 in tertile 1 (lower), 620.19±86.44 in tertile 2 (middle), and 1314±748.94 in tertile 3 (upper). Baseline clinical characteristics, outcomes, and laboratory findings of the patients according to SII tertiles are shown in Table 1. Patients in the upper SII group were older and had a higher prevalence of DM and all-cause mortality (Table 1). The upper and middle SII values were positively associated with higher admission white blood cell count, platelets levels, and neutrophils levels and were negatively associated with lower admission hemoglobin, lymphocytes, serum albumin, and triglycerides levels (Table 1). The prevalence of all-cause mortality was significantly higher among patients in the upper SII group when compared to patients in the lower SII group (Figure 1B).

Ln SII and Ln WBC levels were not associated with the resulted clinical outcomes (Table 1). In the Cox regression analysis, SII, age, and albumin level were found to be predictors of mortality (Table 1). The upper SII group had a higher incidence of all-cause mortality and MI, and significant differences between Kaplan-Meier curves were measured using the log-rank test (Figure 2).

DISCUSSION

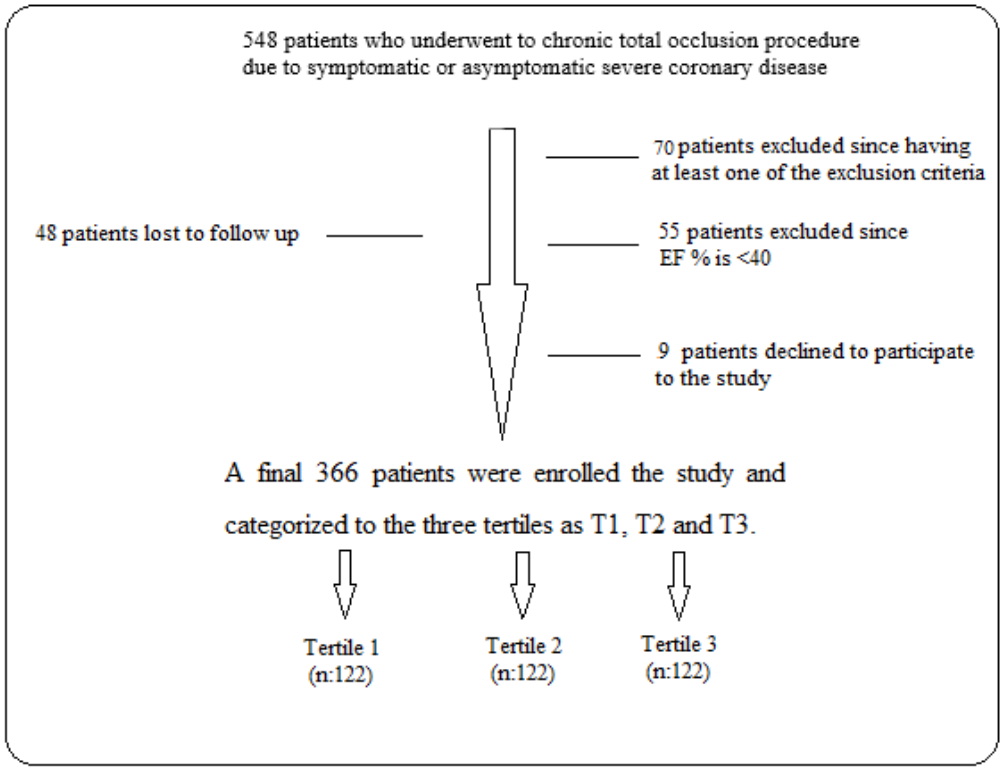
This cohort study was performed in order to determine if SII is independently associated with risks for all-cause death, TVR,

Table 1. Clinical characteristics and outcomes of the patients.

	Total (N=366)	Tertile 1 (N=122)	Tertile 2 (N=122)	Tertile 3 (N=122)	p
Age	62.26±11.09	60.46±10.57	62.39±10.49	63.94±11.95	**0.049**
Male	254 (69.4%)	89 (73%)	89 (73%)	76 (62.3%)	0.114
Hypertension	131 (35.8%)	37 (30.3%)	41 (33.6%)	53 (43.4%)	0.084
Diabetes mellitus	111 (30.3%)	36 (29.5%)	25 (20.5%)	50 (41%)	**0.002**
All-cause death	59 (16.1%)	10 (8.2%)	22 (18%)	27 (22.1%)	**0.01**
Myocardial infarction	32 (8.7%)	10 (8.2%)	6 (4.9%)	16 (13.1%)	0.074
Target vessel revascularization	22 (6%)	8 (6.6%)	6 (4.9%)	8 (6.6%)	0.824
Cerebrovascular event	13 (3.6%)	2 (1.6%)	4 (3.3%)	7 (5.7%)	0.22
Follow-up period (months)	49 (26–74)	46 (26–80)	55.5 (29.75–75)	40 (19–67.2)	**0.02**
Laboratory findings of the patients					
White blood cell count (×10³ µL)	9.58±2.55	8.27±2.28	8.44±1.91	10.45±2.81	**<0.001**
Hemoglobin (g/dl)	13.74±1.89	14.1±1.74	13.95±1.82	13.17±1.98	**<0.001**
Platelets (×10³ µL)	257.77±84.64	218.31±66.45	251.19±61.15	303.81±98.52	**<0.001**
Lymphocytes (×10³ µL)	2.3±0.87	2.84±0.97	2.17±0.63	1.9±0.7	**<0.001**
Neutrophils (×10³ µL)	5.83±2.28	4.39±1.29	5.39±1.34	7.7±2.54	**<0.001**
GFR (mL/min/1.73m²)	85.24±24.61	87.45±24.18	87.13±22.92	81.15±26.29	0.079
Glucose (mg/dl)	143.85±85.24	141.14±75.57	135.09±62.7	155.33±82.19	0.091
Creatine (mg/dl)	1.02±0.72	0.96±0.55	1.01±0.77	1.08±0.82	0.4
Serum albumin (g/dl)	3.64±0.46	3.75±0.42	3.65±0.41	3.51±0.5	**<0.001**
SII (P*N/L)	758±599	340.84±84.65	620.19±86.44	1314±748.94	**<0.001**
Multivariable logistic regression analysis according to the clinical outcomes#					
		Ln SII adjusted		Ln WBC adjusted	
Outcome	n	OR (95%CI)	p	OR (95%CI)	p
TVR	22	0.96 (0.19–4.86)	0.963	0.8(0.16–4.02)	0.790
MI	32	2.52 (0.63–10)	0.192	2.34 (0.59–9.28)	0.226
CVE	13	6.41 (0.78–52)	0.082	2.21 (0.26–18.2)	0.461
Cox proportional hazard regression analysis of all-cause death regression models during 105 months of follow-up in the study population					
		Univariate		Multivariate	
		OR (95%CI)	p	OR (95%CI)	p
Age		1.065 (1.040–1.091)	**<0.001**	1.051 (1.025–1.077)	**<0.001**
Sex		1.24 (0.727–2.113)	0.430		
Hypertension		1.66 (0.996–2.767)	**0.052**	1.075 (0.624–1.850)	0.795
Diabetes mellitus		1.170 (0.682–2.007)	0.568		
Dyslipidemia		0.955 (0.346–2.637)	0.930		
Chronic kidney disease		3.265 (1.603–6.647)	0.001	1.340 (0.594–3.026)	0.481
Smoker		0.681 (0.361–1.284)	0.235		
Albumin		0.252 (0.153–0.415)	**<0.001**	0.418 (0.230–0.761)	**0.004**
Ln SII		5.842 (2.242–15.225)	**<0.001**	2.822 (1.028–7.748)	**0.044**

CI, confidence interval; OR, odds ratio.Bold indicates statistically significant value.
#Ln SII or Ln WBC adjusted with age, sex, hypertension, diabetes mellitus, dyslipidemia, chronic renal failure, and smoking in multivariable logistic regression analysis.

A



B

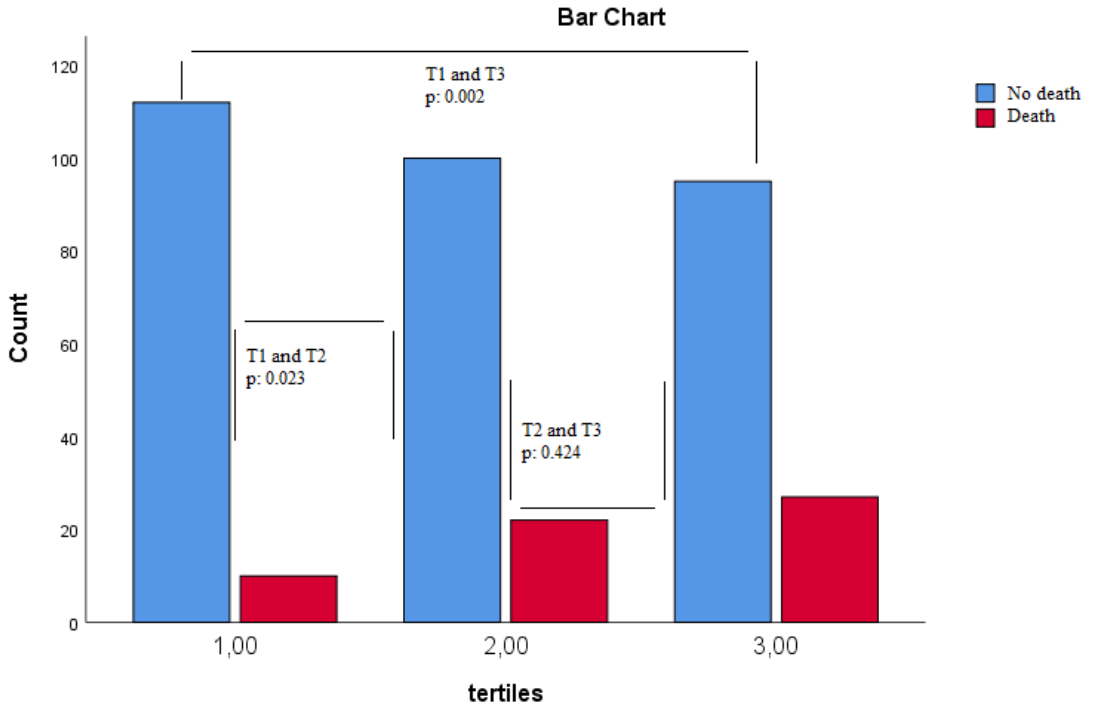


Figure 1. Study flowchart and comparison of groups according to the all-cause death.

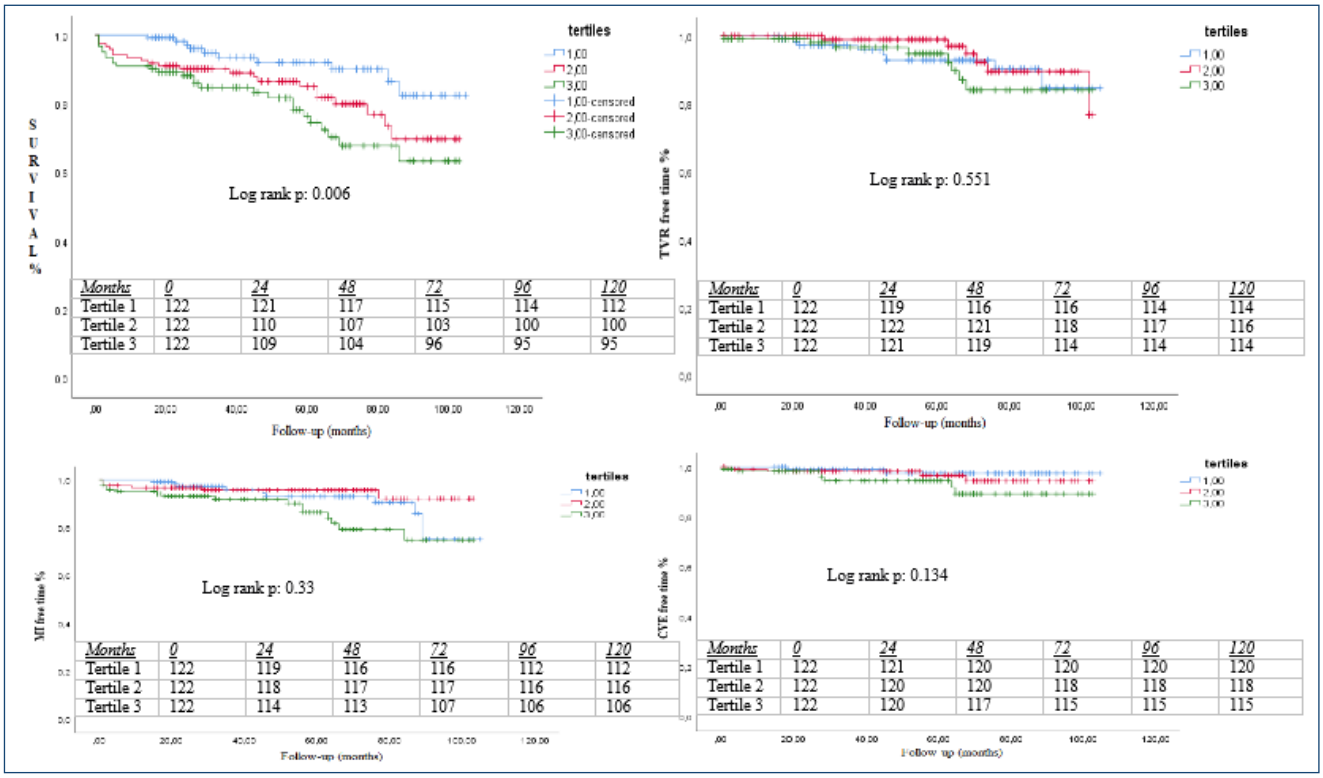


Figure 2. Kaplan-Meier analysis of groups according to the survival, target vessel revascularization (TVR), myocardial infarction (MI), and cerebrovascular events (CVEs).

MI, and CVE in CTO patients. This study presented two main findings: (i) SII was found to be an indicator of survival and (ii) SII was not associated with TVR, MI, and CVE.

Atherosclerosis is strongly associated with inflammation[12,13]. Moreover, atherosclerotic plaque includes a sophisticated interaction between innate immunity and adaptive immunity[14,15]. Components of innate immune system including neutrophils and lymphocytes initiate inflammation in the endothelium. Neutrophils may release pro-oxidant and pro-inflammatory mediators and thereby cause the formation of neutrophil extracellular traps, which have a potential to produce plaque formation and enhance thrombus balance[16]. Platelets also play an important role in the pathogenesis of CAD and acute coronary syndrome[17]. Occlusive platelets aggregate and endothelial damage contributes to the etiology of atherosclerosis. Platelets are biomarkers of CAD that help predict the prothrombotic potential and blood vulnerability[18]. Inflammatory markers with one or two components are relatively poor predictors of prognosis in atherosclerotic diseases[19]. Hence, SII, an inflammatory index calculated from inflammatory cells (e.g., neutrophils, platelets, and lymphocytes), might more comprehensively indicate the balanced status of immune-inflammatory conditions.

Clinical data linking inflammatory markers with the presence of a CTO lesion are highly limited and, to the best of our knowledge, there are very few studies on this subject. Gebhard et al. investigated the prognostic significance of preprocedural leukocyte count and its power to predict cardiovascular risk in CTO patients[20]. Although the study included a larger cohort of 1262 patients (475 of whom had at least a CTO lesion) when compared to our study, the clinical outcomes such as death and adverse cardiac events were evaluated based on only the leukocyte count. In our study, however, these clinical outcomes were investigated with a stronger multiparameter model (i.e., SII). Moreover, in the same study, leukocyte count, age, GFR, and Syntax score were found to be significant predictors of all-cause mortality, while only leukocyte count and Syntax score were significant predictors of major adverse cardiac events (MACEs). In our study, SII, age, and albumin level were associated with all-cause mortality. In addition, unlike in that study, no correlation was found between SII and leukocyte count and adverse cardiac clinical outcomes such as TVR, MI, and CVE. In a study by Okuya et al., a relationship was found between serum uric acid level and TVR[21]. In our study, however, uric acid level was not studied. In another study, a correlation was shown between neutrophil-to-lymphocyte ratio (NLR) and

coronary dissection, instant restenosis, coronary slow-flow phenomenon (CSFP), and MACE ratio in CTO patients[22].

It is difficult to show the specific mechanism on how inflammation affects prognosis in patients with CTO from the results of this observational study. It is known that MI indirectly causes a systemic inflammatory response[23]. Given the low rates of successful percutaneous coronary intervention (PCI) in CTO patients, both the existing ischemia and the inflammation indirectly caused by this ischemia affect the clinical course in CAD and may worsen the prognosis[24]. In our study, however, functional severity of ischemic burden was not determined and thus no causal relationship could be established among MI, inflammatory status, and prognosis in CTO patients.

Our study has some strength. A key finding was that our study was the first to reveal the association of SII with mortality and clinical outcomes including TVR, MI, and CVE in patients CTO, in which SII can be regarded as a mixed indicator of three blood cells in the "cross-talk" of thrombocytosis, inflammation, and immunity in the pathological process of CVEs when compared to other types of blood cells. Second, the follow-up period of the study is relatively long. Finally, the patient population in the study was highly heterogeneous and the study did not focus on a specific patient group but included a wide range of patients such as those who underwent PCI, those who underwent bypass surgery, and those who had a failed CTO intervention and were medically followed up due to SAP, USAP, NSTEMI, and STEMI.

Certain design limitations are also inherent in the present study. First, as a single-center, retrospective study with a small patient cohort, unknown confounding factors might have affected the outcomes regardless of adjustments. Second, only a single value of preprocedural SII was used in the study and no data were available regarding the changes in SII value during subsequent follow-up. Last but the most important limitation, prominent markers of inflammation such as interleukin 6 (IL-6), C-reactive protein (CRP), and erythrocyte sedimentation rate (ESR) were not studied.

CONCLUSIONS

The results indicated that higher SII is independently associated with higher future risk of all-cause mortality in CTO patients, while its relationship with clinical outcomes was not shown. SII improved the risk of mortality compared to traditional risk factors. SII could be used as an easy and practical indicator for identifying high-risk CTO patients. Further multicenter and larger scale studies are needed to perform clinical risk assessment of CTO.

AUTHORS' CONTRIBUTIONS

MD: Conceptualization, Data curation, Formal Analysis, Investigation, Methodology, Project administration, Software, Supervision, Validation, Visualization, Writing – original draft, Writing – review & editing. **MÖ**: Conceptualization, Visualization, Data curation, Investigation, Methodology, Supervision, Validation.

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ORIGINAL ARTICLE

https://doi.org/10.1590/1806-9282.20211105

Evaluation of the rs35996865 polymorphism of the *ROCK1* gene in sepsis

Aykut Kale[1], Elif Funda Şener[2,3], Nahide Ekici Günay[4], Reyhan Tahtasakal[2,3], Seniz Demiryürek[5], Nurullah Günay[1]*, Abdullah Tuncay Demiryürek[6]

SUMMARY

OBJECTIVE: Sepsis is a complex and serious medical condition resulting from the activation of an innate host response to infections. The etiology of sepsis is complex and can be influenced by genetic susceptibility. The purpose of the present study was to investigate a possible association of Rho-kinase 1 (*ROCK1)* gene polymorphism with sepsis in a Turkish population.

METHODS: The study group consisted of 100 unrelated patients with sepsis and 100 healthy controls. Genomic DNA was isolated from peripheral leukocytes from EDTA-containing blood using the QIAamp DNA Blood Mini Kit. *ROCK1* gene rs35996865 and rs112130712 (Lys1054Arg) polymorphisms were analyzed in genomic DNA using the LightCycler 480 II real-time polymerase chain reaction.

RESULTS: There were no significant differences in allele and genotype frequencies for *ROCK1* gene rs35996865 polymorphism between the patients with sepsis and control group ($p>0.05$). Additionally, no association was detected between the rs35996865 polymorphism and mortality in the patient group. No polymorphism was detected with *ROCK1* gene rs112130712 (Lys1054Arg) in our study groups.

CONCLUSIONS: Our data showed that there is no marked association between the rs35996865 polymorphism and sepsis. Therefore, these results suggest that *ROCK1* gene rs35996865 polymorphism is not risk factor for the development of sepsis in the Turkish population.

KEYWORDS: ROCK-I protein kinase. Single nucleotide polymorphism. Mortality. Sepsis.

INTRODUCTION

Sepsis is an extremely complex illness with life-threatening organ dysfunction caused by endogenous mediators in response to infection and is one of the leading cause of mortality worldwide[1]. Septic shock and sepsis are widespread medical emergencies and closely linked with an increased rate of mortality, morbidity, and expensive treatment costs[2,3]. Sepsis is also of great challenges in critical care medicine in the intensive care unit (ICU), where it affects approximately 30% of patients, with high variations between different geographical regions[4]. The estimated worldwide incidence of sepsis admissions has been reported to be 31.5 million cases per year, leading to 5.3 million deaths[5]. The prevalence of sepsis, severe sepsis, and septic shock in ICU in Turkey is reported to be 10.9%, 17.3%, and 13.5%, respectively[6]. Despite significant progress having been made in sepsis management in recent decades, sepsis-related mortality remains as high as 30–50%[2,7]. It is the common cause of death in hospitalized patients and associated with long-term disability in survivors[8]. Sepsis is a multifaceted disease, and its management is complex. There are no drugs approved particularly for the treatment of sepsis, and no definitive therapies present to cure this disease. The treatment of sepsis is mainly supportive in nature, involving the administration of antibiotics, vasoactive substances, intravenous fluids, and oxygen. Genetic epidemiologic studies imply that there is a strong genetic influence on the progression and mortality from sepsis[9-12].

Rho-kinase (ROCK) is a serine/threonine kinase regulated by the small GTPase Rho proteins. It has two isoforms, namely, ROCK1 and ROCK2[13]. While ROCK1 isoform is encoded by 18q11, ROCK2 isoform is located in 2p24 on human chromosomes. Rho/ROCK signaling pathway is involved in regulating various important cellular functions, such as cell migration,

[1]Erciyes University, Faculty of Medicine, Department of Emergency Medicine – Kayseri, Turkey.
[2]Erciyes University, Faculty of Medicine, Department of Medical Biology – Kayseri, Turkey.
[3]Erciyes University, Genome and Stem Cell Center – Kayseri, Turkey.
[4]Kayseri City Hospital, Clinics of Medical Biochemistry – Kayseri, Turkey.
[5]Gaziantep University, Faculty of Medicine, Department of Physiology – Gaziantep, Turkey.
[6]Gaziantep University, Faculty of Medicine, Department of Medical Pharmacology – Gaziantep, Turkey.
*Corresponding author: ngacil@hotmail.com

Conflicts of interest: the authors declare there is no conflicts of interest. Funding: This study was supported by a project (TTU-2020-9781) from the Scientific Research Projects Department of Erciyes University, Kayseri, Turkey.
Received on November 01, 2021. Accepted on February 10, 2022.

cytoskeleton structure, proliferation, apoptosis, and oxidative stress[13]. Experimental studies suggest that ROCK activity regulates sepsis-induced systemic inflammation and organ injury[14,15]. We hypothesize that *ROCK* gene polymorphisms play a role in the risk of sepsis development. Therefore, the goal of the present study was to assess a possible association between *ROCK1* gene polymorphisms and sepsis in a Turkish population.

METHODS

Study design and patients

A total of 200 individuals, including 100 sepsis patients and 100 healthy volunteers, admitted to the Erciyes University Department of Emergency Medicine were enrolled to this study. This research was approved by the Clinical Research Ethics Committee of the Erciyes University (decision no: 2019/581). The patients' relatives and healthy volunteers were asked to give written informed consent for the study procedures prior to participation in the study. This study was conducted in accordance with the Declaration of Helsinki. All genetic analyses were carried out in the Erciyes University Genome and Stem Cell Center (GENKOK).

All consecutive patients consist of those considered to have septic conditions following consultations, investigations, and interventions pursued in the critical care area of the emergency department and decided to be admitted to the ICU or wards. Quick sequential organ failure assessment (qSOFA) score, based on three criteria describing cardiovascular, neurologic, and respiratory dysfunction, was used clinically for screening to identify patients at increased risk for sepsis[16]. The venous blood samples were collected prior to drug administration. Laboratory and clinical parameters elicited in the emergency department including oxygen saturation, arterial blood gases, mean arterial pressure, pulse rate, complete blood count and other biochemical variables, imaging data, and cultures were recorded and analyzed in the routine evaluation as necessary. Data on the clinical courses, diagnoses, mode of disposition, and mortality were abstracted from hospital information system, patients' electronic reports, and patients' relatives and next of kin. Patients who had known or apparent systemic diseases such as heart failure, terminal-stage malignancies, chronic pulmonary, renal or liver diseases, pregnancy, or breastfeeding were excluded. Age range of the study population was set at 18 and 90 years. Control group composed of the healthy, gender- and age-matched volunteers who had no history of medical illness and/or recent surgery, or a diagnosis of genetic, neurologic, psychiatric, liver, infectious, or chronic inflammatory disease. The volunteers for healthy control group were selected from hospital staff and their families.

DNA isolation and genotyping

Venous blood samples (2 mL) were drawn into EDTA-containing tubes from all individuals and were transferred to GENKOK Genome Unit of the Erciyes University. Genomic DNA was extracted from peripheral leukocytes using a QIAamp DNA Blood Mini Kit (Qiagen, Germany), according to instructions of the manufacturer. The samples were stored at -20°C until analyses for each polymorphism. The final DNA concentration was assessed with a micro-volume UV-vis spectrophotometer (BioSpec-nano, Shimadzu, Kyoto, Japan)[11].

To identify *ROCK1* gene rs35996865 and rs112130712 (Lys1054Arg) polymorphisms, genotyping was done using commercially synthesized primers and fluorescently labeled probes and the LightCycler 480 II real-time polymerase chain reaction (PCR) system (Roche Diagnostics GmbH, Mannheim, Germany). Gene polymorphism was determined by analyzing the detailed melting curve of the PCR product obtained.

Statistical analysis

Continuous variable are represented as mean±standard deviation (SD), and categorical variables are expressed as frequencies and percentages. Normal distribution of numerical variables was analyzed with Kolmogorov-Smirnov normality test. Unpaired Student's t-test was used for the comparison of the groups for normally distributed data. Mann-Whitney U test was used for data with the abnormal distribution. Categorical data were analyzed with chi-square test with Yate's correction. The chi-square test was also used to examine deviations from Hardy-Weinberg Equilibrium by comparing the observed and expected genotype frequencies. Differences in allele and genotype frequencies among the controls and cases were analyzed by chi-square with Yate's correction or Fisher's exact tests. Statistical analysis was performed by using Graph-Pad Instat version 3.05 (GraphPad Software Inc., San Diego, CA, USA), and the level of significance was set at $p<0.05$.

RESULTS

A total of 100 patients with sepsis and 100 healthy volunteers were recruited into this case-control study. Table 1 shows the demographic, clinical, and laboratory characteristics of the study population. Sepsis was identified on the basis of microbiological blood culture results. Out of 100 sepsis patients, 43 suffered from Gram negative, 28 from Gram positive, 8 from fungal, and 21 patients displayed a mixed pattern of infections. Compared with

Table 1. Demographic, clinical, and laboratory characteristics of the study cases.

Variables	Patients with sepsis (n=100)	Controls (n=100)	p
Age (years)*	65.1±13.1	62.8±11.5	0.1941
Gender, n (%)			
Male	58 (58.0)	60 (60.0)	0.8857
Female	42 (42.0)	40 (40.0)	
MAP (mmHg)*	66.8±12.2	95.5±10.9	<0.0001
Pulse rate (beats/min)*	98.9±16.9	91.8±17.3	0.0037
Respiratory rate (beats/min)*	28.0±5.9	18.2±9.1	<0.0001
Temperature (°C)*	37.8±1.2	36.2±1.9	<0.0001
qSOFA score†	2.2 (2–3)	-	
GCS score†	13.7 (3–15)	-	
Lactate (mmol/L)*	2.6±2.4	1.3±0.7	<0.0001
SaO_2 (%)*	88.9±8.7	-	
Hemoglobin (g/dL)*	11.8±2.5	12.9±1.9	0.0005
WBC (/μL)*	12777.8±8865.9	9250.0±3704.2	0.0003
Platelet (10^3/μL)*	232.3±148.3	274.3±69.9	<0.0001
Neutrophils (10^3/μL)*	10528.3±8296.5	7106.2±3274.3	0.0002
INR*	1.5±1.1	-	
Glucose (mg/dL)*	171.9±93.8	105.9±20.1	<0.0001
Creatinine (mg/dL)*	1.9±1.7	0.9±0.5	<0.0001
CKD-EPI*	54.2±34.5	-	
AST (U/L)*	33.0±29.3	23.7±9.8	0.0546
ALT (U/L)*	24.1±23.3	21.6±8.8	0.0234
Total bilirubin (mg/dL)*	1.3±1.1	0.6±0.5	<0.0001
Uric acid (mg/dL)*	6.8±3.6	6.4±2.5	0.6972
BUN (mg/dL)*	34.8±25.1	16.1±5.9	<0.0001
D-Dimer (μg/L)*	4395.7±3968.1	-	
C-reactive protein (mg/L)*	146.1±119.6	1.15±1.12	<0.0001
Procalcitonin (ng/mL)*	3.1±4.1	-	

*Data are mean±SD; †Scores are given as median (min–max); MAP, mean arterial pressure; GCS, Glasgow Coma Scale; qSOFA, quick sequential organ failure assessment; SaO_2, oxygen saturation; INR, International Normalized Ratio; WBC, white blood cells; CKD-EPI, chronic kidney disease-epidemiology; AST, aspartate aminotransferase; ALT, alanine aminotransferase; BUN, blood urea nitrogen.

the controls, the average age, gender, aspartate aminotransferase, and uric acid in sepsis group were similar. Pulse rate, respiratory rate, body temperature, lactate, white blood cell and neutrophil counts, glucose, creatinine, alanine aminotransferase, total bilirubin, blood urea nitrogen, and C-reactive protein levels were found to be elevated in the sepsis group when compared to the control. We recorded decreases in mean arterial blood pressure, hemoglobin levels, and platelet counts (Table 1).

Both the control (p=0.9923) and patients (p=0.8713) groups were found to be in Hardy-Weinberg Equilibrium. For the *ROCK1* gene rs35996865 polymorphism, no marked differences in both genotype (T/T, 53.0%; T/G, 41.0%; G/G, 6.0%) and allele (T, 73.5%; G, 26.5%) frequencies in the sepsis group were detected when compared to controls (T/T, 63.0%; T/G, 33.0%; G/G, 4.0%; T, 79.5%; G, 20.5%, p>0.05) (Table 2). Mortality distribution according to genotype frequencies of *ROCK1* gene rs35996865 polymorphism in patient group was also examined at the end of 3 months of hospital admission, but no significant change between survival (T/T, 64.2%; T/G, 70.7%; G/G, 50.0%) and exitus rate (T/T, 35.8%; T/G, 29.3%; G/G, 50.0%, p>0.05) was determined (Table 3).

We have also studied *ROCK1* gene rs112130712 (Lys1054Arg) polymorphism, but no polymorphism was found in both patient and control groups, i.e., only T/T genotype was detected.

Table 2. Genotype and allele frequencies of *ROCK1* gene rs35996865 polymorphism among cases and controls.

Genotypes/alleles	Patients (n=100), n (%)	Controls (n=100), n (%)	p	OR (95%CI)
T/T	53 (53.0)	63 (63.0)		
T/G	41 (41.0)	33 (33.0)	0.2471	0.6771 (0.377–1.217)
G/G	6 (6.0)	4 (4.0)	0.5133	0.5608 (0.150–2.094)
T	147 (73.5)	159 (79.5)		
G	53 (26.5)	41 (20.5)	0.1946	0.7152 (0.449–1.139)

Table 3. Mortality distribution according to genotype frequencies of *ROCK1* gene rs35996865 polymorphism among patients.

Genotypes/alleles	Survive, n (%)	Exitus, n (%)	p	OR (95%CI)
T/T (n=53)	34 (64.2)	19 (35.8)		
T/G (n=41)	29 (70.7)	12 (29.3)	0.6514	0.7405 (0.308–1.779)
G/G (n=6)	3 (50.0)	3 (50.0)	0.6614	1.7890 (0.328–9.760)

DISCUSSION

In this case-control study, we showed no significant association between sepsis and *ROCK1* gene rs35996865 polymorphism, and no significant relationship between the rs35996865 polymorphism and mortality in our Turkish population. To the best of our knowledge, this is the first study to investigate the association of the *ROCK1* gene polymorphism with the risk of developing sepsis. Our data indicate that rs35996865 polymorphism is unlikely to play a role in the sepsis development.

The rs35996865 polymorphism located in the *ROCK1* promoter region, about 2 kb upstream of the transcription start site. However, it is not known whether this polymorphism is able to alter the expression level of the *ROCK1* gene[17]. There are only small numbers of studies related to this polymorphism. The *ROCK1* gene rs35996865 polymorphism mapping to the 5′-UTR has been reported to be significantly associated with colorectal cancer[18,19], obesity-related metabolic syndrome[20], renal cell carcinoma[21], respiratory distress syndrome[22], non-syndromic cleft palate[17], and systemic sclerosis[23], but not with Behçet's disease[24] or Alzheimer's disease[25]. Although no association of this polymorphism was noted with primary open-angle glaucoma in a Turkish population[26], this variant is nominally associated with risk of high-tension glaucoma in a Korean population[27].

Experimental studies showed that ROCK activity regulates sepsis-induced systemic inflammation[14,28]. ROCK inhibitors have been shown to exert beneficial effects in models of sepsis as well as endotoxemic injury in the liver[14,28,29]. It has been shown that specific ROCK inhibitor Y-27632 reduces lung injury from septic rats induced by cecal ligation and puncture[30]. Fasudil, another ROCK inhibitor, improves endothelial permeability and inhibits inflammation, oxidative stress, and cellular apoptosis in order to alleviate acute lung injury in septic rats[15]. Taken together, these studies suggest that ROCK is involved in sepsis-induced organ injury.

CONCLUSIONS

This study indicated that *ROCK* gene rs35996865 polymorphism is not associated with sepsis or sepsis-induced mortality in the Turkish population. Thus, this variant may not influence the risk of sepsis. However, analysis of other polymorphisms in this gene for association with sepsis would be helpful in clarifying the involvement of the *ROCK* gene in sepsis pathogenesis. Future genetic expression analysis and studies in larger populations are needed to elucidate the role of the *ROCK* gene in sepsis susceptibility. This is a pilot study with a lower sample size. We believe that further investigations are also needed to verify these results in different ethnic and independent groups.

AUTHORS' CONTRIBUTIONS

AK: Conceptualization, Data curation, Formal Analysis, Investigation, Methodology, Validation, Visualization, Writing – review & editing. **NEG:** Conceptualization, Data curation, Formal Analysis, Investigation, Methodology, Validation, Visualization, Writing – review & editing. **SD:** Conceptualization, Data curation, Formal Analysis, Investigation, Methodology, Validation, Visualization, Writing – review & editing. **EFŞ:** Data curation, Formal Analysis, Investigation, Methodology, Software, Supervision, Validation, Writing – review & editing. **RT:** Data curation, Formal Analysis, Investigation, Methodology, Software, Supervision, Validation, Writing – review & editing. **NG:** Conceptualization, Data curation, Funding acquisition, Methodology, Project administration, Supervision, Writing – review & editing. **ATD:** Formal Analysis, Visualization, Writing – original draft.

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ORIGINAL ARTICLE

https://doi.org/10.1590/1806-9282.20211174

An international multi-institutional analysis of operative morbidity in patients undergoing elective diverticulitis surgery

Yuksel Altinel[1,2,3*], Paul Cavallaro[1], Rocco Ricciardi[1], Volkan Ozben[4], Ersin Ozturk[5], Ron Bleday[6], Members of the Turkish Diverticulitis Study Group Collaborative[†], Erman Aytac[4], Liliana Bordeianou[1]

SUMMARY

OBJECTIVE: We investigated surgical complications of elective surgery for diverticulitis in international multi-institution to identify a prediction model for potential opportunities of quality improvement.

METHODS: We identified 1225 patients who underwent elective surgery for diverticulitis between January 2010 and January 2018. The data were obtained from the National Surgical Quality Improvement Program and the Turkish Diverticulitis Study Group Collaborative, retrospectively.

RESULTS: We observed that the presence of chronic obstructive pulmonary disease (OR: 3.2, 95%CI 1.8–5.9, p<0.001) or abscess at the time of surgery (OR: 1.4, 95%CI 1.2–1.7, p£0.001) is associated with a higher rate of minor complications, while comorbidities such as dyspnea (OR: 2.8, 95%CI 1.6–4.9, p£0.001) and preoperative sepsis (OR: 4.1, 95%CI 2.3–7.3, p£0.001) are associated with major complications. The centers had similar findings in minor and major complications (OR: 0.8, 95%CI 0.5–1.4, p=0.395). The major independent predictors for complications were malnutrition (low albumin) (OR: 0.5, 95%CI 0.4–0.6, p<0.001) and the American Society of Anesthesiology score (OR: 1.7, 95%CI 1.2–2.4, p=0.002).

CONCLUSION: Regarding the major and minor complications of diverticulitis of elective surgery, the malnutrition and higher American Society of Anesthesiology score showed higher impact among the quality improvement initiatives.

KEYWORDS: Diverticulitis. Complications. Surgery.

INTRODUCTION

The treatment of diverticulitis with elective sigmoidectomy is controversial. Approximately 20% of patients with episodes of diverticulitis enhance recurrences following conservative treatment[1]. Elective resection was recommended for the patients with the second attack of diverticulitis that was considered approximately 60% risk for post-surgical complications[2]. However, prophylactic elective resection for diverticulitis does not assure to decrease postoperative complications[3-5]. Based on the 2006 American Society of Colon and Rectal Surgeons guidelines, the indications for elective resection have been advised as a tailored approach following recurrences and complaints[6,7]. It is equally unclear what happens to patients with diverticulitis who underwent elective surgery, for example, in Western Europe or the United States[8,9]. Similarly, trends in surgical procedures offered and other nuances required to manage the outcomes of diverticulitis in the European and U.S. literature[10,11]. This study is underway to characterize the surgical course of patients who underwent elective surgery based on international multi-institutional data. Our primary goal was to assess the predictive factors that specifically lead to minor and major complications of elective surgery for diverticulitis in order to identify potential targets that may benefit from national efforts toward surgical quality improvement.

METHODS

We queried the database between January 1, 2010, and January 30, 2018. We only included patients who had elective laparoscopic and open surgery for diverticulitis during follow-up. We excluded patients under 18 years old, patients undergoing emergency surgery, and those who underwent a colectomy

[1]Massachusetts General Hospital, Colorectal Surgery Center, Department of Surgery – Boston (MA), United States.
[2]Harvard Medical School, Master in Science Clinical Investigation Program – Boston (MA), United States.
[3] University of Health Sciences, Bagcilar Training and Research Hospital, Department of General Surgery – Istanbul, Turkey.
[4]Acibadem University Atakent Hospital, Department of Surgery – Istanbul, Turkey.
[5]Medicana Bursa University Hospital, Department of Surgery – Bursa, Turkey.
[6]Brigham and Women's Hospital – Boston (MA), United States.
[†]All contributing members of the Turkish Diverticulitis Study Group Collaborative are credited in Chart 1.
*Corresponding author: dryukselaltinel@gmail.com
Conflicts of interest: the authors declare there is no conflicts of interest. Funding: none.
Received on January 09, 2022. Accepted on February 11, 2022.

Chart 1. The Turkish Diverticulitis Study Group Collaborative

Uludag University, Bursa, Region of Marmara	Tuncay Yilmazlar MD., orcid:0000-0003-1924-0795, tunyil@uludag.edu.tr Ozgen Isik MD., 0000-0002-9541-5035, ozgen006@yahoo.com
Medicana Bursa University Hospital Department of Surgery, Region of Marmara	Baris Gulcu MD., orcid:0000-0002-4808-1538, drbarisgulcu@gmail.com, Ersoy Taspinar: orcid;0000-0002-6663-0190
Acibadem University Maslak Hospital Department of Surgery, Region of Marmara	Ismail Ahmet Bilgin MD. Orcid:0000-0002-2073-842X, isahbilgin@hotmail.com
Acibadem University Atakent Hospital Department of Surgery, Region of Marmara	Cansu de Muijnck MD., orcid:0000-0003-0161-5851, cansudemuijnck@gmail.com
Cukurova University Hospital Department of Surgery, South Central Anatolia	Ahmet Rencuzogullari MD. orcid: 0000-0002-5993-9536, rencuzdr@gmail.com
Sultan Abdulhamid Han Research and Training Hospital Department of Surgery Region of Marmara,	İlker Sucullu MD., orcid:0000-0003-3906-6827, suculluilker@yahoo.com Ahmet Ziya Balta MD., orcid:0000-0002-4143-4169 ahmetzbalta@yahoo.com
Bulent Ecevit University Hospital Department of Surgery, Black Sea region	Fatma Ayça Gultekin MD., orcid:0000-0002-4148-5871 faycagultekin@yahoo.com Ramazan Kozan MD., orcid:0000-0002-3835-8759,
Koç University Hospital, Region of Marmara	Emre Balik MD., orcid:0000-0001-5751-1133, ebalik@ku.edu.tr Emre Ozoran MD. Orcid:0000-0002-9371-6811, eozoran@kuh.ku.edu.tr
American Hospital Department of Surgery, Region of Marmara	Dursun Bugra MD., orcid:0003-0316-6818, dursunbugra@yahoo.com Serkan Zenger MD.orcid: 0000-0003-2860-7413, serkanzen@hotmail.com
Gazi University Hospital Department of Surgery, West Anatolia	Sezai Leventoglu MD., orcid:0000-0003-0680-0589 sezaileventoglu@hotmail.com Saygin Altiner MD., orcid:0000-0001-6118-9984, sygn0607@gmail.com
Marmara University Hospital, Department of Surgery, Region of Marmara	Wafi Attaallah, MD. Orcid:0000-0002-3179-4144, drwafi2003@yahoo.com
Izmir Dokuz Eylul University Hospital, Department of Surgery, Eagan Region	Aras Emre Canda MD. Orcid:0000-0002-8257-5881 e-mail: emre.canda@deu.edu.tr

with an underlying diagnosis of colorectal cancer or inflammatory bowel disease (e.g., Crohn's disease and ulcerative colitis). Turkish data were collected by Turkish Collaborative Group. American patients were collected by the National Surgical Quality Improvement Program (NSQIP) database. Approval was obtained from the Partners Institutional Review Board and Partners Colorectal Collaborative for this study.

Clinical characteristics such as body mass index (BMI, kg/m^2), albumin (mg/dL), white blood cell count (10^9/L), sodium (mmEq/L), creatine (mg/dL), platelet (10^3/mm^3), international normalized ratio (INR), aspartate aminotransferase (AST, U/L), alanine aminotransferase (ALT, U/L), and blood urea nitrogen (BUN, mg/dL) were dichotomized based on data review.

The demographic characteristics of patients included age (<59.4 or >59.4 years), gender, and race (i.e., Caucasian, Hispanic, African American, and Asian). The clinical characteristics of patients included smoking status, dyspnea, functional health status, comorbidities (i.e., hypertension, diabetes mellitus, chronic obstructive pulmonary disease [COPD], ventilator dependence, history of myocardial infarction, and bleeding disorder history), steroid immunosuppression, American Society of Anesthesiology (ASA) classification, Charlson comorbidity index (CCI), episode times, previous drainage catheter placement (i.e., interventional radiology [IR]), and laboratory values. Treatment factors included indication for surgery, and operative factors included wound classification, operative approach, concurrent procedures (i.e., small bowel resection, bladder or vagina repair, hysterectomy, or oophorectomy), stoma creation, duration of surgery, length of stay, and the identification of general and colorectal surgeon. Outcomes assessed included minor complications such as superficial surgical-site infection (SSI), postoperative ileus, wound disruption, postoperative urinary tract infection, and prolonged nasogastric use and major complications such as anastomosis leak, deep organ space, SSIs, sepsis, pneumonia, embolism, acute renal failure, myocardial infarction, cardiovascular arrest, cerebrovascular accident, intubation, readmission, reoperation, and mortality. We identified sigmoid colectomy as a segmental resection and low anterior resection (LAR) as an extended resection[12-14].

Statistical analysis

Descriptive statistics were reported as percentages for categorical variables and as mean±standard deviation for continuous variables. Univariate analysis comparing patients with minor and major outcomes was performed using the chi-square test for categorical variables and t-test for continuous variables. Multivariable logistic regression was used to determine variables predictive of minor and major outcomes to control potential confounders. The receiver operating characteristic curve (ROC curve), sensitivity, and specificity were calculated. We used bootstrapping to generate 95% confidence interval (95%CI) of the sensitivity and specificity. A significance level was set at $p<0.05$. All analyses were performed using R software version 3.4.2.

RESULTS

Demographics and operative characteristics

We identified the major and minor complications based on the combined data of 219 Turkish and 1006 American patients who underwent elective colonic resections for diverticulitis. During the follow-up period, 1225 patients underwent elective surgery for diverticulitis. We identified 132 (10.8%) patients who had major complications. The majority (1182 patients, 96.5%) who underwent surgery had minor complications. Of these, 553 (45.1%) were male, and the average age was 59.4 years (Tables 1 and 2).

The patients with major complications were older (58.93 vs. 63.26 years, $p<0.001$) who are having lower albumin (4.02 vs. 3.53 mg/dL, $p<0.001$) and higher ASA classification (0.4% vs. 3.8%, $p<0.001$).

The patients with minor complications also appeared more likely to be taken to the operating room with higher recurrent episodes (>3 attacks; 16.3% vs. 37.9%, $p=0.006$).

The patients with major complications have been performed more likely with open surgeries (52.2% vs. 28.8%, $p<0.001$) and extended resection such as LAR (69.4% vs. 51.5%, $p<0.001$).

Minor complications mainly were seen after LAR (37.2% vs. 68.5%, $p<0.001$). The mean length of hospital stay was shorter (10.58 vs. 6.32 days, $p<0.001$).

Prediction model and performance

On univariate regression analysis, we noted that functional health status, hypertension, ASA score (3–4), advanced age (>59.4 years), persistently elevated white blood cell count (>8.25 × 10^9/L), a higher CCI (>2.08), low albumin levels (>3.97 mg/dL), diabetes mellitus, preoperative sepsis, dyspnea, sodium (>139 mmEq/L), BUN (>14.3 mg/dL), INR (>1.09), reason of surgery (fistula), abscess at the admission, recurrent episode (>3), procedure (laparoscopic), stoma, anastomosis, operative approach (LAR), wound classification (either contaminated or dirty) were associated with major complications (Table 3).

We performed a model for major outcomes in multivariable analysis, such as a higher ASA score (OR: 1.46, 95%CI 1.00–2.12, $p=0.048$), higher CCI (OR: 1.14, 95%CI 1.00–1.30, $p=0.040$), and malnutrition (low albumin) (OR: 0.57, 95%CI 0.41–0.80, $p=0.001$).

The area under the curve (AUC) was 0.690 (95%CI 0.600–0.740), sensitivity was 0.990 (95%CI 0.980–1), and specificity was 0.080 (95%CI 0.030–0.170).

On univariate regression analysis, we noted that functional health status, diabetes mellitus, congestive heart failure (CHF), persistently elevated white blood cell count (>8.25 × 10^9/L), a higher CCI (>2.08), low albumin levels (>3.97 mg/dL), dyspnea, creatine (>0.89 mg/dL), reason of surgery (fistula), abscess at the admission, abscess at the time of surgery, recurrent episode (>3), antibiotic preparation, procedure (laparoscopic), stoma, and anastomosis were associated with minor complications.

We generated a model for minor outcomes in multivariable analysis, such as lower creatine levels (OR: 0.62, 95%CI 0.39–0.91, $p=0.033$), lack of antibiotic preparation (OR: 0.38, 95%CI 0.19–0.78, $p=0.008$), and laparoscopic procedure (OR: 2.34, 95%CI 1.12–4.90, $p=0.024$).

The AUC was 0.700 (95%CI 0.660–0.720), sensitivity was 0.050 (95%CI 0.000–0.100), specificity was 1 (95%CI 1–1). Our model was pretty good at detecting the true negatives but fails in detecting the true positives.

DISCUSSION

This is the first large-scale study comparing clinical characteristics and operative factors for major and minor complications of patients who underwent elective colonic resection for diverticulitis in the international multi-institutional setting. The postoperative major and minor outcomes have been described previously in various distinctive case series, such as infectious or complicated complications[15-17]. Until present, it has been unclear whether the severity of diverticulitis phenotype of patients or the effect of operative management has an impact either alone or combined among the major and minor complications for elective surgery internationally.

The predictive features of complications specific to elective resection for diverticulitis might be inconstant with the studies by Bolkenstein[17], Holmer[18], and Moghadamyeghaneh[19]. It may be challenging to predict before surgery as an underlying cause of the diverticulitis itself. It appears that the recurrent episodes of diverticulitis (>3) did not have an impact on the patients' risk for major and minor complications in our cohort, regardless of its nature of severity. This is controversial but eventually established by additional literature that verified the first episode of complicated diverticulitis or subsequent

Table 1. Demographics and clinical characteristics.

	Major NONE	Major YES	p	Minor NONE	Minor YES	p
	n=1093	n=132		n=43	n=1182	
Demographics						
Age (59.40±12.50)	58.93±12.34	63.26±13.16	**<0.001**	62.53±12.44	59.28±12.49	0.094
Gender (male) (553, 45.1%)	491 (44.9%)	62 (47%)	0.723	17 (39.5%)	536 (45.3%)	0.551
Race						
Asian (6, 0.5%)	6 (0.5%)	0 (0%)		0 (0.0%)	6 (0.5%)	
African American (27, 2.2%)	25 (2.3%)	2 (1.5%)	0.783	1 (2.3%)	26 (2.2%)	0.974
White (1163, 94.9%)	1036 (94.8%)	127 (96.2%)		41 (95.3%)	1122 (94.9%)	
Hispanic (27, 2.2%)	25 (2.3%)	2 (1.5%)	0.462	0 (0.0%)	27 (2.3%)	0.509
Comorbidities						
Diabetes mellitus						
DM Type 1 (42, 3.4%)	29 (2.7%)	13 (9.8%)	**<0.001**	7 (16.3%)	35 (3.0%)	**<0.001**
DM Type 2 (59, 4.8%)	50 (4.6%)	9 (6.8%)		3 (7.0%)	56 (4.7%)	
BMI (28.56±6.13)	28.57±6	28.45±7.17	0.832	27.90±5.54	28.59±6.15	0.472
Smoking (240, 19.6%)	209 (19.1%)	31 (23.5%)	0.282	12 (27.9%)	228 (19.3%)	0.229
ETOH (69, 5.6%)	63 (5.8%)	6 (4.5%)	0.709	5 (11.6%)	64 (5.4%)	0.162
Dyspnea						
At rest (18, 1.5%)	12 (1.1%)	6 (4.5%)	**<0.001**	2 (4.7%)	16 (1.4%)	0.172
Moderate exertion (62, 5.1%)	49 (4.5%)	13 (9.8%)		3 (7.0%)	59 (5%)	
Functional health status						
Independent (1166, 95.2%)	1054 (96.4%)	112 (84.8%)		36 (83.7%)	1130 (95.6%)	
Partially dependent (33, 2.7%)	19 (1.7%)	14 (10.6%)	**<0.001**	5 (11.6%)	28 (2.4%)	**0.001**
Totally dependent (26, 2.1%)	20 (1.8%)	6 (4.5%)		2 (4.7%)	24 (2.0%)	
Ventilator-dependent (18, 1.5%)	13 (1.2%)	5 (3.8%)	**0.05**	0 (0.0%)	18 (1.5%)	0.865
COPD (46, 3.8%)	37 (3.4%)	9 (6.8%)	0.086	3 (7.0%)	43 (3.6%)	0.470
CHF (18, 1.5%)	9 (0.8%)	9 (6.8%)	**<0.001**	1 (2.3%)	17 (1.4%)	1
Hypertension (539, 44%)	469 (42.9%)	70 (53%)	**0.034**	22 (51.2%)	517 (43.7%)	0.420
Open wound (40, 3.3%)	27 (2.5%)	13 (9.8%)	**<0.001**	2 (4.7%)	38 (3.2%)	0.933
Steroid (57, 4.7%)	46 (4.2%)	11 (8.3%)	0.057	3 (7.0%)	54 (4.6%)	0.713
Bleeding disorders (26, 2.1%)	20 (1.8%)	6 (4.5%)	0.085	0 (0.0%)	26 (2.2%)	0.657
Preoperative sepsis						
Sepsis (37, 3%)	23 (2.1%)	14 (10.6%)		2 (4.7%)	35 (3.0%)	
Septic shock (5, 0.4%)	2 (0.2%)	3 (2.3%)	**<0.001**	0 (0.0%)	5 (0.4%)	0.729
SIRS (20, 1.6%)	18 (1.6%)	2 (1.5%)		0 (0.0%)	20 (1.7%)	

BMI: body mass index (kg/m^2); COPD: chronic obstructive pulmonary disease: ETOH: ethyl alcohol; CHF: congestive heart failure; SIRS: Systemic inflammatory response syndrome. Normally distributed data were recorded as mean±standard deviation. Bold values denote statistical significance at the p<0.05 level.

Table 2. Preoperative characteristics and intraoperative findings.

	Major NONE	Major YES	p	Minor NONE	Minor YES	p
	n=1093	n=132		n=43	n=1182	
Operative approach (laparoscopic) (598, 48.8%)	560 (51.2%)	38 (28.8%)	<0.001	17 (39.5%)	581 (49.2%)	0.278
Procedure (LAR) (826, 67.4%)	758 (69.4%)	68 (51.5%)	<0.001	16 (37.2%)	810 (68.5%)	<0.001
Concurrent procedures						
Intestine (12, 1%)	10 (0.9%)	2 (1.5%)	0.122	0 (0.0%)	12 (1%)	0.452
Uro-gynecological (182, 14.9%)	155 (14.2%)	27 (20.5%)		4 (9.3%)	178 (15.1%)	
Stoma						
None (1011, 82.5%)	922 (84.4%)	89 (67.4%)	<0.001	25 (58.1%)	986 (83.4%)	<0.001
Ileostomy (85, 6.9%)	72 (6.6%)	13 (9.8%)		5 (11.6%)	80 (6.8%)	
Colostomy (129, 10.5%)	99 (9.1%)	30 (22.7%)		13 (30.2%)	116 (9.8%)	
Splenic flexura taken down (870, 71%)	780 (71.4%)	90 (68.2%)	0.510	28 (65.1%)	842 (71.2%)	0.485
Anastomosis						
None (141, 11.5%)	41 (18.7%)	31 (23.5%)	<0.001	14 (32.6%)	127 (10.7%)	<0.001
End to end (680, 55.5%)	612 (56%)	68 (51.5%)		20 (46.5%)	660 (55.8%)	
End to side (354, 28.9%)	325 (29.7%)	29 (22%)		4 (9.3%)	350 (29.6%)	
Side to side (50, 4.1%)	46 (4.2%)	4 (3%)		5 (11.6%)	45 (3.8%)	
Wound class						
Clean (89, 7.3%)	81 (7.4%)	8 (6.1%)	<0.001	4 (9.3%)	85 (7.2%)	0.925
Contaminated (645, 52.7%)	596 (54.5%)	49 (37.1%)		22 (51.2%)	623 (52.7%)	
Dirty (228, 18.6%)	209 (19.1%)	19 (14.4%)		7 (16.3%)	221 (18.7%)	
Infected (263, 21.5%)	207 (18.9%)	56 (42.4%)		10 (23.3%)	253 (21.4%)	
Surgeon (colorectal) (901, 73.6%)	808 (73.9%)	93 (70.5%)	0.454	27 (62.8%)	874 (73.9%)	0.146
Surgical duration (min)	160.39±68.82	159.88±73.79	0.937	170.84±72.18	159.95±69.23	0.312
Hospital stay (days)	5.72±4.17	12.64±10.55	<0.001	10.58±7.31	6.32±5.54	<0.001
Laboratory						
Na (139.01±3.30)	139.10±3.24	138.29±3.68	0.008	138.47±3.22	139.03±3.30	0.271
BUN (14.13±7.36)	13.90±7.03	16.04±9.48	0.002	15.85±8.75	14.07±7.30	0.118
AST (25.76±20.40)	25.85±20.04	25.05±23.28	0.672	28.05±21.84	25.68±20.35	0.455
ALT (29.97±24.42)	30.92±24.66	22.13±20.91	<0.001	30.28±23.92	29.96±24.45	0.932
ALB (3.970±.68)	4.02±0.64	3.53±0.85	<0.001	3.54±0.80	3.99±0.67	<0.001
CRE (0.89±0.48)	0.89±0.48	0.90±0.51	0.712	1.24±1.72	0.88±0.36	<0.001
WBC (8.25±3.24)	8.11±3.01	9.45±4.57	<0.001	9.83±4.87	8.19±3.16	0.001
PLT (269.70±87.12)	268.65±84.69	278.32±105.07	0.229	284.26±86.16	269.17±87.14	0.265
INR (1.090±.22)	1.09±0.22	1.15±0.22	0.004	1.14±0.18	1.09±0.22	0.184
Mech bowel prep (646, 52.7%)	587 (53.7%)	59 (44.7%)	0.062	19 (44.2%)	627 (53%)	0.323
Antibiotic prep (311, 25.4%)	278 (25.4%)	33 (25%)	0.998	21 (48.8%)	290 (24.5%)	0.001
Chemotherapy (19, 1.6%)	13 (1.2%)	6 (4.5%)	0.010	3 (7%)	16 (1.4%)	0.021

Continue...

Table 2. Continuation.

	Major NONE	Major YES	p	Minor NONE	Minor YES	p
	n=1093	n=132		n=43	n=1182	
Reason for surgery						
Recurrent episode (700, 57.1%)	655 (59.9%)	45 (34.1%)		13 (30.2%)	687 (58.1%)	
Abscess (284, 23.2%)	227 (20.8%)	57 (43.2%)	<0.001	18 (41.9%)	266 (22.5%)	0.001
Fistula (241, 19.7%)	211 (19.3%)	30 (22.7%)		12 (27.9%)	229 (19.4%)	
Admission for abscess (197, 16.1%)	152 (13.9%)	116 (11.5%)	<0.001	17 (39.5%)	180 (15.2%)	<0.001
Recurrent episode (>3 episode) 455 (37.1)	427 (39.1%)	28 (21.2%)	<0.001	7 (16.3%)	448 (37.9%)	0.006
Abscess						
None (930, 75.9%)	859 (78.6%)	71 (53.8%)		23 (53.5%)	907 (76.7%)	
Present at time of surgery (195, 15.9%)	152 (13.9%)	43 (32.6%)	<0.001	18 (41.9%)	177 (15%)	<0.001
Prior IR drainage (100, 8.2%)	82 (7.5%)	18 (13.6%)		2 (4.7%)	98 (8.3%)	
ASA classification						
I (118, 9.6%)	108 (9.9%)	10 (7.6%)		8 (18.6%)	110 (9.3%)	
II (758, 61.9%)	701 (64.1%)	57 (43.2%)	<0.001	20 (46.5%)	738 (62.4%)	0.087
III (340, 27.8%)	280 (25.6%)	60 (45.5%)		15 (34.9%)	325 (27.5%)	
IV (9, 0.7%)	4 (0.4%)	5 (3.8%)		0 (0.0%)	9 (0.8%)	
CCI (2.08±1.83)	1.98±1.74	2.95±2.25	<0.001	2.72±1.94	2.06±1.82	0.019

Na: sodium; WBC (10^9/L): white blood count; BUN: blood urea nitrogen; AST: aspartate aminotransferase; ALT: alanine aminotransferase; CRE: creatinine; ALB (mg/dL): albumin; PLT: platelet; INR: international normalized ratio; CCI: Charlson comorbidity index; ASA: American Society of Anesthesiology classification. Normally distributed data were recorded as mean±standard deviation. Bold values denote statistical significance at the p<0.05 level.

attacks for ultimate complications[10,11]. Regarding the postoperative adverse outcomes such as morbidity and mortality, we reported that most of our findings among the impact of anastomotic leakage (3.3%) as a major complication (10%) and postoperative ileus (90.4%) and superficial SSI (15.2%) as minor complications (96%), which Moghadamyeghaneh et al.[19], Bordeianou et al.[20], and Bolkenstein et al.[21] correlated the findings of surgical management for diverticulitis. Consistently, major complications following elective diverticulitis surgery had reported with higher ASA score, which is associated with the adverse outcomes on postoperative morbidity and mortality rates following colorectal surgeries such as Hall's study[12].

We reported that higher CCI might express the increasing load of comorbidities in patients with major complications who underwent elective diverticulitis surgery. The possible consequences of the correlation of higher CCI and ASA scores, including malnutrition in diverticulitis patients, previously showed various adverse outcomes in colorectal surgeries[12,19-21]. Regarding our findings, such as malnutrition or hypoalbuminemia, these could be achieved by a supplementary assessment targeting all preoperative patients[21,22]. Significantly, the principles of nutritional support for diverticulitis are a potential intervention that may improve surgical outcomes similar to the study by Van de Wall[23]. We should optimize the preoperative nutritional management as an initial strategy to generate supplementary therapy collectively due to the nutritional risk of diverticular disease similar to the study by Giorgetti[22].

We found factors such as the presence of abscess at admission, presence of anastomosis, ASA score >2, and malnutrition have close association with minor and major complications that are consistent with some studies comparing the selection and outcomes of laparoscopic surgery in the elective or emergent/urgent situations[13,18,24,25].

Unfortunately, despite an increase in laparoscopy, these patients had more minor complications regarding possible higher numbers of laparoscopic procedures and promptly chosen options for elective colon resections similar to the studies by Holmer[18] and Khan[24]. As previously mentioned, prior antibiotic preparation might prevent SSI. Even though they seem to have collaborated with mechanical bowel preparation[13,25],

Table 3. Unadjusted covariates.

	OR	95% confidence interval	p
Major complications			
Age	1.028	1.013–1.044	<0.001
Diabetes mellitus	0.133	0.083–0.212	<0.001
Open wound	4.313	2.167–8.583	<0.001
Dyspnea	0.500	0.187–1.332	0.165
Functional health status	0.106	0.0874–0.129	<0.001
Ventilator-dependent	3.270	1.147–9.324	0.026
Hypertension	1.502	1.045–2.157	0.027
CHF	8.813	3.433–22.619	<0.001
Preoperative sepsis	0.107	0.088–0.130	<0.001
Albumin	0.403	0.316–0.512	<0.001
Na	0.937	0.892–9.845	0.009
BUN	1.034	1.012–1.056	0.001
WBC	1.11	1.059–1.165	<0.001
ALT	0.981	0.971–0.990	<0.001
INR	2.378	1.291–4.381	0.005
Reason surgery	2.069	1.271–3.369	0.003
Chemotherapy	3.956	1.477–10.591	0.006
Admission abscess	3.202	2.149–4.77	<0.001
Recurrent episode	0.419	0.271–0.648	<0.001
ASA class	0.092	0.048–0.176	<0.001
CCI	1.266	1.164–1.376	<0.001
Abscess	1.908	1.499–2.428	<0.001
Wound class	1.662	1.368–2.02	<0.001
Operative approach	1.583	1.015–2.468	<0.001
Stoma	0.096	0.077–0.119	<0.001
Anastomosis	0.611	0.466–0.799	<0.001
Procedure	0.469	0.326–0.676	<0.001
Hospital stay	0.841	0.565–1.251	0.394
Minor complications			
Diabetes mellitus	2.562	2.493–2.634	<0.001
Functional health status	2.635	2.608–2.663	<0.001
CRE	0.584	0.409–0.834	0.003
Albumin	2.172	1.493–3.159	<0.001
WBC	0.890	0.828–0.956	0.001
Reason surgery	0.361	0.162–0.802	0.012
Admission abscess	0.274	0.146–0.516	<0.001
Recurrent episode	3.138	1.385–7.111	0.006
Antibiotic prep	0.340	0.184–0.628	<0.001
Abscess	0.249	0.131–0.471	<0.001
Anastomosis	3.637	1.790–7.391	<0.001
Procedure	3.674	1.956–6.901	<0.001
CCI	0.852	0.744–0.975	0.020
Hospital stay	0.931	0.902–0.961	<0.001
Stoma	0.226	0.112–0.454	<0.001
Chemotherapy	0.182	0.051–0.653	0.008

it was performed even in most of our patients. For example, it appears that our cohort was offered more stomas and laparoscopic approach. Studies by Holmer[18] and Agresta[25] might reflect current strategies on how to handle a patient with a residual abscess, which seem to advocate for a diversion over a primary anastomosis.

Our model appeared to have moderate to high accuracy in predicting overall major and minor complications following elective surgery of diverticulitis. Considering the accuracy of our prediction model, Al-Khamis et al.[14], Bolkenstein et al.[17], and Bordeianou et al.[20] more likely reported the management of the patients' frailty based on the serious adverse outcomes.

The limitations of this study were as follows: (1) nested regression models to generate some imputations for the missing values less than 30% of laboratory results, (2) retrospective analysis including measurement and recall biases, and (3) without stepwise or any other machine learning models. However, this is the first and largest study to identify a prediction model for the minor and major postoperative complications in early settings for elective diverticulitis surgery.

CONCLUSIONS

The preoperative management of nutrition, comorbidities, and invasive interventions might be a helpful clinical tool to better identify the postoperative care for the major and minor outcomes, priorly. In addition, the prediction of postoperative outcomes when accounting for patient comorbidities and patient acuity might add value to the current challenges to improve the quality of care.

ACKNOWLEDGMENTS

We are thankful to members of the Partners Colorectal Surgery Collaboratives.

AUTHORS' CONTRIBUTIONS

YA: Conceptualization, Data curation, Formal Analysis, Investigation, Methodology, Project administration, Software, Validation, Visualization, Writing – original draft. **PC:** Data curation, Investigation, Writing – review & editing. **RR:** Data curation, Writing – review & editing. **RB:** Data curation, Writing – review & editing. **LB:** Investigation, Methodology, Project administration, Writing – review & editing. **VO:** Visualization, Data curation. **EO:** Visualization, Data curation. **EA:** Investigation, Methodology, Writing – review & editing.

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ORIGINAL ARTICLE

https://doi.org/10.1590/1806-9282.20211186

Patient's point of view on the diagnosis, treatment, and follow-up in acromegaly: single-center study from a tertiary center

Ahmet Dirikoç[1], Burçak Polat[1], Birgül Genç[2], Çağlar Keskin[2]*, Bekir Çakır[1]

SUMMARY

OBJECTIVE: We aimed to evaluate the awareness and perspectives of acromegaly patients in the diagnosis and treatment processes and to evaluate basic clinical and demographic features.

METHODS: This cross-sectional study was conducted at the Endocrinology Department of Yildirim Beyazit University between March 2019 and April 2020. A total of 58 acromegalic patients were enrolled. All patients were identified from our database and called for a clinical visit and filling the questionnaire forms.

RESULTS: A total of 58 patients were included in this study (41.4% female). The mean age of the patients was 52±10.8 years. Median year from symptom to diagnosis (min-max) was 2 (1–12). Notably, 55.2% of the patients did not graduate from high school. Of the 58 patients, 30 (51.7%) patients had knowledge about the etiology of their disease. While 12 (20.7%) patients identified their initial symptoms themselves, 75% of the patients reported their symptoms during the clinical history taken by a health care professional. The majority of patients were diagnosed by an endocrinologist (69%). Acromegaly did not affect social life but affected work life and caused early retirement. Transsphenoidal surgery was performed as primary treatment in 96.6% of the patients (n=56). In all, 46 (79.3%) patients received medical treatment with somatostatin receptor ligands (e.g., octreotide or lanreotide long-acting release [LAR]) with or without cabergoline. Overall disease control was achieved in 38 (65.5%) patients.

CONCLUSIONS: Acromegaly is usually detected incidentally by clinicians. The diagnosis of acromegaly is delayed in most patients and disease-related complications have already developed at the time of diagnosis. Therefore, increasing the awareness of the society and health care professionals will reduce both disease-related comorbidities and the economic burden on the health system.

KEYWORDS: Acromegaly. Social life. Perspectives. Questionnaire.

INTRODUCTION

Acromegaly is a rare disease with incidence of 3.3 million per year, and it affects multiple organs and systems[1]. The disease is characterized by excessive growth hormone (GH) production and elevated insulin-like growth factor 1 (IGF-1). The most common etiology is a GH-secreting benign pituitary adenoma. Prolonged exposure to the hormone causes progressive somatic disfigurements, such as enlargement of hands and feet, facial overgrowth due to prognathism, and soft-tissue enlargement. The insidious onset of the symptoms and slow progress often lead to a marked delay in diagnosis, which is reported to be between 5 and 10 years after the onset of symptoms[2-4]. Before the diagnosis, the patients are usually admitted to different specialists and receive treatment for the complications without the holistic diagnosis of acromegaly. When not diagnosed and treated properly, the mortality is increased, and the patient's quality of life (QoL) is decreased. Therefore, early diagnosis of acromegaly is crucial and leads to better outcomes, including reducing overall mortality risk[5]. Timely diagnosis also enables earlier intervention for the comorbidities associated with acromegaly, consequently preventing progression to more advanced disease.

Acromegaly has several adverse effects on QoL, mostly due to musculoskeletal complications, persistent comorbidities, and economic burden of disease. Although previous studies have shown that effective and curative treatment in acromegaly significantly improves QoL, biochemical control does not correlate with clinical well-being and QoL impairments in patients who cannot achieve remission[6,7].

Since acromegaly is a rare disease, the data in the literature about the diagnostic process are scarce. In this study, our aim was to demonstrate the patients' perspective of the disease at the time of diagnosis and during the treatment. We also aimed to determine the demographic characteristics, associated comorbid conditions, and the therapeutic process in our patient group.

METHODS

This study was conducted at the Endocrinology Department of Yildirim Beyazit University between March 2019 and April

[1]Ankara Yıldırım Beyazıt University, Faculty of Medicine, Department of Endocrinology and Metabolic Disease – Çankaya, Turkey.
[2]Ankara City Hospital, Department of Endocrinology and Metabolic Disease – Çankaya, Turkey.
*Corresponding author: caglaron@hotmail.com
Conflicts of interest: the authors declare there is no conflicts of interest. Funding: none.
Received on February 24, 2022. Accepted on February 27, 2022.

2020. A total of 58 patients were enrolled. Before the start of the study, we obtained the local ethical board approval in accordance with principles of the Declaration of Helsinki. All patients were either operated and had histopathology proven or biochemically proven acromegaly. The patients were identified from our database and called for a clinical visit and filling the questionnaire forms. Inclusion criteria were age above 18 years at the time of enrollment, ability to understand and complete the self-reporting questionnaire, and absence of any psychiatric disorder.

The survey was created by the authors participating in the study and performed by a health care professional. The questionnaire was composed of data on the demographic features such as the age, sex, marital status, occupation, and education level. Height, weight, smoking history, diagnostic process such as the specialty and the number of clinicians that the patient visited after the onset of symptoms, reported complaints at the time of diagnosis, duration of the diagnostic process, received treatment modalities, acromegaly-related complications and accompanying comorbid conditions, and follow-up results were also included in the survey.

Statistics

For statistical analysis, SPSS version 22.0 (Statistical Package of the Social Sciences, IBM, Armonk, NY, USA) for Windows was used. Interval-scaled data were described as means and standard deviations (SD), and categorical data were described as percentage. Data were tested for normal distribution by a Shapiro-Wilk test. Free-text answers were categorized and counted. Missing variables were regarded as missing at random. Descriptive analysis was made and given as number of patients and percentage for the categorical variables. For group comparisons, unpaired t-tests or Mann-Whitney U tests for unpaired variables were used. Nominal data were calculated as valid percentage and analyzed by chi-square test or Fisher's exact test.

RESULTS

Patient characteristics

A total of 58 patients were enrolled in the study and filled out the forms. Of these, 34 (58.6%) were male and 24 (41.4%) were female. The mean age of the patients was 52±10.8 years. The oldest patient aged 72 years and the youngest one aged 25 years. Regarding educational level, 28 (48.3%) patients were graduated from primary school, 4 (6.9%) were secondary, 16 (27.6%) were high school, and 10 (17.2%) were university graduates. Out of 58 patients, 50 (86.2%) were married and 8 (13.8%) were either single or widow. Three female patients divorced after the diagnosis, and two declared the disease as the cause of divorce. Regarding occupation, 24 (41.4%) patients were retired, 14 (24.1%) were actively working, and 20 (34.5%) did not have any occupation. Also, 12 (20.7%) patients were active smoker and 46 (79.3%) patients were either non-smoker or ex-smoker. The mean height of the patients was 168±10.6 cm, and mean weight was 88.07±13.34 kg. Of the 58 patients, 22 were obese, 28 were overweight, and 8 were normal according to body mass index (BMI). The demographic features are listed in Table 1.

Table 1. Patient variables regarding the demographic features and diagnostic process.

Sex (female/male)	34 (58.6%)/24(41.4%)
Age (years)	52±10.8
Education level	
Primary school	28 (48.3%)
Secondary school	4 (6.9%)
High school	16 (27.6%)
University	10 (17.2%)
Occupation	
Actively working	14 (24.1%)
Not working	20 (34.5%)
Retired	24 (41.4%)
Smoking status	
Smoker	12 (20.7%)
Non/ex-smoker	46 (79.3)
Height (cm)	168±10.6
Weight (kg)	88.07±13.34
BMI	
Normal	8 (13.7%)
Overweight	28 (48.2%)
Obese	22 (38.1%)
Knowledge of disease etiology (yes/no)	30 (51.7%)/28 (48.3%)
Any close relative or friend who has acromegaly (yes/no)	0 (0%)/58(100%)
Median years from symptom to diagnosis (min-max)	2 (1–12)
Symptoms noticed by	
Self	12 (20.7%)
Relative/friend	4 (6.9%)
Health care professional	42 (72.4%)

Continue...

Table 1. Continuation.

The diagnosis of acromegaly was made by	
Endocrinologist	40 (69%)
Internal medicine	10 (17.2%)
Neurosurgeon	6 (10.2%)
Family doctor	1 (1.8%)
Gynecologist	1 (1.8%)
Initial complaints at diagnosis (number of patients)	
Headache	10
Hypertension	30
Fatigue/lack of energy	32
Heart disease	12
Thyroid nodules	32
Sleep apnea	14
Diabetes	24
Polyposis coli	14
Back pain	5
Neuropathic symptoms	9
Joint pain	30
Mood disorder	16
Visual disturbance	8
Skin problems	22
Menstrual irregularities	5
Weight gain	2
Galactorrhea	2
Excessive body hair	2
Distortion of the facial structures	7
Teeth abnormality	1

Patients' disease perception, symptoms, and diagnostic process

Of the 58 patients, 30 (51.7%) knew the etiology of their disease (that they had a GH-secreting pituitary adenoma), while 28 (48.3%) could not define it. None of the patients knew another acromegaly patient among their family members or close friends.

Median year until diagnosis after symptom onset was 2 years (min-max; 1–12 years). Symptoms were identified by the patient him/herself in 12 (20.7%) cases, by a family member in 4 (6.9%) cases, and with the help of the clinical history taken by a health care professional in 42 (72.4%) cases. The diagnosis of acromegaly was made by an endocrinologist in 40 (69%) patients, by an internal medicine doctor in 10 (17.2%) patients, by a neurosurgeon in 6 (10.2%) patients, and by a family doctor and a gynecologist in 2 patients. Among the initial symptoms, headache was present in 10 patients, hypertension in 30 patients, fatigue or lack of energy was present in 32 patients, heart disease (cardiomyopathy/valvular heart disease) in 12 patients, thyroid nodules in 32 patients, sleep apnea in 14 patients, diabetes in 24 patients, polyposis coli in 14 patients, back pain in 5 patients, joint pain in 30 patients, mood disorder in 16 patients, neuropathic symptoms in 9 patients, visual abnormality in 8 patients, skin problems in 22 patients, menstrual irregularities in 5 patients, weight gain in 2 patients, galactorrhea in 2 patients, excessive body hair growth in 2 patients, distortion of facial structures in 7 patients, and teeth abnormality in 1 patient.

Only 9 of 58 patients reported decreased QoL because of the acromegaly-related symptoms. And the most common disturbing symptoms were headache and arthralgia. Three patients reported negative impact of disease in their social life and personal relationships. The most common reason for this was facial disfigurement. Two patients blamed the disease as a reason for their divorce. Twenty patients were not actively working, but none of them thought acromegaly was an obstacle to the occupation status. There were 24 patients who were retired, of whom 12 were admitted for early retirement option due to acromegaly and were receiving disease-related disability privileges. A total of 38 patients reported that they perceive acromegaly as a lifelong disease without a definite cure.

Treatments and disease control status

Of the 58 patients, 56 (96.6%) underwent surgery as the primary treatment. The histopathology revealed a GH-positive pituitary adenoma in 51 patients. Seven patients had combined staining with prolactin (PRL) and GH. The histopathology reports were lacking the granulation pattern. Notably, 46 (79.3%) patients received medical treatment with somatostatin receptor ligands (SSRLs) (e.g., octreotide or lanreotide LAR) with or without cabergoline. Only three patients had complaints due to SSRLs, mostly gastrointestinal discomfort and pain at the injection side. None of the patients received pasireotide or pegvisomant. Of note, 11 (19.6%) patients received radiotherapy (conventional/gamma knife). Mean disease duration was 11.7±4.97 years. After the diagnosis, all patients reported visits to endocrinologists. In all, 20 reported regular visits in every 6 months and the rest 34 patients reported at least one visit in a year. The other specialties that they regularly consulted were a neurosurgeon (19 patients), ophthalmologist (6 patients), and gastroenterologist (12 patients). The number of patients whose IGF-1 was in the target range in the last

two visits was 38 (65.5%). Of the 58 patients, 52 (89.6%) chose the surgery as the most effective treatment, followed by radiotherapy (6.9%) and medical treatment (3.5%). IGF-1 was used in the follow-up of all patients, whereas glucose GH test was used within the previous year only in 6 patients. IGF levels was measured in each visit every 8.9±3.6 months. The frequency of magnetic resonance imaging (MRI) was every 15.6±6.5 months. The diagnosis of acromegaly caused early retirement in 12 patients and the loss of occupation in 2 patients, whereas no major changes were reported in others. Details of the diagnostic process are shown in Table 1, and treatment and follow-up details are shown in Table 2.

Impact of sex difference

Both male and female patients were compared regarding the time interval between the start of the symptoms and diagnosis, treatment modalities received, and disease control status. The median time from the onset of symptoms to diagnosis was 2.3 years (1.5–12) in females and 1.8 years (1–10) in males (p=0.59). Disease duration was 14.3±4.16 years in females and 10.0±4.8 years in males (p=0.03). Demographic and diagnostic features were similar, except the number of patients was higher among men than women (p<0.001). The choice of treatment modalities, the number of patients operated, and medical treatment percentage were similar between two genders (p=0.55, 0.58, and 0.46, respectively). The number of patients in remission was also similar between two genders (p=0.17) (Table 3).

Table 2. Treatment and follow-up details.

Number of patients operated as primary treatment	56 (99.6%)
Number of patients operated more than once	24 (41.3%)
Number of patients treated with SSRLs	46 (79.3%)
Number of patients received radiotherapy (conventional/gamma knife)	11(19.6%)
Mean disease duration (years)	11.7±4.97
Mean interval between control visits (months)	8.9±3.6
Number of patients going regular control visits to	
Endocrinologist	58 (100%)
Neurosurgeon	19 (32.7%)
Ophthalmologist	6 (10.3%)
Gastroenterologist	12 (20.6%)
Number of patients in remission (IGF-1 in normal range)	38 (65.5%)
Test used in the follow-up	
IGF-1	58 (100%)
Glucose growth hormone suppression test	6 (10.3%)
MR (periodically)	22 (37.9%)

DISCUSSION

In this study, we evaluated the demographic and social features, diagnostic process, access to treatment, follow-up procedures, and perception of disease by the patient in our single-center acromegaly patients. Our hospital is a tertiary center with an experienced endocrinology clinic with registered acromegaly patients. We enrolled 58 of those who gave consent and accepted to fill the detailed study forms and answer the questions.

In this patient cohort, the diagnostic process started with the recognition of the first disease-specific symptom until the exact diagnosis was 2 years (min-max: 1–12). In a previous study, it was reported that the delay was longer, with an average of 5.3±4 years from symptom onset[2]; however in recent studies, it has become shorter, with an average of 2.5 years[4,5]. In a previous cohort with higher number of patients from Turkey, the median period of delay before the initial diagnosis was 24 months and interquartile range was 6.0–48.0 months[8]. The possible explanations for relatively shorter diagnostic process may be due to living in the capital city and easy access of patients to the endocrinologists or internal medicine doctors without loosing time for referral from the family practitioner. Also, it may be due to the "acromegaly awareness" courses and educational workshops for physicians by the Endocrinology and Metabolism society in our country. We did not show any difference between genders, indicating that both genders equally benefit from the health care facilities. This may also be due to similar education levels of two genders.

The education level was similar between the genders, and unfortunately low with >50% of the patients did not graduate from high school. We do not know the educational level of the background population composed of age- and sex-matched

Table 3. Comparison of male and female patients according to diagnosis time and access to treatment.

	Female (24)	Male (34)	
Time to diagnose (years) (median)	2.3 (1.5–12)	1.8 (1–10)	p=0.59
Disease duration (years) (mean)	14.3±4.16	10.0±4.8	p=0.03
The number of patients operated	24 (100%)	32 (94.1%)	p=0.58
Usage of SSRLs or DA	19 (79.1%)	27 (79.4%)	p=0.46
Number of patients in remission	16 (66.6%)	22 (64.7%)	p=0.17

healthy individuals to make a comment. In a recent study, it was reported that the education status of the acromegaly patients was similar to the general population, except a tendency toward lower educational level especially in patients diagnosed before 30 years of age[9].

In the context of daily life, there were no significant changes in personal or social life. The marital status changed only in two female patients because of the acromegaly diagnosis. Half of the patients who were retired had early retirement. Our data support that acromegaly reduces work life and production. In a previous study, it was shown that the comorbid conditions such as diabetes, cardiac disorders, or debilitating arthropathy increase the early retirement, and this rate increases with time and is more prominent in females[10-12]. The number of active workers were higher in males, reflecting the occupation ratios of our reference population. Participants recognized that they had a disease for which the word "cure" does not often apply, particularly if they had to face being on medication for the rest of their life. In our patient group, all the participants reported in one way or another by the degree to which they had educated themselves about the disease via online sources and their own experiences, then additionally through listening to and sharing with each other.

Concerns raised by a doctor or another health care professional prompted the diagnosis in most cases. Patients and close friends or relatives suspected the disease in a low number of cases. In our cohort, most of the patients came to medical attention with nonspecific findings at the time of diagnosis. More specific features such as facial features or extremities were detected less by the patients. So, in most cases, the diagnosis was incidental and caught by the attention of the doctor, as reported in previous studies[4,13,14]. Most of the patients were diagnosed with acromegaly by an endocrinologist or an internal medicine doctor. The diagnosis was made by the suspicion of the physician during examination of related comorbidity or complications, including thyroid nodular disease, diabetes, and hypertension in most cases. The cases detected by the neurosurgeons were mostly admitted with compressive symptoms due to adenoma such as headache or visual abnormality. The number of patients detected by general physicians (GPs) was less and none were referred from the dentist in contrast to previous studies[15,16].

Diagnostic and treatment modalities are in line with international guidelines in our country[17]. The most preferred primary treatment in patients was surgery, which was also perceived as the most effective treatment by the patients. Surgery could not be performed in two patients because of preoperative risk due to advanced cardiopulmonary disease. Almost 40% of the operated subjects underwent recurrent surgeries. Our findings were compatible with the previous reports, suggesting that the remission rates are lower than 60% for macroadenomas[18]. SSRLs and DA were used for medical therapy in patients who could not achieve remission after the surgery. Access to medical treatment and remission rates were similar between male and female patients. The remission rate with medical treatment was over 60%, which was higher than a recent report[19].

CONCLUSION

The symptom in acromegaly patients is usually detected by clinicians incidentally, so diagnosis requires attention, knowledge, and suspicion. Patients do not have severe alterations in daily or social life, but occupation is decreased due to comorbid conditions. To decrease economic burden of the disease, early diagnosis should be supported by increasing disease awareness among health care professionals and society.

AUTHORS' CONTRIBUTIONS

AD: Conceptualization, Methodology, Writing – original draft. **BP:** Methodology, Writing – original draft. **BG:** Data curation, Investigation. **ÇK:** Data curation, Investigation. **BÇ:** Methodology, Writing – review & editing.

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ORIGINAL ARTICLE

https://doi.org/10.1590/1806-9282.2021203

Comparison of arterial stiffness and ultrasound indices in patients with and without chronic obstructive pulmonary disease

XiaoHui Zhang[1]*, ShengTao Zhang[1], QiuLing Huang[1], YunQiu Liu[1], JingNan Chang[1], Peng Liu[1]

SUMMARY

OBJECTIVE: The purpose of this study was to compare arterial stiffness and ultrasound indices in patients with and without chronic obstructive pulmonary disease.

METHODS: In our retrospective study, 83 chronic obstructive pulmonary disease patients were assigned to the chronic obstructive pulmonary disease group and 80 healthy controls were enrolled. Pearson's correlation analysis software was used to analyze the correlation between arterial stiffness (including brachial ankle pulse wave velocity and ankle-brachial blood pressure index) and ultrasound index (including resistance index, pulsatility index, and intima-media thickness) at the carotid artery in chronic obstructive pulmonary disease patients.

RESULTS: The ultrasound resistance index and pulsatility index level of chronic obstructive pulmonary disease group were lower than those of control group (t=6.326, 8.321, p<0.001). Compared with the control group, the chronic obstructive pulmonary disease group had higher intima-media thickness, total plaque area, and number of plaques (t=4.574, 7.493, 5.093, p<0.001). The arterial stiffness and ankle-brachial blood pressure index level in the chronic obstructive pulmonary disease group were higher than those in the control group (t=6.392, 5.109, p<0.001). Moreover, arterial stiffness in patients with chronic obstructive pulmonary disease was negatively correlated with the ankle-brachial blood pressure index, resistance index, and pulsatility index levels (p<0.05), while it is positively correlated with intima-media thickness, total plaque area, and number of plaques (p<0.05).

CONCLUSION: Our results indicated that patients with chronic obstructive pulmonary disease have stiffer arteries compared with healthy control subjects; the ultrasound index could be used as an auxiliary indicator for clinical prediction of arterial stiffness, which is helpful to improve the accuracy of prediction and thus better guide clinical interventions in high-risk groups of chronic obstructive pulmonary disease in time.

KEYWORDS: Chronic disease. Chronic obstructive. Ultrasonography. Vascular stiffnesses.

INTRODUCTION

Chronic obstructive pulmonary disease (COPD) is a chronic respiratory disease characterized by persistent respiratory symptoms and airflow limitation due to airway and/or alveolar abnormalities usually caused by high exposure to noxious particles or gases (usually tobacco smoke but also from environmental and occupational exposures) and influenced by host factors including abnormal lung development[1]. COPD can cause pulmonary hypertension, which can result in enlargement of the right ventricular and may develop to right heart failure, which seriously threaten the life of patients[2,3]. Cardiovascular disease is the most common chronic disease associated with COPD, a major cause of hospitalization, and also one of the leading causes of death[4]. Previous studies have shown that patients with COPD are at increased risk of atherosclerosis, and the mechanism may be related to hypoxemia and inflammation[5-7]. Arterial stiffness is highly relevant to cardiovascular disease and is an important arterial phenotype and an excellent indicator of cardiovascular morbidity and mortality. In clinical practice, measurements of arterial stiffness is currently one of the most commonly used methods to predict cardiovascular risk in patients with COPD[5,7,8]. Of note, early evaluation of arterial stiffness in patients with COPD is of great significance for the treatment and prognosis of the disease. Pulse wave velocity (PWV), defined as the ratio of the distance to transit time between two pressure waves recorded transcutaneous at two arterial sites, is a classic index to reflect arterial stiffness in clinical practice[8-10]. The occurrence of cardiovascular events is very dangerous, and early detection and early prevention play a particularly key role in such diseases. Although the monitoring of PWV has been very applicable in clinical practice, finding and combining with the detection of other early indicators of vascular diseases can only benefit the treatment of cardiovascular diseases. Ultrasound is a commonly used method for measuring arterial stiffness in clinic, but there are few reports on the relationship between other ultrasound indexes and arterial stiffness. Ultrasound, as a widely used clinical tool, might have

[1]Linxi Hospital, Kailuan General Hospital, Department of Respiratory Medicine – Tangshan, China.
*Corresponding author: zhangxiaohui_ys@163.com

Conflicts of interest: the authors declare there is no conflicts of interest. Funding: This work was supported by Medical Science Research Project Plan of Hebei Province in 2019 (grant number 20191343).
Received on February 07, 2022. Accepted on February 08, 2022.

its advantages in evaluating arterial stiffness in some clinical scenarios, especially when PWV was unavailable. The aim of the study was to compare and analyze the arterial stiffness in COPD patients and healthy people by ultrasonic indicators, find the correlation between COPD and arterial stiffness, and provide reference for better clinical prediction of the occurrence and development of COPD.

METHODS

Study design and patients

Consecutive 112 patients with COPD hospitalized in our hospital from August 2017 to August 2019 were retrospectively screened for eligibility. Inclusion criteria were as follows: ① patients meet the clinical diagnostic criteria of COPD[1]; ② patients with cough and progressive dyspnea; ③ patients with history of high exposure to toxic smoke or dust; and ④ patients agree to participate in the study and complete ultrasound and arterial hardness tests. Exclusion criteria were as follows: ① patients with hematological diseases or malignant tumors (n=7); ② patients with autoimmune diseases (e.g., systemic lupus erythematous and rheumatoid arthritis), diabetes, hypertension, or coronary heart disease (n=12); ③ patients with severe liver (bilirubin is two times higher than the normal upper limit, or transaminase was three times higher than the normal upper limit) or kidney dysfunction (hemodialysis, kidney transplantation, or serum creatinine ≥200 μmol/l) (n=4); and ④ patients with hyperlipidemia (total cholesterol ≥5.72 mmol/l or triglycerides ≥1.70 mmol/l) or hyperuricemia (uric acid ≥420 μmol/l) (n=6). In total, 83 patients were included as the COPD group. Meanwhile, 80 health subjects with normal pulmonary function, without history of COPD or other diseases included in the exclusion criteria, were selected as the control group. This study was conducted in accordance with the Declaration of Helsinki and approved by the ethics committee of our Hospital. Written informed consent was obtained from all participants.

Methods

Detection of carotid artery disease with ultrasound

① Detection method: All patients in both groups completed relevant examinations after admission. We explained the disease-related knowledge to patients and their families and informed patients of the importance and necessity of ultrasound examination to improve patients' cooperation. IU22 color Doppler ultrasound (manufacturer: Philips) was used for inspection, and the probe frequency was 2–10 MHz. During the examination, patients took the supine position and fully exposed the neck. The ultrasound probe was placed at the 2 cm position of the carotid artery bifurcation to complete the measurement of carotid artery intima-media thickness (IMT); resistance index (RI) and pulsatility index (PI) were two hemodynamic parameters calculated by flow velocity on ultrasound, which reflected vascular resistance. RI and PI were measured at the bifurcation of the carotid artery 1 cm near the heart and then determine the total plaque area and plaque number. The plaque area was calculated by the following formula: original lumen area — residual lumen area (Figure 1). To improve the accuracy of detection data and reduce the detection error, we measured each subject three times and averaged the results. ② Judgment method: according to the detection results of the two groups, IMT >1.2 mm indicated the patient has atherosclerotic plaque formation[11]. All ultrasound examinations were performed by ultrasound physicians in our hospital.

Measurement of arterial stiffness

① Detection method: BP-203III arterial stiffness tester (manufacturer: Omron) was used to detect brachial-ankle pulse wave velocity (baPWV) and ankle-brachial blood pressure index (ABI). During the test, the temperature in the control room was set at 22–25°C. All subjects wore thin clothes and took a lying posture. The test was started after resting for 5 min. Blood pressure and heart rate were measured first, followed by baPWV and ABI tests. Each case was measured twice and averaged[12]. ② Judgment method: baPWV ≥ 1400 cm/s indicated arterial stiffness; ABI > 1.4 indicated abnormal elevation[11].

Statistics

Statistical software SPSS version 20.0 was used to analyze the data. Normally distributed continuous variables were

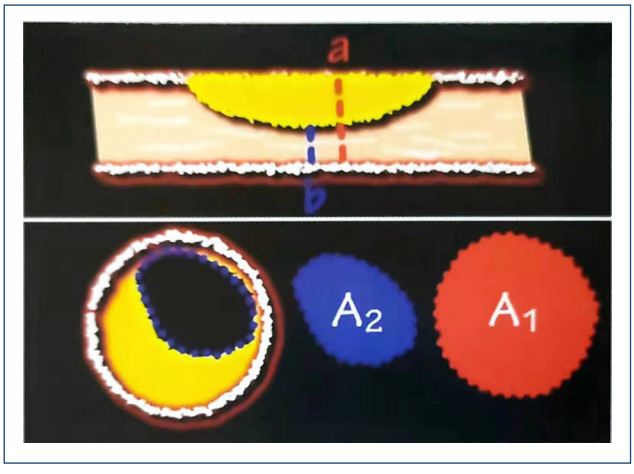

Figure 1. Measurement of patch area.

expressed as mean±standard deviation (SD), and categorical variables were expressed as percentage. An analysis of normality of the continuous variables was performed with the Kolmogorov-Smirnov test. The mean comparison between the two groups was performed by independent sample t-test; the count data were expressed in cases (%), and the comparison between groups was performed by χ^2. Pearson's correlation analysis was used for analyzing the correlation between arterial stiffness and ultrasound index in patients with COPD. The data were analyzed within the 95% confidence interval (CI95%) and p<0.05 was considered statistically significant.

RESULTS

Baseline characteristics of two groups

There were 46 males and 37 females in the COPD group, with an average age of 61.34±2.91 years and body mass index (BMI) of 22.41±2.15 kg/m^2. In the control group, there were 41 males and 39 females, with an average age of 61.87±3.04 years and BMI of 22.32±2.31 kg/m^2. There was no statistically significant difference in general data between the two groups (p>0.05) (Table 1).

Comparison of ultrasound examination results, arterial stiffness, and ABI between the two groups

The levels of RI and PI in the COPD group were lower than those in the control group (p<0.05); IMT level, total plaque area, and number of plaques in the COPD group were higher than those in the control group (p<0.05). The levels of baPWV and ABI in the COPD group were higher than those in the control group (p<0.05) (Table 1).

Correlation analysis of arterial stiffness and color doppler ultrasound index in patients with COPD

Pearson correlation analysis showed that the levels of baPWV and ABI were negatively correlated with RI and PI in patients with COPD (p<0.05), but positively correlated with IMT, total plaque area, and number of plaques (p<0.05) (Table 2).

DISCUSSION

In the present study, we compared arterial stiffness in patients with and without COPD and examined the relationship between ultrasound and arterial stiffness. The main findings can be summarized as follows: (1) compared with the control group, COPD patients had higher IMT, total plaque area, and number of plaques but lower ultrasound RI and PI; (2) the arterial stiffness and ABI level in the COPD group were higher than those in the control group; (3) arterial stiffness in patients with COPD was negatively correlated with the ABI, RI, and PI levels while it is positively correlated with IMT, total plaque area, and number of plaques.

Table 1. Comparison of basic characteristics and ultrasound results between the two groups.

Variables	COPD group (N=83)	Control group (N=80)	p-value
Basic characteristics			
Males, n	46	41	0.59
Age, year	61.34±2.91	61.87±3.04	0.87
BMI, kg/m^2	22.41±2.15	22.32±2.31	0.79
Current smoker, n	47	35	0.06
Current drinkers, n	42	38	0.75
Ultrasound results			
RI	0.62±0.14	0.81±0.22	<0.001
PI	2.61±0.38	2.95±0.36	<0.001
IMT, mm	1.36±0.13	0.94±0.10	<0.001
Total plague area, mm^2	19.75±2.19	5.84±1.32	<0.001
Plaque numbers, n	1.67±0.64	0.82±0.30	<0.001
BaPWV, cm/s	1585.49±14.36	1142.45±10.77	<0.001
ABI	1.63±0.24	1.12±0.16	<0.001

Values are mean±SD for continuous variables or n (%) for categorical variables.

Table 2. Correlation analysis of arterial stiffness and color Doppler ultrasound index in patients with chronic obstructive pulmonary disease.

Related factors	RI R value p-value	PI R value p-value	IMT R value p-value	Patch area R value p-value	Patch numbers R value p-value
baPWV	-0.693 (<0.001)	-0.721 (<0.001)	0.701 (<0.001)	0.668 (<0.001)	0.784 (<0.001)
ABI	-0.712 (<0.001)	-0.689 (<0.001)	0.667 (<0.001)	0.712 (<0.001)	0.722 (<0.001)

Chronic obstructive pulmonary disease is a common respiratory disease characterized by persistent airflow limitation. Its occurrence and development are closely related to the chronic inflammatory reaction caused by the exposure of airways and lungs to toxic substances. Cardiovascular disease is the most common complication in patients with COPD, and more patients die from cardiovascular disease than from respiratory disease[4,13-15]. Therefore, it is important to strengthen the early diagnosis of patients with COPD and timely take clinical intervention to reduce the incidence of COPD.

Arterial stiffness is a noninvasive examination commonly used in clinical prediction of carotid artery disease. Increased arterial stiffness is the early manifestation of arteriosclerosis, which can be effectively diagnosed by ultrasound. The measurement of arterial stiffness in high-risk groups of atherosclerosis can not only detect subclinical vascular structure changes in time but also guide clinical treatment. Previous studies have shown that arterial stiffness is associated with emphysema severity, cardiovascular disease risk, and severity and prognosis in patients with COPD[5,7,16-18]. In this study, we analyzed and compared the arterial stiffness in COPD patients and subjects without COPD by measuring PWV and ABI and detecting carotid artery disease with ultrasound. The results showed that the levels of RI and PI in the COPD group were lower than those in the control group ($p<0.05$); the IMT, total plaque area, and number of plaques in the COPD group were higher than those in the control group ($p<0.05$). The arterial stiffness and ABI level in the COPD group were higher than those in the control group ($p<0.05$), suggesting that the continuous development of COPD may lead to the increase in arterial stiffness and abnormal ultrasound examination.

At present, PWV is the main clinical method for arterial stiffness examination, with the advantages of simple operation, accurate results, and noninvasive, and is suitable for large-scale screening of asymptomatic population[19]. However, pulse wave propagation is affected by arterial stiffness. The greater the segmental arterial stiffness, the faster the PWV[20]. The detection of arterial stiffness is often affected by the nature and thickness of arterial wall. To reduce the influence of other related factors during the examination of arterial stiffness, we further analyzed the relationship between arterial stiffness and ultrasound results in patients with COPD. The results showed that arterial stiffness and ABI levels were negatively correlated with RI and PI levels ($p<0.05$) and positively correlated with IMT, total plaque area, and plaque number ($p<0.05$), suggesting that there was a correlation between arterial stiffness in patients with COPD and the results of ultrasound examination, which could be used as an auxiliary detection index of arterial stiffness.

Arterial stiffness has been increasingly recognized as a strong and independent predictor of cardiovascular events and all-cause mortality by a growing number of clinical and population-based studies[21,22]. Noninvasive arterial PWV, most commonly measured as carotid-femoral PWV (cfPMV), is a simple, robust, and reproducible parameter that is considered the "gold standard" for assessing arterial stiffness[23]. In practice, cfPWV can be calculated as the transit distance divided by the corresponding transit time, which can be reliably determined by Doppler ultrasound[24]. Arterial PWV measured with Doppler echocardiography has also been validated to have a fairly high correlation and agreement with invasive measurements[25]. Given its remarkable breadth, Doppler ultrasound has been recognized as a reliable method for noninvasive assessment of arterial stiffness.

The study has some limitations. First, this study is a single-center retrospective study, and the conclusions drawn need to be further confirmed by clinical studies with a larger sample size. Then, we did not collect all the information of the patients and could not conduct further logistic regression analysis due to the limitations of objective conditions. But we will discuss the problem in our follow-up research.

CONCLUSIONS

This study showed that arterial stiffness in patients with COPD was higher than that in people without COPD, and there is a correlation between arterial stiffness and ultrasonic index in COPD patients. Therefore, we speculated that ultrasonic index could be used as an auxiliary detection method for arterial stiffness to improve the accuracy of prediction of carotid artery lesions and better guide clinical treatment.

ETHICS APPROVAL AND INFORMED CONSENT

This study was conducted in accordance with the Declaration of Helsinki and approved by the ethics committee of Linxi Hospital of Kailuan General Hospital. Written informed consent was obtained from all participants.

AUTHORS' CONTRIBUTIONS

XHZ: Investigation and Methodology, Writing – original draft. **STZ:** Data curation. **QH:** Formal Analysis. **YQL:** Investigation and Methodology. **JNC:** Data curation. **PL:** Writing – review & editing.

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ORIGINAL ARTICLE

https://doi.org/10.1590/1806-9282.20211212

Translation, cross-cultural adaptation, and validation of the heart disease fact questionnaire among the Brazilian population

Walkiria Shimoya-Bittencourt[1], Aldair Darlan Santos-de-Araújo[2], Natália de Castro Corrêa[4], Meire Coelho Ferreira[5], Maria Jacqueline Silva Ribeiro[6], Rodrigo Costa Cutrim[6], Ariane Hidalgo Mansano Pletsch[7], Ana Karolina Franzim Garcia[7], Beatriz Nogueira de Araújo[7], Daniela Bassi-Dibai[3,4]*

SUMMARY

OBJECTIVE: This study aimed to translate, cross-culturally adapt, and validate the Heart Disease Fact Questionnaire into Brazilian Portuguese.

METHODS: The Brazilian version of the Heart Disease Fact Questionnaire was developed through the processes of translation, back-translation, review committee, and pre-test. Test-retest reliability was measured using the intraclass correlation coefficient and the kappa coefficient. Internal consistency was measured using Cronbach's alpha. For construct validity, the total Heart Disease Fact Questionnaire score was correlated with the Diabetes Knowledge Scale and the Diabetes Attitudes Questionnaire. Ceiling and floor effects were also evaluated in this study.

RESULTS: For construct validity and floor and ceiling effect measurements, a total of 100 participants were selected. Reliability was measured using a sub-sample of 30 participants from the total sample. We identified adequate values of reliability (kappa between 0.22 and 1.00 and ICC=0.75) and internal consistency (Cronbach's alpha=0.79). We observed adequate correlations of the Heart Disease Fact Questionnaire score with Diabetes Knowledge Scale (r=0.348) and Diabetes Attitudes Questionnaire (r=0.136). No ceiling or floor effects found.

CONCLUSION: Brazilian Portuguese version of the Heart Disease Fact Questionnaire has adequate psychometric properties according to the best scientific recommendations.

KEYWORDS: Diabetes mellitus. Questionnaire design. Primary health care. Risk factors.

INTRODUCTION

Type 2 diabetes mellitus (T2DM) and cardiovascular diseases (CVD) share many similar pathophysiological characteristics, especially insulin resistance[1], inflammation[2], systemic arterial hypertension[3], and obesity[4]. These characteristics increase the risk of complications and mortality[5,6]. The most recent epidemiological data points to a significant increase in the prevalence of diabetes worldwide, considering that in the past three decades, the number of people diagnosed has more than doubled, with this growing prevalence being associated with a 60% increase in the risk rate attributable to CVDs due to diabetes[7,8]. In addition, it is estimated that by 2035, the number of individuals affected by the pathology will reach the order of 592 million worldwide[9]. Brazil currently ranks fourth in the number of people living with the disease worldwide and first among Latin and Central American countries[10].

In this context, especially in primary care, the use of simple and cost-effective strategies has been desired and encouraged, thus trying to prevent the coexistence of diseases that have high morbidity and mortality and high cost not only for the health system but also for patients[11], as is the case with DM and CVD.

Therefore, the use of questionnaires has been extensively explored not only in the screening and/or screening of various diseases, such as FINDRISK[12], used to screen the risk of developing T2DM, but also as an assessment tool, investigating the level of knowledge about a certain disease and the risk of developing it, such as the Heart Disease Fact Questionnaire (HDFQ).

The Heart Disease Fact Questionnaire (HDFQ) is a 25-item questionnaire that was developed to explore/assess individuals'

[1]Centro Universitário de Várzea Grande – Cuiabá (MT), Brazil.
[2]Universidade Federal de São Carlos, Postgraduate Program in Physical Therapy, Cardiopulmonary Laboratory – São Carlos (SP), Brazil.
[3]Universidade Ceuma, Department of Physiotherapy – São Luís (MA), Brazil.
[4]Universidade Ceuma, Postgraduate Program in Programs Management and Health Services – São Luís (MA), Brazil.
[5]Universidade Ceuma, Postgraduate Program in Dentistry – São Luís (MA), Brazil.
[6]Universidade Ceuma, Department of Medicine – São Luís (MA), Brazil.
[7]Universidade de Cuiabá, Department of Physiotherapy – Cuiabá (MT), Brazil.
*Corresponding author: danielabassifisio@gmail.com
Conflicts of interest: the authors declare there is no conflicts of interest. Funding: none.
Received on February 10, 2022. Accepted on February 11, 2022.

knowledge about the main risk factors for the development of CVD, with a greater focus on diabetics[13]. The HDFQ has already been validated for Turkish[14] and Chinese[15], but has not yet been published for Brazilian Portuguese. Thus, considering the importance of this tool in measuring the level of knowledge about the risk of CVD, this study aimed to translate, cross-culturally adapt, and validate the HDFQ into Brazilian Portuguese.

METHODS

Study design

This was a cross-sectional study on translation and cross-cultural adaptation of a questionnaire. It was conducted in accordance with the Guidelines for the Process of Cross-cultural Adaptation of Self-Report Measures[16] and the COSMIN[17]. This study was approved by the research ethics committee, under opinion number 2.853.570. Participants were recruited through social media, text messages, and emails. All volunteers confirmed their participation after signing the informed consent form.

Participants

The sample size for this study was 100 individuals based on the COSMIN[17]. Individuals of both genders, aged over 18 years, with report of clinical diagnosis of T2DM and regular use of hypoglycemic drugs, without cognitive deficits, or with difficulty reading or writing were included. Exclusion criteria include any situations that made it impossible to answer the questionnaire.

Translation and cross-cultural adaptation of heart disease fact questionnaire

The process of translation and cross-cultural adaptation of HDFQ for Brazilian Portuguese followed the criteria of Beaton et al.[16] and was performed in the following five stages:

1. Translation: Two independent translators, both with Brazilian Portuguese as their native language and fluent in English, translated the original version of the HDFQ into Brazilian Portuguese.
2. Synthesis of translations: After discussions and revisions, the two translators, under observation by one of the researchers, synthesized the two independently translated versions of the questionnaire and produced a single consensual version of HDFQ.
3. Back-translation: Two independent translators (without technical knowledge of the field of health care), both with English as their mother tongue and fluency in Portuguese, translated the Portuguese version of HDFQ back into English, without previous knowledge of the original version of the questionnaire. These translators were not the same as those in phase 1 (English to Portuguese language translation).
4. Expert committee review: Three experts reviewed all the translated and back-translated versions for corrections of possible discrepancies, thus reaching the pre-final version of the HDFQ. At this stage, the criteria for including experts were as follows: time availability, fluency in both languages, clinical expertise with diabetes and heart disease, and interest in collaborating in the study. The pre-final version of HDFQ questionnaire was agreed among all the committee members.
5. Pre-final test: The pre-final version of HDFQ was applied to 30 individuals with diabetes and with Brazilian Portuguese as their mother tongue. The participants read and completed the questionnaire and, at the end of the questionnaire, established that they had understood the pre-final version of HDFQ by selecting check boxes containing "yes" or "no" answers to each question on the questionnaire. To be considered having an adequate degree of understanding, the items must be understood by at least 80% of the participants. After analyzing the pre-final version, the coordinator of the adaptation process thus established the final version of the HDFQ in Brazilian Portuguese.

Heart disease fact questionnaire

Being developed by Wagner et al.[13], the HDFQ is composed of 25 items and assesses how much knowledge an individual has about the risks of developing heart disease, especially in relation to diabetics. The language of the original scale is English. The sentences that build the scale can be true or false with three response options: "Yes," "No," or "I don't know." For each correct answer, a score of 1 is received, while each incorrect or "I do not know" answer receives a score of 0. The total score is calculated by multiplying the number of correct responses by 4. Score on the scale ranges from 4 to 100. Six sentences have different punctuations. The total score is calculated by multiplying the number of correct responses by 4. The higher the final score, the higher the knowledge level.

Other questionnaires

Two other questionnaires that had already been adapted and validated for use in Brazilian Portuguese were applied to verify the validity of the construct concomitantly with HDFQ. Diabetes Knowledge Scale (DKN-A) was validated for the Brazilian population by Torres et al[18]. It is composed of 15 multiple-choice questions on various aspects of general knowledge

related to T2DM. The higher the score, the greater the respondent's knowledge about T2DM.

The Diabetes Attitudes Questionnaire ATT-19 was also validated for Brazilian Portuguese by Torres et al.[18]. It is a self-administered questionnaire about the measure of psychological adjustment for DM. It consists of 19 items arranged in 6 domains: (1) stress associated with DM; (2) receptivity to treatment; (3) confidence in the treatment; (4) personal effectiveness; (5) perception of health; and (6) social acceptance. Questions 11, 15, and 18 start with the reverse score. Each response is measured by a five-point Likert scale. The total score ranges from 19 to 95 points. The higher the score, the greater the positive attitude toward the disease.

Statistical analysis

To characterize the sample, descriptive statistics were performed with the presentation of quantitative data through mean and standard deviation, and qualitative data through absolute number and percentage. The HDFQ reliability analysis was performed using the kappa test with linear weighting, interclass correlation coefficient (ICC), standard error of measurement (SEM), and minimal detectable change (MDC). Internal consistency was assessed using Cronbach's alpha.

For the kappa values, the following interpretations were considered: <0, no agreement; 0.01–0.20, slight; 0.21–0.40, reasonable; 0.41–0.60, moderate; 0.61–0.80, substantial; and 0.81–1, almost perfect[15]. For the ICC values, the following interpretations were considered: <0.40, low reliability; 0.40–0.75, moderate; 0.75–0.90, substantial; and >0.90, excellent[16]. For SEM percentage, the following interpretations were considered: very good: 5% or less; good: >5% and <10%; doubtful: >10% and <20%; and negative: >20%[17]. Pearson's (r) correlation was used to determine construct validity in the correlation between HDFQ and DKN-A, and between HDFQ and ATT-19, following the COSMIN recommendations. The floor and ceiling effect was analyzed.

Data processing was performed using SPSS software, version 17.0 (Chicago, IL, USA).

RESULTS

During the translation and cross-cultural adaptation phase, there were no disagreements or suggested changes to the questionnaire. The translated and adapted version of the HDFQ was unanimously established by the expert committee. This adapted version was then applied to 30 diabetics to assess the level of understanding of the questions. We observed 100% comprehension for all survey items. Thus, we defined the final Brazilian Portuguese version of the HDFQ.

A total of 165 diabetics were recruited and included in the study. From this total sample, a sub-sample with 30 participants was used for the test-retest reliability calculations. Table 1 presents the characteristics of the sample, and it was observed that most of the participants were women, married, overweight, and with more than 10 years of DM. Regarding the reliability (Table 2), when considering each item of HDFQ, we observed adequate values of reliability (kappa ≥0.22). The items 9, 15, 20, 22, and 25 were the least reliable (kappa=0.22), and the items 6, 12, 13, and 16 were the most reliable (kappa=1.00). Considering the total score, we observed adequate reliability (ICC=0.75) and internal consistency (Cronbach's alpha=0.79).

Table 1. Sociodemographic and clinical characteristics of the participants.

Characteristics	Reliability phase (n=30)	Validity phase (n=165)
Age (years)	56.55 (12.78)	58.09 (12.25)
Gender (female)	15 (50%)	105 (63.6%)
Marital status		
Single	7 (23.3%)	48 (51.5%)
Married	22 (73.3%)	85 (51.5%)
Divorced	0 (0%)	14 (8.5%)
Widower	1 (3.3%)	18 (10.9%)
Weight (kg)	69.34 (16.11)	71.31 (13.73)
Height (m)	1.58 (0.08)	1.60 (0.08)
BMI (kg/m^2)	27.67 (6.64)	27.53 (4.88)
Schooling		
Basic education	9 (30%)	67 (40.6%)
High school	19 (63.3%)	64 (38.8%)
Higher education	2 (6.7%)	34 (20.6%)
Medical diagnosis		
SAH and DM	15 (50%)	75 (54.5%)
DM	15 (50%)	90 (54.5%)
Chronicity of DM (years)	10.96 (8.66)	12.12 (9.42)
Type of DM (type 2)	30 (100%)	163 (98.8%)
Physical activity (yes)	14 (46.7%)	60 (36.3%)
Smoker (yes)	3 (10%)	16 (9.7%)
DKN-A (score)	7.51 (2.92)	7.58 (3.03)
ATT-19 (score)	48.44 (9.08)	51.26 (10.68)
HDFQ (score)	79.11 (11.33)	75.61 (14.32)

Values presented in mean (standard deviation) or number (percentage). BMI: body mass index; SAH: systemic arterial hypertension; DM: diabetes mellitus; DKN-A: Diabetes Knowledge Scale; ATT-19: Diabetes Attitudes Questionnaire; HDFQ: Heart Disease Fact Questionnaire.

Table 2. Reliability and internal consistency of items and total score of the Heart Disease Fact Questionnaire (HDFQ) with presentation of mean values, standard deviation (SD), kappa, and Cronbach's alpha.

HDFQ items	Mean (SD)		Kappa	Cronbach's alpha if item excluded
	Test	Retest		
Item 1	0.76 (0.43)	0.76 (0.43)	0.81	0.78
Item 2	0.76 (0.43)	0.90 (0.30)	0.30	0.78
Item 3	0.60 (0.49)	0.76 (0.43)	0.33	0.80
Item 4	0.96 (0.18)	0.93 (0.25)	0.65	0.78
Item 5	0.88 (0.40)	0.93 (0.25)	0.44	0.78
Item 6	1.00 (0.00)	1.00 (0.00)	1.00	0.79
Item 7	0.93 (0.25)	0.93 (0.25)	0.46	0.78
Item 8	0.90 (0.30)	0.93 (0.25)	0.78	0.77
Item 9	0.63 (0.49)	0.93 (0.25)	0.22	0.78
Item 10	0.40 (0.49)	0.36 (0.49)	0.36	0.78
Item 11	0.90 (0.30)	0.90 (0.30)	0.63	0.78
Item 12	0.96 (0.18)	0.96 (0.18)	1.00	0.77
Item 13	0.96 (0.18)	0.96 (0.18)	1.00	0.77
Item 14	0.66 (0.47)	0.76 (0.43)	0.27	0.80
Item 15	0.80 (0.40)	0.93 (0.25)	0.22	0.78
Item 16	0.93 (0.25)	0.93 (0.25)	1.00	0.79
Item 17	0.80 (0.40)	0.96 (0.18)	0.26	0.79
Item 18	0.83 (0.37)	0.66 (0.47)	0.26	0.79
Item 19	0.90 (0.30)	1.00 (0.00)	0.90	0.79
Item 20	0.66 (0.47)	0.46 (0.50)	0.22	0.78
Item 21	0.90 (0.30)	0.93 (0.25)	0.78	0.77
Item 22	0.40 (0.49)	0.26 (0.44)	0.22	0.80
Item 23	0.90 (0.30)	0.96 (0.18)	0.32	0.78
Item 24	1.00 (0.00)	0.96 (0.18)	0.90	0.79
Item 25	0.43 (0.50)	0.23 (0.43)	0.22	0.78

Reliability of the total score of the Heart Disease Fact Questionnaire (HDFQ)

Test	Retest	ICC (95%CI)	SEM (absolute)	SEM (%)	MDC (absolute)	MDC (%)	Cronbach's alpha
79.33 (10.87)	81.60 (12.00)	0.75 (0.48–0.88)	5.72	7.11	15.85	19.70	0.79

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

To assess the construct validity by means of correlation with a validated questionnaire (Table 3), we observed adequate correlations of the HDFQ score with DKN-A (r=0.348) and ATT-19 (r=0.136).

Only, 2 (1.2%) participants achieved a HDFQ maximum score of 100. No participant reached the minimum score of 0 points. Therefore, the ceiling and floor effects were not observed.

Table 3. Correlation between the total score of Heart Disease Fact Questionnaire (HDFQ) and the other questionnaires applied in the study sample (n=165).

Questionnaires	HDFQ
DKN-A	r_s=0.348, p<0.001*
ATT-19	r_s=0.136, p=0.008*

DKN-A: Diabetes Knowledge Scale; ATT-19: Diabetes Attitudes Questionnaire. *Statistically significant correlation (p<0.05, Spearman's correlation coefficient).

DISCUSSION

The HDFQ in the Brazilian Portuguese version showed an adequate level of understanding according to the study sample. The values for internal consistency, validity, and reliability proved to be acceptable. In reliability, the kappa values, when considered item by item, ranged from 0.22 to 1; when considering the total score, a substantial ICC value (0.75) was found. Internal consistency, measured using Cronbach's alpha, was 0.79.

This questionnaire was translated, cross-culturally adapted, and validated for other countries, with a Turkish[14] and a Chinese[15] version. Other psychometric properties were also verified, such as reliability, internal consistency, and construct validity.

The translation and back-translation processes were used to create the Turkish and Chinese versions (C-HDFQ). Method similar to the guidelines used in the translation and cross-cultural adaptation process of this version is based on COSMIN criteria. Both versions adapted relevant expressions, present in the scale, to terms more suited to their own culture.

The Turkish version[14] used the Rasch measurement model to verify reliability, considering the Person Separation Index (PSI). A value of 0.77 was found for reliability, according to the Rasch analysis model. The C-HDFQ reliability was assessed using a test-retest; however, Chow and Wong did not make it clear which values were considered in this measurement. According to him, the Chinese version has good reliability (r=0.92), according to Kuder-Richardson Formula 20 internal consistency coefficient analysis. The reliability of the Brazilian version of the HDFQ was verified by test-retest, according to the C-HDFQ; however, unlike these studies, the values of kappa, ICC, SEM, and MDC were considered, following the international recommendations for psychometric analysis of instruments, i.e., the COSMIN[17].

However, the construct validity was analyzed using Pearson's coefficient correlated to two other instruments, i.e., DKN-A and ATT-19. However, as mentioned above, this method has been used to verify the reliability of the Chinese version. The HDFQ in the Turkish version used confirmatory factor analysis (CFA) as a verification method, considering a supposed unidimensionality of the construct.

The factor loadings found in the Turkish version of the HDFQ were higher than 0.51, according to the CFA, which is considered adequate in the literature. However, according to the study by Prinsen et al.[17], CFA is recommended to verify the internal factor structure of an instrument. This occurs with the aim of investigating whether the items that make up the tool reflect its dimensionality and respond to its construct[19].

Internal consistency, measured using Cronbach's alpha in the Brazilian version, was 0.79. Chow et al.[15] analyzed the internal consistency of the Chinese version of the HDFQ through the Kuder-Richardson Formula 20 and found the resulting value as 0.86, which was considered adequate.

Finally, the clinical implications of this questionnaire are supported by the fact that the diabetic population is more susceptible to developing CVD[20] and the focus of this questionnaire is on the knowledge of this population about the main risk factors for the development of CVD. Additionally, it is known that the greater the knowledge about the disease and its consequences, the smaller the impaired of the same can be.

This study has some limitations. We did not verify the accuracy or response capacity for the HDFQ. In addition, the sample in this study was specific to a city in the Northeast of the country. It is recommended that other psychometric properties be verified, such as the structural validity of the HDFQ, and we suggest that this instrument be applied to larger samples and different regions of the country.

CONCLUSION

Brazilian Portuguese version of the HDFQ has adequate psychometric properties according to the best scientific recommendations.

ACKNOWLEDGMENTS

The authors wish to thank all the individuals interviewed for taking the time and agreeing to participate in the research. They also thank the Ceuma University.

AUTHORS' CONTRIBUTIONS

DB-D: Conceptualization, Funding acquisition, Formal Analysis, Investigation, Methodology, Resources, Supervision, Writing – original draft preparation, Writing – review & editing. **WS-B:** Conceptualization, Funding acquisition, Methodology, Writing – review & editing. **MCF:** Conceptualization, Funding acquisition, Methodology, Writing – review & editing. **MJSR:** Conceptualization, Funding acquisition, Methodology, Writing – review & editing. **NCC:** Formal Analysis, Investigation, Writing – original draft preparation. **RCC:** Formal Analysis, Investigation, Writing – original draft preparation. **AHMP:** Formal Analysis, Investigation, Writing – original draft preparation. **AKFG:** Formal Analysis, Investigation, Writing – original draft preparation. **BNA:** Formal Analysis, Investigation, Writing – original draft preparation. **ADS-d-A:** Methodology, Writing – review & editing.

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ORIGINAL ARTICLE

https://doi.org/10.1590/1806-9282.20211260

Seating system for scoliosis in nonambulatory children with cerebral palsy: a randomized controlled trial

Merve Damla Korkmaz[1*], Murat Korkmaz[2], Nalan Capan[3], Goktug Sanli[4], Yasar Tatar[5], Ayse Resa Aydin[3]

SUMMARY

OBJECTIVE: This study aimed to investigate the effect of an adaptive seating system on pelvic obliquity and spinal coronal/sagittal balance in children with nonambulatory cerebral palsy and scoliosis.

METHODS: This was a single-blind, prospective, randomized interventional study. Nonambulatory children aged 6–15 years with cerebral palsy and scoliosis were included. The seating system was used for 4 h/day, and exercises were performed 3 days/week for 12 weeks. The Cobb angle, spinopelvic parameters, pelvic obliquity, Reimer's migration index, and Sitting Assessment Scale were measured before and after treatments.

RESULTS: A total of 29 participants were randomized into two groups, namely, the seating system+exercise group (SSE-group; n=15) and the exercise group (E-group; n=14). There was no significant change in Cobb angle and Reimer's migration index for both hips in SSE-group, but there was a significant increase in E-group (p=0.002, 0.049, and 0.003, respectively). The sagittal vertical axis, pelvic incidence, and pelvic obliquity decreased in SSE-group. However, there was no difference in the other sagittal parameters and Sitting Assessment Scale-total scores among groups.

CONCLUSION: The adaptive seating system was found to be superior in reducing the progression of Cobb angle and hip subluxation/dislocation, decreasing pelvic obliquity, and improving the sagittal balance of the spine/pelvis compared with exercise therapy.

KEYWORDS: Cerebral palsy. Sitting. Scoliosis. Spine. Pelvis.

INTRODUCTION

Cerebral palsy (CP) is the most common cause of serious pediatric disabilities. Children with CP have different levels of activity limitations[1]. According to the Surveillance of Cerebral Palsy in Europe, approximately 40% of children with CP are classified into Gross Motor Function Classification System (GMFCS) levels IV–V, which are nonambulatory[2]. These patients are at risk of spinal deformity, especially scoliosis[3], hip subluxation/dislocation, and musculoskeletal deformities[4,5].

It is considered that seating is a fundamental position for function and health in CP[6]. Seating systems are one of the nonoperative modalities for neuromuscular scoliosis and pelvic obliquity (PO)[4]. Since the 1960s, many types of seating systems, such as seat inserts, three-point trunk supports, and modular seating systems, have been used to improve postural control and sitting posture[4,5]. The correction of PO is also aimed in these systems to reduce the progression of spinal curvature[3].

According to the literature, the spinal balance is also very important to maintain posture[7,8]. Evaluating spinopelvic parameters and Cobb angles (CAs) radiographically reveals the effect of treatments more clearly. There are very few studies showing the effect of seating systems on the spinal stability/balance, and these studies have low methodological quality[5].

The purpose of this study was to demonstrate the effects of a custom-molded adaptive seating system (ASS) on PO and the coronal and sagittal spinal balance in nonambulatory children aged 6–15 years with CP and scoliosis.

METHODS

Participants

Children with CP and scoliosis aged 6–15 years who were admitted to the Pediatric Rehabilitation Outpatient Clinic were recruited in this study. The inclusion criteria were as follows: being classified as GMFCS levels IV–V CP, having mild-to-moderate scoliosis (between 10º and 40º), and the absence of severe contracture in the lower extremity to prevent

[1]University of Health Sciences, Kanuni Sultan Suleyman Training and Research Hospital, Department of Physical Medicine and Rehabilitation – Istanbul, Turkey.
[2]Istanbul University, Istanbul Faculty of Medicine, Department of Orthopedics and Traumatology – Istanbul, Turkey.
[3]Istanbul University, Istanbul Faculty of Medicine, Department of Physical Medicine and Rehabilitation – Istanbul, Turkey.
[4]Marmara University, Faculty of Sports Sciences – Istanbul, Turkey.
[5]Marmara University, Faculty of Medicine, Department of Physical Medicine and Rehabilitation – Istanbul, Turkey.
*Corresponding author: mervedml@gmail.com
Conflicts of interest: the authors declare there is no conflicts of interest. Funding: none.
Received on December 10, 2021. Accepted on February 12, 2022.

sitting. The exclusion criteria were as follows: having a rigid deformity in the spine and/or pelvis, previous history of the spine and/or hip surgery, the use any other seating devices and/or trunk orthoses within 6 months, having severe scoliosis (CA >40º), and history of uncontrolled epileptic seizures.

The study protocol was approved by the Clinical Research Ethical Board in conformity with the Declaration of Helsinki. All participants and their parents were informed about the study. This study was registered at https://clinicaltrials.gov.

Study design

This study was designed as a single-blind, prospective, randomized controlled 12-week interventional trial, which was conducted between April 2016 and March 2019.

The participants who met the inclusion criteria were randomized into two groups according to the order of admission to the department using computer-generated random numbers: the ASS and exercise group (SSE-group) and the exercise-only group (E-group).

All treatments and initial evaluations were performed by the same investigator. However, after treatment, evaluations and radiologic measurements were performed by a different investigator who had at least 5 years' experience and was blinded to the treatments.

Intervention

All participants received general exercises for spinal mobilization, stretching of back muscles (for convex side), strengthening of the back (for concave side), and abdominal muscles, passively. In the initial evaluation, these basic spinal correction exercises were taught practically to the parents and participants in a 1-h training session. An exercise diary was also given, and controls were made weekly to ensure the accuracy and continuity of the exercise therapy. The program was performed 3 days/week, with 10 repetitions for each exercise in a set for 12 weeks. The home exercise program was created because the participants had difficulty coming to the hospital 3 days/week.

In addition to the exercises, in the SSE-group, a custom-molded ASS was used for 4 h/day. The ASS included custom-designed "seating elevations," ranging from 1 to 2.5 cm. These elevations were used to equalize the pelvis of participants with PO. The height of the elevation was adjusted by measuring the horizontal PO angles on the pelvic radiographs. "A thoracic support" with pads at different levels was also used to maintain the upright posture and spinal alignment. "A head support" was added if necessary. "A hip block" was used to keep the hips in the correct position (Figure 1). The usage time of the ASS was checked via weekly phone calls and at each follow-up examination.

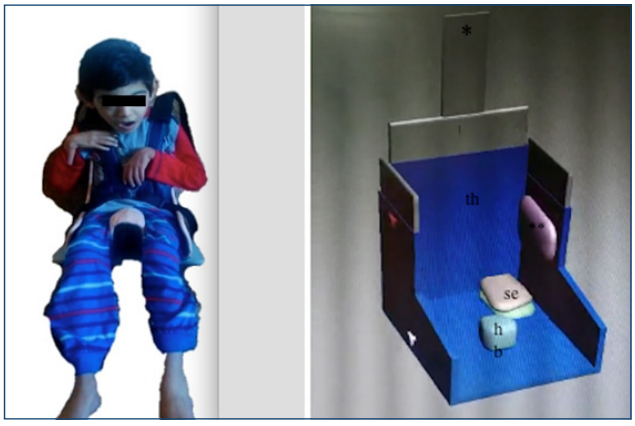

Figure 1. The seating system with a thoracic support (th), adjustable lateral supports (**), adjustable sitting elevation (se), a hip block (hb), and head support (*) if necessary.

Outcome measures

The demographic and clinical characteristics were all recorded at the initial examination.

The primary outcomes such as CA, sagittal spinopelvic parameters (i.e., thoracic kyphosis [TK] angle, lumbar lordosis [LL] angle, the sagittal vertical axis [SVA], pelvic tilt [PT], pelvic incidence [PI], and sacral slope [SS]), and PO angles were measured using the Surgimap® program. All radiographs were taken in sitting position.

The secondary outcomes were Reimer's migration index (RMI) for hip displacement and the Sitting Assessment Scale (SAS)[9] for evaluating sitting functional control. The SAS evaluation was not filmed because the parents of participants did not give consent. Instead, an assistant was included in the study who supervised the examination.

All evaluations and measures were performed before and after treatment.

Statistical analysis

Statistical analysis was performed using the IBM SPSS software version 23.0 (Statistics for MacOs). The normality of distribution was determined using histograms and the Shapiro-Wilk test. For inter-group analysis, the independent samples t-test or the Mann-Whitney U test was used, and for within-group analysis, Wilcoxon signed-rank test or the paired-samples t-test was used depending on the distribution analysis.

For the sample size, the confidence interval was 95%, and $p<0.05$ was considered statistically significant.

RESULTS

A total of 56 participants aged 6–15 years with nonambulatory CP and scoliosis who presented to the Outpatient Clinic

were evaluated for eligibility. Of these, 32 participants met the inclusion criteria. Two participants refused to participate in the study due to the distance from their city of residence. The remaining 30 children participated in the study. One participant dropped out of the study because of not attending follow-up examinations. Finally, the study was completed with 29 participants. The demographic and clinical characteristics of the participants are shown in Table 1.

The mean age of the study population was 10.24±2.72 years. There was no significant difference between the groups in terms of age, sex, age of menarche and puberty, GMFCS levels, Risser signs, and Tanner stages. No adverse effects were identified in either groups.

Inter-group analysis

Upon comparison of the two groups, there was a statistical difference in terms of CA (p=0.001), SVA (p=0.033), PI (p=0.037), PO (p=0.002), and RMI for both hips (p=0.026 and p=0.001, respectively). No statistical differences were identified in terms of TK, LL, PT, SS, and SAS-total scores (Table 2); only hand/

Table 1. Demographic and clinical characteristics of the participants.

Variable	SSE-group (n=15)	E-group (n=14)	p-value
Age (year)	9.67 (0.55)	10.86 (0.56)	0.084
Sex *(male/female)*	10/5	7/7	0.3
Type of CP			
Spastic	14	13	
Dyskinetic	1	1	
Tanner stages			0.51
Stage 1	9	5	
Stage 2	3	3	
Stage 3	2	3	
Stage 4	1	3	
Stage 5	0	0	
In puberty	3	7	
GMFCS levels			0.591
Level IV	4	2	
Level V	11	12	
Risser sign			0.51
Level 0	11	7	
Level 1	2	2	
Level 2	2	3	
Level 3	–	2	

SSE-group: seating system with exercise group, E-group: exercise group, CP: cerebral palsy, GMFCS: Gross Motor Functional Classification System.

Table 2. Effects of treatments on outcome measures at initial evaluation and after 12 weeks.

	SSE-group (n=15)	E-group (n=14)	p-value [b]
	Mean (SD)	Mean (SD)	
Cobb angle (°)			
BT	23.77 (12.98)	26.31 (9.99)	0.001*
PT	21.52 (11.64)	30.46 (12.10)	
p-value [a]	0.088	0.002	
Pelvic obliquity (°)			
BT	6.46 (3.15)	7.39 (4.28)	0.002*
AT	4.39 (2.34)	9.74 (5.49)	
p-value [a]	0.013	0.074	
Thoracic kyphosis (°)			
BT	33.75 (11.95)	41.07 (9.97)	0.354
AT	36.91 (14.47)	40.94 (10.98)	
p-value [a]	0.307	0.975	
Lumbar lordosis (°)			
BT	36.25 (9.90)	36.16 (9.43)	0.847
AT	40.43 (13.59)	37.90 (8.21)	
p-value [a]	0.691	0.451	
Sagittal vertical axis (mm)			
BT	10.93 (7,46)	13.48 (6.58)	0.033*
AT	8.02 (7,13)	15.26 (8.89)	
p-value [a]	0.016	0.331	
Pelvic tilt (°)			
BT	20.99 (13.62)	13.37 (7.86)	0.747
AT	18.69 (11.8)	13.5 (8.87)	
p-value [a]	0.910	0.826	
Sacral slope (°)			
BT	31.04 (14.93)	31.84 (11.4)	0.270
AT	27.16 (12.39)	33.1 (12.31)	
p-value [a]	0.100	0.802	
Pelvic incidence (°)			
BT	52.4 (11.9)	45.22 (11.34)	0.037*
AT	45.46 (10.33)	46.6 (5.97)	
p-value [a]	0.011	1.000	
Reimer's migration index (%)			
Right hip			
BT	26.27 (11.20)	22.85 (7.65)	0.026*
AT	24.80 (10.28)	28.29 (8.65)	
p-value [a]	0.345	0.049	
Left hip			
BT	39.80 (22,28)	32.43 (9.70)	0.001*
AT	37.00 (24,19)	40.28 (9.42)	
p-value [a]	0.310	0.003	

Continue...

Table 2. Continuation.

	SSE-group (n=15)	E-group (n=14)	p-value [b]
	Mean (SD)	Mean (SD)	
Sitting Assessment Scale			
Head control			
BT	2.9 (1.1)	2.1 (0.8)	0.561
AT	3.0 (1.0)	2.1 (0.8)	
p-value [a]	0.317	0.317	
Trunk control			
BT	1.9 (0.9)	1.5 (0.7)	0.384
AT	3.0 (1.1)	1.8 (0.9)	
p-value [a]	0.008	0.046	
Foot control			
BT	1.5 (0.6)	1.1 (0.4)	0.642
AT	1.7 (1.0)	1.3 (0.5)	
p-value [a]	0.102	0.157	
Arm control			
BT	2.2 (0.8)	1.6 (0.6)	0.030*
AT	2.7 (0.9)	1.7 (0.7)	
p-value [a]	0.005	0.157	
Hand control			
BT	1.6 (0.7)	1.3 (0.6)	0.003*
AT	2.5 (1.0)	1.4 (0.6)	
p-value [a]	0.006	0.317	
Total score			
BT	10.1 (3.3)	7.6 (2.7)	0.072
AT	12.2 (4.4)	8.3 (2.9)	
p-value [a]	0.002	0.026	

SSE-group, seating system with exercise group; E-group, exercise group; SD, standard deviation; BT, before treatment; AT, after treatment. *p<0.05, statistically significant difference. [a]p-value by Mann-Whitney U test or independent t-test. [b]p-value by Wilcoxon signed-rank test or paired samples t-test.

arm scores were significantly different among groups (p=0.003 and 0.030, respectively).

Intra-group analysis

The mean values of the CA and RMI for both hips were significantly increased in the E-group after treatment (p=0.002, 0.049, and 0.003, respectively). However, there was no significant difference in the SSE-group (Table 2).

In the SSE-group, there was a significant decrease in the mean values of SVA, PI, and PO (p=0.016, 0.011, and 0.013, respectively), whereas no significant differences were identified in the E-group. The remaining spinopelvic parameters were not statistically significant within each group (Table 2).

Sitting Assessment Scale-trunk, arm, hand, and total scores in the SSE-group and trunk and total scores in the E-group were significantly increased (Table 2).

DISCUSSION

The treatment of scoliosis in CP remains very challenging due to associated comorbidities[10]. It is known that surgical treatment is required in severe cases. Surgery for neuromuscular scoliosis has the highest mortality and morbidity rates. However, conservative treatment methods are very limited[11]. In this study, it was aimed to create a nonoperative treatment method for neuromuscular scoliosis, so the mid-term effects of an ASS on the spine and pelvis were assessed.

In several studies, different types of ASSs have been used to improve postural control and sitting posture in neuromuscular scoliosis[12-14]. However, few studies have evaluated the effects on the coronal spinal balance. Holmes et al.[15] evaluated the effects of three alternative arrangements of lateral support pads on spinal coronal alignment and achieved the most correction in coronal plane with a three-point force system. In this study, supporting both the trunk and the pelvis with the ASS reduced the CA progression. The participants in our study spend most of their daily lives lying or sitting in an inclined position. This result may have been achieved due to sitting in an upright position.

The spine maintains a mechanical balance on sagittal alignment with minimum energy consumption. This balance is achieved by the harmonious relationship of spine and pelvic anatomy[16]. In a study that compared spinopelvic parameters between patients with CP and healthy participants, the patients with CP had lower PT and greater SS, LL, and TK than healthy participants[7]. It can be said that the evaluation of sagittal spinopelvic parameters would be beneficial for the treatment of scoliosis in CP. Hayden et al.[17] found that pelvic motion caused a significant change in sagittal parameters. In our study, maintaining the PO and upright sitting posture improved sagittal balance.

Opinions about whether the PI angle is a dynamic or static parameter are conflicting[8,18,19]. It was stated that the PI increased during skeletal growth and became fixed after skeletal maturity occurred[8]. Recently, some studies reported that the PI was a dynamic parameter that could change with pelvic positions[18,19]. In our study, a significant decrease in PI was observed. This may be due to the incomplete skeletal maturity of the participants; spinal balance will be preserved in children who use the ASS at an early age and mild-moderate scoliotic period. SVA is a good parameter for analyzing spinal sagittal balance[20]. In our

study, the decrease in SVA in the SSE-group can be explained by sitting in an upright position. Vekerdy et al.[12] showed that there was no significant change in TK and LL, which play an important role in sagittal balance, after using a seating device. Similarly, there was no difference in both parameters in our study.

Pelvic obliquity is one of the potential factors that cause spinal asymmetry during the spinal growth, especially in nonambulatory CP[21]. In an experimental study, it was found that a trunk support had no significant effect on PO in nonambulatory children with CP and scoliosis[15]. In this study, using the ASS, which also maintained the pelvic levels, decreased PO. This result is noteworthy for future studies because it contributes to the relationship between the correction of PO and scoliotic curvatures.

As GMFCS levels increase, the incidence of hip displacement increases[22], resulting in gait abnormalities and impaired sitting balance[23]. Positive results were obtained in several studies that evaluated the effect of ASSs on hip dislocation[13,14]. In our study, ASS prevented progression of hip dislocation by maintaining the hip position.

Seated postural control is very important for the functionality in CP[6]. Considering the natural history of scoliosis in CP, it is possible to have a postural collapse in the absence of sitting balance[24]. It was found that a seating system had no effect on postural control[13]. Similarly, the ASS had no significant effect on postural control in our study. It can be suggested that the 12-week treatment period was not sufficient for maintaining postural control. Otherwise, the system provided significant improvement in holding or grasping objects compared with exercise therapy alone. Cimolin et al. observed that trunk-supported sitting systems improved the voluntary upper extremity function in severe CP[25]. This can be explained by the fact that ASS provided the conditions for nonambulatory children to use their hands to reach any objects.

To the best of our knowledge, this is the first randomized controlled study to demonstrate the effect of an ASS on the sagittal balance and PO in children with nonambulatory CP and scoliosis. Blinding the assessors, close monitoring of treatment adherence, and having a control group can be considered the strengths of this study. The result that only 4-h sitting in an upright position with maintained pelvic levels improved spinal alignment in CP is notable. It is important to present an alternative method to surgery for the treatment of neuromuscular scoliosis.

This study has some limitations. First, the participants could be selected only in CP with GMFCS level V. Second, the short follow-up period can be counted as a limitation.

CONCLUSIONS

This study demonstrated the positive effects of an ASS on the spinal sagittal/coronal balance and PO in nonambulatory children with CP and scoliosis. However, no effect was found on postural control.

ETHICAL APPROVAL

The study protocol was approved by the Clinical Research Ethical Board of Istanbul University Istanbul Faculty of Medicine (approval no: 2016/72) in conformity with the Declaration of Helsinki. The study was registered at https://clinicaltrials.gov (ID number: NCT03862625).

AUTHORS' CONTRIBUTIONS

MDK: Conceptualization, Data curation, Formal Analysis, Writing – original draft. **MK**: Data curation, Formal Analysis, Writing – review & editing. **NC**: Data curation, Writing – review & editing. **GS**: Data curation, Formal Analysis. **YT**: Conceptualization, Data curation, Formal Analysis. **ARA**: Conceptualization, Data curation, Writing – review & editing.

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ORIGINAL ARTICLE

https://doi.org/10.1590/1806-9282.20211267

Psychiatric emergency units in Brazil: a cross-sectional study

Cintia de Azevedo-Marques Périco[1,2], Roberto Mendes dos Santos[2], Leonardo Rodrigo Baldaçara[3], Camila Santos Símaro[1,2], Renata Costa Junqueira[1,2], Maria Olivia Pozzolo Pedro[1,2*], João Mauricio Castaldelli-Maia[1,2,5]

SUMMARY

OBJECTIVES: This study aimed to identify the infrastructure (e.g., availability, resources, and staff), basic metrics, and problems (e.g., network, overcrowding, resources, and infrastructure) of the psychiatric emergency services in Brazil.

METHODS: This is a cross-sectional study assessing psychiatric services (n=29) listed by the Brazilian Psychiatric Association in 2019.

RESULTS: Almost all the units reported 24 h/7-day availability having psychiatrists, nurses, and social workers, with 8.8 (SE=2.2) and 2.8 (SE=0.3) consultations and hospitalizations per day, respectively. Separated room for contention was reported by the minority of the services (38%). The most commonly reported problems were insufficient structure for child/adolescent care (83%), increasing patient demand (72%), housing referral for homeless (72%), excessive prescription demand (69%), short-term room overcrowding (59%), court orders for inpatient treatment (59%), lack of vacancies for inpatients hospitalization (59%), and referral to primary care (56%).

CONCLUSIONS: Similar to the United States, the Brazilian psychiatric emergency units are decreasing and encompass the shortcomings of the Brazilian mental health care network.

KEYWORDS: Health services research. Medical emergency services. Psychiatric emergency services.

INTRODUCTION

Emergency situations can be defined as those that involve essential life or social risk, requiring immediate and unavoidable interventions. In comparison, urgent situations deal with less risk, requiring short-term intervention[1]. Psychiatry emergencies (PEs) are all behavioral changes that result in real and significant risk and require immediate and essential therapeutic intervention to prevent harmful evolution for the patient and third parties[2].

In the past decades, the psychiatric practice has undergone profound changes in Brazil, aiming to elaborate therapeutic plans to prevent long-term hospitalization. A proposal of reformulating mental health care had been organized to introduce a network of services that seeks to manage the patient in psychosocial care units (*Centros de Atenção Psicossocial*), with greater integration of the patient with the community. Beyond the supply of outpatient care and the approximation of the psychiatric services with general hospitals, there was also the need to amplify the services and functions of PE services (PES) to deal with patients in crises[3,4]. Until the creation of the first PES, the Psychiatric Emergency Room of the Psychiatric Institute of the National Center at Rio de Janeiro, cases of PE were characterized as "police cases"[5]. Before these proposals for restructuring mental health care, patients in an acute crisis had, at best, low-quality assistance. Most of the time, they were managed in nonpsychiatric health services or in asylum hospitals existing at the time[6]. Several PES have been created in all Brazilian regions in the following decades. Even though it is considered an important service for the organization of mental health network, Brazilian data of PES are scarce, with little information regarding the distribution of these centers in the territory. Consequently, less is known about the organization of emergency teams and the problems they face on a daily basis[7,8].

The objective of this research was to collect information about the infrastructural characteristics and basic metrics of the Brazilian PES, as well as the main difficulties faced to provide proper acute psychiatric care to the Brazilians.

METHODS

Study design

This was a quantitative cross-sectional study. We invited the heads of all the PES listed by the Brazilian Psychiatric Association to

[1]Centro Universitário de Saúde FMABC, Medical School, Department of Neuroscience – Santo André (SP), Brazil.
[2]Centro ABC de Estudos de Saúde Mental – Santo André (SP), Brazil.
[3]Hospital Universitário Lauro Wanderley – João Pessoa (PB), Brazil.
[4]Universidade Federal do Tocantins – Palmas (TO), Brazil.
[5]Universidade de São Paulo, Medical School, Department of Psychiatry – São Paulo (SP), Brazil.
*Corresponding author: maria.oliviapozzolo@gmail.com
Conflicts of interest: the authors declare there is no conflicts of interest. Funding: none.
Received on December 16, 2021. Accepted on February 27, 2022.

participate in a survey (one per PES). The study included all PES over the national territory that accepted and signed the consent term to participate. We have considered PES a mental health care unit designed to provide immediate care for acute cases of psychiatric symptoms.

Sample

The respondents were directors, coordinators, or technical leaders who had extensive experience in the routine of the PES and voluntarily agreed to participate in the research. For each PES, only one professional, who was familiar with the practice and had a great knowledge of the service and structures, was offered a questionnaire developed by the authors of the study.

Procedures

Because the study involves humans, all the requirements proposed by the National Health Council/Ministry of Health were attended through Resolution #466/2012[9]. Therefore, the data collection started after the appreciation of the Research Ethics Committee of the Fundação do ABC. The research team informed the respondents about the objectives and procedures of the study before the latter had signed the Informed Consent Term, guaranteeing them anonymity, confidentiality, and informing them of the ethical procedures.

Measures/Analysis

The questionnaire was developed by members of the PE section of the Brazilian Psychiatric Association composed of specific questions about the profile of the health care professionals (e.g., psychiatrists, nurses, and nursing technicians), the PES physical structure, and the main problems faced by the health team of the emergency care. Data were collected through self-administered questionnaires answered by health professionals who had a working relationship with the PES in analysis at the time of the response. The results collected were tabulated, and we carried out a descriptive analysis by categories and subcategories, as follows:

- Infrastructure: availability, resources, and staff
- Metrics
- Problems: network, overcrowding, resources, infrastructure, and other

RESULTS

Figure 1 presents the flowchart of PES invited to participate in this study. The Brazilian Psychiatric Association listed 83 possible PES. Among these, 66 were found to be still active. Only 52 services were considered PES; the other 14 units were excluded from the study for not meeting the criteria of PES. From these 52 locations, 29 accepted to participate and answered the questionnaire. Most of them were academic training sites.

Table 1 presents infrastructure, metrics, and problems of Brazilian PES. Regarding availability, 93% of these services work 24 h/day, evaluate children and adolescents, and accept patients from other municipalities. Responses on resources showed that almost 66% apply a screening protocol for risk classification and have a procedures protocol and a clinical analysis laboratory. In addition, 79% have adequate material for mechanical containment, but only 38% have a separate room for physical restriction. Almost all (97%) have an observation room for the patients. Concerning the staff, all teams are composed of psychiatrists, nursing technicians, and social workers, and almost all have nurses and administrative employees (97%). Psychologists (69%) and occupational therapists (48%) are less present. In addition, we found that 86% of the PES have guards.

There was an average of 8.8 and 2.8 consultations and hospitalizations per day, respectively. The team is formed by an average of 9.2 psychiatrists, 5.4 internal medicine physicians, and 1.5 psychiatrists per 12-h period. The mean number of beds per service was 6.8. In addition, we found an average of two consultancy rooms per service.

Among the problems previously selected by the survey, the item "insufficient/absent structure for childhood and/or adolescence" was reported by 83% of services. Furthermore,

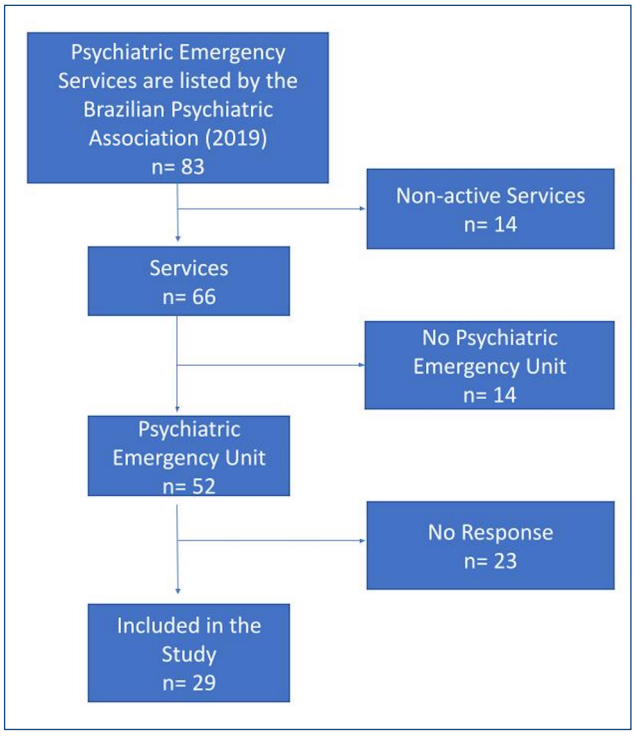

Figure 1. Flowchart of psychiatric emergency services invited to participate in this cross-sectional study, Brazil, 2019.

Table 1. Infrastructure, metrics, and problems of psychiatric emergency units in Brazil, 2019.

Infrastructure	n	%
Availability		
Open 24 h/7 days	27	93.1
Any restriction in consultations	13	44.8
Serves children and adolescents	27	93.1
Accept patients from other municipalities	27	93.1
Resources		
Performs risk rating	19	65.5
Uses service protocols	19	65.5
Uses medical records	29	100.0
Separated room for contention	11	37.9
Containment equipment	23	79.3
Short-term inpatient room	28	96.6
Laboratorial tests available	19	65.5
Staff		
Psychiatrists	29	100.0
Psychologists	20	69.0
Nurses	28	96.6
Nurse technicians	29	100.0
Social workers	29	100.0
Security staff	25	86.2
Occupational therapist	14	48.3
Administrative officer	28	96.6
Other professionals	5	17.2

Metrics	Mean	SE
Number of consultations per day	8.8	2.2
Number of hospitalizations per day	2.8	0.3
Psychiatrists in the team	9.2	1.2
Internal medicine physicians in the team	5.4	1.4
Psychiatrists per 12-h period	1.5	0.1
Beds	6.8	1.1
Consultancy room	2.0	0.2

Problems	n	%
Network		
Related to primary care	16	55.17
Related to specialized health system	14	48.28
Related to substance use care units	10	34.48
Related to mental health care units	11	37.93
Related to housing (homeless)	21	72.41
Related to therapeutic communities	4	13.79
Inpatient removal for hospitalization	7	24.14
Overcrowding		
Increasing patient demand	21	72.41
Excessive prescription demand	20	68.97
Short-term room overcrowding	17	58.62
Court orders for inpatient treatment	17	58.62
Resources		
Lack of vacancies for inpatients hospitalization	17	58.62
Lack of medicines at the emergency service	13	44.83
Lack of medicines in public health system	15	51.72
Lack of internal medicine support	9	31.03
Lack of employees (other than psychiatrists)	15	51.72
Replacement of psychiatrists by nonspecialized physicians	2	6.90
Insufficient training	11	37.93
Infrastructure/other		
Inadequate physical structure	14	48.28
Inadequate physical containment	12	41.38
Insufficient structure for child and adolescence care	24	82.76
Aggression	11	37.93
Others	2	6.90

72% had the following problems: "increased patients demand" and "homeless people." In addition, 69% declared "excessive demand for recipes," and 59% declared "lack of hospital beds," "patients presenting court orders for hospitalization," and "overcrowding of the observation room." Moreover, 55% pointed as a problem "contact with the basic service network," and 52% pointed to "lack of employees (nonpsychiatrists)" and "lack of medication in the health network." Other items were less identified as problems, such as contact with the specialized service network (48%), contact with CAPS AD (34%), contact with the CAPS (38%), insufficient team training (38%), contact with therapeutic communities (14%), transfer to hospital (24%), lack of medication in the emergency unit (45%), inadequate physical structure (48%), lack of support of internal medicine physicians (31%), problems due to inadequate physical restraint (41%), deaths during psychiatric hospitalization while the patient was still in the psychiatric emergency department (17%), agitated patients (38%), exchange of psychiatrists for physicians from another specialty (7%), and other problems (7%).

DISCUSSION

This study identified major flaws for proper PE care. In spite of the majority of the Brazilian PES providing 24 h/7 days care, a lack of adequate infrastructure to children and adolescents and overcrowding related to the shortcomings of the mental health care network were largely reported. The lack of medications was also reported by most of the services. However, we also found some strength. All the PES had a social worker as part of the team, making it possible to obtain a better collection of social and family data and act on social and economic issues. Almost all the PES were also available for patients from other cities. This is important because of the absence of PES in most of the regions of the country.

In Brazil, there is no consolidated information regarding the distribution of PES in our territory or also the difficulties that they encounter on a daily basis[6,9]. There are insufficient official data on such locations, and most states do not have information available in official media. Thus, despite being a fundamental and essential service[10], PES are still incipient and insufficient to serve a population of more than 212 million habitants, an alarming data found in this study.

The decrease in the number of Brazilian active PES has also been noted in the United States. A very recent study showed that the availability of U.S. psychiatric "walk-in" services has been declining by 15.8% from 2014 to 2018[11]. There was also a decrease of 7.5% in crisis services during the same period[11]. The problems related to the shortcoming of the mental health care network found in this study are also found in the United States[12]. Interestingly, some of our findings were similar to those of a survey with the U.S. PES in 1998[13]. The majority of the U.S. PES were academic training sites. Almost all the PES were open 24 h/7 days and had a psychiatrist present at some point of the day. Nearly 70% of respondents reported inadequate referral options for patients with substance abuse[13].

These findings support the importance of updating the PES data and, based on that, understanding the flaws and the problems faced. But, conversely, it is crucial to identify the positive aspects of each service that could serve as a model for other regions with similar demands.

CONCLUSION

Similar to the United States, the Brazilian PES are decreasing in number and encompassing the shortcomings of the Brazilian mental health care network. Data collection enables the better organization and updating of services in the national territory, facilitating new research in the area. Given the importance of the PES, it is necessary to accelerate improvements in services and the construction of public policies to care in a qualified and preestablished form for acute cases. In addition, through this study, it is feasible to talk about the possibility of making the distribution of these services more homogeneous in our regions, thus resulting in better access to services and adherence to treatment of our patients.

AUTHORS' CONTRIBUTIONS

CA-MP: Conceptualization, Investigation, Methodology, Project administration, Supervision, Validation, Visualization, Writing – original draft, Writing – review & editing. **RMS:** Conceptualization, Data curation, Methodology, Project administration, Resources, Supervision, Writing – original draft, Writing – review & editing. **LRB:** Conceptualization, Investigation, Methodology, Project administration, Supervision, Validation, Visualization, Writing – original draft, Writing – review & editing. **CSS:** Data curation, Formal Analysis, Investigation, Resources, Validation, Visualization, Writing – original draft. **RCJ:** Data curation, Formal Analysis, Investigation, Resources, Validation, Visualization, Writing – original draft. **MOPP:** Data curation, Formal Analysis, Investigation, Resources, Validation, Visualization, Writing – original draft, Writing – review & editing. **JMC-M:** Conceptualization, Formal Analysis, Investigation, Methodology, Project administration, Supervision, Validation, Visualization, Writing – original draft, Writing – review & editing.

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ORIGINAL ARTICLE

https://doi.org/10.1590/1806-9282.20211279

Factors affecting the clinical outcomes in pediatric post-cardiotomy patients requiring perioperative peritoneal dialysis

Ahmet Hulisi Arslan[1*], Tamer Aksoy[2], Murat Ugur[3], Hasim Ustunsoy[1]

SUMMARY

OBJECTIVE: Fluid overload is associated with increased mortality and morbidity in pediatric cardiac surgery. In the pediatric age group, peritoneal dialysis might improve postoperative outcome with avoiding fluid overload and electrolyte imbalance. It preserves hemodynamic status with the advantage of passive drainage. In this study, we are reporting our results of peritoneal dialysis after cardiac surgery.

METHODS: In this retrospective study, we evaluated the patients who underwent pediatric cardiac surgery in our hospital between December 2010 and January 2020. Patients who required peritoneal dialysis during hospitalization period were included in the study. Patients' clinical status and outcomes were evaluated.

RESULTS: Peritoneal dialysis was performed to 89 patients during the study period. The age varies from the newborn to 4 years old. The indication of peritoneal dialysis was prophylactic in 68.5% (n=61) and for the treatment in 31.5% (n=28). There were 31 mortalities. The risk factors for the mortality were preoperative lower age, longer cardiopulmonary bypass time, lengthened intubation, lengthened inotropic support, and requirement of extracorporeal membrane oxygenation (p<0.0001).

CONCLUSION: Earlier initiation of peritoneal dialysis in pediatric cardiac surgery helps maintain hemodynamic instability by avoiding fluid overload, considering the difficulty in the treatment of electrolyte imbalance and diuresis.

KEYWORDS: Congenital heart defects. Renal insufficiency. Dialysis.

INTRODUCTION

In pediatric patients, the risk of renal failure after cardiopulmonary bypass (CPB) varies between 20% and 64%[1, 2]. CPB causes fluid overload, hemodilution, capillary leakage, and release of pro-inflammatory mediators during the cardiac surgery. Fluid overload and edema, which are associated with the increased morbidity and mortality, might develop after the cardiac surgery even in the absence of renal dysfunction in pediatric patients[3, 4].

Renal replacement therapy might be initiated as soon as possible in the patients with acute kidney injury (AKI), who had undergone cardiac surgery[5]. The indications of the renal replacement therapy included fluid overload, prevention of fluid overload, acute renal failure, electrolytic abnormality, metabolic acidosis, oliguria, and increasing of urea[6-8]. In the postoperative period, fluid restriction and keeping the general balance negative contribute to recovery. In cases where there is no response to these treatments, continuous renal replacement therapy might be performed to gain hemodynamic stability, remove toxins, and control fluid balance[4].

In the pediatric age group, peritoneal dialysis catheter might be applied for renal replacement therapy[3]. Peritoneal dialysis is a low-cost, easy-to-apply method with a low risk of hemodynamic instability and is effective in reducing fluid overload[9]. It treats uremia and electrolyte imbalance via passive drainage[1]. It provides an opportunity for optimal ultrafiltration in newborns without affecting the hemodynamic status[3]. Early peritoneal dialysis reduces the need for vasoactive drugs and mechanical ventilation[1]. In some centers, prophylactic usage was reported to decrease the risk of acute renal injury[2]. It was reported that peritoneal dialysis is superior to diuretics in providing diuresis in the postoperative period in infants[10]. In this retrospective study, clinical outcomes of pediatric post-cardiotomy patients in which peritoneal dialysis was performed and the factors affecting these outcomes were investigated.

METHODS

Patients who underwent congenital heart surgery in our hospital between December 2010 and January 2020 (n=1404) were retrospectively investigated. The study was initiated after the approval of the institutional review board. Patients who underwent peritoneal dialysis during the perioperative period

[1]Anadolu Medical Center, Department of Cardiovascular Surgery – Kocaeli, Turkey.
[2]Anadolu Medical Center, Department of Anesthesiology and Reanimation – Kocaeli, Turkey.
[3]University of Health Sciences, Sancaktepe Sehit Professor Doctor Ilhan Varank Education and Research Hospital, Department of Cardiovascular Surgery – Istanbul, Turkey.
*Corresponding author: ahmet.arslan@anadolusaglik.org
Conflicts of interest: the authors declare there is no conflicts of interest. Funding: none.
Received on February 10, 2022. Accepted on February 27, 2022.

were included in the study. Demographic information, operative information, and laboratory results of the patients were obtained from the patient records. Mortality and morbidity rates were examined in patients who underwent peritoneal dialysis by examining the records of the patients.

In our clinic, peritoneal dialysis is initiated prophylactically in the operating room as well as in the intensive care unit (ICU) for the treatment. The indications of prophylactic peritoneal dialysis are longer than 90 min CPB time and perioperative oliguria. In case of prolonged CPB and intraoperative fluid overload, we place the peritoneal dialysis catheter prophylactically in the operating room. In intensive care follow-ups, we place peritoneal dialysis catheter in cases of oliguria (<0.5 mL/kg/h for more than 4 h), fluid overload, electrolyte imbalance, and creatinine value above 1.2 mg/dL. We considered edema, weight gain, and positive overall balance as signs of fluid overload.

The data were evaluated by using the Analyse-it version 4.20.1 program. Categorical variables were expressed as numbers and percentages, and continuous variables were expressed as mean±standard deviation.

RESULTS

Peritoneal dialysis was performed to 89 patients during the study period. The preoperative demographic and laboratory findings of the patients are shown in Table 1. Different surgical procedures were performed based on the underlying pathologies. The diagnoses of the patients and the surgical procedures are detailed in Table 2.

Peritoneal dialysis was used as prophylactic in 61 patients and for the treatment in 28 patients. There were 31 mortality rates in the follow-up period; dialysis was initiated in 19 patients as prophylactic, and in 12 patients for the treatment. There is no statistically significance for indications of dialysis, i.e., for the mortality (p=0.282). Preoperative lower age, lower body surface area (BSA), lower weight, longer CPB time, lengthened intubation period, and lengthened inotropic support were found statistically significant for the mortality (p<0.0001). Extracorporeal membrane oxygenation (ECMO) was performed in 18 patients. Mortality rate in patients undergoing ECMO was 89% (p<0.0001). In 11 of 16 mortality with ECMO, dialysis was initiated prophylactically.

Table 1. Preoperative variables in 89 patients with peritoneal dialysis.

Variable	Values
Age (months)	11.7 ± 37.6
BSA (m^2)	0.25 ± 0.2
Weight (g)	4971 ± 4698
Preoperative Hb (g/dL)	13.6 ± 3
Preoperative Htc (%)	40.1 ± 9
Preoperative creatinine (mg/dL)	0.47 ± 0.2
Preoperative SaO_2 (%)	88.6 ± 9.1
Preoperative PaO_2 (mmHg)	54.5 ± 48.3

BSA, body surface area; Hb, hemoglobin; Htc, hematocrit; PaO_2, partial pressure of arterial oxygen; SaO_2, oxygen saturation.

DISCUSSION

Preoperative cyanosis, polycythemia, congestive heart failure, prolonged CPB, hypothermia, and low cardiac output are the increasing risk factors for AKI in congenital cardiac surgery[8]. Fluid overload and usage of nephrotoxic drugs are the other risk factors that increase the risk of tubular damage[11]. In this study, we found that lower age, lower BSA, lower weight, longer CPB time, lengthened intubation period, and lengthened inotropic support are the risk factors for the mortality in the patients who needs dialysis. In these patients, increased inflammatory response to prolongation of CPB, low cardiac output, and inotropic drugs increased the necessity of the renal replacement therapy.

It was reported that the risk of renal injury increased seven times when the CPB duration exceeds 2 h[12]. In case of CPB duration longer than 90 min and total circulatory arrest longer than 60 min, insertion of a peritoneal catheter is suggested[8]. In our study, we started peritoneal dialysis prophylactically in the patients who had longer than 90 min CPB time. Mortality rates of the patients according to the indications of dialysis were similar. We can predict that earlier initiation of peritoneal dialysis in the lengthened CPB time decreases the risk of AKI and related complications during the congenital cardiac surgery.

Myocardium is extremely sensitive to fluid overload, electrolyte imbalance, and acid-base imbalance in the postoperative period of cardiac surgery[8]. Prevention of fluid overload is important to preserve myocardial functions. Fluid overload and AKI are associated with increased mortality and morbidity. Fluid overload is an independent risk factor that negatively affects congenital cardiac surgery[2]. There are different methods such as ultrafiltration, peritoneal dialysis, and fluid restriction in the treatment of fluid overload[2]. The first option for the treatment of postoperative fluid overload is intravenous diuretic administration[11]. Continuous renal replacement therapy is required in patients whose renal function does not improve with diuretics[13]. In our clinical approach, we started

Table 2. Cardiac pathology and surgical procedures.

Diagnosis	n	Surgical procedure
Aorta stenosis	1	Valvuloplasty
Aorta stenosis + hypoplastic arcus aorta	1	Valvuloplasty + repair of hypoplastic arcus aorta
CAVSD	5	Repair of CAVSD
CAVSD + hypoplastic arcus aorta	1	Repair of hypoplastic arcus aorta + pulmonary artery banding
CAVSD + PS		BCPC + pulmonary valvuloplasty
CAVSD + TOF	2	Repair of CAVSD + pulmonary valvuloplasty
CAVSD + TOF	1	BT shunt
DORV + PS	1	RVOTR
DORV + PS	1	Rastelli procedure
DORV + PS	1	BCPC
Hypoplastic arcus aorta	1	Repair of hypoplastic arcus aorta + VSD repair
Hypoplastic arcus aorta	1	Repair of hypoplastic arcus aorta + pulmonary banding
Hypoplastic right ventricle + PS	1	Central shunt
Hypoplastic right ventricle + TAPVC	1	BCPC + TAPVC Repair
Hypoplastic left heart syndrome	10	Norwood I procedure
Hypoplastic left heart syndrome	2	Repair of hypoplastic arcus aorta + pulmonary banding
Hypoplastic left heart syndrome	1	Pulmonary banding
Interrupted arcus aorta	1	Repair of hypoplastic arcus aorta + pulmonary banding
Interrupted arcus aorta	1	Repair of hypoplastic arcus aorta + VSD Repair
Interrupted arcus aorta + VSD	1	Norwood I procedure
PS	1	RVOTR
Pulmonary venous stenosis	1	Pulmonary venous reconstruction
TAPVC	1	Correction of TAPVC
TGA	21	Arterial switch
TGA	2	Senning procedure
TGA	1	Rastelli procedure
TGA	1	Arterial switch+ VSD repair
TGA + DORV	1	Senning procedure + VSD repair
TGA + hypoplastic arcus aorta	1	Repair of hypoplastic arcus aorta + pulmonary banding
TGA + PS	1	Senning procedure
TGA + VSD + interrupted arcus aorta	1	Repair of arcus aorta + pulmonary banding
TOF	1	BT Shunt
TOF	10	Total correction of TOF
TOF	2	RVOTR
TOF	1	BCPC
Tricuspid atresia	1	Closure of pulmonary artery
Tricuspid atresia	1	Fontan procedure
Truncus arteriosus	1	Rastelli procedure
VSD + coarctation of aorta	1	Repair of VSD and coarctation
VSD + coarctation of aorta	1	Repair of hypoplastic arcus aorta and VSD
VSD + coarctation of aorta	1	Repair of hypoplastic arcus aorta and VSD + pulmonary banding
VSD + pulmonary band	1	Repair of VSD + pulmonary debanding

BCPC, bidirectional cavopulmonary connection; BT, Blalock-Taussig; CAVSD, complete atrioventricular septal defect; DORV, double-outlet right ventricle; PS, pulmonary stenosis; RVOTR, right ventricle outflow reconstruction; TAPVC, total anomalous pulmonary venous connection; TGA, transposition of great artery; TOF, tetralogy of Fallot; VSD, ventricular septal defect.

renal replacement therapy with peritoneal dialysis, who has insufficient reply to diuretics and volume overload.

Acute kidney injury after cardiac surgery is associated with prolonged ventilation and hospital stay and increased mortality. It increases the risk of mortality five times after cardiac surgery[11]. A 20% mortality has been reported in patients undergoing peritoneal dialysis after pediatric cardiac surgery[3, 8, 12]. Earlier treatment of the AKI improves postoperative outcome and avoids postoperative complications. The tendency to initiate the peritoneal dialysis in early postoperative period, in the patients at risk of being affected by rapid fluid change and those who do not response to diuretic therapy and prolonged CPB duration, was started in order to maintain fluid balance[11, 14]. Peritoneal dialysis is a safe and easy method to prevent postoperative AKI and fluid overload with the advantages of not requiring anticoagulation and vascular intervention[1, 2, 10]. Short-term and low-volume peritoneal dialysis (10 mL/kg every hour) might be performed safely with a low risk of hemodynamic instability[8]. Peritoneal dialysis prevents capillary leakage, which is one of the effects of CPB. It also drains the fluid accumulated in the extravascular area[10]. Peritoneal dialysis improves the electrolyte imbalance and reduces the need for mechanical ventilation and inotropic support by providing negative fluid balance in a short time. In a prospective, randomized controlled study, peritoneal dialysis is superior to diuretics in fluid management, controlling the electrolyte imbalance, and reducing the need for inotropic support and mechanical ventilation[10]. In our clinic, we aim to reduce postoperative morbidity and mortality by performing peritoneal dialysis as prophylactic in prolonged CPB duration in the operating room and as earlier treatment of fluid overload in intensive care follow-ups. When examined all of our patients who underwent congenital cardiac surgery, we observed that the patients with longer than 90 min CPB time underwent prophylactic peritoneal dialysis. There were patients whose CPB duration was longer than 90 min in the treatment group for dialysis indication. In these patients, we did not prefer to insert a catheter intraoperatively because of negative balance and without the signs of fluid overload. The mortality rate of our patients was 34.8%. It was 31.1% for prophylactically dialysis and 42.8% for the patients whose dialysis was initiated in the ICU.

Gist et al.[2] reported the prophylactic peritoneal dialysis avoids fluid overload after arterial switch operation. Prophylactic peritoneal dialysis after arterial switch operation reduces mechanical ventilation time by 42% and hospital stay by 34%, improving the postoperative recovery and reducing hospital cost[2]. We performed peritoneal dialysis prophylactically in all 22 patients who underwent arterial switch operation in our clinic, and our mortality rate was 13.5% (n:3) in these patients.

Patients under treatment of ECMO have a high risk of fluid overloading and renal damage due to the patient's primary disease (i.e., sepsis, ischemia, respiratory and cardiac failure, and vasopressor support). Acute renal damage occurs in 70–85% of the patients with ECMO, and 50% of these patients require renal replacement therapy[7]. Initiation of renal replacement therapy in the earlier period without fluid overloading in the patients with ECMO increases the rate of survival[15]. In the patients with peritoneal dialysis, base deficit, lower pH, and higher lactate levels increase the risk of mortality. Extracorporeal support systems might be beneficial in these patients[16]. In patients undergoing ECMO, the need for dialysis is an independent risk factor for mortality and increases mortality four times[9]. Peritoneal dialysis with ECMO is an effective and safe method to prevent fluid overload and electrolyte abnormality[7]. ECMO was required in 20% (n:18) of our patients who underwent peritoneal dialysis, and two of the patients with ECMO survived.

In this study, there is a lack of the nature of the retrospective studies and as a result no definitive conclusions can be drawn by these results. We included all patients with congenital cardiac defects in the study. Our study includes the patients in the age range from newborn to 288 months, and those weighing up to 12 kg were evaluated. Assessment of age- and weight-related dialysis requirement could not be done and therefore we could not suggest any risk value of age or weight for dialysis. Further prospective studies should be performed with sub-analyses in different age groups and according to diagnosis and treatment modalities.

CONCLUSION

Peritoneal dialysis is a safe and easy method to avoid fluid overloading and AKI after the pediatric congenital cardiac surgery. It might be initiated in earlier period in the operating room in the conditions of fluid overloading and lengthened CPB time. It improves postoperative outcomes with decreasing mechanical ventilation period, need of inotropic support, and length of hospital stay.

AUTHORS' CONTRIBUTIONS

AHA: Conceptualization, Data collection. **AHA, MU:** Methodology, Writing – original draft. **TA:** Software, Investigation. **HU:** Validation, Formal Analysis. **TA, HU:** Writing – review & editing.

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ORIGINAL ARTICLE

https://doi.org/10.1590/1806-9282.20211336

Telematics program of breathing exercises and mindfulness for post-coronavirus disease 2019 patients

Marta de la Plaza[1*], María Blanco Morales[1], Guillermo García Pérez de Sevilla[1], Ángel Gonzalez de la Flor[1], Carlos Romero Morales[1], Margarita Rubio[1]

SUMMARY

OBJECTIVE: The coronavirus disease 2019 pandemic is an economic, social, and health challenge. During the coronavirus disease 2019 lockdown, a telematics platform for respiratory physiotherapy and mindfulness was created, aiming to reduce dyspnea and anxiety and to increase quality of life in post-coronavirus disease 2019 patient.

METHODS: A quasi-experimental study was performed on post-coronavirus disease 2019 patients, with breathing exercises and mindfulness with remote supervision by a respiratory physiotherapist. Dyspnea on exertion (Mahler Scale), quality of life (EuroQol-5D score), and anxiety (State-Trait Anxiety Inventory questionnaire) were measured before and after the rehabilitation program.

RESULTS: A total of 20 subjects completed the program, with a significant decrease in the measures of dyspnea on exertion ($p<0.001$), state anxiety ($p=0.004$), and trait anxiety ($p=0.001$) and a significant increase in quality of life ($p=0.016$).

CONCLUSIONS: Coronavirus disease 2019 should be treated using a multidisciplinary approach that includes respiratory rehabilitation. At present, there are few studies on respiratory rehabilitation and mindfulness in post-coronavirus disease 2019 patients. The results of this study showed that the implementation of breathing exercises and mindfulness with remote supervision was effective in decreasing dyspnea and anxiety and in increasing quality of life in post-coronavirus disease 2019 patients during confinement.

KEYWORDS: COVID-19. Coronavirus. SARS-Cov-2. Mindfulness. Breathing exercises. Telerehabilitation.

INTRODUCTION

The coronavirus disease 2019 (COVID-19) pandemic is an economic, social, and health challenge. The mobility restrictions have affected millions of people around the world, the high level of contagiousness and sanitary collapse has driven new sanitary realities to control the pandemic, and telehealth has been recommended by the post-COVID-19 patient rehabilitation guidelines[1].

Severe acute respiratory syndrome coronavirus 2 (SARS-Cov-2) is a complex virus, with 10% of the cases requiring hospitalization. SARS-Cov-2 combines high transmissibility with high morbidity and mortality, showing a highly variable course between asymptomatic and fulminant lethal cases. Scientific evidence shows that 80% of infected patients present complications and sequelae after overcoming the acute period of illness. Among the most important sequelae are fatigue (58%), dyspnea (24%), headaches (44%), attention disorder (27%), anxiety (13%), depression (12%), and many other symptoms[2].

The most severe forms of COVID-19 can leave sequelae of pulmonary fibrosis in 5% of patients who have presented bilateral pneumonias[3]. A significant number of patients who have suffered COVID-19 require rehabilitation, with the severity of the disease being a key factor that determines the type of rehabilitation. To treat COVID-19 patients, multidisciplinary rehabilitation teams should perform cardiopulmonary rehabilitation, musculoskeletal rehabilitation, neurorehabilitation, and psychological rehabilitation[4].

As respiratory function can be altered, dyspnea is a common symptom[5]. We also found decreased tidal volume and compliance, ventilatory imbalance, alveolar collapse, decreased respiratory muscle strength, increased airway resistance, and decreased coughing ability[6]. Chest physiotherapy helps to restore the patient's lung function and improve ventilation, efficiency of the respiratory muscles, and readaptation to exertion[7]. With few exceptions, patients do not require bronchial lavage techniques, but respiratory muscle training will be important if they are assisted by a ventilator in order to increase the success of weaning if the patient is hospitalized in the acute phase in the intensive care unit (ICU)[8].

Previous studies on the sequelae of SARS showed a decrease in lung function with restrictive patterns, muscle

[1]Universidad Europea de Madrid – Madrid, Spain.
*Corresponding author: marta.delaplaza@universidadeuropea.es
Conflicts of interest: the authors declare there is no conflicts of interest. Funding: none.
Received on December 29, 2021. Accepted on March 03, 2022.

weakness, cardiorespiratory deficit, and decreased musculoskeletal performance as sequelae[9], which are similar to the COVID-19 sequelae[2].

Few studies on post-acute COVID-19 syndrome recommend slow and deep breathing, rib cage expansions, abdominal breathing, pursed-lip exhalations, and drainage of secretions if necessary[10]. In addition to breathing, stretching techniques, progressive muscle relaxation, and mindfulness session are also recommended. The use of breathing techniques may help control the anxiety levels[11], and mindfulness stimulates the parasympathetic nervous system, thereby altering neuronal function in specific areas of the brain and reducing the release of stress chemicals[12].

Mindfulness is also effective in improving many biopsychosocial conditions, including depression, anxiety, stress, insomnia, addiction, psychosis, pain, hypertension, and weight control. Mindfulness has been proposed as potentially effective in alleviating mental health problems related to the COVID-19[13].

During the COVID-19 lockdown in Spain, a telematics platform of respiratory physiotherapy and mindfulness for post-COVID-19 patients was launched as an altruistic initiative. The aim of the program was to improve the patient's dyspnea sensation, anxiety, and quality of life in the recovery phase of COVID-19.

METHODS

Study design and participants

This quasi-experimental study was performed on April 2020. On April 6, 2020, the program was launched through social networks, and people interested in participating in the study contacted the physiotherapist.

Inclusion criteria to participate in the study were as follows: a positive PCR test result for the COVID-19 virus, more than 10 days having passed since the initial diagnosis, no fever, hemodynamically stable, patients with dyspnea, and being able to remain seated for 1 h.

Ethical considerations

This study was conducted under the guidance of the Helsinki ethical statements. All the participants read the study criteria and signed the informed consent form.

Measurements

Before starting the rehabilitation program, and after completion of the intervention, each patient filled the following questionnaires: EuroQol-5D quality-of-life score[14], Mahler dyspnea index[15], and State-Trait Anxiety Inventory (STAI) anxiety questionnaire[16], through the Google Forms platform.

Intervention

Ten sessions were remotely supervised through a digital platform by a physiotherapist trained in chest physiotherapy and mindfulness. This program was based on respiratory physiotherapy guidelines[10].

The program consisted of 10 sessions of respiratory physiotherapy with remote supervision, carried out three times a week, each session lasting 45 min. Before the session, the patient's dyspnea was monitored with the Borg scale[17]; patients who increased their dyspnea during the exercises by more than 3 points stopped the session.

The sessions consisted of (1) 10 abdomino-diaphragmatic respirations: The rhythm of each breath was slow, inhaling to high lung volume[1]; (2) 10 costal expansion exercises with upper limb flexion and abduction; (3) three self-passive stretching of the rib cage and accessory respiratory neck muscles, aiming to increase the flexibility of the muscles to improve vital capacity; (4) progressive Jacobson's relaxation contracting according to the procedure recommended by Bernstein and Borkovec[18]; and (5) final mindfulness, focusing on breathing instructions during 10 min, based on the study by Arch and Craske[12].

Statistical analysis

The frequencies of the categorical variables were expressed as absolute numbers and percentages. The quantitative variables that were non-normally distributed were summarized as median and interquartile range (IQR) using the Shapiro-Wilk test. For the comparison of the data corresponding to the quantitative variables measured before and after the physical therapy sessions, the Wilcoxon signed-rank test was used. The significance level was set at alpha <0.05. Data analysis was performed using the IBM SPSS Statistics for Windows, version 23.0 (IBM Corp., Armonk, NY, USA).

RESULTS

A total of 20 patients participated in the study, and all of them completed the 10 sessions of respiratory physiotherapy. The mean age was 48.5 years (IQR 39.2–60.5), 50% were female, and the median body mass index (BMI) was 23.9 kg/m^2 (IQR 22.7–26.4).

Table 1 shows the clinical characteristics of the patients. Most of them reported having had or having fever (85%)

and/or cough (75%), and 75% had been diagnosed with pneumonia. Notably, 60% of the patients had been hospitalized due to the COVID-19 infection, but none of them required ICU admission. Also, 35% (7 patients) had required oxygen therapy.

A comparative analysis of the measures assessed before and after the chest physiotherapy and mindfulness virtual intervention is shown in Table 2. A significant decrease in state anxiety (p=0.004), trait anxiety (p=0.001), and dyspnea was achieved after the intervention (p<0.001), and a significant increase in quality of life was found (p=0.016) after the intervention.

DISCUSSION

The results of the virtual physiotherapy program met the objectives of improving dyspnea and quality of life and decreasing anxiety in post-COVID-19 patients. The exercises used were based on consensus and expert guidelines that promote the application of pulmonary rehabilitation[17].

Coronavirus disease 2019 impedes gas exchange due to exudate in the alveolar space. The virtual respiratory rehabilitation program consisted of different types of breathing, such as abdomino-diaphragmatic respirations, costal expansion exercises, stretching, progressive muscle relaxation, and final mindfulness. The participants improved their dyspnea symptoms, so it could be an effective strategy to improve gas exchange due to increased ventilation of the deep lung[19]. The effects of Jacobson's progressive muscle relaxation exercises as well as mindfulness on dyspnea and fatigue have been successfully tested in people with lung disease[20].

There are currently few studies on respiratory rehabilitation in COVID-19, with the first study being that by Liu et al.[21], in which a 6-week respiratory physiotherapy program consisting of respiratory muscle training, cough exercises, diaphragmatic training, stretching exercises, and home exercises showed improved spirometric parameters, the 6-min walk test score, and quality of life of the participants.

Due to the variability of the sample, the program was based on breathing exercises that were adaptable to most of the patients. As described above, a safety limit was established in order to carry out the exercises in the most controlled way possible, since not all the subjects had measurement systems, and the telematics route could be a limitation to maintain safety.

A previous study, similar to this research, used telerehabilitation in the acute phase in patients with mild or moderate symptomatology. The intervention lasted for 1 week, thus improving the 6-min walk test score, the dyspnea, and the functionality of the experimental group[22]. Although more trials are needed, telerehabilitation seems an adequate approach during the COVID-19 pandemic.

Table 1. Characteristics of the participants.

Variables	n=20
Fever	17 (85%)
Cough	15 (75%)
Anosmia	9 (45%)
Ageusia	9 (45%)
Pneumonia	15 (75%)
Currently with pneumonia	6 (30%)
Previously hospitalized COVID-19	12 (60%)
Currently hospitalized COVID-19	2 (10%)
Days of hospitalization, median (IQR)	9 (5.7–12.2)
Oxygen therapy during illness	7 (35%)
Admission to ICU	0
Previous respiratory pathology	4 (20%)
Asthma	1 (5%)
Bronchiectasis	3 (15%)

Table 2. Pre- and post-intervention comparative analysis.

	Pre-intervention Median (IQR)	Post-intervention Median (IQR)	p
Anxiety status	19.5 (13.3–19.3)	17.5 (10.3–22.5)	0.004*
Anxiety trait	17 (10.5–23.5)	14 (8.5–21.5)	0.001*
Quality of life	0.8 (0.7–1)	1 (0.8–1)	0.016*
Dyspnea	8 (2–11)	11.5 (10–12)	<0.001*

*Significance of p<0.05 was considered. The Wilcoxon signed-rank test was used.

CONCLUSION

Remotely supervised respiratory physiotherapy seems to be an effective approach for post-COVID-19 patients to decrease the sensation of dyspnea and anxiety and to increase the quality of life.

AUTHORS' CONTRIBUTIONS

MPSF: Investigation, Methodology, Writing. **MBM:** Writing-review and editing. **GGPS:** Approval final version. **ÁGF:** Writing-review and editing. **CRM:** Data curation, Project administration. MRA: Formal Analysis, Validation.

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ORIGINAL ARTICLE

https://doi.org/10.1590/1806-9282.20211368

An inconvenient status in anti-osteoporotic treatment process: corticosteroid use

Ercüment Öztürk[1*], Ahmet Çiğiloğlu[1], Güzin Çakmak[1], Zeynel Abidin Öztürk[1]

SUMMARY

OBJECTIVE: There are limited studies investigating the comparison of the efficacy of anti-osteoporotic drugs in different conditions resulting in osteoporosis in older adults. This study aimed to compare the effectiveness of anti-osteoporotic agents in older adults with or without glucocorticoid-induced osteoporosis.

METHODS: This retrospective study included 364 patients with osteoporosis, aged 65 years and older. Bone mineral density measurement was performed, and the percent change from baseline was calculated at month 24.

RESULTS: Of the 364 patients, 80 were glucocorticoid users. Similar changes in the bone mineral density of the lumbar spine and femoral neck and fracture risk were found in patients with or without glucocorticoid-induced osteoporosis. There was no significant difference in bone mineral density changes between the groups in terms of anti-osteoporotic agents used.

CONCLUSIONS: This study demonstrated that the response to anti-osteoporotic agents was similar in older adults with glucocorticoid-induced osteoporosis and those without glucocorticoid-induced osteoporosis. The results of our study may guide osteoporosis treatment in older individuals with glucocorticoid-induced osteoporosis.

KEYWORDS: Elderly. Osteoporosis. Glucorticoid effects. Alendronate. Zoledronic acid. Denosumab. Teriparatide.

INTRODUCTION

Osteoporosis is a skeletal disorder characterized by low bone mass, microarchitectural disruption, and bone fragility, resulting in increased fracture risk. The social and economic burden of osteoporosis is increasing constantly due to the aging of the world population[1] Glucocorticoid-induced osteoporosis (GIOP) is the most common type of secondary osteoporosis[2]. An important characteristic of GIOP is rapid bone loss immediately after initiation of glucocorticoid (GC) therapy[3]. Fracture is the most common serious and preventable adverse event associated with GCs. The use of approximately 5 mg of prednisone or its equivalent for 3 months has been shown to result in a measurable increase in fracture risk[4].

Bisphosphonates are recommended as an initial anti-osteoporotic therapy because of their efficacy, favorable cost, and long-term safety[5]. Alendronate, risedronate, ibandronate, and zoledronic acid have been shown to improve bone mineral density (BMD) in postmenopausal women with osteoporosis[6]. Denosumab can be preferred as initial therapy in certain patients who are at high risk for fracture and intolerant or unresponsive to other therapies like intravenous bisphosphonates, or who have markedly impaired renal function. Denosumab improves BMD and reduces fracture risk in postmenopausal women with low BMD[7]. Denosumab may be an alternative in some patients with GIOP, especially those who are at high risk due to advanced age. Both the features of superiority to the bisphosphonates and the similarity of the adverse events make denosumab an appropriate alternative for these patients[8].

Teriparatide is recommended for patients who have severe osteoporosis (low BMD [T-score <-2.5] and at least one fragility fracture) or who do not have improvements with the previous therapy[9]. Teriparatide directly stimulates osteoblastogenesis and inhibits osteoblast apoptosis; therefore, it could be another alternative as anabolic therapy in patients who are receiving long-term GCs and are at high risk for fracture[10]. Teriparatide is also superior to bisphosphonates in increasing BMD of the lumbar spine, total hip, and femoral neck in patients with GIOP[11].

In this study, we aimed to compare the efficacy of anti-osteoporotic medications in osteoporotic older adults with or without GIOP.

METHODS

Participants

This retrospective study included 412 patients, aged 65 years or older and diagnosed with osteoporosis, who visited our geriatric medicine outpatient clinic between January 1, 2018, and March 1, 2019. Notably, 29 patients with insufficient data and

[1]Gaziantep University, Faculty of Medicine, Department of Internal Medicine, Division of Geriatric Medicine – Gaziantep, Turkey.
*Corresponding author: ercument37@yahoo.com
Conflicts of interest: the authors declare there is no conflicts of interest. Funding: none.
Received on February 09, 2022. Accepted on February 11, 2022.

19 patients without dual-energy x-ray absorptiometry (DXA) scan at month 24 were excluded. The study was completed with 364 participants. The sample size was calculated using the Epi Info software, and the minimum sample size was 120 participants, with 80% power at the level of α=0.05. Exclusion criteria were renal impairment, primary or metastatic bone tumor, and bone diseases other than osteoporosis. BMD measurement of the lumbar spine and proximal femur was performed by DXA method (using Hologic scanners) before treatment and at month 24. The percentage change from the baseline BMD was calculated at month 24. Drugs administered included the following: alendronate 70 mg/week orally, zoledronic acid 5 mg/year intravenously, denosumab 60 mg/every 6 months subcutaneously, and teriparatide 20 µg/day subcutaneously. All patients were prescribed 1000 mg of calcium and 800 IU of vitamin D per day. GC use was considered the use of ≥5 mg/day prednisolone or equivalent for ≥3 months.

Statistical analysis

Statistical analyses were performed using SPSS for Windows version 22.0 (IBM SPSS Statistics, Armonk, NY, USA). The distribution of normality was checked using the Shapiro-Wilk test. We used the Mann-Whitney U test and independent samples t-test to compare two independent groups of variables, the chi-square test to assess the relationship between categorical variables, and Spearman's rank correlation coefficients between numerical variables. Logistic regression analysis was used to determine the independent predictors of low BMD. A p<0.05 was accepted as statistically significant.

RESULTS

In this study, the mean age of 364 older adults was 69.9±5.4 years, and 90.4% were women. Most of the participants (82.1%) were in the age group 65–74. Twenty-eight were smokers and none of them consumed alcohol. The proportion of those with diabetes mellitus and coronary artery disease was significantly higher in the non-GC-user group. C-reactive protein level was higher in GC-users; however, there was no difference between the groups in terms of age, gender, anti-osteoporotic agents used, and other laboratory tests (Table 1).

Baseline BMD of the lumbar spine and femoral neck, as well as BMD changes were similar between the groups (Table 2). There was no significant difference in BMD changes between the GC-users and the non-GC-users in terms of anti-osteoporotic agents used (Table 3). In addition, it was observed that parenteral anti-osteoporotic agents were more effective in BMD improvement compared with alendronate, although there was no statistically significant difference.

Age, the number of comorbidities, and medications were not correlated with the BMD change and fracture risk reduction. A statistically significant strong positive correlation was found between femur neck BMD change and major osteoporotic and hip fracture risk reduction percentage (p=<0.001, r=0.961 and p=<0.001, r=0.962, respectively). In addition, there was a statistically significant negative correlation between the baseline femur neck and the BMD changes (p£0.001, r=–0.292), between major osteoporotic and hip fracture risk reductions (p£0.001, r=–0.335, and p£0.001, r=–0.274, respectively), and between the baseline BMD and BMD change in the lumbar spine (p£0.001, r=–0.232).

According to the multivariate logistic regression analysis, BMD change of the femoral neck was an independent variable for both major osteoporotic (p=0.000, OR=4.11) and hip fracture risk reductions (p=0.000, OR=4.01).

DISCUSSION

In our study, it was noticeable that BMD changes of the lumbar spine and femur neck showed similar responses to treatment agents in both the groups who received and who did not receive GC medication. Major osteoporotic and hip fracture risk reductions were also similar in both the groups. Parenteral anti-osteoporotic agents were found to be more effective in BMD improvement, although there was no statistically significant difference.

Glucocorticoid-induced osteoporosis is characterized by a greater reduction in osteoblastic activity at different levels of the bone, leading to reduced bone formation dramatically when compared with postmenopausal osteoporosis[12]. "Similar responses to the treatment" is a rather remarkable result, especially when we consider expectations for better responses to the treatment in patients with GIOP. Another cause of these similar responses may be ongoing GC treatment of the GC-receiving group. While a dramatic improvement in BMD is expected with anti-osteoporotic therapy after cessation of GC drugs, ongoing GC therapy may cause a slowdown in anti-osteoporotic treatment response. With this point of view, especially for those who have to continue their GC treatment, we can conclude that depending on GC doses and the condition of the underlying disease, one of the second-line anti-osteoporotic agents may be preferred as a first-line option or earlier than bisphosphonates therapy in GIOP treatment[13]. Oral bisphosphonates are generally the first-line

Table 1. Sociodemographic characteristics and laboratory analysis results of the participants.

	GC-user (n=80)	Non-GC-user (n=284)	p	Total (n=364)
Gender				
Female	73 (91.3%)	256 (90.1%)	0.480	329 (90.4%)
Male	7 (8.8%)	28 (9.9%)		35 (9.6%)
Age (years) #	69.0±4.5	70.1±5.6	0.092	69.9±5.4
65–74	74 (92.5%)	225 (79.2%)	0.016*	299 (82.1%)
75–84	4 (5.0%)	51 (18.0%)		55 (15.1%)
≥85	2 (2.5%)	8 (2.8%)		10 (2.7%)
Treatment agent				
Alendronate	32 (40.0%)	79 (27.8%)	0.130	111 (30.5%)
Zoledronic acid	23 (28.7%)	98 (34.5%)		121 (33.2%)
Denosumab	24 (30.0%)	94 (33.1%)		118 (32.4%)
Teriparatide	1 (1.3%)	13 (4.6%)		14 (3.8%)
Other comorbidities				
Hypertension	30 (37.5%)	119 (41.9%)	0.521	149 (40.9%)
Diabetes mellitus	8 (10.0%)	65 (22.9%)	0.011*	73 (20.1%)
Coronary artery disease	4 (5.0%)	39 (13.8%)	0.031*	43 (11.8%)
Asthma/COPD	10 (12.5%)	19 (6.7%)	0.103	29 (8.0%)
Cancer	2 (2.5%)	17 (6.0%)	0.268	19 (5.2%)
Smoker	4 (5.0%)	24 (8.5%)	0.306	28 (7.7%)
Serum 25-OH vitamin D (nmol/L) #	35.9±6.4	34.0±5.7	0.158	34.4±6.2
Parathyroid hormone (pg/ml) †	56	48	0.167	49
Serum calcium (mg/dl) # ‡	9.7±0.6	9.7±0.5	0.579	9.7±0.6
Serum phosphorus (mg/dl) #	3.7±0.6	3.6±0.4	0.601	3.6±0.5
C-reactive protein (mg/dl) †	3.0	2.6	0.017*	2.8
Erythrocyte sedimentation rate (mm/h) †	18	17	0.461	17
Serum creatinine (mg/dl) #	0.73±0.24	0.70±0.18	0.201	0.71±0.20

*p≤0.05. #Data are presented as mean±SD; †Data are presented as median; ‡, Albumin-adjusted calcium. GC: glucocorticoid; COPD: chronic obstructive pulmonary disease.

Table 2. Comparison of the dual-energy x-ray absorptiometry scan assessments, bone mineral density changes, and fracture risk reduction.

.	GC-user (n=80)	Non-GC-user (n=284)	p	Total (n=364)
Lumbar spine				
Baseline T score#	-2.90±0.78	-2.98±0.84	0.460	-2.97±0.83
Baseline BMD (g/cm^2) #	0.73±0.09	0.72±0.09	0.658	0.72±0.09
24th month BMD (g/cm^2)#	0.76±0.09	0.75±0.09	0.508	0.75±0.09
BMD change (%)†	3.68	3.99	0.581	3.93
Femur neck				
Baseline T score#	-2.36±0.72	-2.39±0.75	0.355	-2.39±0.75
Baseline BMD (g/cm^2) #	0.59±0.08	0.58±0.09	0.394	0.59±0.08
24th month BMD (g/cm^2)#	0.61±0.08	0.60±0.08	0.734	0.60±0.08
BMD change (%)†	3.57	2.93	0.770	2.99
Major osteoporotic fracture risk reduction (%)†	6.67	9.09	0.642	8.33
Hip fracture risk reduction (%)†	10.31	14.28	0.399	13.72

#Data are presented as mean±SD; †Data are presented as median. BMD: bone mineral density.

Table 3. Comparison of the bone mineral density changes between treatment agents.

Treatment agent		Lumbar spine BMD change (%)	p	Femur neck BMD change (%)	p
Alendronate (n=111)	Non GC-user (n=79)	3.27	0.984	2.28	0.607
	GC-user (n=32)	3.38		2.31	
Zoledronic acid (n=121)	Non GC-user (n=98)	4.41	0.746	2.79	0.761
	GC-user (n=23)	3.55		5.57	
Denosumab (n=118)	Non GC-user (n=94)	3.61	0.784	3.79	0.721
	GC-user (n=24)	3.40		3.64	
Teriparatide (n=14)	Non GC-user (n=13)	8.19	0.143	3.16	0.429
	GC-user (n=1)	30.5		15.19	

BMD: bone mineral density; GC: glucocorticoid. Data are presented as median.

therapy for GIOP in most patients due to their proven efficacy, good safety, and low cost. However, the superiority of teriparatide to oral bisphosphonates especially in increasing BMD and reducing fracture risk may provide an advantage for GIOP patients who have ongoing GC treatment[14,15]. Giving high-dose teriparatide may be another way to provide a faster and greater BMD increase in GIOP patients. In a recent study, patients receiving high-dose teriparatide treatment achieved clinically meaningful and rapid gains in hip and spine BMD[16]. Moreover, some studies indicate that cyclic administration of teriparatide either alone or in combination with ongoing bisphosphonates may achieve the best outcomes for patients with severe osteoporosis[17,18]. The small number of patients receiving teriparatide in our study may be the reason for the lack of significant difference in BMD changes.

Most of our patients were using intravenous zoledronic acid, which is more effective than risedronate in increasing lumbar spine BMD and reducing serum bone turnover markers (BTM). Therefore, treatment of GIOP patients with intravenous zoledronic acid may be more reasonable than the oral forms of other bisphosphonates. Denosumab can be considered as one of the therapeutic options for GIOP patients, especially when the efficacy of bisphosphonate treatment is diminished or teriparatide treatment is discontinued[19].

This study has many limitations. First, there is a lack of BTM measurement at baseline and month 24 in both the groups. Second, a much longer follow-up may better show the differences in fracture incidence. Third, we need more teriparatide-receiving patients in both the groups in order to acquire more accurate comparisons and achieve a treatment approach. Despite these limitations, our study has some strength. First, our study includes only older patients. Second, we compared the effects of the anti-osteoporotic agents among themselves, while most previous studies compared the effects of the drugs with placebo. Similarities in laboratory test results and sociodemographic characteristics between groups were also important for a clearer comparison of treatment response.

CONCLUSIONS

This study showed that older adults with GIOP had a similar anti-osteoporotic treatment response compared to those without GIOP. Even though the second-line anti-osteoporotic agents have particular indications to use as anti-osteoporotic treatment, it can be considered to use these agents as the first-line treatment options in patients with GIOP in order to achieve more effective BMD responses. Furthermore, among osteoporotic patients, considering that GIOP is a more destructive process, alternative treatments like high-dose teriparatide can be given as an anti-osteoporotic treatment. However, further studies are needed to obtain more strong data to support our results.

ETHICS APPROVAL

All procedures performed in studies involving human participants were in accordance with the ethical standards of the institutional research committee and with the 1964 Helsinki Declaration and its later amendments or comparable ethical standards. Approval for the study was granted by the Local Ethics Committee.

AUTHORS' CONTRIBUTIONS

EÖ: Investigation, Project administration, Resources, Writing – original draft. **AÇ:** Data curation, Validation. **GÇ:** Methodology, Visualization. **ZAÖ:** Conceptualization, Supervision, Writing – review & editing.'

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ORIGINAL ARTICLE

https://doi.org/10.1590/1806-9282.20211369

Differentiation of affected and nonaffected ovaries in ovarian torsion with magnetic resonance imaging texture analysis

Tumay Bekci[1]*, Ismet Mirac Cakir[1], Serdar Aslan[1]

SUMMARY

OBJECTIVE: This study aimed to evaluate the feasibility of texture analysis on T2-weighted axial images in differentiating affected and nonaffected ovaries in ovarian torsion.

METHODS: We included 22 torsioned ovaries and 19 healthy ovaries. All patients were surgically proven ovarian torsion cases. On T2-weighted axial images, ovarian borders were delineated by the consensus of two radiologists for magnetic resonance imaging-based texture analysis. Statistical differences between texture features of affected and nonaffected ovaries were assessed.

RESULTS: A total of 44 texture features were extracted from each ovary using LIFEx software. Of these, 17 features were significantly different between affected and nonaffected ovaries in ovarian torsion. NGLDM_Coarseness and NGLDM_Contrast, which are the neighborhood gray-level difference matrix parameters, had the largest area under the curve: 0.923. The best cutoff values for the NGLDM_Contrast and NGLDM_Coarseness were 0.45 and 0.01, respectively. With these cutoff levels, NGLDM_Contrast had the best accuracy (85.37%).

CONCLUSION: Magnetic resonance imaging-based texture analysis on axial T2-weighted images may help differentiate affected and nonaffected ovaries in ovarian torsion.

KEYWORDS: Artificial intelligence. Diagnostic techniques. Obstetrical and gynecological.

INTRODUCTION

Ovarian torsion (OT) is defined as a partial or complete turn of the ovary and ovarian vascular pedicle on its long axis[1,2]. OT results venous blood flow obstruction, edema, and consequent necrosis of ovarian tissue because of subsequent arterial blood flow obstruction[2]. Its nonspecific symptoms and a wide differential diagnosis of pelvic abdominal pain make it difficult to diagnose OT, even in experienced hands, with the use of multimodality screening tools. Furthermore, the reliability of ultrasonography (US) and magnetic resonance imaging (MRI) assessments in the diagnosis of OT is limited by the variety of experience of radiologists[1,2]. An increased incidence of OT, especially in pregnant women, children, and women undergoing ovulation induction therapy, draws attention to this issue[1]. In contrast, timely diagnosis and management of OT is crucial for the preservation of ovarian reserve and fertility[1]. Thus, an accurate, noninvasive method that does not use contrast media or radiation to predict OT preoperatively is essential for the overall treatment of OT, especially in children and pregnant women.

Texture analysis (TA) is an emerging technique that allows for the analysis of the distribution of pixel intensities and transforms digital medical images into mineable data by extracting quantitative features mathematically[3-18]. TA has recently been investigated for the identification of brain, renal, lung, and ovarian tumors and diseases[6,8]. However, to the best of our knowledge, there is still no study in the literature that uses TA to differentiate affected and nonaffected ovaries in OT. TA is a promising method, and the texture data obtained can be used in deep learning algorithms for rapid diagnosis and treatment of OT in emergency settings. The most obvious example of this is artificial intelligence-based algorithms used in stroke patients[19]. OT, in contrast, is a difficult process to diagnose, and the fact that the torsed and nontorsed ovaries can be differentiated by TA can provide rapid diagnosis and treatment of OT with deep learning applications in emergency settings. We think that TA may help differentiate affected and nonaffected ovaries based on lesion signal intensity characteristics in MRI. Accordingly, we aimed to investigate the feasibility and accuracy of TA for differentiating affected and nonaffected ovaries in OT on T2-weighted MR images.

METHODS

A flowchart of the TA model is shown in Figure 1.

[1]Giresun University Faculty of Medicine, Department of Radiology – Giresun, Turkey.
*Corresponding author: tmybkc@gmail.com

Conflicts of interest: the authors declare there is no conflicts of interest. Funding: none.
Received on January 30, 2022. Accepted on January 03, 2022.

Patients

This retrospective study was approved by the institutional review board of our university hospital, and written informed consent was waived (OMU/KAEK-2016/49). The database of our university hospital was reviewed to identify surgically proven OT patients with preoperative MRI examinations between January 2015 and April 2020. The inclusion criteria were surgically proven OT, MRI examination prior to surgery, and having an axial T2-weighted MRI (n=22). The exclusion criterion was MR images with motion artifacts (n=1) and torsion cases with paraovarian cysts neoplasms (n=3).

MR image acquisition and ovarian segmentation

A 1.5-T MRI Scanner (Siemens Magnetom Symphony Quantum, Erlangen, Germany) equipped with phased-array coils was used for MRI examinations. The standard T2-weighted MRI protocol was used.

The affected and nonaffected ovaries were manually segmented by the consensus of two radiologists with 9 and 8 years of experience in abdominal imaging using LIFEx software (www.lifex-soft.org). LIFEx software is a free, multiplatform, and easy-to-use freeware called LIFEx, which enables the calculation of conventional, histogram-based, textural, and shape features from PET, SPECT, MR, CT, and US images, or from any combination of imaging modalities. Axial T2-weighted MR images were exported in Digital Imaging and Communications in Medicine (DICOM) format from the hospital database to LIFEx software. The region of interest included the largest cross-sectional, two-dimensional area of ovaries in axial planes selected on T2-weighted MR images (Figure 2)[16]. All ovarian tissue was used, including cysts and necrosis. Paraovarian cysts neoplasms, which cause some adnexal torsion cases, were excluded (n=3). After ovarian segmentation, texture feature extraction was performed.

Texture feature extraction

Texture analysis was obtained from two-dimensional images of segmented ovaries on axial plain using LIFEx software. Preprocessing steps including spatial resampling, gray-level discretization, and intensity rescaling were performed for all MR images after ovarian segmentation. To create homogeneity for the voxel values, spatial resampling was performed, and after calculating their means±standard deviations, *X-Y-Z* directions

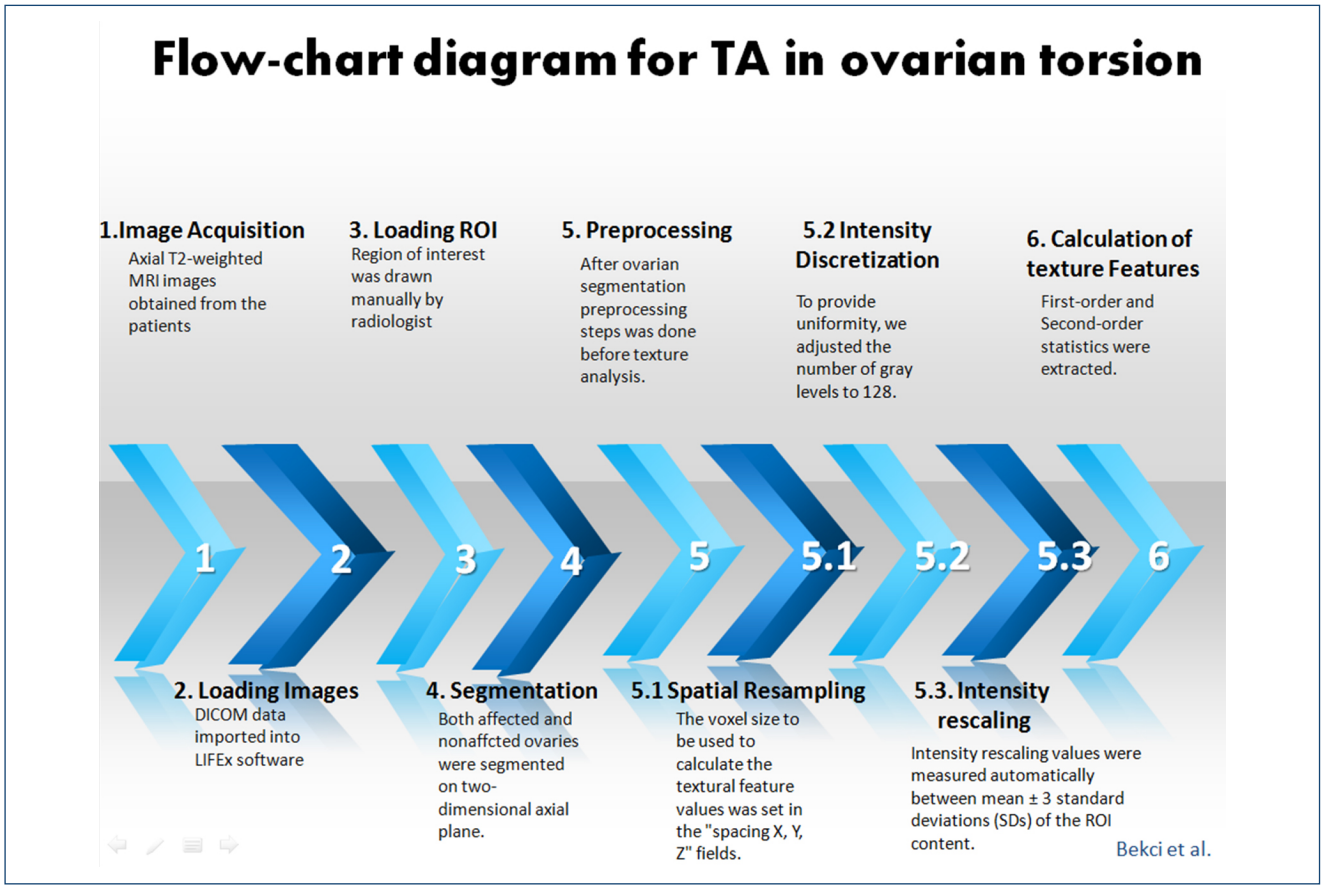

Figure 1. Flowchart diagram for texture analysis in ovarian torsion.

were rescaled as 0.87, 1.07, and 5, respectively. A gray-level range between 1 and 128 bits/pixel was used for intensity discretization to ensure uniformity for TA. The ±3 sigma technique was used for intensity rescaling to minimize different MRI protocol effects. A total of 44 texture features were extracted. Notably, 12 first-order features were derived from discretized, conventional, histogram, and shape features, and 32 second-order features were derived from gray-level co-occurrence matrix (GLCM) features, gray-level run-length matrix (GLRLM) features, neighborhood gray-level different matrix (NGLDM) features, and gray-level zone length matrix (GLZLM) features.

Statistical analysis

Statistical analyses were performed using IBM SPSS version 23. Normality distributions of quantitative parameters were analyzed using the Shapiro-Wilk test. The Mann-Whitney U test was used to compare data that did not conform to normal distributions. Receiver operator characteristic (ROC) analysis was performed for diagnostic test evaluation, and sensitivity and specificity were evaluated. Data are expressed as mean (95% confidence interval). A $p<0.05$ was considered statistically significant.

In the power analysis performed with reference to the results of the Bekci et al.'s study, which is evaluated diffusion-weighted MRI features of torsioned and normal ovaries, with a test power to be 95%, a total of 22 cases are required, with 11 cases in each group[20].

RESULTS

Patient characteristics

The median age of the patients was 27 (range 5–65). In all, 26 surgically proven OT patients were evaluated. A total of 41 ovaries were included in the study in 22 patients, excluding the cases with motion artifact (n=1) and paraovarian cyst neoplasm (n=3), which were the exclusion criteria. Three OT patients had previous oophorectomy. A total of 22 torsioned ovaries and 19 healthy ovaries were evaluated.

Texture features

A total of 1 first-order and 16 second-order features, including 1 DISCRETIZED_HISTO_Entropy_log2 feature, 5 GLCM features, 4 GLRLM features, 3 NGLDM features, and 4 GLZM features, demonstrated statistically significant difference between affected and nonaffected ovaries on T2-weighted axial MR images in OT patients. NGLDM_Coarseness and NGLDM_Contrast, which are the NGLDM parameters, had the largest area under the curve: 0.923 (Figure 3). The best cut-off values for NGLDM_Contrast and NGLDM_Coarseness were 0.45 and 0.01, respectively. With these threshold values, sensitivity, specificity, and accuracy values were 86.36% (65.09–97.09%), 84.21% (60.42–96.62%), 85.37% and 36.36% (17.2–59.34%), 100% (82.35–100%), and 65%, respectively. NGLDM_Contrast had the best accuracy (85.37%).

DISCUSSION

Magnetic resonance imaging-based TA analysis on T2-weighted axial images for the differentiation of affected and nonaffected ovaries in OT was investigated in this study for the first time in the medical literature. A total of 17 TA features were significantly different between affected and nonaffected ovaries, with ROC values ranging between 0.679 and 0.923. Our results demonstrate that NGLDM_Contrast, which is the NGLDM parameter, has excellent differentiation accuracy, with an area under curve (AUC) of 0.923 for affected and nonaffected ovaries

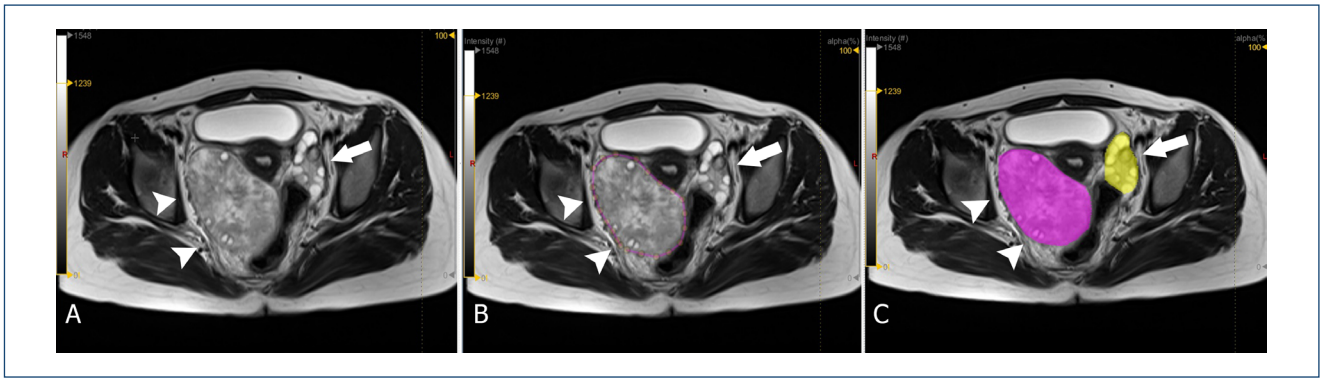

Figure 2. A. 30-year-old women with right-sided surgically proven ovarian torsion. T2-weighted axial magnetic resonance imaging demonstrate enlarged right ovary with peripherally located cysts [arrowheads]. Arrow indicates normal ovary on the left. **B.** The region of interest included the largest cross-sectional, two-dimensional area [arrowheads] of ovary in axial plane selected on T2-weighted magnetic resonance imaging. **C.** Both affected [arrowheads] and nonaffected ovaries [affected] manually segmented by the consensus of two radiologists using LIFEx software.

in OT. NGLDM_Coarseness and NGLDM_Contrast values of 0.45 and 0.01 were the best diagnostic parameters for predicting OT, respectively. With these threshold values, sensitivity and specificity reached 86.36% and 100%, respectively.

Ovarian torsion is increasingly prevalent, especially in children and pregnant women[2]. Although US is the first choice of imaging modality used in the diagnosis of OT, for further investigation, MRI is used as an advanced imaging method in most cases[1,2]. However, both the user-dependent diagnostic performance of US and the varying accuracy of MRI have required the development of a new method for the diagnosis of OT[1]. In addition, the need for the use of contrast agents during the classical evaluation of OT with MRI presents a disadvantage for pediatric cases and pregnant women. At this point, TA plays an important role in the diagnosis of OT without using contrast media or radiation exposure.

Texture analysis is a mathematical method that allows the examination of changes in intensity that cannot be detected with the human eye in MR images[9-12]. Texture features can be divided into five groups: size- and shape-based features, descriptors of the image intensity histogram, descriptors of the relationships between image voxels (e.g., GLCM features, GLRLM features, NGLDM features, and GLZLM features), and fractal features[13]. We used TA only on axial T2-weighted images. Using only a single MRI sequence for MRI examination is essential in terms of time management, which is important in the diagnosis and treatment of OT. After careful segmentation of ovaries by the consensus of two radiologists, texture features were extracted. Our study demonstrated that 17 parameters consisting of first- and second-order features differ significantly with TA of axial T2-weighted images. Of these, NGLDM_Contrast, which is a second-order feature, was able to predict torsed ovaries with the highest accuracy. A neighboring gray tone difference matrix quantified the difference between a gray value and the average gray value of its neighbors within distance[3,4]. Contrast is a measure of a spatial intensity change, but it is also dependent on the overall gray-level dynamic range[15,17,21]. Contrast is high when both the dynamic range and the spatial change rate are high, i.e., an image with a large range of gray levels, with large changes between voxels and their neighborhood[15,21]. From a mathematical point of view, NGLDM_Contrast reflects how much the gray levels of neighboring regions differ[15,21]. In our

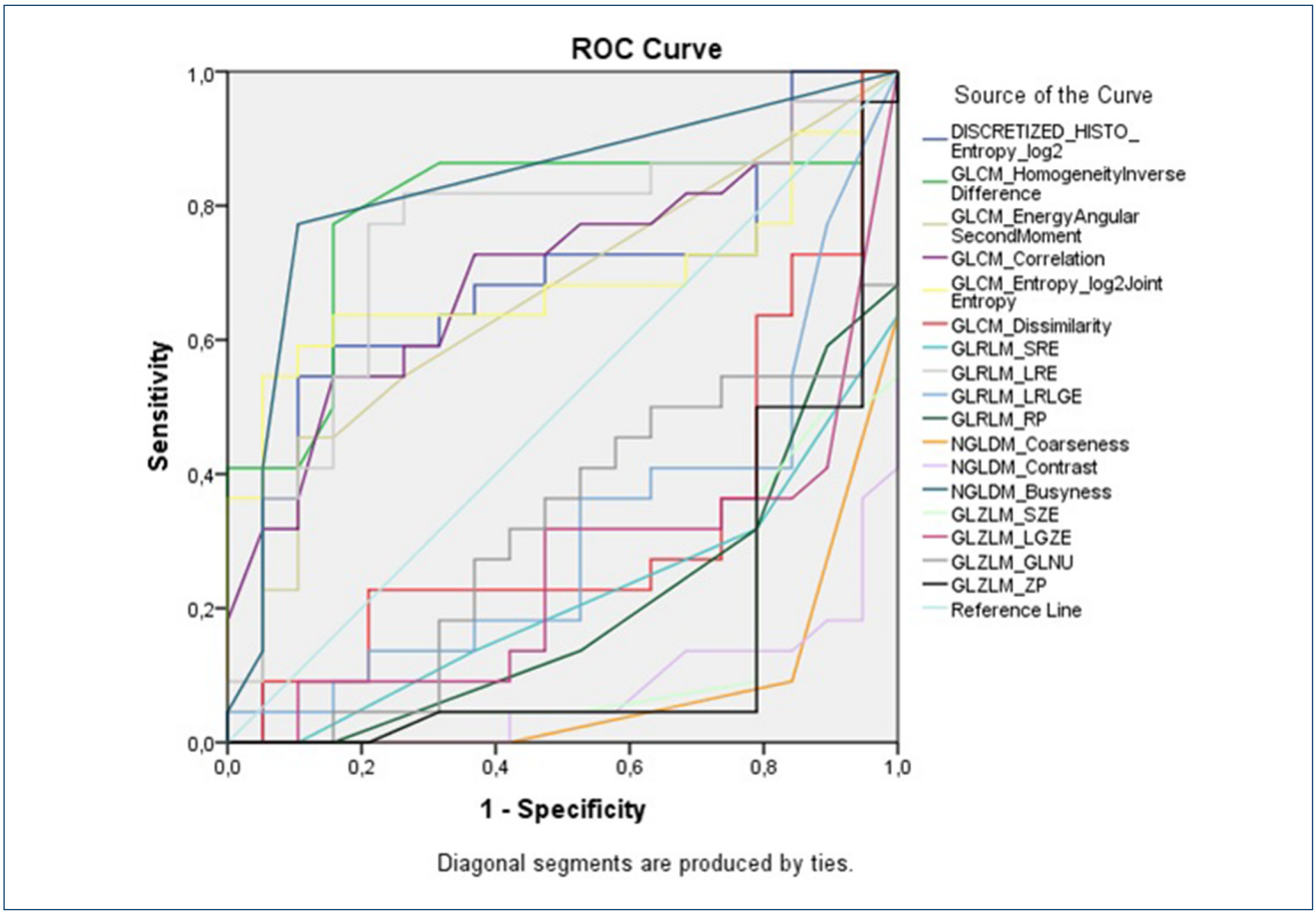

Figure 3. Receiver-operating characteristics curve of texture analysis parameters for differentiating affected ovary from nonaffected ovary.

study, torsioned ovaries showed lower contrast. We could, therefore, hypothesize that OT presents a more homogeneous parenchymal texture. This may be associated with edema caused by venous congestion in the torsed ovaries. Edema caused by congestion develops in almost all torsed ovaries, and this finding is consistent with the pathophysiological and morphological features of OT.

This study has some limitations. The first limitation is the relatively small number of cases examined. Second, we used only T2-weighted images for TA. Using or combining other MRI sequences, such as contrast-enhanced or diffusion-weighted images, may expand the feature pool and improve the diagnostic performance of texture features. Additionally, combining conventional features with texture features and to calculate added value might be useful. Third, we did not study interobserver agreement to test the reproducibility of the method. In the future, it is necessary to study using multisequence texture features and conventional features of OT with larger samples.

CONCLUSIONS

Our study results show that MRI-based TA can be used to differentiate affected and nonaffected ovaries in OT. A set of parameters, especially NGLDM_Contrast, can predict torsioned ovaries with high accuracy. By implementing the defined parameter with high diagnostic accuracy into artificial intelligence applications, early diagnosis and treatment of OT can be enabled in emergency settings. The data we obtained in our study should be supported by new studies and the feasibility of using it in the diagnosis of OT should be evaluated by using it in artificial intelligence applications in further studies. TA may be an important part of diagnosis of OT in daily practice.

ETHICAL CONSIDERATIONS

This study was approved by the Ethics Committee of our hospital. Due to the prospective nature of the study, informed consent for prospective data analysis was taken by the institutional review board.

AUTHORS' CONTRIBUTIONS

TB: Conceptualization, Writing – original draft. **IMC:** Data curation, Formal Analysis. **SA:** Formal Analysis, Writing – review & editing.

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ORIGINAL ARTICLE

https://doi.org/10.1590/1806-9282.20220001

Artichoke for biochemistry, histology, and gene expression in obstructive jaundice

Salih Celepli[1*], Bayram Çolak[2], Pınar Celepli[3], İrem Bigat[4], Hatice Gül Batur[5], Furkan Soysal[6], Serdar Karakurt[5], Sema Hücümenoğlu[3], Kemal Kismet[7], Mustafa Şahin[2]

SUMMARY

OBJECTIVE: This study aimed to evaluate the hepatoprotective effect of artichoke leaf extract (*Cynara scolymus*) in experimental obstructive jaundice.

METHODS: Rats were separated into three groups, namely, sham, control, and artichoke leaf extract. Ischemia was created for 60 min, and then liver tissue and blood samples were taken at the 90th minute of reperfusion. Artichoke leaf extract was given at a 300 mg/kg dose 2 h before the operation. Antioxidant enzyme activities and biochemical parameters were examined from the tissue and serum. Histopathological findings of the liver were scored semiquantitatively.

RESULTS: Antioxidant enzyme activities in the artichoke leaf extract group were statistically significantly higher than that in the other two groups. Biochemical parameters, which show hepatocellular damage, were found to be similar in both sham and artichoke leaf extract groups. Although the values in the sham group were higher than the artichoke group in terms of protein and gene expressions, no statistically significant difference was found between these two groups. Regarding the hepatocellular effects of obstructive jaundice, the artichoke leaf extract group showed lower scores than the control group in all histopathological scores.

CONCLUSION: The results of this study showed that artichoke leaf extract had a hepatoprotective effect that was associated with the antioxidant and anti-inflammatory effects of artichoke leaf extract.

KEYWORDS: Liver. Obstructive jaundice. *Cynara scolymus*. Protective agent. Antioxidant.

INTRODUCTION

Obstructive jaundice (OJ) is the obstruction of the common bile duct due to complications associated with surgery, idiopathic diseases, and metabolic diseases[1]. It has been shown that bile acids and harmful substances eliminated by bile accumulate in hepatocytes and blood in OJ. As a result, chronic liver damage and fibrosis develop due to cell death[2]. If OJ is not treated appropriately, disturbances in reticuloendothelial system (RES) functions, suppression of the immune system, inhibition of the detergent and antibacterial effects of bile salts, disruption of the intestinal mucosal barrier, bacteremia, and endotoxemia develop[3]. Numerous experimental and clinical studies have been conducted to prevent or reverse oxidative stress and inflammation, which have a significant effect on the pathogenesis of OJ. However, there are still no drugs that are widely used in clinical practice[4].

Oxidative stress is characterized by a disruption in the pro-oxidant-antioxidant balance, in which the formation of reactive oxygen species (ROS) exceeds the capacity of the enzymatic and nonenzymatic antioxidant defense systems[5]. ROS in high concentrations damage all major cell structures, including proteins, lipids, and DNA. Phenolic substances in the antioxidant defense system act as a protective shield against oxidative damage in biological molecules such as proteins, lipids, and DNA[6].

The main phenolic compounds in artichoke (*Cynara scolymus*) leaf extract (ALE) are caffeic acid derivatives, including caffeoylquinic acid derivatives[7]. The antimicrobial, hepatoprotective, choleretic, hypocholesterolemic, hypoglycemic, and

[1]Gulhane Training and Research Hospital, Department of General Surgery – Ankara, Turkey.
[2]Selcuk University, Faculty of Medicine, Department of General Surgery – Konya, Turkey.
[3]Ankara Training and Research Hospital, Department of Pathology – Ankara, Turkey.
[4]TOBB University of Economics & Technology, Graduate School of Science and Technology, Department of Biomedical Engineering – Ankara, Turkey.
[5]Selcuk University, Science Faculty, Biochemistry Department – Konya, Turkey.
[6]Ankara Yıldırım Beyazıt University, Faculty of Engineering and Natural Sciences, Department of Chemical Engineering – Ankara, Turkey.
[7]Selcuk University, Faculty of Nursing, Department of Surgical Nursing – Konya, Turkey.
*Corresponding author: dr.salih.celepli@gmail.com
Conflicts of interest: the authors declare there is no conflicts of interest. Funding: none.
Received on January 08, 2022. Accepted on February 27, 2022.

anticancer effects of ALE have been shown in previous studies[8-10]. It has also been reported that ALE significantly prevented oxidative damage in hepatocyte membranes[11].

This study aimed to evaluate the hepatoprotective effect of ALE in experimental OJ, a subject that has not been previously studied.

METHODS

The study was carried out following the principles of the National Laboratory Animal Use and Care Directive, with the approval of the XXX University Experimental Medicine Research Center Animal Ethics Committee. A total of 30 adult male Wistar albino rats included in the study were cared for under the conditions determined by XXX University Experimental Medicine Research and Application Center. The groups were organized as follows:

Group 1 (sham group, n=10): After laparotomy, the common bile duct was released from the surrounding tissues in rats in this group, no other procedure was performed, and no treatment was given.

Group 2 (control group, n=10): After the common bile duct was freed from the surrounding tissues in rats in this group, it was double tied with 5-0 silk and cut between the sutures, no other procedure was performed, and no treatment was given.

Group 3 (ALE group, n=10): After the common bile duct was freed from the surrounding tissues in rats in this group, it was double tied with 5-0 silk and cut between the sutures, then 300 mg/kg/day artichoke extract was given via orogastric tube for 10 days.

After the surgical procedures were completed, the rats were sacrificed on postoperative day 10, and liver tissue and blood samples were taken. The obstructive jaundice model in the study is a model that has been widely used by both our team members and other researchers[12-14].

The ALE used in this study was prepared in XXX University, Faculty of Engineering and Natural Sciences, Department of Chemical Engineering. The dose of ALE to be used in the study was determined as 300 mg/kg, which is preferred in studies in the light of various articles scanned in the literature. Furthermore, in the literature, it was seen that the extract is mainly applied as oral gavage[15,16].

Supply of tissues

Liver tissue and blood samples were taken on postoperative day 10. The tissues were placed on ice and, to remove blood, were washed with cold distilled water and physiological saline, then packed sterile and frozen in liquid nitrogen. In the Science Faculty Biochemistry Department Research Laboratory, the tissues were maintained at -80°C, blood was centrifuged at 10,000 rpm for 5 min at 4°C, and sera were obtained and stored at -80°C until assay.

Biochemical studies

Total protein from the tissues was extracted, the protein concentration of protein lysate was determined, and Western blot analyses were performed. For evaluating antioxidant enzyme activities, catalase, superoxide dismutase, and glutathione peroxidase activities were determined. Serum aminotransferases (AST and ALT), serum lactate dehydrogenase (LDH) activity, serum alkaline phosphatase (ALP), creatine kinase (CK), total protein (TPROT) and albumin (ALB), total bilirubin (TBIL), direct bilirubin (DBIL), and C-reactive protein (CRP) levels were also measured.

Microsomal proteins were separated with the SDS-polyacrylamide gel electrophoresis (SDS-PAGE) method by applying the vertical electrophoresis technique for determination of expression at protein level. RNA isolation from the tissues obtained to determine the effects of the study plant components on the gene expression levels of the enzymes was performed using the RNA TRIZOL method. cDNA from total RNAs was synthesized using 18 nucleotide long oligo d(T) primer and Moloney-Murine Leukemia Virus Reverse Transcriptase. The expression of the mRNAs of the relevant genes was determined in the Bio-rad qRT-PCR device using iTaq Universal SYBR Green Supermix (Cat. No.: 172-5124).

Histopathological examination

The samples were evaluated by the same pathologist blinded to the groups. Histopathological examination of the samples was made using an OLYMPUS brand BX51TF model light microscope. Bile duct proliferation, focal ("spotty") necrosis, inflammation, and granuloma formation were evaluated semi-quantitatively in the liver section.

Statistical analysis

Biochemical data were analyzed using the Statistical Package for Social Sciences (SPSS) for Windows software, version 25.0 (SPSS Inc., Chicago, IL, USA). Statistical analysis of pathological scores was performed using R 3.6.0 (https://www.r-poject.org).

RESULTS

General

One rat from Group 2 and Group 3 died during the study, and no new rats were added in their place.

Biochemical results

Total phenolic/flavonoid antioxidant amounts of artichoke extract

The total phenolic content of the artichoke methanol extract was 38.03±0.95 µg GAE/mg, and the total flavonoid amount was 18.11±0.26 µg QE/mg.

Antioxidant enzyme activities

SOD, catalase, and GPx enzyme activities in the artichoke group were statistically significantly higher than that in the other two groups ($p<0.05$) (Table 1).

Other biochemical parameters

According to these results, all parameters were statistically significantly higher in the control group compared to the other groups ($p<0.05$). Although the CRP levels were higher in the artichoke group than the sham group, no statistically significant difference was found between these two groups ($p>0.05$). However, all other parameters were statistically significantly higher in the artichoke group compared to the sham group ($p<0.05$).

Protein and gene expression study results

When albumin and globulin protein expressions and albumin, globulin, and prothrombin gene expressions were evaluated, it was observed that the values for each parameter in the control group were statistically significantly lower than that in the other two groups ($p<0.05$). In terms of protein and gene expressions, although the values in the sham group were higher than in the artichoke group, no statistically significant difference was found between these two groups ($p>0.05$) (Figure 1).

Histopathological results

There was a statistically significant association between biliary duct proliferation/spotty necrosis and the study groups ($p<0.001$ for both).

There was a statistically significant association between inflammation and the study groups ($p<0.001$). The proportion

Table 1. Antioxidant enzyme activities of the study groups.

Groups	SOD	Catalase	GPx
Sham (Group 1)	15.43±1.97[a]	260.58±28.98[a, g]	34.53±2.80[a, g]
Control (Group 2)	19.52±4.09[b]	315.06±28.98[b]	58.87±3.25[b]
Artichoke (Group 3)	25.35±2.41	377.51±13.67	94.37±4.30

[a] Significantly different, Group 1 vs. Group 3, $p<0.05$; [b] Significantly different, Group 2 vs. Group 3, $p<0.05$; [g] Significantly different, Group 1 vs. Group 2, $p<0.05$.

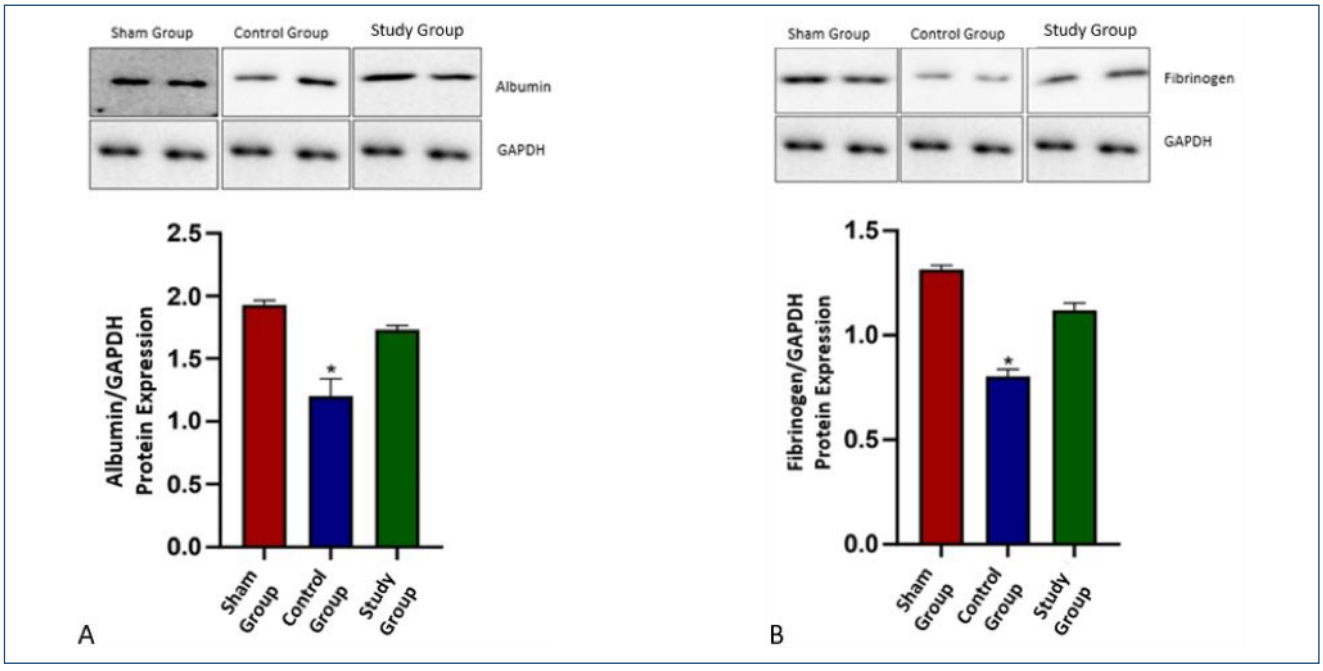

Figure 1. A. Albumin protein expression (*$p<0.05$). **B.** Fibrinogen protein expression (*$p<0.05$).

of no inflammation was higher in Group 1 (n=8, 80%) compared to Groups 2 and 3.

There was a statistically significant association between granuloma and the study groups (p<0.001). The proportion of no granuloma was higher in Groups 1 and 3 compared to Group 2. Conversely, the proportion of existing granuloma was higher in Group 2 (n=7, 87.5%) compared to Group 1 (n=0, 0%) and Group 3 (n=1, 12.5%).

The histopathological differences between Groups 2 and 3 are shown in Figure 2.

DISCUSSION

In OJ, increased bile acids promote the expression of free oxygen radicals from neutrophils and macrophages and induce oxidative damage by stimulating free oxygen radical formation from mitochondria[17]. Quantitative analysis in animal studies has shown that supplementation with ALE can increase SOD, CAT, GSH, and GPx in the liver[18]. In this study, SOD, CAT, and GPx enzyme activities were measured and found that all three antioxidant activities in the ALE group were significantly higher than in the other two groups (p<0.05). These data suggested that ALE is effective in preventing damage by increasing the antioxidative effect against oxidative damage (Table 1).

Elevated circulating levels of ALT, AST, ALP, LDH, and OCT enzymes suggest hepatocellular damage[19]. It was demonstrated that ALE reduced serum ALT and AST levels in a carbon tetrachloride (CCl4)-induced hepatotoxicity model in mice[20]. In this study, the values of liver function tests were significantly higher in the control group than that in the other groups (p<0.05). CRP values indicating inflammation were highest in the control group, followed by the ALE group, and were lowest in the sham group. The higher CRP values in the control group compared to the other two groups are significant in showing inflammation caused by hepatocellular damage due to OJ.

Low protein and albumin levels or high prothrombin time or INR indicate decreased synthetic function and hepatic decompensation[21]. When the albumin and globulin protein expressions and albumin, globulin, and prothrombin gene expressions were evaluated in this study, it was observed that the values of each parameter in the control group were lower than in the other two groups, showing a statistically significant difference (p<0.05). In terms of protein and gene expressions, although the values in the sham group were higher than in the artichoke group, no statistically significant difference was found between these two groups (p>0.05) (Figure 1). These data suggested that ALE protects the synthetic function of liver and helps in compensation.

Mehmetcik et al.[22] reported that administration of ALE to rats significantly reduced transaminase activity and alleviated histopathological change. In this study, there was a statistically significant correlation between the formation of bile duct proliferation and the study groups (p<0.001). While bile duct proliferation was not seen in the sham group, it was evident in the other two groups, and significantly more severe bile duct proliferation was observed in the control group than in the ALE group. There was a statistically significant correlation between spotty necrosis and the study groups (p<0.001). Spotty necrosis was not seen in the sham group but was mild in the ALE group and moderate-severe in the control group. Inflammation was seen in all groups. While mild inflammation was observed in very few samples in the sham group, mild-to-moderate inflammation was more common in the control group than in the ALE group. Although the ALE group showed lower scores than the

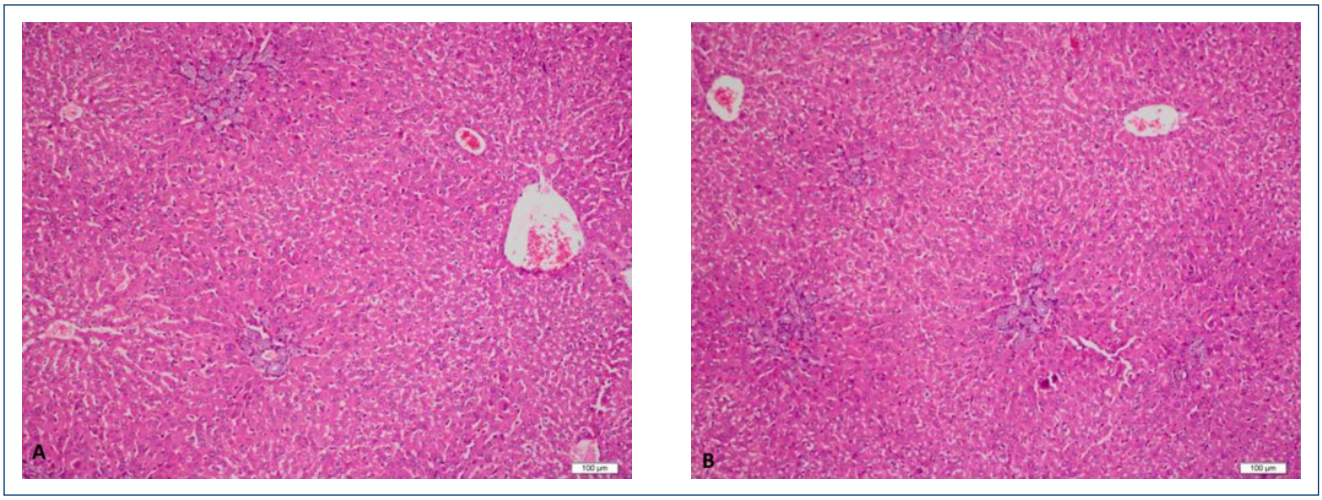

Figure 2. A. B. Milder bile duct proliferation, spotty necrosis, and inflammation were observed in Group 3 compared to Group 2 (H&E, ×100).

control group in all histopathological scores in determination of hepatocellular effects of OJ, the most significant difference was seen in granuloma formation. Granuloma showing chronic inflammation was not seen in the sham group but was more intense in the control group than in the ALE group.

CONCLUSION

In the light of these results, it was concluded that artichoke extract has a positive effect on OJ and this effect is related to the antioxidant and anti-inflammatory effects of artichoke.

ETHICAL COMMITTEE APPROVAL

In accordance with Research and Publication Ethics, Ethics Committee approval was received from Selçuk University Experimental Medicine Application and Research Center on June 28, 2019, with the decision number 2019-25.

ACKNOWLEDGMENTS

We thank Asst. Prof. Muslu Kazım KÖREZ for statistical analysis.

AUTHORS' CONTRIBUTIONS

SC: Conceptualization, Investigation, Methodology, Writing – original draft. **BÇ:** Investigation, Resources. **PC:** Methodology, Resources. **İB:** Data curation, Investigation, Visualization, Writing – original draft. **HGB:** Investigation, Resources. **FS:** Resources, Validation. **SK:** Supervision, Validation. **SH:** Supervision, Validation. **KK:** Investigation, Methodology, Supervision, Visualization. **MŞ:** Writing – review & editing.

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ORIGINAL ARTICLE

https://doi.org/10.1590/1806-9282.20220005

Does asporin have a role in polycystic ovary syndrome? A pilot study

Yusuf Özay[1], Ali Cenk Özay[2], Özlen Emekçi Özay[2*], Oğuzhan Edebal[3]

SUMMARY

OBJECTIVE: Asporin is secreted by theca cells in the mouse ovaries and is an effective marker at the gonadotropin-independent stage in secondary follicle development. It has an inhibitory effect on transforming growth factor beta and bone morphogenic proteins, which are involved in androgenesis process. Our aim was to compare serum asporin levels of polycystic ovary syndrome and control groups and examine the relationship between asporin and hyperandrogenism.

METHODS: A total of 60 patients, i.e., 30 polycystic ovary syndrome group and 30 controls, were included in the study. The demographic characteristics, hormonal status, and serum asporin levels of patients were evaluated and compared for each group. In addition, polycystic ovary syndrome patients were analyzed according to the presence of hyperandrogenism. Receiver operating characteristic curve analysis was performed for asporin levels in order to distinguish polycystic ovary syndrome patients from controls.

RESULTS: Body mass index, serum asporin and androgen levels, free androgen index, and insulin resistance values were statistically significantly higher in polycystic ovary syndrome group. Serum asporin levels were statistically significantly higher in hyperandrogenic polycystic ovary syndrome patients compared to non-hyperandrogenic polycystic ovary syndrome women (p=0.010). Receiver operating characteristic curve analysis was done for serum asporin levels to distinguish between polycystic ovary syndrome patients and healthy controls (area under the curve=0.676, standard error: 0.070, 95%CI: 0.539–0.812, p=0.019, 63.3% sensitivity, and 70% specificity).

CONCLUSION: The elevation of serum asporin levels in patients with polycystic ovary syndrome may be associated with the pathogenesis of this syndrome, or it may be the consequence of the disease. This relationship may be explained through the androgen mechanism.

KEYWORDS: Polycystic ovary syndrome. Hyperandrogenism. Asporin.

INTRODUCTION

Polycystic ovary syndrome (PCOS) is the most common endocrinopathy of the reproductive age, with its incidence rate of approximately 10%[1]. PCOS not only affects the reproductive system but also causes clinical and biochemical effects by affecting many structures, such as the cardiovascular system, adipose tissue, and metabolic system[2,3]. Rotterdam criteria are the most frequently used method for diagnosis, including oligo-anovulation, hyperandrogenism, and polycystic ovary appearance in ultrasound. PCOS affects so many systems, but these effects are not included in the Rotterdam diagnostic criteria[4].

The underlying mechanism in PCOS etiopathogenesis is unclear and a real challenge[5]. Cellular studies have mostly been done on granulosa cells (GCs) and androgen metabolism disorders. Interaction between GC and oocyte plays an important role in ensuring oocyte maturation[6]. In addition to being effective in normal folliculogenesis, GCs also play a role in pathological folliculogenesis conditions such as PCOS[7]. In PCOS, dominant follicle development is impaired and GC function differs from normal in folliculogenesis steps. Increased proliferation of GCs has been demonstrated in murine PCOS models and in women diagnosed with PCOS[8,9]. During the folliculogenesis process, GC and theca cell (TC) interact and TC is where androgen production occurs in the ovary. Although the exact cause is unknown, it has been shown that TCs are overactive in PCOS, probably due to genetic/epigenetic reasons, and consequently, intraovarian androgen production is increased[10].

Asporin, which consists of 380 amino acids and belongs to the small leucine-rich repeat proteoglycan family, was identified in 2001 by three different independent groups[11-13]. It has been shown that asporin is synthesized in different tissues such as articular cartilage, periodontal ligament, connective tissues, aorta, and uterus[11-13]. Previous studies have examined the functions of asporin and concluded that asporin inhibits transforming growth factor-beta (TGF-β) in articular cartilage tissue, suppresses bone morphogenic protein (BMP)-related cytodifferentiation in periodontal ligament, affects TGF-β/SMAD2-3 pathway in colorectal cancer, and plays a role on tumor metastasis via BMP in mesenchymal stromal cells[14-17].

[1]Adıyaman University, Department of Medical Biology – Adıyaman, Turkey.
[2]Near East University Hospital, Department of Obstetrics and Gynecology – Nicosia, Cyprus.
[3]Near East University Hospital, Department of Biochemistry – Nicosia, Cyprus.
*Corresponding author: ozlenemekci@yahoo.com
Conflicts of interest: the authors declare there is no conflicts of interest. Funding: none.
Received on March 02, 2022. Accepted on March 03, 2022.

Androgen synthesis in TCs takes place as a result of a complex process in which many biochemical markers play a role in steroidogenesis steps. In this process, many triggering factors such as insulin-like growth factor-1 (IGF-1)[18,19], inhibin[18], stem cell factor/kit ligand[20], as well as proteins with inhibitory effects such as TGF-β[21], BMP[22,23], and activin[24] are involved. For these reasons, any disturbance in the functioning of TCs will affect the female reproductive system.

One study in 2019 reported that asporin is secreted by TC/interstitial cells in the mouse ovaries and is an effective marker at the gonadotropin-independent stage in secondary follicle development[25]. This study found that asporin has an inhibitory effect on the TGF-β/SMAD2-3 cascade and suggested that asporin may play an autocrine/paracrine role in folliculogenesis[25]. Moreover, asporin may also affect androgen production through similar pathways.

Our hypothesis is that considering the suppressing effect of asporin on TGF-β and BMPs, it may play a role in hyperandrogenism in PCOS patients and, therefore, serum asporin levels will be high in PCOS patients. With this point of view, we aimed to compare serum asporin levels of PCOS and control groups and examine the relationship between asporin and hyperandrogenism.

METHODS

This study was conducted between July 2019 and July 2020 at Department of Obstetrics and Gynecology, Near East University. Ethics committee approval was obtained from the local ethics committee for the study (project number: YDU/2019/71-875), and informed consent was obtained from all patients.

In this pilot study, a total of 60 patients, i.e., 30 PCOS and 30 controls, were included. Post-hoc analysis of the pilot study data revealed that effect size was 1.22, and 22 individuals were required in each group for attaining 0.95 power with 0.05 alpha error probability. The diagnosis of PCOS was made according to Rotterdam criteria[4]. Medical history, age, height, weight, and blood pressure values of all patients were recorded. Body mass index (BMI) was calculated by dividing body weight in kilograms by the square of height in meters. All patients were nulligravid, and transvaginal ultrasonography was performed on all of them after gynecological examination within the first 5 days of menstruation. In patients with oligomenorrhea after pregnancy was ruled out, menstruation was induced by administering 5-mg medroxyprogesterone acetate twice a day to create progesterone-withdrawal bleeding.

Serum glucose, insulin, thyroid-stimulating hormone (TSH), prolactin (PRL), follicle-stimulating hormone (FSH), luteinizing hormone (LH), estradiol (E2), androstenedione, dehydroepiandrosterone sulfate (DHEAS), sex hormone-binding globulin (SHBG), free testosterone (fT), and total testosterone (TT) values were analyzed from the blood sample taken in the morning fast from all patients. One tube of these blood samples was centrifuged and stored at −80°C for each participant until the day when serum asporin level is measured.

The free androgen index (FAI) was obtained by multiplying the ratio of serum total testosterone level to serum SHBG level by 100 (i.e., 100×TT/SHBG). Homeostatic Model Assessment-Insulin Resistance (HOMA-IR) was calculated as follows: fasting glucose × fasting insulin/405.

Serum asporin level was analyzed with Human Asporin sandwich Enzyme-Linked ImmunoSorbent Assay (ELISA) assay (catalog no.: abx150758, Abbexa Ltd., Cambridge, UK).

Exclusion criteria were as follows: age >35 and <18 years, hyperprolactinemia, thyroid dysfunction, pregnancy status, congenital adrenal hyperplasia, use of drugs that affect the hypothalamic-ovarian axis or hormones, history of ovarian surgery, use of any hormones including combined oral contraceptives in the past 6 months, having a disease affecting the skeleton and cartilage system, any malignancy, smoking, and alcohol use. The presence of follicles larger than 10 mm in the ovary or the detection of ovarian cysts was also considered exclusion criteria.

Statistical analysis

Social Sciences Statistics Program (SPSS) version 16 was used for statistical analysis. Kolmogorov-Smirnov test was performed to show the distribution of data. Mann-Whitney U test was used for continuous variables that have non-normal distributed. Data were expressed as median (interquartile range) and p-values. For correlation of asporin and androgens, Spearmen's correlation was performed. A $p<0.05$ was considered statistically significant.

RESULTS

The demographic characteristics and laboratory results of the patients with PCOS and the healthy group are shown in Table 1. BMI, asporin, LH/FSH, DHEAS, androstenedione, free testosterone, FAI, and HOMA-IR values were statistically significantly higher in PCOS group.

When PCOS patients were divided into two groups according to their hyperandrogenism status, we found that serum asporin levels were significantly higher in the hyperandrogenic PCOS group (Table 2).

There was no statistically significant correlation between the serum androgen levels and asporin in PCOS patients with hyperandrogenism. In addition, correlation analysis was performed between BMI and asporin for both PCOS and healthy patients, but no correlation was detected.

Table 1. Comparison of polycystic ovary syndrome and healthy groups.

	PCOS (n=30)	Control (n=30)	p
Age	22.00 (21.0–25.0)	23.50 (21.0–25.25)	0.633
BMI (kg/m²)	22.7 (20.45–25.55)	20.19 (19.21–21.93)	0.003
Asporin (ng/mL)	31.85 (7.46–51.45)	19.31 (2.91–29.88)	0.019
LH/FSH ratio	1.34 (0.87–2.13)	0.91 (0.83–1.10)	0.004
DHEAS (µg/dL)	304.55 (229.38–400.40)	167.65 (142.80–275.98)	<0.001
Androstenedione (ng/dL)	136.70 (91.55–175.22)	70.40 (61.83–78.70)	<0.001
Free testosterone (pg/mL)	1.56 (1.16–2.32)	0.91 (0.80–1.05)	<0.001
FAI	3.01 (1.85–4.93)	1.10 (0.84–1.37)	<0.001
HOMA-IR	1.70 (1.10–2.60)	1.27 (0.89–1.45)	0.001

BMI: body mass index, LH: luteinizing hormone, FSH: follicle-stimulating hormone, DHEAS: dehydroepiandrosterone sulfate, FAI: free androgen index, HOMA-IR: Homeostatic Model Assessment-Insulin Resistance. Bold indicates statistically significant values.

Table 2. Comparison of polycystic ovary syndrome patients according to hyperandrogenism.

	HA+ (n=19)	HA– (n=11)	p
Age	22.00 (21.0–24.0)	24.00 (22.0–27.0)	0.127
BMI (kg/m²)	22.5 (20.8–25.5)	23.40 (20.3–26.7)	0.846
Asporin (ng/mL)	43.12 (24.88–58.02)	6.85 (0.74-42.78)	0.010
LH/FSH ratio	1.38 (0.87–2.12)	1.27 (0.86–2.17)	0.846
HOMA-IR	1.70 (1.0–2.09)	1.10 (1.81–2.90)	0.576

BMI: body mass index, LH: luteinizing hormone, FSH: follicle-stimulating hormone, HOMA-IR: Homeostatic Model Assessment-Insulin Resistance. Bold indicates statistically significant values.

Receiver operating characteristic (ROC) curve analysis was made for serum asporin levels in distinguishing between PCOS patients and healthy controls (area under the curve=0.676, standard error: 0.070, 95%CI: 0.539–0.812, p=0.019; 63.3% sensitivity and 70% specificity). The comparison of the ROC curve of serum asporin is shown in Figure 1.

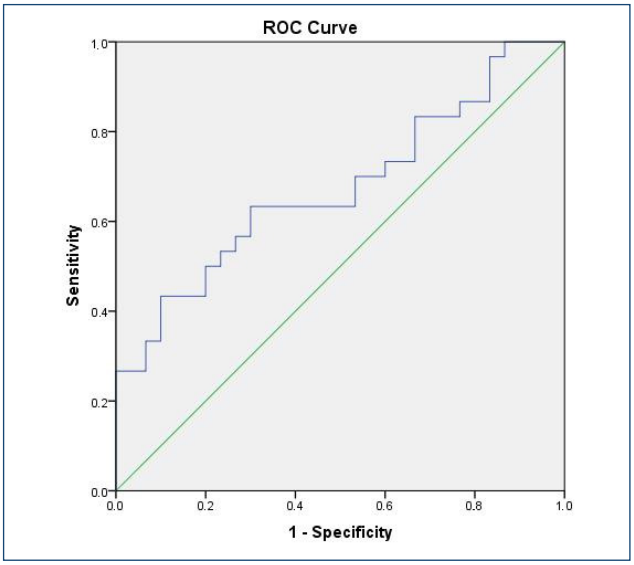

Figure 1. Receiver operating characteristic curves of serum asporin for differentiating polycystic ovary syndrome patients from healthy women.

DISCUSSION

It has long been known that hyperandrogenism, obesity, and high insulin resistance are more common in PCOS. In our study, significant increases were found in the PCOS group in terms of these data as expected. However, the most important result of this study is that the serum level of asporin, which is synthesized in TCs and stated to play a role in folliculogenesis steps, was significantly higher in patients with PCOS compared to healthy women.

Studies on asporin in the past mostly focused on cartilage tissue, bone tissue, and cancer. Unlike the examples in the literature, Aoyama et al. investigated that asporin is secreted from TCs in the mouse ovarian and stated that it may have a role in folliculogenesis[25]. In this study, it has been shown that asporin antibody arrested secondary follicle development and induced the TGF-β signaling[25]. With these findings, it was concluded that asporin has an inhibitory effect on TGF-β and plays an

important role in secondary follicle development[25]. TGF-β has been shown to suppress androgen production in TCs of humans[21]. Also, TGF-β plays a role in steroidogenesis steps in TCs and dysregulation of this molecule is one of the responsible factors for increase in stromal thickness and hyperandrogenism in PCOS[26]. Asporin, which was found to be high in PCOS patients in our study, may play a role in the pathogenesis of this syndrome by contributing TGF-β pathway.

Theca cells have been relatively neglected in PCOS pathogenesis studies. There are many molecules involved in the stages of steroidogenesis and folliculogenesis in TCs. For example, BMPs have an inhibitory effect on the steps from cholesterol to androstenedione production in TCs[27]. Asporin, which affect the cytodifferentiation in different tissues via BMPs, can have a similar effect in ovaries[14-17]. Tomoeda et al. have concluded that asporin binds BMP[15]. Glister and Campbell reported that BMPs 2/4/6/7 all significantly decreased androstenedione production from TCs[22,23]. In the light of these data, the findings of Aoyama et al.[25] and results of our study can conclude that asporin may have a role in androgen production in TCs by suppressing BMPs. In our study, although serum asporin levels were found to be significantly higher in hyperandrogenic PCOS patients compared to normoandrogenic PCOS patients, the lack of correlation between serum asporin and androgen levels may be due to the relatively low number of patients.

There are some studies in the literature that reveal the relationship between asporin and cartilage tissue. It has been stated in the literature that asporin is expressed in cartilage tissue and is associated with osteoarthritis, and this relationship is mediated by TGF-β[28-31]. In addition, studies have shown that cartilage tissue is thicker in PCOS patients than in healthy women; nevertheless, the possibility of osteoarthritis is increased in relation to hyperandrogenism[32,33]. Considering the fact that asporin and hyperandrogenism seen in PCOS are associated with cartilage tissue, the high serum asporin levels that we detected in the PCOS group in our study may not be solely of ovarian origin, and further studies are needed to reveal this issue.

Our study was the first to show that serum asporin level was significantly higher in PCOS patients, although its mechanism is not known exactly. PCOS is a syndrome with a complex pathogenesis and many unknowns. The finding of this study may be a step in revealing the pathogenesis of PCOS. This study consisted of well-diagnosed patient and control groups. However, the small number of participants and the fact that other markers such as TGF-β that may be affected by asporin have not been studied can be considered the limitations of this study.

CONCLUSIONS

According to results of our study, the elevation of serum asporin levels in PCOS patients may be associated with the pathogenesis of this syndrome. This relationship might be due to the androgen mechanism. Further studies with high patient numbers are needed to elucidate this situation, especially involving the patients with hyperandrogenic PCOS phenotypes.

ACKNOWLEDGMENTS

The authors declare no financial relationship with the any organization. They have full control of all primary data. Ethics committee approval was obtained from Ethics Review Board of the Near East University and it is available for review by the Editor-in-Chief of this journal upon request.

AUTHORS' CONTRIBUTIONS

YÖ: Conceptualization, Formal Analysis, Funding acquisition, Methodology, Validation, Visualization, Writing – review & editing. **ACÖ:** Data curation, Formal Analysis, Methodology, Project administration, Supervision, Validation, Visualization, Writing – original draft, Writing – review & editing. **ÖEÖ:** Data curation, Investigation, Resources, Supervision, Validation, Visualization, Writing – original draft, Writing – review & editing. **OE:** Data curation, Formal Analysis, Methodology, Software, Visualization, Writing – original draft, Writing – review & editing.

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ORIGINAL ARTICLE

https://doi.org/10.1590/1806-9282.20220026

Fantastic Lifestyle Questionnaire applied to undergraduate medical students during the COVID-19 pandemic: a factor analysis

João Mateus Silva Martins[1], Esther Angélica Luiz Ferreira[1*], Cristina Ortiz Sobrinho Valete[1], Hendrick Henrique Fernandes Gramasco[2]

SUMMARY

OBJECTIVE: To identify what structure represents life style in medical students, in a public university, with the application of the Fantastic Lifestyle Questionnaire.

METHODS: This is a cross-sectional exploratory study. The Fantastic Lifestyle Questionnaire was applied online to medical students. Factorial analysis was realized and factors were extracted by principal components method. Rotation was conducted by Varimax method.

RESULTS: Sixty-one questionnaires were analyzed. Students were male in 45.9%, single in 88.5%. The model was composed of three factors that explained 63.5% of all observed variance. The factors related to sleep perception, nutrition and stress, followed by relationships and entertainment and then, activity. Cronbach's alpha was 0.81, which was considered good.

CONCLUSION: The model composed by the three factors observed in this group of students represented the construct quality of life, evaluated by the Fantastic Lifestyle Questionnaire. This result may provide substrate to actions that aim to improve quality of life and well-being in medical students from this university.

KEYWORDS: Factor analysis. Medical students. Lifestyle. Quality of life. COVID-19.

INTRODUCTION

Health is a global concept that encompasses physical, mental and social well-being and not just the absence of illnesses[1]. In this context, medical students may have their health compromised due to a set of specificities, such as a tiring schedule, lack of sleep, exposure to human suffering, financial issues, and even the poor relationship between students. These situations can result in physical and psychological suffering[2,3].

The set of habits and behaviors in response to everyday situations, learned through the socialization process and often reinterpreted throughout life, which define the lifestyle, has been pointed out as the greatest direct determinant of an individual's health. In addition, it can collectively influence health, denoting the importance of its study and evaluation[4]. Some studies indicate that the lifestyle of medical students is not beneficial to their health. Problems related to the quality of sleep, food and physical activity, among others, have been pointed out[5,6].

The Fantastic Lifestyle Questionnaire (FLS), an instrument that was developed in 1984 at McMaster University, Canada, used to analyze lifestyle, and is validated for use in Brazil[7,8]. This questionnaire has already been applied to science health students, being considered a reliable instrument[9].

Objective

Identify which structure represents the lifestyle of medical students at a public university, using the FLS questionnaire.

METHODS

This is an exploratory cross-sectional study, with a non-probabilistic sample, from which an exploratory factor analysis was performed. The inclusion criteria of the participants were: being a student from the first to the sixth year, with active enrollment in the undergraduate Medicine course, over 18 years of age, and a regular attendee of undergraduate curriculum activities. Exclusion criteria were: inaccurate or incorrect filling out of the questionnaire.

Students were invited to participate in the study through an invitation letter sent through digital communication media, such as email, WhatsApp and Facebook, from September 1, 2020 to June 30, 2021. All students agreed and signed the free,

[1]Universidade Federal de São Carlos, Departamento de Medicina – São Carlos (SP), Brazil.
[2]Universidade Estadual Paulista Júlio Mesquita Filho, Faculdade de Medicina de Botucatu, Departamento de Neurologia, Psicologia e Psiquiatria – Botucatu (SP), Brazil.
*Corresponding author: estherferreira@ufscar.br
Conflicts of interest: the authors declare there is no conflicts of interest. Funding: none.
Received on January 06, 2022. Accepted on February 08, 2022.

prior and informed consent document, and were fully informed about the objectives and purposes of the study, in addition to the guarantee of anonymity, as well as the guarantee of access to an electronic copy of the consent document. The answers were registered in the research administration application, which has security mechanisms, such as the non-identification of students in the form, restriction of access to answers through e-mail and password access by researchers.

The instrument used to measure the students' lifestyle was the Brazilian version of the FLS questionnaire. This questionnaire consists of nine domains: family and friends, physical activity, nutrition, smoking and drugs, alcohol, sleep, stress and safe sex, type of behavior, introspection and work. Data regarding gender, age, skin color and marital status of the participants were also collected.

Statistical analysis was performed using factor analysis, a multivariate method that provides for the reduction of a group of variables into a smaller set of factors that represent the underlying latent structural dimensions. The methodological basis of factor analysis resides in the assumption that some underlying factors, in smaller numbers than the observed variables, are responsible for the covariation between the set of variables. In this way, it is possible to identify constructs that summarize or explain the set of variables observed. For this purpose, the adequacy of the database, the extraction technique and the type of factor rotation must be observed[10].

For the analyses, the Stata program version 13.0 (Statacorp, L.C.) was used. Qualitative variables are presented in percentages. For the factor analysis, the correlations between the variables were initially observed, and correlations with values greater than 0.3 in the matrix were considered adequate and the others excluded. Of the 19 variables, 10 remained in the model. This number of variables in the model in relation to the sample size resulted in a 1:5 ratio, considered appropriate. Bartlett's test of sphericity was applied, which was significant ($p<0.001$). Subsequently, the Kaiser-Meyer-Olkin (KMO) test was applied on the selected matrix, to show the proportion of the common variance. This initial analysis revealed that factorization would be adequate.

The extraction of factors was performed using the principal components model, to estimate the best combination of variables that would explain most of the observed variance. The factors were selected by the latent root criterion (Eigenvalue), keeping those with eigenvalues greater than 1.0. The Eigenvalues were observed by the Scree graph. The rotation of the factors to adjust the loads was performed using the Varimax method. The variables were related to the factors according to their highest rotated loads and the factors were named according to the variables with the greatest weight in their construction. For the construction of this model, parsimony was used. Variances, commonalities and factor loadings are presented.

The study was approved by the Research Ethics Committee (CAAE: 31527020.3.0000.5504).

RESULTS

The sample consisted of 61 participants and their characteristics are shown in Table 1. Regarding the global assessment of the FLS questionnaire, one participant (1.63%) had a score between 70 and 84-very good; 34 (55.73%) between 55 and 69-good; 24 (39.34%) between 35-54-regular, and two (3.27%) between 0 and 34-needs improvement.

Ten variables participated in the factor analysis:

1. I have someone to talk to about the things that are important to me;
2. I give and receive affection;
3. I am vigorously active for at least 30 minutes a day;

Table 1. Characteristics of the participants.

Feature	N	Frequency (%)
What is your birth sex		
Male	28	45.9
Female	33	54.1
What is your marital status		
Single	54	88.5
Married	6	9.8
Common-law marriage	1	1.7
What is your skin color		
White	35	57.4
Brown	20	32.8
Black	3	4.9
Others	3	4.9
What is your religion		
None	25	41.0
Catholic	20	32.8
Evangelical	6	9.8
Spiritist	5	8.1
Umbanda	1	1.6
Others	4	6.7
With whom you live		
With family members	33	54.1
Alone	20	32.8
In a student republic	8	13.1

4. I am moderately active;
5. I eat a balanced diet;
6. I often eat in excess: sugar, salt, animal fat, junk food, snacks;
7. Healthy weight range;
8. I sleep well and feel rested;
9. I am able to handle the stress of my day-to-day life;
10. I relax and enjoy my leisure time. The correlation matrix was inspected and generated a moderate KMO test (0.78). Bartlett's test of sphericity (approximate χ^2 186.66; $p<0.001$) indicated that the correlational matrix was not an identity matrix, which was followed by a factor analysis.

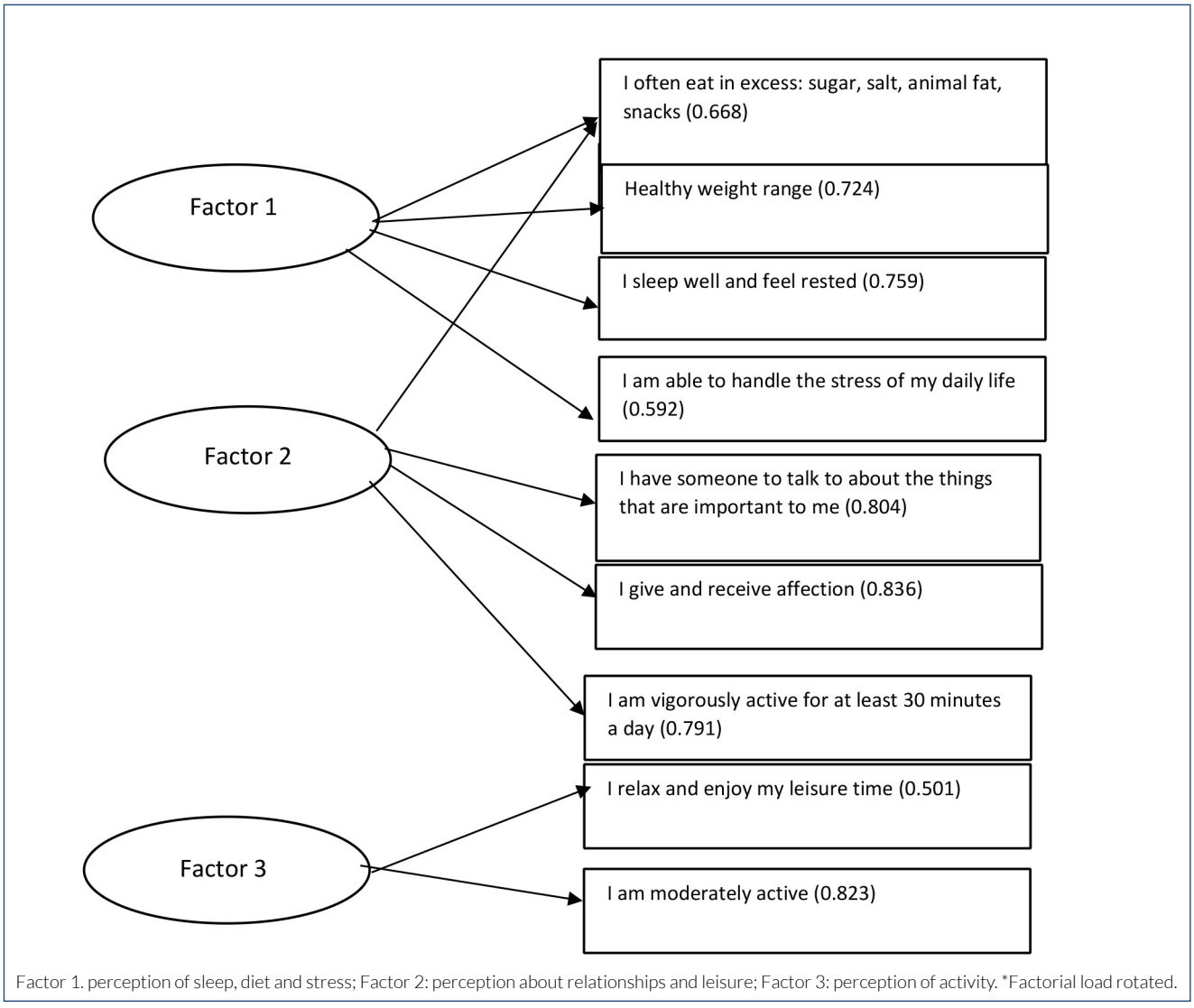
The analysis of eigenvalues suggested the existence of three main factors (Table 2), which can be confirmed by the Scree graph (Figure 1).

The factor analysis model identified three factors that were named taking into account the factor loadings obtained. Thus, Factor 1 refers to the perception of sleep, diet and stress, Factor 2 refers to the perception of relationships and leisure and Factor 3 refers to the perception of activity (Figure 1). These three factors accounted for the structure found in the analyzed questionnaires.

The three factors identified explained 63.50% of the total variance observed. Varimax rotation was performed, and the summary of the results of the factor analysis is also found in Table 2.

Table 2. Results of the analysis of factor eigenvalues, proportion of explained variance and accumulated variance factor followed by the factor solution with rotated loads, commonalities, percentage of explained variance of the Fantastic Lifestyle Questionnaire applied to medical students.

Results of the analysis of factor eigenvalues, proportion of explained variance and accumulated variance				
Factor	**Eigenvalue**	**Variance**	**Accumulated Variance**	
Factor 1	3.875	0.387	0.387	
Factor 2	1.420	0.142	0.529	
Factor 3	1.070	0.107	0.636	
Factor 4	0.813	0.081	0.718	
Factor 5	0.716	0.071	0.789	
Factor 6	0.557	0.055	0.845	
Factor 7	0.509	0.050	0.896	
Factor 8	0.409	0.040	0.937	
Factor 9	0.381	0.038	0.975	
Factor 10	0.246	0.020	1.000	
Factor solution with rotated loads, commonalities, percentage of explained variance of the Fantastic Lifestyle Questionnaire applied to medical students				
Variable	**Factor 1**	**Factor 2**	**Factor 3**	**Commonality**
1		0.804		0.751
2		0.863		0.756
3			0.791	0.686
4			0.823	0.709
5	0.618			0.664
6	0.668			0.570
7	0.724			0.551
8	0.759			0.634
9	0.592			0.574
10		0.501		0.475
Eigenvalue	2.444	1.995	1.927	
explained variance (%)	0.244	0.199	0.192	Total=63.50
Number of variables	5	3	2	
Cronbach's Alpha	0.760	0.71	0.69	Total=0.81



Factor 1. perception of sleep, diet and stress; Factor 2: perception about relationships and leisure; Factor 3: perception of activity. *Factorial load rotated.

Figure 1. Model resulting from the factor analysis of the Fantastic Lifestyle Questionnaire, consisting of three factors.

DISCUSSION

This study involving medical students from a public university analyzed the multidimensional characteristics of the quality of life construct. The model resulted in three factors that explained 63.40% of all observed variance. These factors were related to the perception of sleep, food and stress, relationships, leisure and activity.

The internal consistency of the FLS questionnaire, in the context analyzed, measured by Cronbach's alpha was 0.81. This internal consistency denotes the degree of internal relationship between the items in the questionnaire and the consistency of the responses of the studied group. It has been recommended over the years that the cut-off point for the value of this statistic should be 0.70[11]. Thus, the value reached in this study was good, revealing consistency of information.

The components of food, sleep and stress self-control were correlated and revealed great importance in this study. This result suggests that these variables were very important to determine the quality of life in this group of individuals. High factor loadings were observed for the variables "being in the range of weight considered healthy" and "sleeping well and feeling rested". This relationship has also been described in the literature. Vernia et al. discussed the complex interrelationship that exists between sleep disorders and their relationship to poor eating habits. In fact, these disorders are considered "triggers" for digestive disorders. On the other hand, individuals who eat poorly generally sleep less and not well. All these circumstances affect the quality of life and deserve attention[12].

The second factor identified in medical students was formed by the components of relationships, affection and leisure. It is

essential to rescue the importance of this component for the construction of quality of life, especially during the COVID-19 pandemic, where people around the world underwent a process of reinvention and needed to give new meaning to their interpersonal relationships. Self-care, represented by leisure activities, was also part of this factor. It has already been pointed out that, in medical students, resilience is positively correlated with quality of life, whereas psychological stress is negatively correlated[13]. Also, self-care and work-life balance have been identified as essential in medical students not only for quality of life, but for the delivery of effective care. Medical professors must be proactive in supporting these practices in students, particularly in critical periods, such as the COVID-19 pandemic[14,15].

In the present study, the participant's daily activity dimension constituted the third factor, which refers to domain A of *activity*, which makes up the name FANTASTIC. In a Brazilian multicenter study that included twenty-two medical schools, it was observed that 40% of students reported not having time for physical activity. Furthermore, an association between quality of life and physical activity was revealed, including a dose-effect relationship (the greater the activity, the better the quality of life)[16].

It is interesting to identify that the domains related to the use of cigarettes and drugs, alcohol and career (which represent domain C of FANTASTIC) did not participate in the making of this construct. It is worth remembering that this particularity refers to this group of individuals, as it is known that the consumption of these substances is negatively associated with quality of life. Among nursing students in Australia, alcohol consumption, physical inactivity and skipping breakfast were associated with poor quality of life[17]. In the present study, career or work were not very important, possibly because they were students.

This study has limitations. First, it was carried out during the COVID-19 pandemic and, therefore, the forms were filled out online, voluntarily. The sample refers to a single public university, making it difficult to generalize the results. The small sample size may have influenced the results. However, given the lack of studies on this topic, especially in Brazil, this study contributes to the reflection on the lifestyle of medical students. Future studies with a larger sample size and after the COVID-19 pandemic may contribute to a greater understanding of the topic.

CONCLUSION

This study evaluated the components of the FLS in order to identify, in this group of medical students, which elements shape its construct. Thus, components related to the perception of sleep, food and stress, relationships, leisure and activity were identified. This result can provide substrate for actions to improve the quality of life and well-being of students at this university.

AUTHORS' CONTRIBUTIONS

JMSM: Conceptualization, Data curation, Formal Analysis, Writing – review & editing. **EALF:** Conceptualization, Data curation, Formal Analysis, Writing – review & editing. **COSV:** Data curation, Formal Analysis, Writing – review & editing. **HHFG:** Formal Analysis, Writing – review & editing.

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ORIGINAL ARTICLE

https://doi.org/10.1590/1806-9282.20220037

Is the tumor-stroma ratio a prognostic factor in gallbladder cancer?

Mehmet Ali Uzun[1,2*], Metin Tilki[1], Aylin Gönültaş[3], Fügen Aker[3], Sevcan Alkan Kayaoglu[1], Gülten Çiçek Okuyan[1]

SUMMARY

OBJECTIVE: This study aimed to examine the prognostic effect of the tumor-stroma ratio, which has been shown to have prognostic value in various cancers, in patients with gallbladder cancer who have undergone curative resection.

METHODS: The records of gallbladder cancer patients who underwent surgical treatment in our clinic between December 2005 and March 2021 were analyzed retrospectively. The hematoxylin and eosin-stained sections representing the tumors were evaluated under light microscopy to determine tumor-stroma ratio, and based on the results, <50% was defined as the stroma-rich and ≥50% as the stroma-poor groups.

RESULTS: A total of 28 patients, including 20 females and 8 males, with a mean age of 64.6 years, were included in this study. Stroma-poor and stroma-rich tumors were detected in 15 and 13 patients, respectively. There was no statistically significant relationship identified between tumor-stroma ratio and advanced age, gender, serum levels of carbohydrate antigen 19-9 and carcinoembryonic antigen, incidental or nonincidental diagnosis, jaundice, adjacent organ or structure resection, tumor location, grades 1–2 or 3, T1/T2 or T3/T4, N0 or N1/N2, M stage, *American Joint Committee on Cancer* stage, lymphovascular invasion, and perineural invasion. The stroma-poor and stroma-rich groups had a 5-year survival rate of 30% and 19.2% and a median overall survival of 25.7 and 15.1 months, respectively, with no statistically significant difference between the groups (p=0.526).

CONCLUSIONS: A low tumor-stroma ratio tended to be a poor prognostic factor in gallbladder cancer, although not to a statistically significant degree. This can be considered one of the preliminary studies, as further studies involving larger groups are needed.

KEYWORDS: Gallbladder neoplasms. Prognosis. Tumor microenvironment.

INTRODUCTION

Gallbladder cancer (GBC) is generally considered to have a very poor prognosis. Surgical resection is the only treatment with curative potential and success that depends on the stage and biology of the tumor and the completeness of the resection[1]. The effect of many clinicopathological factors on prognosis, however, is still a matter of discussion.

Tumor tissue consists of carcinoma cells and the stroma that surrounds them. The tumor stroma, associated with tumor initiation, progression, and metastasis, has a prognostic value[2], with the tumor-stroma ratio (TSR) expressing the proportion of tumor cells to stroma in tumor tissue. A low TSR implies a high proportion of stroma and has recently been identified as a poor prognostic factor in many tumor types[3,4]. In contrast, the prognostic value of TSR in GBC has been examined in only two studies to date, and so further studies are needed[5,6].

This study aimed to examine the prognostic value of TSR through a retrospective review of GBC patients who underwent surgery for an R0 curative resection.

METHODS

A retrospective analysis was made of GBC patients who underwent surgery in our clinic between December 2005 and March 2021 and who met the inclusion criteria. The study was approved by the Institutional Ethics Committee of the University of Health Sciences Haydarpasa Numune Research and Training Hospital (2021/65-2).

[1]University of Health Sciences Turkey, Haydarpasa Numune Training and Research Hospital, Department of General Surgery – Istanbul, Turkey.
[2]University of Health Sciences Turkey, Sisli Hamidiye Etfal Training and Research Hospital, Department of General Surgery – Istanbul, Turkey.
[3]University of Health Sciences Turkey, Haydarpasa Numune Training and Research Hospital, Department of Pathology – Istanbul, Turkey.
*Corresponding author: drmauzun@gmail.com

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

PATIENTS

The inclusion criteria were the achievement of R0 resection through surgical treatment and the availability of appropriate material for TSR assessment in the pathology laboratory. Patients who received neoadjuvant chemotherapy and/or radiotherapy, those who died within 30 days of surgery, those with insufficient records, and those were lost to follow-up were excluded from the study.

The American Joint Committee on Cancer (AJCC) Cancer Staging Manual, 8th Edition (AJCC, 8th Ed.) was used for clinical and pathological staging of the cases[7]. Standard radical cholecystectomy was sufficient to achieve R0 resection in most cases, while some advanced cases required extended radical resections. The patients were evaluated using a multidisciplinary approach, and cases were referred to postoperative adjuvant treatment where necessary.

DATA COLLECTION

The patient details were collected from the registered information in our hospital. The following patient data were extracted: age at the time of diagnosis, gender, complaints, preoperative and postoperative radiological and laboratory data, operative findings and surgical procedures, morbidity and mortality, TNM stage (AJCC, 8th Ed.), tumor location, histopathological type, and grade, lymphovascular invasion (LVI), perineural invasion (PNI), and long-term follow-up data.

HISTOPATHOLOGICAL SCORING

All hematoxylin and eosin (H&E)-stained sections from the tumors that were used to diagnose the resection pieces of the patients were retrieved from the archive of the pathology laboratory and reevaluated under light microscope. Sections that were unsuitable for evaluation were resectioned with a 4-micron section thickness from paraffin blocks and stained with H&E. Multiple H&E-stained sections representing the tumors were examined under a light microscope using a 4× objective, and the most invasive sections of the tumors were determined. These sections were examined with a 10× objective according to the TSR assessment criteria recommended in the study by Van Pelt et al.[8]. A stroma-rich microscopic area surrounded by tumor cells at four corners was determined in the most invasive tumor area, which is deemed most suitable for evaluation. The proportion of stroma in this area was assessed by two independent pathologists in a blinded manner and scored per 10-fold percentage. Following the assessment, inconsistent results were determined by consensus. A 50% cutoff value was accepted as described by Mesker et al.[9]. Accordingly, TSR was defined as follows: TSR-low <50% and TSR-high ≥50%. The TSR-low cases were defined as the stroma-rich group, and the TSR-high cases were defined as the stroma-poor group.

STATISTICAL ANALYSIS

A Shapiro-Wilk test was used to analyze whether the normal distribution assumption was met. Categorical data were expressed as numbers (n) and percentages (%), while quantitative data were presented as median (25th–75th) percentiles. The kappa coefficient was calculated to determine the level of agreement between the TSRs established by two independent pathologists. A Kaplan-Meier survival analysis with a log-rank test was used to determine whether the TSR had a statistically significant effect on overall survival (OS). Cumulative 1-, 3-, 5-, and 10-year survival rates; median life expectancy; and 95% confidence intervals were also calculated. The differences in continuous variables between the groups were compared with a Mann-Whitney U test. A continuity-corrected χ^2 test was used for all 2×2 contingency tables to compare categorical variables when one or more of the cells had an expected frequency of 5–25, and a Fisher's exact test was applied when one or more of the cells had an expected frequency of ≤5. For all R×C contingency tables to compare categorical variables, the Fisher-Freeman-Halton test was used when 25% or more of the cells had an expected frequency of ≤5. Data analysis was performed using IBM SPSS Statistics (version 25.0; IBM Corp., Armonk, NY, USA). A $p \leq 0.05$ was considered statistically significant.

RESULTS

The 28 eligible GBC patients had a mean age of 64.6 years and included 20 (71.4%) females and 8 (28.6%) males. Of the total, 10 (35.7%) patients were diagnosed incidentally by cholecystectomy for cholelithiasis or polyps, while 18 (64.3%) had a nonincidental diagnosis. All patients underwent R0 curative resection, with a standard radical cholecystectomy in 24 (85.7%) and extended radical resection in 4 (14.3%) (hepatopancreatoduodenectomy in 3 and right hepatic trisectionectomy in 1) patients. Of the total, 14 (50.0%) patients required en-bloc adjacent organ or structure resection to achieve R0 resection. Histological assessment

Table 1. Demographic and clinicopathological characteristics of cases by tumor-stroma ratio value.

	Stroma-poor n: 15 (53.6%) n (%) or mean (95%CI)	Stroma-rich n: 13 (46.4%) n (%) or mean (95%CI)	p
Age ≥60 years	10 (66.7)	10 (76.9)	0.686†
Gender			0.686†
Male	5 (33.3)	3 (23.1)	
Female	10 (66.7)	10 (76.9)	
CA 19-9 (U/mL)	10.03 (2.04–26.73)	30.54 (6.75–320.25)	0.126‡
CEA (U/mL)	3.20 (1.67–7.52)	3.09 (1.96–9.56)	0.755‡
Nonincidental	10 (66.7)	8 (61.5)	>0.999†
Jaundice	3 (20.0)	3 (23.1)	>0.999†
Adjacent organ or structure resection	8 (53.3)	10 (76.9)	0.254†
Location			0.751¥
Fundus	3 (20)	3 (23.1)	
Corpus	9 (60)	5 (38.5)	
Neck	1 (6.7)	2 (15.4)	
Multiple	0 (0.0)	1 (7.7)	
Diffuse	2 (13.3)	2 (15.4)	
Grade			>0.999†
1–2	11 (73.3)	10 (76.9)	
3	4 (26.7)	3 (23.1)	
AJCC, 8th Ed. Stage			0.316¥
I	2 (13.3)	0 (0.0)	
II	3 (20.0)	1 (7.7)	
III	3 (20.0)	6 (46.2)	
IV	7 (46.7)	6 (46.2)	
T stage			0.114†
T1/T2	7 (46.7)	2 (15.4)	
T3/T4	8 (53.3)	11 (84.6)	
N stage			0.322¶
N0	9 (60.0)	4 (33.3)	
N1–N2	6 (40.0)	8 (66.7)	
M stage			>0.999†
M0	12 (80.0)	11 (84.6)	
M1	3 (20.0)	2 (15.4)	
LVI	9 (60.0)	8 (61.5)	>0.999¶
PNI	7 (46.7)	10 (76.9)	0.212¶

CA 19-9: serum carbohydrate antigen 19-9; CEA: serum carcinoembryonic antigen; AJCC, 8th Ed.: *The American Joint Committee on Cancer (AJCC) Cancer Staging Manual*, 8th Edition; LVI: lymphovascular invasion; PNI: perineural invasion. † Fisher's exact test; ‡ Mann-Whitney U test; ¥ Fisher-Freeman-Halton test; ¶ continuity-corrected χ^2 test.

revealed adenocarcinoma in 25 (89.3%) patients, squamous cell carcinoma in 2 (7.1%) patients, and neuroendocrine carcinoma in 1 (3.6%) patient.

The results of the histopathological TSR scoring showed an almost-perfect agreement between the two independent pathologists, with a kappa of 0.929. A high TSR (stroma-poor) and a low TSR (stroma-rich) were detected in 15 (53.6%) and 13 (46.4%) patients, respectively. The other demographic and clinicopathological characteristics of the cases related to TSR are presented in Table 1. A comparison of the stroma-poor and stroma-rich groups revealed no statistically significant difference in advanced age (≥60 years), gender distribution, serum levels of carbohydrate antigen 19-9 (CA 19-9) and carcinoembryonic antigen (CEA), incidental or nonincidental diagnosis, jaundice, adjacent organ or structure resection, tumor location, a grade 3 rather than grades 1–2, a T stage of T1/T2 or T3/T4, an N stage of N0 or N1/N2, M stage, AJCC stage, LVI, and PNI.

The median follow-up of the patients was 15.6 (range, 2.3–145.6) months. The 1-, 3-, 5-, and 10-year survival rates and the expected median OS are presented in Table 2 for the stroma-poor, stroma-rich, and overall patient groups. As can be seen, the stroma-rich group tended to have lower expected survival rates and a shorter median OS, although the difference was not statistically significant (p=0.526). Kaplan-Meier survival curves of the patient groups are presented in Figure 1.

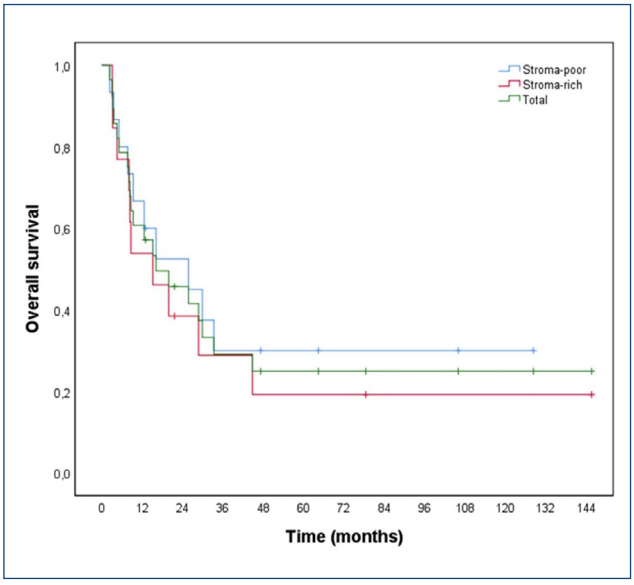

Figure 1. Kaplan-Meier survival curves for overall survival according to tumor-stroma ratio (stroma-poor versus stroma-rich) and the total number of patients.

Table 2. Kaplan-Meier survival analyses of overall survival with the log-rank test.

	N	Cumulative survival rates				Life expectancy	Log-rank	p
		1 year	3 years	5 years	10 years	Median (95%CI)		
TSR							0.402	0.526
Stroma-poor	15	66.7	30.0	30.0	30.0	25.7 (3.0–48.4)		
Stroma-rich	13	53.8	28.8	19.2	19.2	15.1 (1.6–28.6)		
Total	28	60.7	29.1	24.9	24.9	16.1 (0.3–31.8)		

CI: confidence interval; TSR: tumor-stroma ratio.

DISCUSSION

Recent studies have analyzed tumor cells and tumor microenvironments to identify additional biomarkers with a high prognostic and/or predictive value, investigating molecular mechanisms, tumor cell structure, genetic mutations, tumor immune response, and gene expression, although the transcriptomic and genetic data collection in these methods leads to high costs[10-12]. The traditional pathological approach to analysis using a microscope is simple, inexpensive, and effective and so a microscopic analysis-based biomarker is desirable. TSR was first reported in 2007 to have potential in meeting this need due to its prognostic effect on colon cancers[9]. Subsequent studies put forward TSR as a promising outcome prediction tool, which demonstrates its prognostic effect on other cancer types, such as rectal cancer, breast cancer, hepatocellular carcinoma, and esophageal cancer[3,4]. While studies of TSR are increasing day by day, only two studies have been published to date for GBC[5,6]. Among these studies, Li et al.[5] reported median OS of 6 and 17 months for the stroma-rich and stroma-poor groups, respectively (p=0.004), and suggested TSR as an important prognostic factor in GBC. However, the authors also reported that TSR was not an independent prognostic factor for OS, with only the operative technique being an independent prognostic factor. The said study evaluated 51 patients, of which 37.3% underwent palliative resection. It should not be ignored that patients undergoing palliative resection, who should have been excluded from the study in our opinion, might have affected the results. Goyal et al.[6], in turn, examined the associations among TSR, tumor budding (TBd), and desmoplastic stromal reaction (DSR) with conventional prognostic factors and OS, in 96 patients, all of whom underwent curative resection. The authors, using the mean value instead of the median for OS, reported 18.9 months for the stroma-rich group and 89.5 months for the stroma-poor group (p<0.001) and showed TSR to be a prognostic factor for OS. The multivariate analysis also identified a low TSR along with the presence of metastases and positive surgical margins as independent poor prognostic factors for OS. Our study included only patients undergoing R0 curative resection, and despite the tendency for lower survival rates and shorter median OS in the stroma-rich group, the difference was not statistically significant. That said, the low number of patients in our study might have prevented our results from reaching statistical significance.

A meta-analysis study evaluating the effect of TSR on OS in various solid tumor patient groups established that a low TSR resulted in significantly poorer OS in patients with colorectal cancer, non-small cell lung cancer, hepatocellular carcinoma, breast cancer, and esophagus cancer, while no such effect was identified in cervical cancer patients[3]. The same study evaluated TSR according to the clinical stage subgroups and found a high TSR to be a positive predictor of OS in the stages I–IV, I–III, and II–III groups, while no such effect was identified in the stages I–II group[3]. The stage-specific effect of TSR was not assessed in this study due to the small sample size, and no such assessment was made also in the other two studies[5,6].

In this study, an analysis of the relationships between TSR and demographic and clinicopathological characteristics revealed no statistically significant relationship. In contrast, Li et al.[5] examined the relationships between TSR and gender, age, pathology type, differentiation grade, pTNM stage, surgical margins, and operative techniques and found only the stroma-rich group to be statistically significantly associated with higher T stages. Goyal et al.[6], in turn, reported TSR to be significantly associated with T stage, AJCC stage, LVI, PNI, resection margins, TBd score and category, and the type of DSR. The stroma-rich group was significantly associated with immature DSR, and the stroma-poor group with fibrotic

DSR[6]. No evaluation of the TBd score or the category or type of DSR was made in this study.

The underlying mechanism of the prognostic effect of TSR has yet to be clarified. The components of tumor-related stroma are complex, including the extracellular matrix (ECM), various cell types, and different secreted factors. While ECM helps cancer cells to communicate with stromal cells, it has been shown that the abnormal expression of some secreted protein factors that activate ECM may promote tumorigenesis[13]. Factors such as matrix metalloproteinases that degrade the ECM also facilitate tumor initiation and invasion[14]. In several types of cancer, activated fibroblasts, known also as cancer-associated fibroblasts (CAFs), are the predominant cell type within the tumor tissue rather than cancer cells. In the early stages of tumor progression, CAFs act as suppressors of contact inhibition in cancer cells by increasing the formation of gap junctions among activated fibroblasts. In later stages, CAFs function as promoters of tumor growth and progression after activation by several tumor-secreted factors[15]. Stromal cells also promote angiogenesis and metastasis and thus have a significant negative impact on prognosis[16]. Clarifying the relationship between the stromal component and cancer cells and the impact of this relationship on cancer progression may also be beneficial to the development of new therapeutic approaches in the future and should be evaluated from this perspective[3].

This study has some limitations, primarily including its retrospective design and the associated risk of selection bias. Second, the number of eligible patients was relatively low, which did not allow for subgroup assessments.

CONCLUSION

In this study, a low TSR (stroma-rich) tended to be a poor prognostic factor in GBC, although not to a statistically significant degree. Further studies should be conducted with larger patient groups. If the prognostic effect of TSR is strongly proven, its inclusion in routine pathological assessment as a simple, inexpensive, and useful method may be recommended.

AUTHORS' CONTRIBUTIONS

MAU: Conceptualization, Data curation, Formal Analysis, Investigation, Methodology, Project administration, Supervision, Validation, Writing – original draft, Writing – review & editing. **MT**: Conceptualization, Data curation, Formal Analysis, Investigation, Validation, Writing – original draft, Writing – review & editing. **AG**: Conceptualization, Data curation, Formal Analysis, Investigation, Methodology, Validation, Visualization, Writing – original draft, Writing – review & editing. **FA**: Conceptualization, Data curation, Formal Analysis, Investigation, Methodology, Validation, Visualization, Writing – review & editing. **SAK**: Conceptualization, Data curation, Formal Analysis, Investigation, Validation, Writing – review & editing. **GÇO**: Conceptualization, Data curation, Formal Analysis, Investigation, Validation, Writing – review & editing.

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ORIGINAL ARTICLE

https://doi.org/10.1590/1806-9282.20220047

Maternal-fetal alloimmunization: perinatal outcomes in a reference hospital in Northeastern Brazil

Úlima Rates Duete[1], Denise Menezes Brunetta[2,3], Edward Araujo Júnior[4,5*], Gabriele Tonni[6], Francisco Herlânio Costa Carvalho[1]

SUMMARY

OBJECTIVE: To assess the prevalence of maternal alloantibodies in pregnant women at a maternity hospital in northeastern Brazil and describe their perinatal outcomes.

METHODS: A retrospective cohort study reviewed maternal and newborn medical records between January 2017 and October 2018 to assess for the presence of maternal alloantibodies.

RESULTS: The following maternal alloantibodies were found in the 41 cases surveyed: anti-D, 28 cases (45%); anti-C, 7 cases (11%); anti-c, 1 case (1.6%); anti-E, 4 cases (6.4%); anti-Cw, 1 case (1.6%); anti-K, 2 cases (3.2%); anti-Jka, 1 case (1.6%); anti-M, 3 cases (4.8%); anti-Fya, 2 cases (3.2%); anti-Fyb, 1 case (1.6%); anti-Lea, 5 cases (8%); anti-Leb, 3 cases (4.8%); and anti-Dia, 4 cases (6.4%). Anti-D antibodies were the most frequent cause of erythrocyte alloimmunization (80%). Fetal anemia was observed in four pregnancies based on the peak systolic velocity of the middle cerebral artery. In one case, the mother showed anti-M, and anti-Lea alloimmunization, but the direct antiglobulin test results for the newborn were negative, and no unfavorable neonatal outcomes were observed. In one case of a mother with anti-C and anti-D alloimmunization, the neonate showed anti-D antibodies only in the serological panel and required phototherapy. Neonates with plasma antibodies and jaundice requiring phototherapy only had a serological panel with anti-D, anti-C, anti-c, and anti-E antibodies. Intervention was required for 2.5% of pregnant women with positive antibody screens and 81% of newborns with positive direct antiglobulin test results.

CONCLUSION: Despite being a rare condition, maternal alloimmunization by irregular antibodies can result in high perinatal morbidity and mortality.

KEYWORDS: Fetal erythroblastosis. Antibodies. Fetal outcomes.

INTRODUCTION

Maternal alloimmunization during pregnancy occurs when the pregnant woman has an immune response to a fetal erythrocyte antigen inherited by the father, which is not present in the maternal erythrocytes[1]. Although prophylaxis with anti-D immunoglobulin has been recommended by the World Health Organization (WHO) since the 1970s, the most common immunization is still against the Rh-D antigen[2].

Widespread use of anti-D immunoglobulin has significantly reduced cases of maternal Rh-D alloimmunization. However, no prophylactic immunoglobulin exists to prevent the formation of maternal antibodies against other erythrocyte antigens—non-anti-RhD alloimmunization—which also contributes to perinatal morbidity and mortality[3].

Several reported erythrocyte antigens are associated with perinatal hemolytic disease[3]. In addition to the anti-D antibody, those most commonly associated with fetal anemia are anti-c, anti-E, and anti-Kell[4]. Others, such as anti-C, e, Kidd, Duffy, and MNS blood group antibodies, can lead to fetal disease, but more rarely, and usually with mild outcomes[5].

The consequences of alloimmunization during pregnancy depend on antibody type, quantification, and affinity for the corresponding antigen, and can result in pregnancies without fetal impairment until hydrops fetalis or intrauterine fetal death[4]. Perinatal hemolytic disease in the newborn should be suspected when prenatal screening for maternal alloimmunization is positive and/or ultrasound scans show hydrops fetalis or anemia; severe or rapidly progressive hyperbilirubinemia

[1]Universidade Federal do Ceará, Maternidade Escola Assis Chateaubriand, Serviço de Medicina Fetal – Fortaleza (CE), Brazil.
[2]Universidade Federal do Ceará, Maternidade Escola Assis Chateaubriand, Unidade Transfusional – Fortaleza (CE), Brazil.
[3]Centro de Hematologia e Hemoterapia do Ceará – Fortaleza (CE), Brazil.
[4]Universidade Federal de São Paulo, Escola Paulista de Medicina, Departamento de Obstetrícia – São Paulo (SP), Brazil.
[5]Faculdade de Medicina, Universidade Municipal de São Caetano do Sul, Bela Vista Campus, São Paulo (SP), Brazil.
[6]Azienda Unità Sanitaria Locale di Reggio Emilia, Department of Obstetrics and Gynecology – Reggio Emilia, Italy.
*Corresponding author: araujojred@terra.com.br
Conflicts of interest: the authors declare there is no conflicts of interest. Funding: none.
Received on January 12, 2022. Accepted on February 1, 2022.

when no history of maternal prenatal alloimmunization is observed; or when major anemia or hemolysis is detected in laboratory tests and/or in the case of positive direct antiglobulin test (DAT) results[6].

This study aimed to assess the prevalence of positive antibody screens and the types of clinically significant maternal alloantibodies present in pregnant women at a reference service in Northeast Brazil, as well as the perinatal outcomes of each case.

METHODS

A retrospective cohort study was conducted using the medical records from the Hematology and Hemotherapy Center of Ceará. Serological panels were conducted to detect antibodies among the patients of Assis Chateaubriand School Maternity, Universidade Federal do Ceará (UFC), specifically pregnant and postpartum women with positive antibody screens and/or newborns with positive DTA results. This study surveyed 84 serological panels with maternal alloantibodies from January 2017 to October 2018. This study was approved by the Ethics Committee of UFC under No. 34115320.6.0000.5050.

Maternal serological panels were assessed as follows.

1. ABO and RhD typing was performed in tubes, with anti-A, anti-B, anti-D, and Rh control sera (Fresenius) and A1 and B red blood cells (Revercel, Fresenius);
2. Antibody screens were performed using a LISS/Coombs IgG ± C3d gel card centrifuge (Bio-Rad) with DiaCell I-II red cells (Bio-Rad);
3. Polyspecific DAT was performed using a LISS/Coombs gel card centrifuge containing antibodies against human IgG + C3d (Bio-Rad);
4. Erythrocyte phenotyping was performed for C, c, E, e, K, k, Kpa, Kpb, Jka, Jkb, M, N, S, s, Fya, Fyb, P1, Lua, Lub, Lea, and Leb antibodies using an Rh + Kell card and ID-Antigen Profiles I, II, and III (Bio-Rad).

Neonatal serological panels were assessed as follows.

1. ABO, RhD typing, and DAT were performed using Bio-Rad's newborn card;
2. Erythrocyte phenotyping was performed for antigens corresponding to maternal antibodies C, c, E, e, K, k, Kpa, Kpb, Jka, Jkb, M, N, S, s, Fya, Fyb, P1, Lua, Lub, Lea, and Leb using an Rh + Kell card and ID-Antigen Profiles I, II, and III (Bio-Rad);
3. In cases of positive DAT results, eluate testing using the glycine-acid technique was performed with the DiaCidel kit (Bio-Rad), according to the manufacturer's instructions.

The eluate was tested with red blood cells from DiaPanel and DiaPanel P (Bio-Rad) and red blood cells from Revercel diluted at 1% with diluent 2 (Bio-Rad), when the newborn was not O, for testing in a gel card centrifuge. If the eluate tested negative in newborns with DAT results from alloimmunized mothers and the phenotyping of the newborn was positive for the corresponding antigen, the eluate test results were considered a false negative. In these cases, the maternal antibody with specificity for the antigen expressed in the neonate's red blood cells was implicated as a cause of perinatal hemolytic disease.

After the serological panels were analyzed, information was collected from the medical records of 41 pregnant women with maternal alloantibodies, except for those with anti-RhD only, who gave birth at the institution or were followed up in high-risk prenatal care.

RESULTS

A total of 1052 antibody screens were performed in 2017, 40 of which were positive (3.8% prevalence rate). Between January and October 2018, 1339 antibody screens were performed, 20 of which were positive (1.4% prevalence rate), for an overall prevalence of 2.5%.

Of the 60 patients with positive antibody screens between January 2017 and October 2018, 45 medical records were analyzed, with the following prevalence: anti-D 53.3% (24); anti-C 15.5% (7), anti-c 2.2% (1), anti-E 6.7% (3), anti-Cw 2.2% (1), anti-K 4.4 % (2), anti-Jka 2.2% (1), anti-M 6.7% (3), anti-Fya 4.4% (2), anti-Fyb 2.2% (1), Anti-Lea 11.1% (5), anti-Leb 6.7% (3), anti-Dia 6.7% (3).

A survey of 84 alloantibody serological panels (including pregnant women, postpartum women, and newborns) was carried out from January 2014 to October 2018. From these 84 panels, 41 clinical cases of alloimmunization by non-anti-D alloantibodies were analyzed (Table 1). Serological panels of pregnant women, postpartum women, or newborns alloimmunized with anti-D only were discarded, and those with an alloantibody other than anti-D were included in the analysis.

During prenatal care, fetal anemia was detected in four pregnancies by measuring the mean peak systolic velocity of the middle cerebral artery (MCA-PSV). In case 1, the mother was alloimmunized with anti-M antibodies, and in case 8 by anti-Lea and anti-Leb antibodies; however, in both cases, the newborns' DAT results were negative and no unfavorable neonatal outcomes were observed.

In case 12, the mother was alloimmunized with anti-C and anti-D antibodies, but the newborn's serological panel revealed

Table 1. Types of maternal alloantibodies and perinatal outcomes for 41 alloimmunized pregnant women.

Case	Maternal alloantibodies	Gestational complications related to the presence of maternal alloantibodies	Newborn's DAT result	Newborn alloantibodies	Perinatal outcomes related to the presence of maternal alloantibodies
1	Anti-M	Fetal anemia	NEG	–	–
2	Anti-c	–	POS	Anti-c	Phototherapy
3	Anti-Lea	–	NEG	–	–
4	Anti-Leb	–	NEG	–	–
5	Anti-C, anti-D	–	POS	Anti-C, anti-D*	Transfusion
6	Anti-Lea	–	NEG	–	–
7	Anti-Lea	–	NEG	–	–
8	Anti-Lea, anti-Leb	Fetal anemia	NEG	–	–
9	Anti-K	–	NEG	–	–
10	Anti-Fya, anti-Dia	–	POS	Anti-Fya*	–
11	Anti-Leb	–	NEG	–	–
12	Anti-C, anti-D	Fetal anemia	POS	Anti-D	Phototherapy
13	Anti-C, anti-D, anti-E, anti-Dia	–	POS	Anti-D, anti-E	Phototherapy, exchange transfusion
14	Anti-E	–	POS	Anti-E	Phototherapy
15	Anti-C, anti-D	–	POS	Anti-D	Phototherapy
16	Anti-c, anti-E	–	POS	Anti-c	Phototherapy
17	Anti-Dia, anti-E	–	NEG	–	–
18	Anti-Cw	–	POS	Anti-Cw	Phototherapy
19	Anti-Dia	–	NEG	–	–
20	Anti-M	–	Not performed	–	Fetal death
21	Anti-Jka	–	POS	Anti-Jka	–
22	Anti-Lea	–	NEG	–	–
23	Anti-M	–	NEG	–	–
24	Anti-Fy3	–	POS	Not possible to identify antibody	Phototherapy
25	Anti-E	–	NEG	–	–
26	Anti-D, anti-C, anti-K	–	NEG	–	–
27	Anti-D, anti-C	–	NEG	–	–
28	Anti-C	–	POS	Anti-C	Phototherapy
29	Anti-M	–	NEG	–	–
30	Anti-Dia	–	NEG	–	–
31	Anti-M	–	NEG	–	–
32	Anti-M	–	NEG	–	–
33	Anti-f	–	POS	Anti-f	Phototherapy
34	Anti-M	–	NEG	–	–
35	Anti-Fya, anti-G	Fetal anemia	POS	Anti-Fya, anti-G	Phototherapy, transfusion, exchange transfusion
36	Anti-D, anti-C	–	POS	Anti-D	Phototherapy
37	Anti-E, anti-c	–	POS	Anti-c	Phototherapy
38	Anti-Fy3	–	POS	Anti-Fy3*	-
39	Anti-D, anti-C, anti-K, anti-E, anti-S	–	POS	N/A	Phototherapy
40	Anti-E, anti-Fyb	–	NEG	–	–
41	Anti-K	–	NEG	–	–

DAT: direct antiglobulin test; N/A: not available; NEG: negative; POS: positive.
*Not identified by the eluate technique.

anti-D antibodies only, with phototherapy being required. In case 35, the mother was alloimmunized with anti-Fya and anti-G antibodies, and the same antibodies were detected in the newborn, resulting in unfavorable neonatal outcomes requiring phototherapy, blood transfusion, and exchange transfusion.

In one case, fetal death occurred at 25 weeks of gestation in a primigravida without comorbidities, alloimmunized with anti-M antibodies, but the newborn's DAT was negative. Anti-K was present in maternal blood in cases 9, 26, and 41, but the newborn's DAT was negative, since all neonates were K negative.

Of the 41 alloimmunized pregnant women described in Table 1, 18 had newborns with positive DAT. Only 3 of these 18 newborns, which is equivalent to a percentage of 16.7%, did not need any type of intervention during pregnancy or postpartum. The other 83.3% required phototherapy, blood transfusion, or exchange transfusion. Of the 32 pregnant women alloimmunized with non-anti-D antibodies only, 11 had newborns with positive DAT, of which 9 newborns required at least phototherapy.

DISCUSSION

Among the alloimmunized pregnant women reviewed in this study, the prevalence of anti-D antibodies was much higher than that of other types, supporting previous findings that the most frequent cause of erythrocyte alloimmunization is anti-D (80%)[7]. Also highly prevalent were antibodies that have demonstrated an important association with severe hemolytic disease, such as anti-E and anti-K[4].

In case 8, we have the presence of maternal antibodies anti-Lea and Anti-Leb, but the newborns' DAT results were negative. Because the erythrocyte antigens Lea and Leb are poorly developed at birth, these antibodies are not associated with the development of perinatal hemolytic disease, and pregnant women with anti-Lea and anti-Leb alloimmunization do not require follow-up[8].

Anti-Fya and anti-G were detected in the newborn in case 35, resulting in phototherapy, blood transfusion, and exchange transfusion. The Duffy blood group system consists of the five antigens, and the most important are Fya and Fyb. Although anti-Fyb antibodies are unrelated to perinatal hemolytic disease, anti-Fya antibodies do show an association[3]. Antigen G is usually present when antigens D and/or C are also present, and absent when both are absent[9]. In initial serological tests, anti-G antibodies can mimic anti-D and anti-C. Anti-G alloimmunization can also be associated with perinatal hemolytic disease, must be identified, and also requires follow-up during pregnancy[10,11].

Newborns who had detectable antibodies in the plasma and developed jaundice requiring phototherapy only had a panel including those antibodies with the most clinical significance: anti-D, anti-C, anti-c, and anti-E. Anti-K, despite being one of the non-anti-RhD antibodies most strongly associated with perinatal hemolytic disease, was present in maternal plasma but did not lead to neonatal DAT positivity or any unfavorable fetal or neonatal outcomes, since all neonates were K negative[4].

The MNS blood group system consists of several erythrocyte antigens, but anti-M, -N, -S, -s, and -U antibodies are most strongly associated with perinatal hemolytic disease[3]. In this study, fetal death occurred in a primigravida alloimmunized with anti-M antibodies, but the newborn's DAT was negative. In a case reported by Lin et al.[12], a newborn with severe hemolytic disease caused by anti-M alloimmunization initially presented negative DAT results. Yasuda et al.[13] found a rate of up to 79% negative direct Coombs results in cases of MN incompatibility.

With the spread of anti-D immunoglobulin prophylaxis since the 1960s, maternal alloimmunization rates have decreased[3], but non-anti-RhD antibodies, such as anti-c, anti-E, and anti-Kell, have also been identified as causes of perinatal hemolytic disease, usually with mild to moderate presentations. Despite the predominance of anti-D antibodies among the alloimmunized patients in this study (53.3%), other types of antibodies also showed significant prevalence rates.

This study has an important limitation due to the lack of data on fetal genotyping and some neonatal phenotyping. These tests are important to confirm whether the maternal alloantibody is clinically relevant to the fetus or newborn.

CONCLUSION

To avoid adverse perinatal outcomes, it is critical to reinforce the use of immunoprophylaxis for anti-D alloimmunization in pregnant women. Additionally, given the association of non-anti-D antibodies with the development of perinatal hemolytic disease, it may be warranted to request an antibody screen (indirect Coombs's test) for all pregnant women, even those who are D-positive, and DAT (direct Coombs's test) for newborns whose mothers have an alloantibody other than anti-D, to diagnose non-anti-D maternal alloimmunization.

AUTHORS' CONTRIBUTIONS

URD: Data curation. **DMB**: Methodology. **EAJ**: Writing – original draft. **GT**: Formal Analysis. **DMB**: Formal Analysis. **FHCC**: Investigation, Supervision.

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ORIGINAL ARTICLE

https://doi.org/10.1590/1806-9282.20220063

Discussion of the Brazilian neurologists about sudden unexpected death in epilepsy

Amanda Mosini[1,2*], Ively Guimarães Abdalla[3], Michele Longoni Calió[2], Ana Claudia Fiorini[4], Carla Alessandra Scorza[3], Maria Alice Susemihl[1], Josef Finsterer[5], Fúlvio Scorza[3]

SUMMARY

OBJECTIVE: This study aimed to evaluate the concept of health professionals affiliated with the Brazilian League of Epilepsy on whether or not to inform patients about the risk factors related to the occurrence of sudden unexpected death in epilepsy.

METHODS: A descriptive research of inquiry was conducted with direct survey on the Brazilian neurologist's view, regarding medical behavior in the health area to report or not about the risk of sudden unexpected death in epilepsy. Data collection consisted of a structured questionnaire available online.

RESULTS: The study population consisted of a sample of 44 Brazilian League of Epilepsy members who answered the questionnaire, of which 25 (56.8%) were men and 19 (43.2%) were women. Among the analyzed questionnaires, 79.5% reported that they were aware of the risk factors for sudden unexpected death in epilepsy and 18.2% admitted not knowing the potential risk factors for sudden unexpected death in epilepsy. Notably, 59.1% of these professionals thought that an early discussion with the patient about sudden unexpected death in epilepsy must be considered. The majority (70%) felt that the neurologist should do this, and 22% believed that the subject should be discussed with psychologists. It was noted that 84.1% of respondents did not discuss or discussed only with some of their patients about the risk factors for sudden unexpected death in epilepsy.

CONCLUSIONS: There is a need for encouraging early discussion of sudden unexpected death in epilepsy with epilepsy patients if the patient asks about the risks related to epilepsy and its treatment, when treatment adherence is low, in cases of intractable epilepsy with strong indication for surgical treatment, and when polytherapy is needed.

KEYWORDS: Epilepsy. SUDEP. Health care. Medical care.

INTRODUCTION

Epilepsy, affecting over 70 million people worldwide, is one of the most common and disabling chronic neurologic conditions which is characterized by a lasting brain predisposition to generate spontaneous and recurrent epileptic seizures. Epilepsy has several neurobiological, cognitive, and psychosocial consequences[1]. For example, epilepsy patients have an increased risk of premature mortality. On June 19, 1773, George Washington documented the death of his stepdaughter on his diary as "at home all day About five o'clock poor Patcy Custis died suddenly"[2]. In 1868, Bacon wrote in *Lancet Neurology* that "the immediate cause of death in epilepsy is a matter which is not always easily solved, and one which is not often discussed in works on medicine, most probably from lack of information"[3]. Years later, in 1904, William Spratling noticed that almost 4% of deaths in epilepsy patients resulted directly from epileptic seizures without any explanation, even after the autopsy was performed[4]. Only in 1996, the term "sudden unexpected death in epilepsy" (SUDEP) was defined by Nashef, at the International Congress on Epilepsy and Sudden Death[5].

Sudden unexpected death in epilepsy is defined as an unexpected, witnessed, or unwitnessed death in patients with epilepsy, with or without evidence of a seizure, excluding documented epilepticus, drowning or trauma status, and without toxicological or anatomic cause for death found on postmortem examination[5]. Besides being responsible for 7.5–17% of all epilepsy deaths, SUDEP incidence varies between 1:500 and 1:1000 adult patients per year[6] and accounts for 12% of all children epilepsy-related deaths[7]. From a statistical standpoint, Holst and colleagues (2013) reported 27 times higher incidence of sudden death in young adults with epilepsy

[1]Associação Brasileira de Epilepsia – São Paulo (SP), Brazil.
[2]Universidade Federal de São Paulo, Departamento de Fisiologia – São Paulo (SP), Brazil.
[3]Escola Paulista de Medicina/Universidade Federal de São Paulo, Disciplina de Neurologia Experimental – São Paulo (SP), Brazil.
[4]Escola Paulista de Medicina/Universidade Federal de São Paulo, Departamento de Fonoaudiologia – São Paulo (SP), Brazil.
[5]Messerli Institute, Klinikum Landstrasse – Vienna, Austria.
*Corresponding author: amandacfmosini@gmail.com
Conflicts of interest: the authors declare there is no conflict of interest. Funding: none.
Received on January 14, 2022. Accepted on January 23, 2022.

compared to the general population of the same age group[8]. Several factors are associated with an increased risk of developing SUDEP, including male gender, alcohol or psychotropic medication usage, long history of epilepsy, high seizure frequency, structural findings on neuropathology or EEG with epileptiform discharges, cognitive deficits, number and long duration of generalized tonic-chronic seizures, preexisting respiratory diseases and refractory epilepsy, low number of antiepileptic drugs (AEDs) or nonadherence to AED treatment, and abrupt medication changes[9].

Despite the importance of the subject, talking about SUDEP with patients and their families is a sensitive matter, creating an emotional burden and anxiety not only for the patient but also for the physician. Thus, the SUDEP topic is still avoided by many physicians who believe that discussing the subject will solely escalate patients and their family's concerns.

In consonance with Abdalla and colleagues (2013)[10], 76% of the Brazilian epileptologists discuss the risk of SUDEP with a minority of their patients, 14% discuss with the majority of their patients, and 10% with none of them. In contrast, 90% of the patients wished the SUDEP discussion for themselves and over 70% wished SUDEP discussion with people for whom they are responsible[11].

A study performed with English neurologists by Beran and colleagues (2004) showed that 4.7% of physicians discuss SUDEP with all their patients, 25.6% with the majority, and 7.6% with the minority or none of their patients[12]. A study performed in 2011 showed that 35% of the Michigan neurologists never discussed SUDEP with their patients, while 38% reported to have discussed this subject only when patients are at risk[13].

The awareness of risk factors for SUDEP by health professionals, who deal with people with epilepsy, has grown in recent years, but there is still uncertainty regarding whether to discuss this subject with patients. Additionally, Henning and colleagues (2018) reported that 90% of epilepsy patients and their caregivers longed for information about epilepsy-related risks like death or injuries. Out of this group, 47% of those with epilepsy and 55% of carriers affirmed that they had obtained useful information about this topic[14].

To talk about the risk of SUDEP, the neurologist should be well informed about it. The aim of this study was to investigate through a questionnaire if members of the Brazilian League of Epilepsy (LBE) know about the risk factors related to SUDEP and if they feel prepared to talk with their patients about it.

METHODS

Participant characteristics

A physician questionnaire and a consent term were mailed via individualized email to 293 members of the LBE who were invited to participate in the study. The confidentiality of the identity of each participant was ensured by the national and international ethical standards of the LBE.

Of this total, 234 had one or more email addresses and 54 did not have an email address. Four of the subjects contacted by email sent a printed questionnaire. Personalized and parameterized emails were sent to 234 professionals in the LBE database six times in a 2-month period.

Measures

A questionnaire was devised. The design and use of the respondent-completed questionnaires were developed by using Microsoft Office Access Database software. The questionnaire contained closed alternatives aiming to identify the level of understanding of professionals about SUDEP and their opinion on whether or not to inform patients about the risk of SUDEP and to acquire information on how and when patients can be informed about SUDEP. Anonymous results of the questionnaires were stored in an encrypted database and analyzed independently.

In brief, questions were the following:

a. What is your area of expertise in neurology?
b. What is your experience in treating patients with epilepsy?
c. How many epilepsy patients are you assessed on a monthly basis?
d. Do you know the possible risk factors for SUDEP?
e. If so, what sources and authors do you use (or) to inform/update on the topic?
f. In your opinion, should the patient with epilepsy be accompanied by a multidisciplinary team?
g. If the answer is yes, should these professionals be aware of the risks of the phenomenon of SUDEP?
h. In your opinion, which professional from this multiprofessional team should discuss the risks of SUDEP with the patient? Why?
i. Do you think there should be an incentive to advance discussion of SUDEP with patients?
j. If you answered yes to the question, which patients should be encouraged for an early discussion of SUDEP?

After obtaining the answers, a descriptive analysis of the results was made.

RESULTS

Specialties of the interviewed professionals

Of the 234 invitations sent, we received 44 responses (19% response rate), being 25 (56.8%) men and 19 (43.2%) women with an average age of 46.7 years. The majority (33.79%) identified themselves as epileptologists, followed by 28.38% who identified themselves as adult or pediatric neurologists. Many of the doctors had more than one specialty.

Experience in the treatment of epilepsy and knowledge about sudden unexpected death in epilepsy

The majority (91%) of doctor's respondents affirmed that they are experienced in treating epilepsy patients, 7% assumed to have a moderate knowledge, and only few responded that they have less experience on the subject, although everyone works with epilepsy. Of these doctors, 68.2% reported attending up to 69 patients per month, while 20.5% attending up to ≥110 patients per month.

Of the 44 doctors, 8 admitted having no knowledge about the possible risk factors of SUDEP, while 35 reported having knowledge about risk factors (Figure 1). Only one individual did not answer the question.

Need for monitoring by a multidisciplinary team

Among all those interviewed, 43 (97.7%) replied that the patient must be followed up by a multidisciplinary team. Among these, 42 (95%) also think that the professionals involved in the multidisciplinary team must have knowledge about the risks of SUDEP, including those who admitted that they did not know about it.

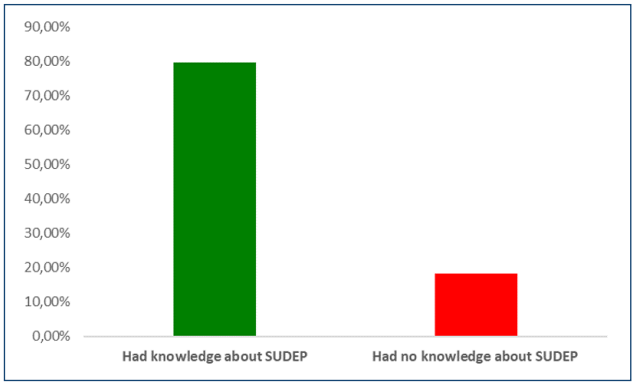

Figure 1. Distribution of the knowledge about the possible risk factors for sudden unexpected death in epilepsy.

Discussing sudden unexpected death in epilepsy with the patient

Regarding to which professional of the multidisciplinary team should discuss about the risks of SUDEP with the patient, the majority affirms that the doctor should do this, the second option is the psychologist. Only a minority affirms that the physiotherapist, nurses, social assistant, or another member of team can discuss the topic with the patients after training. Among them, 26 affirmed that there should be an incentive for early discussion about SUDEP (Figure 2).

When asked if they ever discussed the topic SUDEP with their patients, 81.81% of subjects answered "yes," 11.36% answered "no," and 6.83% did not answer.

DISCUSSION

The aim of this survey was to evaluate the concept of LBE members about informing epilepsy patients about the risk factors related to SUDEP. Pioneered in Brazil, this study represents an opportunity to approach an important little-discussed issue like SUDEP. Although SUDEP is an uncommon complication, it is a source of considerable concern for patients, taking into account that there is an important insecurity among professionals about how to demystify the subject[15]. While the study was limited by a relatively low response rate, as typical of many Internet-based surveys, the answers of the 44 professionals were carefully interpreted and demonstrate the real situation of medical advice regarding the risks of SUDEP.

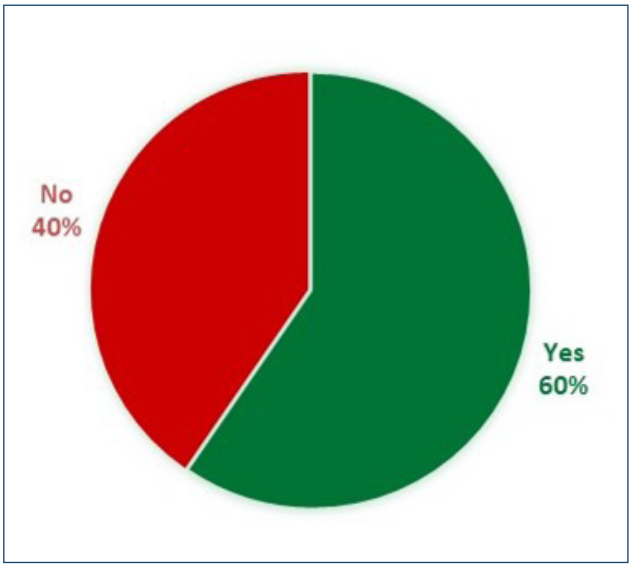

Figure 2. Recognition of the need for early discussion about sudden unexpected death in epilepsy with patient.

The survey data show that most of the subjects evaluated are well informed and well updated on the subject, as 79.5% of the interviewed know the risks related to SUDEP and update themselves on the topic from scientific articles and congresses as the main source of information. Nevertheless, there is a strong consensus on the need for a multidisciplinary team to deal with this issue with epilepsy patients, revealing an understanding of the complexity of preventing SUDEP. Almost 98% of the subjects affirmed that epilepsy patients must be accompanied by a trained multidisciplinary team prepared with knowledge about risk factors of SUDEP.

According to our data, there was an agreement between 59% of the subjects encouraging the discussion about SUDEP with epilepsy patients. The majority (70.45%) affirms that the doctor should discuss the risks of SUDEP with the patient, 22.2% propose the psychologist to explain the topic to the patient, and the minority (7.35%) affirms that physiotherapists, nurses, social assistants, or other members of the team should discuss the topic with patients after training. As stated by Gayatri and colleagues (2010)[16], the information about SUDEP must be given by the doctor and accompanied by an information leaflet. This conclusion about the need for the information leaflet in the guidance on the risks of SUDEP may perhaps minimize the negative reactions described by professionals in our work. Nair and colleagues (2016)[17] emphasized that with regard to the individual responsible for the diagnosis and subsequent development of the patients long-term plan of care, neurologists should establish a therapeutic alliance with the patients and their families and thus should lead the discussion about SUDEP.

The decision to discuss the topic SUDEP with patients remains a sensitive issue of debate worldwide. Based on the findings of the few studies that investigated counseling of epilepsy patients, health professionals prefer not to discuss the risk of SUDEP[18]. This fact is against the guidelines that recommend disclosure as part of the educational intervention to patients with epilepsy[17]. Even though most of the participants in our study have stated that there should be an incentive for early discussion of SUDEP, 40.9% were against such an incentive, showing that opinions were well balanced. These results are in line with the international literature, where the discussion about whether and when to talk about SUDEP with patients is one of the most debated topics among epileptologists. The National Institute for Clinical Excellence Publication (2004) recommends epilepsy patients and their families and/or caregivers having access to information about SUDEP[19]. The Scottish Intercollegiate Guidelines Network (SIGN) developed clinical evidence-based guidelines for the National Health Service (NHS) in Scotland. In this sense, it is possible to observe the relevance of the study in our country, as it is the beginning for more discussions and research on the subject to develop.

Contrary to the study by Morton and colleagues (2006)[15] who reported that neurologists and epileptologists do not expose routinely information about SUDEP, nearly 82% of our subjects affirmed that they ever discussed with their patients about the topic. The reasons for discussing SUDEP included moral accountability, practical accountability, proactivity, and reactivity[20]. As reported by Abdalla and colleagues (2013)[10], 76% of 44 subjects discussed the risk of SUDEP with their patients, while only 24% of 44 subjects discussed the topic with a minority or none of their patients.

CONCLUSIONS

This study may help obtain an overview of the doctors' view about explaining the risks of SUDEP to their patients. The results showed that SUDEP is an extremely important subject but still stigmatized. Congresses and extension courses focused on SUDEP should be organized and made available to health professionals (doctors and non-doctors), with the aim of helping them start this difficult discussion with patients, thus building a partnership to improve the treatment of epilepsy.

ACKNOWLEDGMENTS

This study has been supported by grants from FAPESP (Fundação de Amparo à Pesquisa do Estado de São Paulo), CNPq (Conselho Nacional de Desenvolvimento Científico e Tecnológico), FAPESP/FAPEMIG, and FAPESP/CNPq/MCT (Instituto Nacional de Neurociência Translacional).

AUTHORS' CONTRIBUTIONS

AM: Formal Analysis, Resources, Visualization, and Writing – original draft. **IGA**: Conceptualization, Data curation, Formal Analysis, Investigation, Methodology, Project administration, Resources, and Visualization. **MLC**: Resources, Visualization, and Writing – original draft. **ACF**: Conceptualization, Validation, and Visualization. **CAS**: Validation, Visualization, and Writing – original draft. **MAS**: Validation, Visualization, and Writing – review & editing. **JF**: Validation, Visualization, and Writing – review & editing. **FS**: Conceptualization, Funding acquisition, Software, Validation, Visualization, and Writing – review & editing.

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ORIGINAL ARTICLE

https://doi.org/10.1590/1806-9282.20220152

Expression of endoglin, CD105, in conjunctival melanocytic nevi: Is it suspicious like in thyroidology? *Oculi plus vident quam oculus*?

Dzenana Detanac[1*], Snezana Jancic[2], Demet Sengul[3], Ilker Sengul[4,5], Dzemail Detanac[6]

SUMMARY

Objective: The aim of this study was to evaluate the expression of endoglin and its correlation with histopathological and clinical findings in conjunctival nevi.

Methods: The study included archival formalin-fixed, paraffin-embedded tissue sections of 44 patients with conjunctival nevi. Immunohistochemical staining for CD105 had been performed with monoclonal mouse antihuman CD105 antibodies. The intratumoral microvessel density for quantification of tumoral vascularization had been determined by this marker.

Results: The expression of CD105 was positive in 30 (68.2%) cases. There was a statistically significant difference in the level of CD105 expression regarding the histological type of nevus (p=0.03) and intralesional cysts status (p=0.02). Spearman's rho (ρ -0.316) revealed a significant negative correlation between the expression of endoglin and the histological type of nevus (p=0.03) and between the expression of endoglin and the presence of intralesional cysts (ρ -0.380, p=0.01).

Conclusion: This study suggests that endoglin could be a useful diagnostic and prognostic marker in differentiating between benign and malignant melanocytic ocular lesions.

Keywords: Endoglin. Conjunctiva. Nevus, Pigmented. Immunohistochemistry. Thyroid gland. Thyroidology.

INTRODUCTION

Conjunctival tumors frequently originate from pigment cells, usually possessing the structural configuration of melanocytic nevi[1,2]. Debate is still ongoing on the accurate differential diagnosis of the benign and malignant melanocytic proliferation of the conjunctiva. However, accuracy in the mentioned issue is crucial as it implies diverse ocular and systemic prognoses[3]. Ad initio, many studies recommended immunohistochemical markers to provide additional and supportive diagnostic and prognostic pieces of information, to date. Ad hoc, immunohistochemical expression of S100A1, S100A6, S100B, MelanA, CEA, HMB-45, MART-1, CD45, CD68, CD1a, Ki-67 nuclear proliferation protein, p16, p53, WT, and Bcl2 in conjunctival melanocytic lesions had been investigated, but still, this topic continues to receive serious needs for further investigations[4-12].

In the present study, it is purposed to investigate the endoglin (CD105) expression and its correlation to the histopathological and clinical features in the conjunctival nevi.

Endoglin is a homodimeric transmembrane glycoprotein, a component of the receptor complex of transforming growth factor beta1 (TGF-β1), a multifunctional cytokine with an important role in cell proliferation, differentiation, and migration[13]. Inhibition of CD105 expression enhances the ability of TGF-β1 to suppress growth and migration of cultured endothelial cells, and their capacity to form capillary tubes[14]. The evaluation of neovascularization by CD105 staining was found to be a useful prognostic indicator in different solid malignancies. In contrast to some other markers, expressed on endothelial cells of blood vessels in both normal tissue and malignant tumors, endoglin is mostly expressed on the peritumoral and intratumoral blood vessels, which makes it a potential molecular target for therapy[15].

The expression of endoglin has been investigated in uveal melanoma[6], cutaneous melanoma[7,8], and cutaneous melanocytic lesions[9]. There have been no published reports on CD105 expression in human conjunctival nevi so far.

[1]General Hospital Novi Pazar, Department of Ophthalmology – Novi Pazar, Serbia.
[2]University of Kragujevac, Faculty of Medical Sciences, Department of Pathology – Kragujevac, Serbia.
[3]Giresun University, Faculty of Medicine, Department of Pathology – Giresun, Turkey.
[4]Giresun University, Faculty of Medicine, Division of Endocrine Surgery – Giresun, Turkey.
[5]Giresun University, Faculty of Medicine, Department of Surgery – Giresun, Turkey.
[6]General Hospital Novi Pazar, Department of Surgery – Novi Pazar, Serbia.
*Corresponding author: dzenana.detanac@gmail.com
Conflicts of interest: the authors declare there is no conflicts of interest. Funding: none.
Received on February 03, 2022. Accepted on February 04, 2022.

METHODS

This retrospective histopathological and immunohistochemical study of 44 surgically excised conjunctival nevi was conducted at the Institute for Pathology of the Faculty of Medicine, University of Kragujevac, Serbia. A total of 44 patients, 25 (56.8%) females and 19 (43.2%) males, who carried the diagnoses of conjunctival nevi, were examined and surgically treated in the tertiary referral center, Clinic for Eye Diseases, Clinical Center of Serbia, Belgrade, during the period from January 2000 to December 2002. The archival consultation files and 10% formalin-fixed, paraffin-wax-embedded tissue sections from the Eye Pathology Laboratory of the Clinic for Eye Diseases, Belgrade, were collected and retrospectively reviewed with approval from the institutional Ethics Committee of the University of Belgrade for the purposes of this study (approval nº:1009/3). The tumor data had also included intralesional cysts status, in terms of presence or absence. The patient charts had been reviewed for specific data as follows: gender, age at the time of excision, anatomic location of the lesion, duration of the process, clinical indications for excision, and follow-up period. These data had been collected and analyzed after the histopathological and immunohistochemical findings were determined.

Archival in 10% formalin-fixed, paraffin-embedded tissue sections was cut at 3 µm. Representative paraffin sections, mounted on high adhesive slides (Star Frost, Waldemar Knittel GmbH, Braunschweig, Germany), were heated at 55ºC to melt the paraffin, deparaffinized in xylene (three times, 5 min each), and rehydrated with a graded series of alcohol. Standard hematoxylin-eosin staining for the type of nevus differentiation and Alcian Blue-Periodic Acid Schiff pH 2.5 (AB-PAS) staining for testing and differentiation of neutral (red) from the acid (blue) mucins were performed in separate sections.

Antigen retrieval was enhanced by autoclaving of slides in sodium citrate buffer (pH 6.0) for 30 min. After cooling for about 30 min, the slides were washed again in phosphate-buffered saline (PBS). Endogenous peroxidase activity was blocked by treating the sections with 0.3% (v/v) H_2O_2 in methanol for 25 min and then the slides were washed again. The sections were then incubated with the primary antibodies overnight at 4ºC. Staining was performed with antibodies for the identification of CD105 (monoclonal mouse anti-human CD105, endoglin, Clone SN6h, 1:50, DAKO, Glostrup, Denmark). Incubation with secondary antibody was performed with Vectastain Elite ABC Kit (Vector Laboratories, Burlingame, CA, USA) at room temperature for 1 h. Visualization of immune complexes was performed with 3,3'-diaminobenzidine (DAB) chromogen solution. Slides were counterstained with Mayer's hematoxylin and mounted on Canada balsam. For negative controls, the primary antibody was replaced by PBS.

The microvessel density (MVD) was calculated by immunostaining for CD105, by searching the most vascularized area ("hotspots") at low magnification (200×) using light microscope (Olympus BH-2). Then, CD105-positive vessels in five of these fields at high magnification (400×) were counted according to the Weidner's procedure[10]. A countable single microvessel was considered any immunopositive (clearly stained) endothelial cell or endothelial cell cluster that is separated from the adjacent microvessels, tumor cells, and other connective tissue elements[10]. The mean of the vessels in five fields was used as MVD. The immunohistochemical staining intensity was graded as follows: negative: –, weak/mild: +, moderate: ++, or strong: +++, depending on the expression of endoglin (–: absent; +: 1–5 positive cells; ++: 5–10 positive cells; +++: more than 10 positive cells). The immunohistological specimens were evaluated by two independent experienced pathologists; in all cases, agreement was reached.

SPSS version 20.0 (SPSS Inc., Chicago, IL, USA) was used for statistical data processing. The results were analyzed by using the descriptive statistics and Mann-Whitney U test or the Kruskal-Wallis test depending on the distribution and number of compared groups. Nonparametric variance analysis was performed by Spearman's rank correlation coefficient calculation. A value of $p<0.05$ was considered statistically significant.

RESULTS

In this study, 44 nevi in 44 patients, 25 (56.8%) females and 19 (43.2%) males, with a mean age 31.36±18.715 years (range 7–73 years), were included. Excision of conjunctival melanocytic lesion was done in all patients. One or more clinical indications for excision were as follows: suspicious clinical appearance, accelerated growth, or color change of the lesions. Bulbar conjunctiva was the most common location of the tumor. In all, 28 (63.6%) of 44 nevi was located on nasal quadrant and 16 (36.4%) on temporal region. The tumor anterior margin was located on the edge of the cornea in 9 (20.5%) lesions and on plica semilunaris in 7 (15.9%) cases.

Follow-up examinations were made at 6- to 12-month intervals, and the patients were followed up for a mean of 8.9 years. During the follow-up period, there were no recorded data on recurrence or malignancy.

Histopathologically, the 44 excised lesions had revealed the compound nevus in 33 (75.0%) patients, subepithelial nevus in 7 (15.9%) patients, combined nevus in 2 (4.5%) patients,

junctional nevus in 1 (2.3%) patient, and ceruleus nevus in 1 (2.3%) patient. The cysts were noted in 9 (20.5%) nevi, of which 7 (15.9%) were compound nevi and 2 (4.5%) were subepithelial nevi.

The expression of CD105 was positive in 30 (68.2%) cases. Out of these, 24 (80%) were compound nevi, 2 (6.7%) combined nevi, 2 (6.7%) subepithelial nevi, 1 (3.3%) junctional nevus, and 1 (3.3%) ceruleus nevus. The majority of CD105-positive conjunctival nevi showed weak CD105 expression, with 27 (61.4%) cases showing the weak (+) CD105 staining intensity and 3 (6.8%) cases, including 1 compound nevus, 1 junctional nevus, and 1 combined nevus, showing moderate (++). The CD105-positive vessels were absent in 14 (31.8%) conjunctival nevi (Figure 1).

We have investigated the association of the presence of CD105-positive blood vessels with histology. There was statistically significant difference in the level of CD105 expression regarding the histological type of nevus (p=0.04). The CD105 expression was significantly higher in compound nevi. Of all subepithelial nevi, only one showed a low (+) CD105 expression, and in other subepithelial nevi, the CD105-positive vessels were absent (Figure 2).

The CD105 expression was moderate (++) in 3 (6.8%) of 44 conjunctival nevi, 1 junctional nevus, 1 compound (Figure 3) nevus with the presence of marginal mitotic activity, and 1 combined nevus in which the greater part of the lesion was in a deeper subepithelium, composed of spindle-shaped cells and strongly pigmented.

We have also investigated the association between the presence of CD105-positive blood vessels and the intralesional cysts status. There was statistically significant correlation between the CD105 expression and intralesional cysts status in conjunctival nevi (p=0.03). The CD105 expression was significantly lower in nevi with intralesional cysts. The CD105-positive vessels were present in three of nine nevi with intralesional cysts. The statistical analysis showed that there was no significant correlation between CD105 expression and nevi location (p=0.43).

Nonparametric variance analysis by Spearman's rho (ρ -0.316) revealed significant negative correlation between expression of endoglin and histological type of nevus (p=0.03), which means that as nevus is in deeper layers of the conjunctiva, the expression of endoglin is weaker. A significant negative correlation between expression of endoglin and the presence of intralesional cysts was also confirmed with nonparametric variance analysis by Spearman's rho (ρ -0.380, p=0.01), which means that the more the intralesional cysts, the weaker the expression of endoglin.

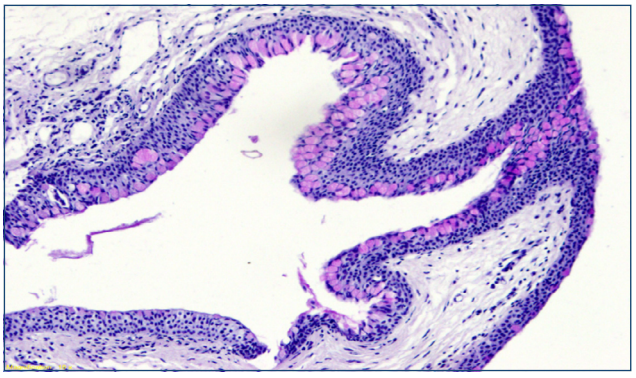

Figure 2. The naevus subepithelial plica semilunaris with cystic formation that is in continuity with cover epithelium. In superficial third of the epithelium (periluminal), mucinous epithelium transformation with PAS+ neutral mucins is present and the CD105 expression is negative (Immunohistochemistry, AB-PAS; Original magnification, 200×).

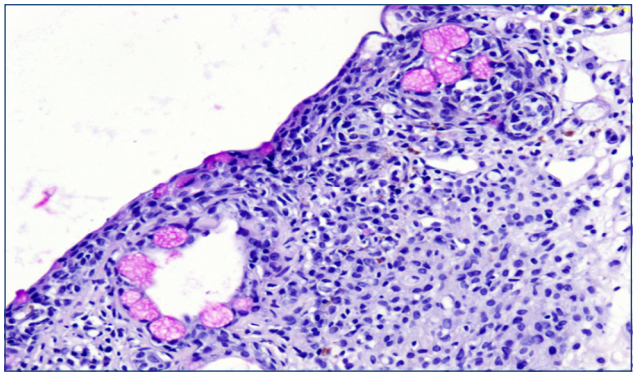

Figure 1. The naevus compositus conjunctivae associated with chronic conjunctivitis and mucinous cysts and filled with PAS+ neutral purple-red mucins. A focal mucinous metaplasia is present on the surface of epithelium and the CD105 expression is negative (Immunohistochemistry, AB-PAS; Original magnification, 400×).

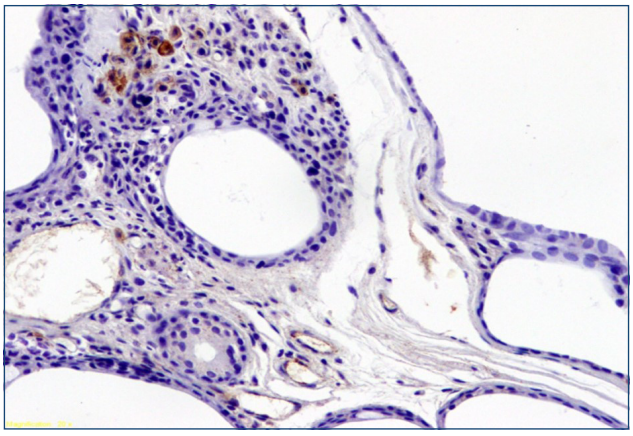

Figure 3. A compound nevi with a moderate expression of CD105 in the individual endothelial cells.

DISCUSSION

In a study, CD105 immunolabeling has been investigated with 35 uveal melanomas[6] and concluded that, since the staining for some nonendothelial cells has been described in benign cutaneous melanocytic lesions[9], further specific investigations are needed to confirm the CD105 specificity for proliferating endothelial cells in ocular melanocytic tumors. To the best of our knowledge, since the expression of endoglin in human conjunctival nevi has not been studied to date, we were interested to do that investigation. Our clinical characteristics of the investigated nevi and histopathological distribution of the types of nevi were quite similar to other studies. Compound nevus was the most common diagnosis, and bulbar lesions were the most common site[2,11,12]. In 30 out of 44 lesions, endoglin was weakly or moderately positive while it was not identified in 14 (31.8%) lesions. The association between the number of CD105-positive nevi and the histological type of conjunctival nevi was investigated in our study. The evolution of conjunctival nevi starts from an initial junctional phase to a compound and finally subepithelial nevus. Junctional nevi, characterized of nevus cells located at the epithelium and substantia propria interface, are found only early in life. In compound nevi, nevus cells are located in the substantia propria and junctional area. Subepithelial nevus, over time, becomes located in substantia propria, entirely beneath the epithelium[2]. Our study showed a statistical significant correlation between CD105 expression and the histological type of conjunctival nevi. The CD105 expression was significantly higher in compound nevi compared to subepithelial and becomes weaker as nevus cells pass into the deeper layers of the conjunctiva. These results correspond to the fact that subepithelial nevus is characterized by calm epithelium in which there is no nevus cells, or any cell activity, and never shows malignant transformation[2].

The presence of intralesional epithelial cysts is very characteristic and diagnostically useful feature of conjunctival nevi[11]. Intralesional epithelial cysts are less frequent in early lesions. In long-standing nevi, cysts may occupy most of the volume of the lesion and the melanocytic component may not be apparent and their presence may help differentiate such conjunctival nevi from other amelanotic conjunctival lesions. In contrast, conjunctival cysts are extremely rare in primary acquired melanosis and melanoma[2,11]. When we analyzed the correlation of the presence of CD105-positive blood vessels with the intralesional cysts status, results showed that expression of CD105 was significantly lower in nevi with intralesional cysts and that the more intralesional cysts are present when the expression of endoglin becomes weaker.

Many ophthalmology studies evaluated MVD using biomarkers such as CD34, CD31, vWF, and CD105 and demonstrated that CD105 is specifically overexpressed on endothelial cells of all angiogenic tissues, including tumors, but only weakly or not at all on those of normal tissues[3,6,16,17]. In recent years, the antiangiogenic therapy represents a promising approach for cancer treatment[18,19]. How to improve the benefit from these therapies and how to check patient response are leading goals for investigators. The value of using tumor MVD as a prognostic and antiangiogenic treatment efficacy indicator for a wide range of cancers is still the aim of many studies[20]. To date, bevacizumab is an antiangiogenic antibody approved for clinical indications. However, essentiality is ongoing in order to develop more antibodies that have targets highly expressed on tumor endothelium. CD105 represents a promising marker of angiogenesis that requires to be further investigated, in terms of its therapeutic relevance in cancer. In this context, Karmani et al.[21] suggest, in vivo, that the potential use CD105, in terms of indirectly iodinated anti-CD105 mAbs (D-KRYRR peptide as a linker [I125-KRYRR-anti-CD105-mAbs]) regarding its directly usage (125-anti-CD105 mAbs) for the thyroid tumor imaging and for therapeutic purposes in thyroidology. Understanding and recognizing the benefits and limitations of microvessel density, further investigations of characteristics of molecules expressed by endothelial cells will certainly improve the efficacy of antiangiogenic agents and proper guidelines for effective therapy in human malignancies. The importance of evaluating the CD105 expression in some ocular tumors has been already indicated, but there is a need for further detailed investigations of endoglin expression in the eye in order to determine its importance as a prognostic and antiangiogenic treatment efficacy indicator.

CONCLUSION

Herewith, in the present study, the first demonstrating the CD105 expression in conjunctival nevi, weak expression of endoglin was exhibited in the majority of investigated nevi. As such, this study demonstrated a statistically significant correlation of endoglin and histological type of nevus, also a statistically significant correlation of endoglin and the presence of intralesional cysts. Of note, this association suggests that endoglin could be a useful diagnostic and prognostic marker for ocular melanocytic lesions, but the further confirmatory study is required in order of affirming its specificity in differentiating between benign and malignant melanocytic ocular lesions and its clinical, predictive, and therapeutic potential.

AUTHORS' CONTRIBUTIONS

DD: Conceptualization, Data curation, Formal Analysis, Investigation, Methodology, Project administration, Resources, Software, Validation, Visualization, and Writing – original draft. **SJ**: Conceptualization, Data curation, Formal Analysis, Investigation, Methodology, Project administration, Resources, Software, Validation, Visualization, and Writing – original draft. **DS**: Investigation, Methodology, Project administration, Software, Supervision, Validation, Visualization, Writing – original draft, and Writing – review & editing. **IS**: Investigation, Methodology, Software, Supervision, Visualization, Writing – original draft, and Writing – review & editing. **DD**: Investigation, Methodology, Software, Supervision, Visualization, Writing – original draft, and Writing – review & editing.

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ORIGINAL ARTICLE

https://doi.org/10.1590/1806-9282.20220160

Management of appendicitis in coronavirus disease 2019, severe acute respiratory syndrome coronavirus 2, pandemic era: decreasing incidence with increasing complicated cases?

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

SUMMARY

OBJECTIVE: This study aimed to examine the impact of the coronavirus disease 2019 (COVID-19) pandemic on appendicitis and the relevant outcomes in a tertiary hospital, designated as a "pandemic institution" by the Ministry of Health, between pre-COVID-19 and post-COVID-19, i.e., between 2019 and 2020, of the identical period in terms of the annual schedule.

METHODS: The data of cases with acute appendicitis, who were followed up at the Department of General Surgery, a 400-bed, tertiary care, a university-affiliated education and research hospital, providing health care to a population of approximately 450,000 people, during the novel coronavirus SARS-CoV-2, during the identical time intervals of pre-COVID-19 (March 12, 2020 to November 12, 2020) and post-COVID-19 (March 12, 2019 to November 12, 2019), were retrospectively analyzed in a detail.

RESULTS: Of the 212 appendectomy operations in total, 99 (46.7%) were performed in the pre-COVID-19 and 113 (53.3%) were performed in post-COVID-19. Compared to the pre-pandemic period, patients who had undergone appendectomies in post-COVID-19 revealed significantly lower neutrophil counts and significantly greater appendix diameters ($p<0.001$ for both). A significantly lower ($p=0.041$) acute appendicitis with abundant gangrenous appendicitis and phlegmonous appendicitis ($p=0.043$ and $p=0.032$, respectively) was recognized in post-COVID-19 compared with pre-COVID-19 interval.

CONCLUSION: The number of appendectomy operations decreased in the COVID-19 pandemic. Patients operated during the pandemic period had wider appendix diameter and lower neutrophil levels. The pathological diagnosis was less frequent acute appendicitis, more frequent gangrenous appendicitis, and phlegmonous appendicitis in the pandemic period.

KEYWORDS: Pandemic. COVID-19. SARS-CoV-2. Appendectomy. Appendix. Appendicitis.

INTRODUCTION

Acute appendicitis, defined as inflammation of the vermiform appendix, remains the most frequent emergency face of abdominal pain, accounting for 4.5% of all relevant cases[1]. Common factors that complicate definitive diagnoses, such as gynecological disorders in young women, difficulty in patient-physician relationship, delayed administration to health care institutions, and impediments in the referral chain may contribute to delayed or late diagnosis, progression of inflammation, and even perforation. In addition, the effects of extraordinary national or global events, e.g., the novel coronavirus disease 2019 (COVID-19) strain, that burden the local and global health care system on a massive scale can be disastrous for the human being, due to the augmentation in the relevant morbidity and mortality rates[2-4]. Crucial alterations have occurred in the health policies of countries worldwide due to the outbreak of the novel severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2), which has been declared a global pandemic by the World Health Organization (WHO)[5]. Many countries have planned to attenuate the spread of the disease through measures of quarantining at-risk individuals and travel restrictions after the onset of the pandemic. However, some concerns about the patients that may be reluctant to seek essential health care due to these restrictions and also personal preferences have appeared[6]. Attenuation in admissions to emergency service[6,7], delayed or late admission of acute appendicitis cases[8-10], and an augmented frequency of complicated appendicitis cases[6,11] all these led to worsening appendicitis-related outcomes and post-operative consequences of appendectomy[6,11]. This study aimed to evaluate the appendectomies that had been performed in a tertiary hospital, designated as a pandemic institution by the

[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: ilker.sengul.52@gmail.com
Conflicts of interest: the authors declare there is no conflicts of interest. Funding: none.
Received on February 09, 2022. Accepted on February 09, 2022.

Ministry of Health, during the COVID-19 pandemic period, i.e., 2020, in comparison to the same period in the previous year, i.e., 2019. Our objective was to compare the effect of SARS-CoV-2 on appendicitis and its outcomes between pre-COVID-19 and post-COVID-19 of the identical period in terms of the annual schedule.

METHODS

This study was a retrospective, backward-looking, cohort investigation of acute appendicitis at a 400-bed, tertiary care, a university-affiliated education and research hospital, providing health care to a population of approximately 450,000 people, during the novel coronavirus SARS-CoV-2. Variables collected included patient age, gender, imagings, labs, histopathology, and length of stay. We identified all adult and pediatric admissions to our pandemic hospital by enrolling the documents, which were identified via searching each through electronic databases of the hospital that are kept in real time, of the consecutive cases with uncomplicated and complicated acute appendicitis during the COVID-19 pandemic (March 12, 2020 to November 12, 2020), in comparison to those for the same period before the pandemic in Turkey (March 12, 2019 to November 12, 2019). *Ab initio*, March 11 was accepted as the threshold/initiation, since the first confirmed COVID-19 case in Turkey was reported on March 10, 2020. The primary outcome of this study was to identify the numerical value presenting with acute appendicitis pre-COVID-19 and post-COVID-19 associated restrictions and the proportion of cases with complicated acute appendicitis disease. All the statistical analysis was performed using SPSS, version 22 (IBM SPSS Statistics for Windows, version 21.0; Chicago, IL, USA). The descriptive statistics were displayed as mean± standard deviation or median (first quartile to third quartile) percentage unless stated otherwise for categorical variables. Univariable statistics were generated using the Shapiro-Wilk test, Student's t-test, and Mann-Whitney U test. A two-tailed $p<0.05$ was considered statistically significant.

RESULTS

We identified that a total of 212 patients who had been admitted with acute appendicitis to our institution during the study period. Of these, 113 (53.3%) patients were performed in the post-COVID-19 and 99 (46.7%) were performed in pre-COVID-19, in comparison with the same period of the previous year. Demographic and clinical characteristics for the study population are depicted in Table 1. The mean neutrophil count was 10.83 (7.9–13.01)

Table 1. Demographic and clinical characteristics during the period of admission.

	Period		p
	Pre-COVID-19 (n=113)	Post-COVID-19 (n=99)	
Sex, n (%)			
Female	35 (30.97)	37 (37.37)	0.326
Male	78 (69.03)	62 (62.62)	
Age (years)	36.0 (27.0–52.0)	35.0 (25.0–51.0)	0.269
White blood cell count ($\times10^3/\mu l$)	13.72±4.33	12.87±55.54	0.222
Neutrophil count ($\times10^3/\mu l$)	10.83 (7.91–13.01)	8.33 (5.78–10.20)	<0.001
Diameter of the appendix (mm)	9.10 (8.00–10.00)	11.00 (10.00–12.20)	<0.001
Perforation, n (%)	8 (7.08)	11 (11.11)	0.305
Extraluminal air, n (%)	7 (12.28)	9 (16.07)	0.563
Pathological diagnosis, n (%)			
Acute appendicitis	97 (85.84)	74 (74.75)	0.041
Gangrenous appendicitis	4 (3.54)	11 (11.11)	0.043
Phlegmonous appendicitis	3 (2.65)	9 (9.09)	0.032
Suppurative appendicitis	1 (0.88)	3 (3.03)	0.252
Lymphoid hyperplasia	4 (3.54)	2 (2.02)	0.506
Length of stay (days)	2.0 (2.0–2.0)	2.0 (1.0–3.0)	0.335

Data were given as mean±standard deviation or median (first quartile to third quartile) for the continuous variables according to the normality of distribution and as frequency (percentage) for the categorical variables.

×10³/µl in the pre-COVID-19 and 8.33 (5.78–10.20) ×10³/µl in the post-COVID-19 period, with the latter being less significant (p<0.001) (Figure 1). The median appendix diameter (first quartile to third quartile) was 11 (10.0–12.2) mm in the post-COVID-19 and 9.1 (8.0–10.0) mm in pre-COVID-19, with the former being significantly higher (p<0.001). Histopathologically, pre-COVID-19 and post-COVID-19 have been recognized to comprise acute appendicitis (85.8/74.8%), gangrenous appendicitis (3.5/11.1%), and phlegmonous appendicitis (2.7/9.1%) (Figure 2). Last but not least, a comparison of histopathological outcomes of performed appendectomies in 2020 vs. 2019 revealed significantly lower (p=0.041) acute appendicitis with abundant gangrenous appendicitis and phlegmonous appendicitis (p=0.043 and p=0.032, respectively) in the post-COVID-19 period.

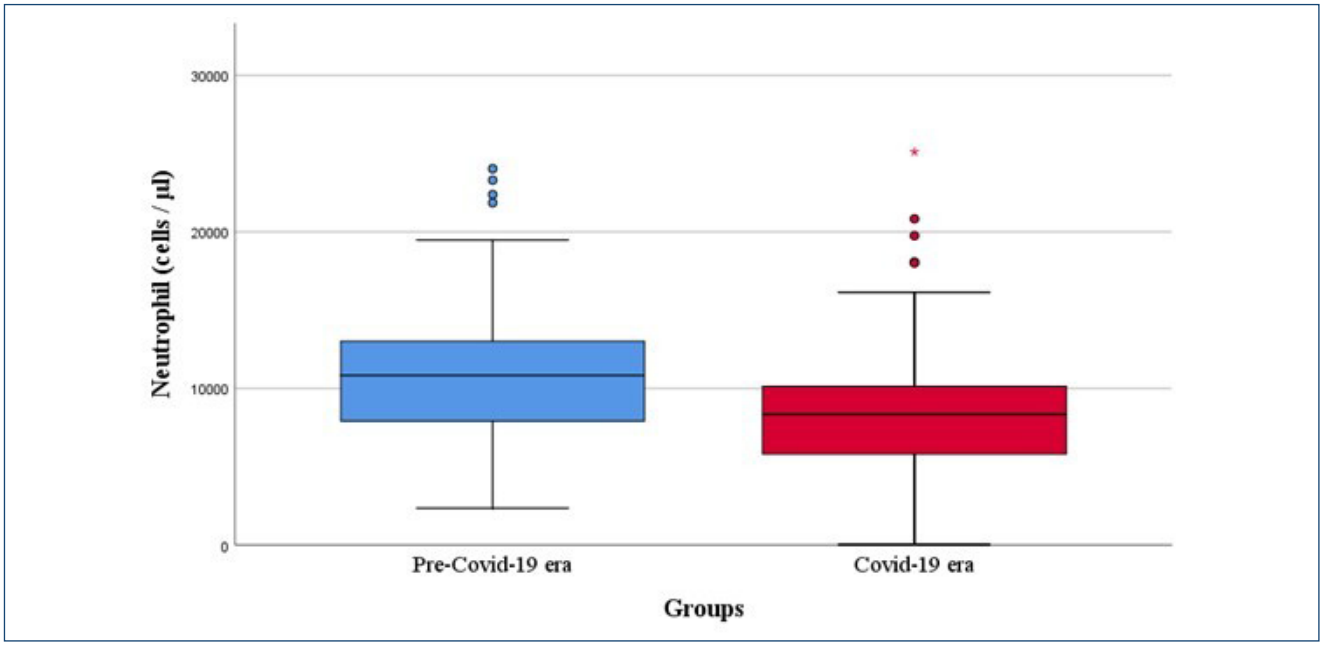

Figure 1. The box-plot of the neutrophil counts for pre-COVID-19 era and post-COVID-19 era.

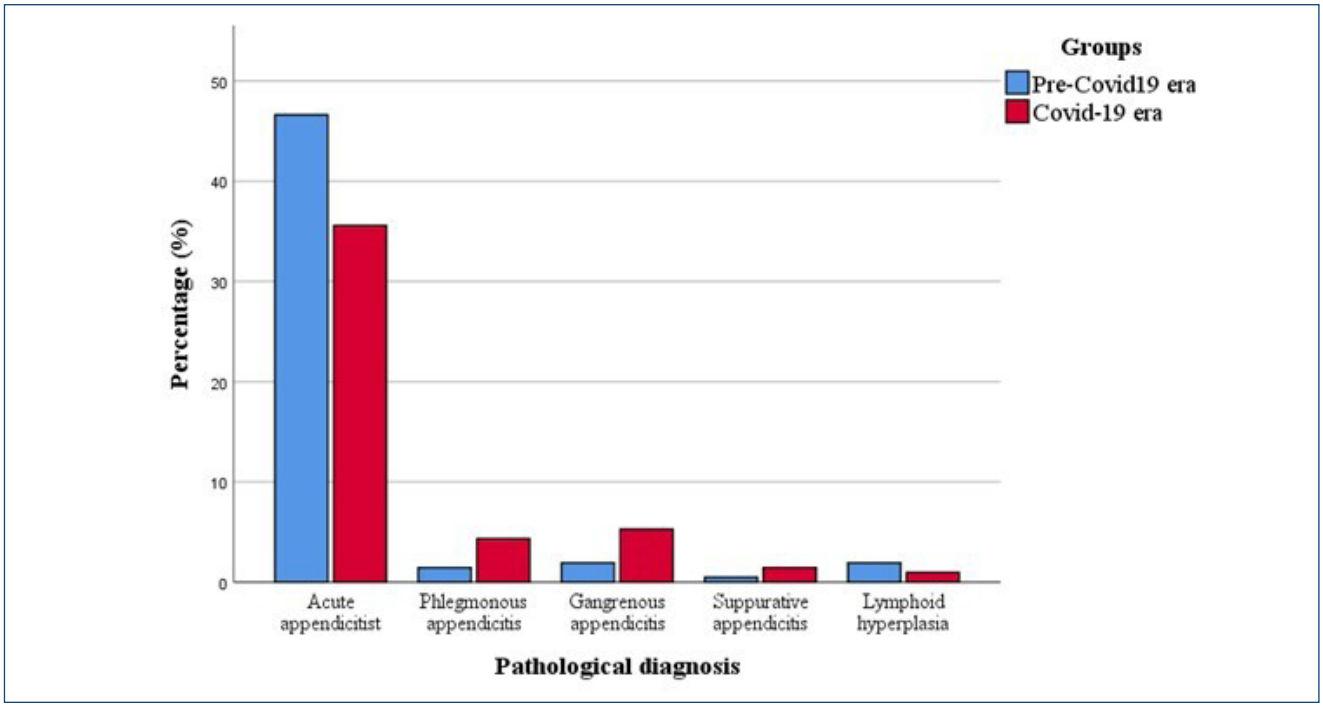

Figure 2. The box-plot of the appendix diameters for pre-COVID-19 era and post-COVID-19 era.

DISCUSSION

Since WHO declared SARS-CoV-2 as a global public health emergency in January 2020, the pandemic has profoundly affected the health care systems and the economies worldwide[5]. Acute surgical emergencies are inevitable, and these cases should be dealt with in a timely and logical manner. The COVID-19 pandemic has had many implications in the management of emergency cases. In this context, postponing all elective surgical and endoscopic cases has been recommended in current guidelines[12,13]. *Hic et ubique terrarum*, many security measures have been implemented to refrain from the spread of the virus. On the other side of the coin, since most individuals were concerned about contracting COVID-19 and some groups were restricted to staying in their homes, they may have been reluctant to seek medical care until their health status would reach a serious level, necessitating hospital admission.

In the present study, the relevant surgical procedures had been performed by using the same operating room that had been sanitized concerning the COVID-19 protocol. *A posteriori,* the lower neutrophil levels with the greater vermiform appendix diameters were revealed for the cases in the post-COVID-19 compared with pre-COVID-19 period. Moreover, less acute appendicitis with more gangrenous and phlegmonous appendicitis was recognized as another outcome in post-COVID-19, in terms of histopathology. An Italian study reported that pediatric emergency admissions being decreased by 88% during the pandemic period[7]. Another study conducted in Colombia asserted a 57% decrease in the frequency of computed tomography (CT) scans that were ordered to confirm acute appendicitis during the SARS-CoV-2 infection. In contrast, the authors reported acute appendicitis was being diagnosed more frequently in CT scans and the mentioned cases had possessed more severe disease[6].

Due to the limitations of this study, the possible cases treated conservatively had not been analyzed. Various studies have reported that surgeons may be more inclined to apply conservative treatment under pandemic conditions and concluded that utilizing nonsurgical therapeutic options in nonessential situations may be beneficial[14,15]. In other words, the main impact of the pandemic may be ascertained as an increase in conservative treatment and a decrease in surgical treatment, which is much more likely than an overall decline in the number of acute appendicitis cases during this period.

Many factors that emerged in the pandemic era have contributed to some delays in hospital admission, directly or indirectly contributing to the development of more severe clinical conditions among the cases. A study conducted in New York City reported that the patients with suspected acute appendicitis had a considerable delay in hospital admissions; therefore, the duration of symptoms before admission was longer and the patients who were admitted for appendectomy procedure had more severe clinical pictures[15]. A study conducted in Israel exhibited that the frequency of complications doubled in acute appendicitis cases that had undergone surgery during the COVID-19 pandemic[10]. In addition, different studies conducted in Spain[16], Australia[17], Brazil[18], and Nepal[19] observed that the hospital admissions of patients with symptoms of acute appendicitis were delayed, the number of complicated appendicitis cases had increased, the severity of appendicitis cases had increased, and length of hospital stay was prolonged during the pandemic period compared to the previous year. Consistent with previous studies, compared to the pre-pandemic period, we recognized the frequency of complicated cases and the diameters of the appendixes had significantly increased in the post-COVID-19. Previous studies have shown that the relevant admission delay is a multifactorial problem, even under normal conditions, that may be associated with many variables, involving health perception, socioeconomic status, and educational status[15]. Of note, the clinical presentation of patients may have also changed according to the characteristics of the region, preventive measures in practice, and the approach of the local population, for each study, to the relevant health care services.

Appendicitis is an inflammatory condition, and an augmentation in the inflammation markers is expected in cases, regardless of the presence or absence of complications[1]. It is well-established that white blood cell count, neutrophil levels, fever, even C-reactive protein (CRP) levels are higher in complicated appendicitis cases than the uncomplicated ones. Considering that complicated cases increased during the pandemic period, we would have expected to observe relatively elevated neutrophil levels in the pandemic period. Nevertheless, contrary to expectations, the mentioned neutrophil levels were expressed to be significantly lower in the relevant literature findings[20-22].

The most important limitation of the present study was possessing retrospective pattern and single-centered design. The cases who would have normally applied to our pandemic hospital may have preferred not to, and some may not have been able to access our facilities during the SARS-CoV-2 pandemic due to various restrictions (e.g., prohibition of going out and traveling). To this end, the cases were examined in two different time intervals, which might have regional differences that could have altered characteristics. We also did not questionnaire the previous COVID-19 infection status directly and the cases were not analyzed according to these characteristics. Since our hospital was designated as a pandemic hospital,

any individuals with a COVID-19 diagnosis would have been referred to us for surgical treatment. Herein, it is unlikely that screening for COVID-19 would have altered the results considerably. Of note, the early pandemic period and later pandemic period may have had significant differences in terms of patient characteristics, since the restrictions were much greater in the early period of disease spread. We could not examine whether the infection imitated appendicitis clinic or led to it. Last but not least, we did not evaluate acute appendicitis cases treated conservatively, without surgery, which may have had marginal effects on the distribution of patient characteristics. Notwithstanding, emergency surgery remains its significance in the era of emergency cases, prevalently[23-25].

CONCLUSIONS

Compared to the previous year, the numerical value of appendectomy attenuated in the COVID-19 era. Patients who had undergone surgery in the post-COVID-19 had greater appendix diameters and lower neutrophil levels. The distribution of histopathological diagnoses had changed in favor of complicated cases, with a lesser frequency of acute appendicitis and a higher frequency of gangrenous and phlegmonous ones, in the post-COVID-19 era. Hereinbefore, in any SARS-CoV-2 pandemic era, early detection of life-threatening situations with maximum adherence to protective precautions may be critical and vital to reducing complicated cases of both frequent and substantial causes of acute abdomen appendicitis.

ACKNOWLEDGMENTS

We thank all the participants involved in this study.

AUTHORS' CONTRIBUTIONS

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

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ORIGINAL ARTICLE

https://doi.org/10.1590/1806-9282.20220172

Physicians' income in Brazil: a study on information sources

Mário Scheffer[1], Felipe Oliveira Pinto Ribeiro[1], Mário Dal Poz[2], Lucas Andrietta[1*]

SUMMARY

OBJECTIVE: Data on physicians' income are relevant for well-informed health policies, both due to their strategic role and the volume of resources that their activities represent to health systems. In Brazil, multiple sources of data measure the income of these professionals, each one with singularities that generate a complex and heterogeneous picture. This study explores the methodological aspects of different data sources, pointing to potentials and limitations to measuring the income of physicians.

METHODS: We use the sources' documentation and data on the average monthly income in 2019, by gender and macro region, from four distinct surveys: Continuous Pnad (National Household Sample Survey), RAIS (Annual Listing of Social Information), Medical Demographics, and IRPF (Personal Income Tax).

RESULTS: The results confirm the heterogeneity of definitions, variables, and methodologies. The data set can evidence phenomena such as the income difference between men and women. Regional inequalities are evident; however, the data interpretation is less assertive.

CONCLUSIONS: Although eventual gaps and discrepancies among sources can limit some strong conclusions, the analysis of different methodologies employed can suggest relevant hypotheses for in-depth studies.

KEYWORDS: Salaries and fringe benefits. Economics, medical. Health workforce. Methods.

INTRODUCTION

Universal and robust health systems require investments in human resources, including the improvement of data, evidence, and knowledge about physician and other healthcare labor markets. In this perspective, the Ninth World Health Assembly adopted the "Global Strategy on Human Resources for Health: Workforce — 2030"[1], which includes, among its objectives, the implementation of National Health Workforce Accounts, with the purpose of facilitating the standardization of health workforce information systems toward interoperability. Improving the capacity of using and exchanging health workforce data in broader health information systems (either regional or national), as well as in international information systems, allows countries to make policy decisions based on (or informed by) evidence on the health workforce[2].

Information on physicians' income is especially relevant, both due to the strategic role of these professionals in certain structures and levels of care of the health system and the volume of resources that their activities and salaries represent in public and private health expenditure[3].

Physicians' income can be influenced by education, supply of professionals, and human resources policies, and it can reflect on the services' quality, productivity, and health system organization[4].

The income can be associated with choices on work location and medical specialties, job permanence, or turnover[5].

Studies on income usually refer to multiple data sources and approach macroeconomic policies, employment, multiple income composition (e.g., labor and capital), salary inequalities, and correlation between income and training, occupation, and other variables[6,7]. However, there are few studies on the income of specific professions that also aggregate both social relevance and expressive investment, as it is in the case of physicians.

The number of physicians has grown greatly in the past decade in Brazil, along with the establishment of medical courses and classes, the stronger presence of women, persistence of regional supply inequalities, and unbalances between public and private healthcare services. Physicians keep earning high salaries compared to other higher education professions; however, there was an increase in the number of simultaneous jobs and weekly workload of professionals[8].

[1]Faculdade de Medicina da Universidade de São Paulo – São Paulo (SP), Brazil.
[2]Instituto de Medicina Social da Universidade do Estado do Rio de Janeiro – Rio de Janeiro (RJ), Brazil.
*Corresponding author: lucasandrietta@gmail.com

Conflicts of interest: the authors declare there is no conflicts of interest. Funding: The study relied on the contribution of the research project: ProvMed Study 2030 – OPAS/MS/FMUSP (agreement letter no. SCON2020-00001).
Received on February 07, 2022. Accepted on February 09, 2022.

This article addresses the possibilities of measuring the economic income of Brazilian physicians. Preliminary exploring available databases, we expect to indicate their potentials and limitations for income studies as a tool to guide policy decisions and health workforce planning.

METHODS

This descriptive and exploratory study aims at presenting the strength and limitations of four different data sources on physicians' income in Brazil, while it drafts income characteristics, trends, and scenarios of these professionals.

The initial criterion for selecting sources was the availability of the number of physicians covered/registered and the monthly income per capita. Next, we selected variables that met two requirements, namely, the presence in different databases and comparability potential. Thus, the data obtained were disaggregated by gender and macro region. When possible, the income obtained exclusively from the professional exercise of Medicine was prioritized. We considered the available time series, the update frequency, and chose 2019 as the reference year to approach and illustrate the analysis on databases' methodological aspects.

The article used the following sources, whose characteristics are also compared in "Results" section:

- National Household Sample Survey: Performed by the Brazilian Institute of Geography and Statistics (IBGE), it aims at generating indicators on workforce fluctuations in the country. With a quarterly frequency and national coverage of 3,500 cities, Pnad's sampling plan uses and stratifies primary sampling units (UPA), with each one of them having at least 60 permanent private households (DPP)[9]. We used Pnad microdata for the fourth quarter from 2012 to 2020, focusing on the variable V4019 "Usual income at all jobs." The sample was filtered by Occupation Code, including the "general physicians" and "specialist physicians." The 95% confidence intervals were calculated considering the variation of the number of interviewed physicians at each quarter.
- Annual Listing of Social Information: This is an administrative registry of the Ministry of Work and Social Security (MTP) for the characterization of the formal labor market, at national level and up to a municipal level breakdown. It is performed annually, mandatory to all employers. The RAIS database contains the original statements on current amount of jobs and the fluxes of employed labor (both admissions and terminations), by gender, age group, education degree, average income, and income ranges in minimum wages[10]. In this study, all active job contracts from 2010 to 2019 in the following groups of the Brazilian Classification of Occupations (*CBO2002*): clinical physicians, surgical specialties physicians, and diagnosis and therapeutic medicine physicians.
- Personal Income Tax Returns: This is composed of the active returns presented by taxpayers, regardless of being or not selected to go through tax audits. With the purpose of reducing the effects of inconsistent amounts, data are filtered by the Federal Revenue, in order to remove distorted figures regarding incomes, deductions, payments, assets, and others. Once fiscal confidentiality rules are observed, the "Greater Figures of Personal Income Tax Returns (DIRPF)" are made available, with semi-disaggregated data and general indicators according to state, gender, income ranges, and other variables[11]. This study obtained, by means of the Law on Access to Information (LAI), filtered data from 2012 to 2017 of statements that answered *Physician* in the field *Main Occupation* of the annual tax return survey.
- Brazilian Medical Demography: This includes survey on physicians' sociodemographic, education, labor, and practice data, conducted by the Scholl of Medicine of the University of São Paulo (FMUSP), supported by the Federal Council of Medicine (CFM), Brazilian Medical Association (AMB), and National Commission of Medical Residency[8]. This study produced income data from a telephone survey, using a probability sample of 2,400 doctors, carried out in 2019 by DMB. Income was considered within the period of 1 month, resulting from the practice of Medicine, considering all works, job contracts, and activities of physicians. The income is self-reported by interviewees, who were previously presented to six income ranges.

All data extracted from various databases were deflated by the Broad Consumer Price Index (IPCA) to constant values of December 2020.

RESULTS

The main available sources for measuring the income of physicians in Brazil have distinct origins, objectives, and methodologies (Table 1). Regarding the generating institution,

all databases involve public agencies, such as IBGE, MTP and Federal Revenue, Federal Council of Medicine, and the University of São Paulo.

As to the objectives, the databases aim to monitor the evolution of workforce (Pnad), characterization of the formal labor market (RAIS), taxation of individuals (DIRPF), and trends and scenarios related to the population of physicians in Brazil (DMB).

Regarding methods, Pnad and DMB use probabilistic sampling, with a residential survey and population survey of physicians, respectively; and DIRPF and RAIS use the group of physicians who are present in notarial records or mandatory administrative statements.

Table 1. Methodological aspects of data sources for physicians' income studies.

Databases	Continuous PNAD	RAIS/caged system	Medical demographics	Personal Income Tax Returns (DIRPF)
Description	Continuous survey on general characteristics of the population, education, job market, income, and housing in Brazil	Administrative database that gathers information on employee hiring, termination, and transfers made by companies that operate according to the regime of the Brazilian Consolidation of Labor Laws (CLT).	Study on sociodemographic, training, and work characteristics of physicians in Brazil	Mandatory statement sent to the Federal Revenue by every taxpayer who has obtained taxable income
Nature of the survey	Official research by a sample of households	Mandatory administrative registry	Survey, sectional study	Taxation data aggregated and complemented by the Law on Access to Information (LAI)
Analysis unit	Household and Individual	Formal employment tie and establishment	Individual	Individual
Institution	IBGE	Ministry of Work and Social Security	CFM/FMUSP	Federal Revenue
Frequency	Quarterly	Monthly	Biannually	Annually
Collection method / information source	In-person survey answered by a person living in the household	Electronic form filled out by companies	Telephone survey voluntarily answered by physicians and other official databases	Compilation of data from annual Federal Revenue tax returns
Territorial scope	National	National	National	National
Maximum territorial disaggregation	State and metropolitan regions	City	Macro region	State
Relevant variables	Location (state, capital, metropolitan region, urban/rural area), gender, age group, ethnicity, education, occupation, monthly income, worked hours/week, number of jobs, possession or not of a specialist title	Location, monthly, employment period, number of contracted working hours per week, age of professional, personal information, hires, and terminations	Location (state, age, countryside/capital, region, rural/urban area), gender, time since graduation, possession or not of a specialist title, specialty, number of vacancies in graduation, number of vacancies in medical residence, physicians doing medical residence, field of activity, work in the public/private sector, work characteristics, number of employment ties, monthly salary, location of residence, location of work	State, state capital, nature of occupation (i.e., self-employed professional), gender, age group, taxable income, assets and rights, donations, inheritance, salary (monthly salary), total income, taxable income, main occupation
Target population	People living in private and permanent households in the area of research scope	Employees working under the formal employment tie regime (CLT)	Physicians with an active professional registry in a Regional Board of Medicine (CRM)	Individuals with taxable income

Source: Own elaboration based on official documentation[7-10].

There are currently 500,000 physicians in Brazil[8]. The larger number of physicians (392,492) is covered by DIRPF. The size of samples varies from 771 persons in Pnad to 2,400 in DMB. In the case of RAIS, which has the formal job contract as unit of analysis, 262,618 records were considered (Table 2).

The monthly income of physicians ranged from R$16,438.00 (PNAD) to R$32,677.00 (DIRPF). In the case of RAIS, the average salary from formal employment ties was R$10,219.00. In the DMB, whose method does not allow establishing a general average, the self-reported income median is within the range from R$17,120.00 to R$22,470.00.

All databases indicate lower income for women in comparison to men, though there are discrepancies due to the nature of the source. RAIS indicates that the average salary paid to women is almost equivalent to men's (93.7%). In Pnad, women's income corresponds to 73.4% of men's. The greatest difference is seen in DIRPF, where the reported women's income reaches 64.3% of men's income. In DMB, women are concentrated in lower income ranges, having their median value within the second range (R$11,770.01–R$17,120.00).

There are differences in physicians' incomes according to macro regions, but variations, in the comparison between databases, are not always coincident.

In Pnad, Northeast and North regions present an average income that is notably higher to the national average; South and Midwest present a lower average; and Southeast is close to the national average.

In DMB, we could highlight the higher frequency of physicians in the Northeast and Midwest regions in the superior range (>R$34,200 per month) when compared to the remaining regions. We emphasize that in the DMB, the participation of each income range varies among regions, and there is a significant overlap of confidence intervals for the regional comparison (Table 3).

In the DIRPF, the income is higher in the South and Midwest regions, when compared to the North and Northeast. Likewise, in RAIS, the South and Midwest overcome other regions.

DISCUSSION

The four sources considered provide relevant information for the study of physicians' income in Brazil. The differences between databases can be explained by the objectives, parameters, and criteria previously established by the institutions generating the information, as well as by the diversity of collection methods, concepts, variables, and units of analysis.

Table 2. Selected physicians' income indicators by gender and macro region, 2019.

Original variables and research scope	All physicians	Gender			Macro region				
		Women (W)	Men (M)	Ratio (W/M)	North	Northeast	Southeast	South	Midwest
Pnad									
Usual monthly income from all jobs (R$)	16,438	14,463	18,244	***79.3%***	17,978	17,325	16,645	14,806	14,933
Error margins (95% confidence interval)	±1,216	±1,653	±1,551		±4,887	±3,231	±1,739	±2,026	±2,754
Sample size (N)	771	418	353		61	143	324	171	72
RAIS									
Average monthly income from employment ties (R$)	10,219	9,871	10,533	***93.7%***	10,536	9,345	9,838	12,358	11,095
Participation in the total (N=262,618 employment ties)	100%	48%	52%		5%	19%	53%	12%	10%
DIRPF*									
Average monthly income from all sources (R$)	32,677	25,158	39,156	***64.3%***	29,873	31,047	32,550	34,495	35,648
Participation in the total (N=392,432 statements)	100%	46%	54%		4.6%	18.9%	52.6%	15.9%	8.0%

Source: Own elaboration with data from IBGE, RAIS/CAGED, and Federal Revenue. *IRPF data specific to the medical category were obtained by means of the Law on Access to Information. All values adjusted to R$ of December 2020.

Table 3. Percentage distribution of physicians by income range, gender, and macro region, 2019.

Income range	Percentage distribution (%)							
	All physicians	Gender		Macro region				
		Women	Men	North	Northeast	Southeast	South	Midwest
Up to R$11,770.00	21.7 (±1.8)	30.6 (±3.0)	14.8 (±2.1)	13.4 (±7.4)	19.7 (±4.1)	23.8 (±2.6)	21.8 (±4.5)	17.5 (±5.5)
R$11,770.01–R$17,120.00	23.6 (±1.9)	28.7 (±3.0)	19.5 (±2.3)	18.3 (±8.4)	21.1 (±4.2)	25.3 (±2.6)	22.4 (±4.5)	23.0 (±6.1)
R$17,120.01–R$22,470.00	19.3 (±1.7)	21.6 (±2.7)	17.5 (±2.2)	28.0 (±9.7)	20.3 (±4.1)	18.4 (±2.4)	20.0 (±4.3)	17.5 (±5.5)
R$22,470.01–R$28,890.00	14.4 (±1.5)	10.8 (±2.0)	17.4 (±2.2)	17.1 (±8.1)	14.0 (±3.6)	14.6 (±2.1)	14.2 (±3.8)	13.7 (±5.0)
R$28,890.01–R$34,240.00	7.4 (±1.1)	4.1 (±1.3)	9.9 (±1.8)	12.2 (±7.1)	9.0 (±2.9)	6.0 (±1.4)	7.9 (±2.9)	8.7 (±4.1)
Above R$34,240.01	13.6 (±1.5)	4.3 (±1.3)	20.9 (±2.4)	11.0 (±6.8)	15.9 (±3.8)	11.9 (±2.0)	13.6 (±3.7)	19.7 (±5.8)
Total	100.0	100.0	100.0	100.0	100.0	100.0	100.0	100.0

Source: Own elaboration with data from Medical Demographics. Margins calculated to the 95% confidence interval. Total sample size: 2,003 people interviewed. Income ranges deflated to R$ in December 2020.

The income reported by physicians in the surveys (Pnad and DMB) has a relative convergence and tends to better express earnings resulting exclusively from the professional exercise of medicine, though the self-reported information may cause some measurement biases. In DMB, for instance, 16.1% of physicians refused to answer on their income[8].

Statements for income tax purposes tend to overestimate the income related to medical activities, while salary recorded in formal job contracts underestimate it.

Unlike DMB, the individual income from all works registered in Pnad (R$16,438.00) allows deeper breakdowns. However, due to the reduced samples, even more so in Pnad than in DMB, results in large confidence intervals, inadequate for certain interpretations, and cross-referencing.

The result from RAIS (R$10,219.00) has the limitation of measuring only formal jobs (CLT) which, definitely are not the only and, possibly, not even the main component of physicians' income currently in Brazil.

In DIRPF, the amount of R$32,677.00 refers to the physicians' incomes resulting from other sources besides their medical activities: interest rates, profits, rent fees, and companies. It is not possible to access data on the income composition from various sources, although they exist. Information in lower breakdown levels must be obtained through the Law on Access to Information. Brazil's alignment to international initiatives of tax microdata disclosure could contribute to the quality of surveys and public policy[12].

Income inequality according to gender was confirmed in all databases. The intermediate results obtained in Pnad and DMB seem to better represent the category set. RAIS indicates that formal contracts have a narrower income gap between men and women. DIRPF shows that patrimonial income tends to significantly emphasize the disparity in favor of men. This result reiterates the higher probability of men obtaining a higher salary than women in Medicine[13], confirming recent studies made in Brazil[14], Iran[15], Peru[16], New Zealand[17], and Italy[18].

Regarding the physicians' income according to macro regions, there are more significant divergences among databases. Notably, the existence of contrast between RAIS and DIRPF or approximations between Pnad and DMB. The comparisons should be done cautiously for this variable and can become more difficult both given the nature of databases and multiple factorial phenomena: distinct socioeconomic characteristics, regional inequalities in physician supply with impact on salary policies, health services profiles and demanded specialties, work productivity, the magnitude of public and private subsystems, and other aspects.

CONCLUSIONS

The available sources provide relevant and incipiently explored information for the study of physicians' income in Brazil.

The distinct purposes, methodologies, and operational aspects of surveys suggest that single-sourced analyses may have distorted results and conclusions. Therefore, future studies on this subject must use different sources to guide the research within the discrepancies found.

It is desirable to improve existing databases toward a higher level of standardization of the main indicators on physicians and other health professionals, which requires the creation of a harmonized and integrated income information system, allowing interoperability, data exchange, and comparison among sources.

The Brazilian medical workforce is currently going through pronounced changes, such as an increasing number of professionals, shortage of specialized training, dissemination of precarious and outsourced jobs, feminization, and greater inclusion of professionals from lower income families or self-declared black and brown[8]. In contrast, recent economic crises emphasize the

chronic underfunding of the Brazilian Unified Health System (SUS) and seasonal retraction of private health insurance coverage[19], which impacts the medical labor market.

In face of these endogenous and exogenous transformations of the profession, and due to representing a significant portion of resources necessary to the operation of universal and effective health systems, physicians' income remains an unavoidable study object in the human resources and health policies research fields.

ETHICS

The study was approved by the Research Ethics Committees of the Faculty of Medicine of the University of São Paulo, under the title Medical Demographics in Brazil: the profile, distribution, work, and specialization of physicians (CAAE: 35140914.7. 0000.0065).

ACKNOWLEDGMENTS

The authors thank Aline Guilloux, Alex Cassenote, and Alexandre Guerra for contributing on labor market data curation from DMB.

AUTHORS' CONTRIBUTIONS

MCS: Conceptualization, Investigation, Writing – original draft. **FOR**: Data curation, Writing – original draft. **MDP**: Validation, Writing – review & editing. **LSA**: Supervision, Conceptualization, Data curation, Writing – review & editing.

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REVIEW ARTICLE

https://doi.org/10.1590/1806-9282.20211136

Application and prospect of enhanced recovery after surgery in patients with arthroplasty in China

Yun Fei[1], Xueyun Li[1]*

INTRODUCTION

Enhanced recovery after surgery (ERAS) was first proposed by Danish scholar Henrik kehlet in 1997[1]. In the actual promotion process, researchers have found and verified that ERAS can not only accelerate the recovery of patients and reduce the incidence of complications but also reduce medical costs, shorten the length of hospital stay, and increase patient satisfaction[2-4].

In 2007, ERAS was introduced into China by Professor Li Jieshou[5], and its application scope gradually expanded from abdominal surgery to orthopedics, urology, and other fields. In 2016, a Chinese expert consensus about hip and knee arthroplasty[6-8] pointed out that a key of ERAS in hip and knee arthroplasty is to improve the operation technology and optimize the perioperative management. Compared with the traditional hip and knee arthroplasty perioperative management strategy, ERAS has made great progress not only in concept but also in the actual development process. Specific projects have also been clearly subdivided.

METHODS

Search strategy

A literature search using PubMed, MEDLINE, China National Knowledge Infrastructure (CNKI), and the Wanfang databases on November 20, 2020, was performed using the Medical Subject Headings terms and the following search words in combination with Boolean "AND" and "OR" phrases: "enhanced recovery after surgery," "enhanced recovery pathways," "ERAS," "fast-track surgery," "arthroplasty," and "joint replacement." A total of 48 articles were retrieved, including 19 randomized controlled trials and a total of 19 retrospective studies. A total of 1741 cases outcomes were summarized.

Inclusion criteria

Inclusion criteria were as follows: (1) population — undergoing hip joint replacement, knee joint replacement, and spinal surgery for general osteoarthritis; (2) intervention — ERAS vs. conventional care; (3) outcomes — primary outcomes (e.g., mortality rate, transfusion rate, range of motion [ROM]) and secondary outcomes (e.g., 30-day readmission rate, complication rate, length of stay [LOS]).

Exclusion criteria

Case reports, review articles, or other works without original data and studies investigating only multimodal analgesia or comparing the efficacy of various analgesic medications were excluded.

Data extraction

We reviewed abstracts and titles, read the full text carefully according to prespecified inclusion criteria, and extracted relevant clinical, study, and other information, including authors, year of publication, sample size, age and gender of subjects, ERAS-specific recovery measures, surgical site, postoperative complications, LOS, and readmission rates after 30 days for patients in the group and non-ERAS groups.

Definition of outcome events

The primary outcome events were mortality, transfusion rate, and ROM. Secondary events were postoperative LOS, 30-day readmission rates, and overall complication rates and other reported outcomes.

[1]The Affiliated Hospital of Nanjing University Medical School, Nanjing Drum Tower Hospital, Department of Anesthesiology – Nanjing, China.
*Corresponding author: xyll66@21cn.com
Conflicts of interest: the authors declare there is no conflicts of interest. Funding: Project name: A controlled study of ERAS concept in promoting rapid recovery in patients with hip replacement surgery.
Received on February 15, 2022. Accepted on February 16, 2022.

RESULTS

Review of enhanced recovery after surgery program

Preoperative education and counseling

Most patients with arthroplasty have anxiety and fear before an operation. Positive communication with patients, preoperative psychological education, and intervention is very important.

One study found that explicit pre-anesthesia education can significantly relieve anxiety and emotional stress before hip or knee replacement[9]. Preoperative education helps improve patients' confidence, satisfaction, early rehabilitation, and discharge[10]. Louw and other scholars reported that preoperative patients with more knowledge of pain science and preoperative education courses may be more effective in controlling postoperative pain[11].

Preoperative evaluation

Anemia is a common complication in hip and knee replacement patients[12], which can lead to adverse clinical outcomes, such as stroke, periprosthetic inflammation, and postoperative mortality. In China, prior to joint replacement, the patients are suggested to have screening for anemia.

Diabetes is very common in patients with hip and knee arthroplasty and may have adverse effects on the outcome of hip and knee replacement[13]. Literature on diabetic patients with arthroplasty and its relationship with prognosis shows that diabetes increases the risk of postoperative death[14, 15]. Therefore, based on the ERAS concept, patients with diabetes should be screened and identified before joint replacement, and the endocrine pathway should be optimized to improve the clinical outcomes.

Multimodal analgesia

Pain is the main complication after hip and knee replacement. Beswick and other scholars found that 7–23% of total hip arthroplasty (THA) patients and 10–34% of total knee arthroplasty patients have persistent pain after surgery[16]. In China, the multimodal, opioid-sparing techniques are advocated as the basis for postoperative pain control. Multimodal analgesia is an effective way to manage arthroplasty pain. It has a good analgesic effect by combining different drugs with different mechanisms[17]. In addition, ice can also reduce inflammation and swelling, thereby reducing the incidence of pain[18].

Selection of intraoperative anesthesia techniques

The choice of anesthesia mode for patients with arthroplasty is of great significance to the safety and rapid recovery of patients[19]. There is a physiological view that regional anesthesia is the optimal ERAS technique for hip and knee arthroplasty. Axonal anesthesia is adequate for surgery. It provides sympathetic block, inhibits the release of stress hormones, and attenuates the release of insulin after nerve conduction[20, 21]. A lot of evidence demonstrates a lower incidence of postoperative complications when hip or knee arthroplasty is performed under normal/regional compared general with anesthesia. Pulmonary embolus, pulmonary compromise, renal injury, infection, need for transfusion, and LOS are all significantly lower after neuraxial anesthesia[22, 23]. A recent meta-analysis of 29 studies (including 10,488 patients) found that axial anesthesia reduced hospital stay by nearly half a day compared with the general anesthesia group[24]. A multi-institution retrospective study found that the use of general anesthesia increased the risk of moderate-to-severe postoperative pain by 8.5 times and the risk of persistent pain after hip surgery by 2.5 times[25, 26].

In addition, the combined sevoflurane inhalation anesthesia and lumbosacral plexus block under the guidance of Gas Man software can provide relatively accurate anesthesia management for elderly patients undergoing hip arthroplasty and promote rapid postoperative recovery. For elderly patients with poor tolerance, intraspinal anesthesia is also a better choice. Zheng Quan et al. found that the cognitive impairment of patients after spinal anesthesia was reduced, and the visual analog scale (VAS) score was decreased 48 h after operation[27]. Thus, spinal anesthesia is a better choice for joint replacement, which can promote faster recovery of patients.

Prevention and treatment of postoperative nausea and vomiting

Postoperative nausea and vomiting (PONV) may be more distressing than pain[28]. The risk factors of PONV included female, non-smoking status, exercise history, or previous history of PONV[29]. The treatment of PONV may be avoiding general anesthesia and minimizing opioids.

Early mobilization

Early mobilization is a key component of ERAS. Adverse physiological effects of long-term bed rest include increased insulin resistance, myopathy, decreased pulmonary function, impaired tissue oxygenation, and thromboembolism[30]. Safe and effective analgesia is a prerequisite for encouraging postoperative activities. A recent meta-analysis showed that ambulation within 24 h after surgery reduced hospital stay (by 1.8 days)[31]. The early activity of knee replacement was also related to the

improvement of functional recovery[32]. Early joint activity plays a positive role in improving prognosis. Despite these benefits, it is unclear whether early mobilization is associated with other complications.

Current obstacles of enhanced recovery after surgery in China

There are many obstacles in the process of ERAS promotion, which mainly focus on policy support, team building, evaluation process, scheme formulation, insufficient effect evaluation, and so on[33]. A meta-analysis published in 2017 that included seven randomized controlled or clinically controlled studies involving a total of 8346 patients undergoing total hip replacement or total knee replacement showed that arthroplasty ERAS significantly reduced the length of hospital stay by 1.44 days compared to controls. However, the ERAS-related departments did no close cooperation in China, each link is not to achieve optimization, and early experience accumulation stage, basic-level hospital looking forward and developed, and the system of specific measures in accordance with the arthroplasty characteristics is not clear; thus, further practice and exploration efforts were needed. In addition, among the patients who have carried out ERAS (including all and part of ERAS), some patients expressed dissatisfaction with the current situation. The dissatisfaction mainly focused on PONV, application of tourniquet, and optimization of analgesia scheme.

DISCUSSION

In foreign countries, one of the reasons for the limited clinical development of ERAS is the difficulty of some of the contents of expert consensus. Some experts believe that the lack of team human resources will also hinder the development of ERAS. At present, in our country, the design and implementation of the specific composition, operation management, collaboration mode, and diagnosis and treatment process of ERAS are still in the exploratory stage. Enhanced recovery requires multidisciplinary optimization and cooperation, which is the optimal management of the perioperative "process."

It is required that the medical staff of various disciplines participating in ERAS pay attention to the perioperative management of patients, do a good job in the optimization measures of this discipline, and strengthen the cooperation and communication with relevant departments of ERAS[34]. In the application of the concept of fast-track surgery in the perioperative management of hip and knee arthroplasty, we should strictly implement the fast-track measures, reduce the surgical stress and complications, shorten the length of hospital stay and reduce the cost of hospitalization, and pay more attention to the rehabilitation effect and follow-up work after discharge. Based on the above two points, we should strengthen the research on the process and clinical pathway of ERAS and innovate and construct the organization and management[35]. Based on the optimization strategy of ERAS, at the level of diagnosis and treatment team, we should establish a multidisciplinary ERAS diagnosis and treatment team, including surgery, anesthesiology, operating room, nutrition, and rehabilitation, and clarify the responsibilities and rights between disciplines; the objectives are to establish a follow-up system for discharged patients with ERAS, understand the rehabilitation of patients after discharge, provide necessary feedback for the mechanism research of the ERAS, and promote the development of ERAS concept in orthopedic hip and knee arthroplasty. In short, with the strengthening of the application of ERAS in orthopedic theory and practice, the concept of rapid rehabilitation will benefit patients better. This will make ERAS better and more reasonable localization promotion, more standardized and more effective implementation, promote the promotion and application of ERAS in China, and provide high-level and high-quality medical services for patients.

CONCLUSION

We need to proceed from our own reality, hold the attitude of seeking truth from facts, carry out more and more reliable clinical exploration, and obtain more and more feasible solutions in the process of promotion. All this will make ERAS better and more reasonable localized promotion, more standardized and more effective implementation, and provide high-level, high-quality medical services for patients.

AVAILABILITY OF DATA AND MATERIALS

All data generated or analyzed during this study are included in this article.

The data that support the findings of this study are available from the corresponding author upon reasonable request.

ETHICS APPROVAL

This study was conducted in accordance with the Declaration of Helsinki and was approved by the Ethics Committee of our hospital.

AUTHORS' CONTRIBUTIONS

YF: Conceptualization, Data curation, Formal Analysis, Funding acquisition, Validation, Visualization, Writing – original draft, Writing – review & editing. **XL:** Investigation, Methodology, Project administration, Resources, Software, Supervision, Writing – original draft, Writing – review & editing. All authors wrote and gave final approval of the manuscript.

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REVIEW ARTICLE

https://doi.org/10.1590/1806-9282.20220009

Scientific evidence on malnutrition in children in Brazilian Quilombola: an integrative review

Luan Pereira Lima[1], André Pontes-Silva[2*], Lucas da Silva Sousa[3], Fernando Rodrigues Peixoto Quaresma[1], Erika da Silva Maciel[1]

INTRODUCTION

Studies show that childhood obesity is increasingly evident[1-3], as sedentary lifestyle and malnutrition during childhood are becoming common[4]. Other studies[5,6] point to physical activity as a protective factor against various chronic diseases (e.g., obesity) and human development facilitator for children.

Malnutrition is a pathological condition caused by deficient or inadequate intake of calories and/or proteins[7]. This means that the overweight or obese child may also be malnourished, as this condition is related to the type of food consumed (e.g., the ultra-processed)[8]. Calories from ultra-processed foods are often "empty." An individual who consumes a high amount of calories but lack macronutrients can contribute to malnutrition, a condition related to the absence of nutrients. Childhood malnutrition causes damage to the central nervous system (i.e., cerebellar cortex and hippocampus)[9].

There is a relationship between family influence and children's good/bad habits[10-12]. In the nutritional context, some family members allow the children to choose the type of food (usually ultra-processed), time, and the amount ingested. In terms of physical activity, sedentary family members raise sedentary children. Some still believe that exercise is contraindicated for children. There are some attitudes that build bad habits in life[10-12]. Absence of instructions, on the part of family members and teachers, favors the development of bad habits and chronic diseases[5,13].

Another problem in this context is the lack of exercise. Increasingly, the opportunities, spaces, and time devoted to active play are being neglected in favor of school education (i.e., one in which the child spends the day at school sitting)[4,14]. In addition, contemporary violence and the reduction of public spaces for the practice of physical and leisure activities further restrict children, such as keeping them locked at home, leaving them with cell phones, and videogames (in the case of urban areas). In contrast, there is children residing in rural areas (e.g., quilombolas), which are less investigated[15,16].

A quilombola child lives far from the urban area (in places difficult to access)[17]. For this reason, studies on childhood malnutrition and obesity in quilombola children are lacking, and this prevents us from presenting the current scenario. In addition, to the best of our knowledge, there are still no descriptions that quilombola children fulfill the amount of exercise recommended by the World Health Organization, such as the need for moderate physical activity (e.g., walking, family outings, and recreational activities with movement) or vigorous (e.g., running and sports' games) for at least 1 h daily, in order to add a total of 300 min of physical activity (exercise) at the end of the week[18].

In this context, family members and teachers are the drivers[19] or inhibitors of the child development[20]. According to the United Nations Children's Fund (UNICEF) and the Statute of Children's and Adolescents (ECA), every child has the right to movement and right to play, and whether, in urban or rural areas, this should be encouraged[4]. Thus, the question arises: Are family members and teachers encouraging good habits to promote quality of life for quilombola children?

This study aimed to determine whether studies with quilombola children evaluated the influence of family members and teachers on childhood malnutrition and obesity.

METHODS

For the elaboration of an integrative review, it is necessary to adopt phases that present methodological rigor in search of evidence on a given subject. These phases comprise some steps: select the question for review (i.e., guiding question); select the

[1]Universidade Federal do Tocantins, Programa de Pós-Graduação em Ensino em Ciências e Saúde (Mestrado) – Palmas (TO), Brazil.
[2]Universidade Federal de São Carlos, Programa de Pós-Graduação em Fisioterapia (Doutorado) – São Carlos (SP), Brazil.
[3]Universidade Federal do Tocantins, Discente da graduação em Medicina – Palmas (TO), Brazil.
*Corresponding author: contato.andrepsilva@gmail.com
Conflicts of interest: the authors declare there is no conflicts of interest. Funding: none.
Received on February 19, 2022. Accepted on February 22, 2022.

surveys that will constitute the study sample; represent the characteristics of the studies reviewed; analyze the findings according to the inclusion and exclusion criteria established in the project; interpret the results; and present and disseminate the results[21].

Based on the guiding question (i.e., "Are family members and teachers encouraging good habits to promote quality of life for quilombola children?"), the process of reading, collecting, and extracting data in the search engine and databases began. The keywords raised according to the proposed theme and after having been refined through the vocabulary of the Decs (Descritores em Ciências da Sáude) were "Atividade física," "Desnutrição," "Obesidade," "Quilombolas," and "Crianças." The keywords for MeSH (Medical Subject Headings) were "Physical activity," "Malnutrition," "Obesity," "Quilombola," and "Children." Descriptor "quilombola" does not change even though its term is used in English.

After defining the descriptors, they were grouped into the following search terms: A1: "Atividade Física" AND "Quilombolas" AND Crianças; B1: "Physical Activity" AND "Quilombolas" AND Children; C1: Desnutrição AND Obesidade AND "Quilombolas" AND Crianças; D1: Malnutrition AND Obesity AND "Quilombolas" AND Children.

We performed the search in Google Scholar, Fiocruz's institutional arch-repository, PubMed, Periódicos Capes, and BVS databases. This search was performed between August and November 2020. Later, the data extracted from the selected articles were arranged in table format in the Word 2013 Program of the Office Suite.

Inclusion criteria were as follows: articles, monographs, dissertations or theses, works written in Portuguese or English, having published between 2010 and 2020, and studies carried out in quilombola communities or vulnerable populations located near or outside the urban area. Duplicate articles were excluded from the study.

Data extraction was performed as follows: first, papers not related to the research topic were excluded by reviewing simply the title; second, the researchers read the abstracts of papers to confirm whether these papers were related to the proposal in question; and third, to confirm whether the works were in fact related to the theme, all the works selected from the abstracts were read in full.

Finally, articles in the form of handouts, letters, and editorials which do not meet the necessary criteria for scientific research were excluded from this research, as the focus of this study was to seek scientific evidence on the subject. Articles that were not available in full were also excluded.

Data extracted from each selected article were arranged in table format in the Word Program (Office 2013 package) and divided into items as follows: authors, title, objective, methods, results, influence of subjects involved with children, environmental influence, main associated factors, conclusion, and notes (i.e., researchers' perception of each article, such as whether the objectives of the review were addressed, or whether it contained all the other items in the table).

RESULTS

We observed a small number of studies on quilombola children. Most recruited articles (11/12) were retrieved via Google Scholar, in which only one was selected from the BVS database (supplementary document).

Some of the selected articles did not include all the items described in the table, e.g., six articles (corresponding to 50%) did not assess the influence of family members and teachers on childhood malnutrition and obesity.

Environmental influences refer to issues of infrastructure and basic sanitation; regarding the influence of the subjects involved with the children, we observed that lack of knowledge is one of the factors mentioned in the studies described (Tables 1, 2 and 3).

Table 1. Information extracted from selected articles (part a).

Title	Influence of individuals involved with children	Environmental influence	Associated factors
Conhecimento de crianças quilombolas sobre hábitos cardiológicos saudáveis[17].	NA	Quilombola children do not have access to knowledge related to the prevention of cardiovascular diseases; this is perceived by the number of children who do not recognize simple habits for preventing these diseases, such as having adequate nutrition and practicing physical activities.	Instruction/knowledge about healthy eating habits and physical activity; low education and family income, precarious conditions of food education, and preventive health.
Estado nutricional e crescimento de crianças quilombolas de diferentes comunidades do estado do Pará[31].	As for community agents, there is only one (in most of the communities studied) that serves this population.	Restricted access to health services; lack of basic sanitation; there is no structure for health care (e.g., health post or health unit). In contrast, many of them receive family allowances and monthly basic food baskets.	They do not have basic sanitation; lack of structure and trained health professionals; untreated water; socioeconomic conditions.

Continue...

Table 1. Continuation.

Title	Influence of individuals involved with children	Environmental influence	Associated factors
Perfil epidemiológico da obesidade infanto-juvenil em uma comunidade quilombola: relação entre televisão, atividade física e obesidade[32].	Both parents and teachers are not encouraging the practice of physical activities by children. It is recommended that workshops be offered to these subjects (i.e., parents, teachers, and schoolchildren) to encourage them to use fruits, natural juices, and vegetables produced in the community, thus reducing the consumption of industrialized foods. In addition, motivating children to engage in some sporting activity that gives them pleasure.	The community is located close to the state capital, favoring access to manufactured foods, especially soft drinks and fast food.	Insufficient physical activity, high consumption of processed foods, especially soft drinks and fast foods, geographic location conducive to the consumption of unhealthy foods, in addition to high screen exposure, especially television.
Consumo alimentar e estado nutricional de pré-escolares das comunidades remanescentes dos quilombos do estado de Alagoas[26].	The families, despite receiving the Bolsa Família from the federal government, do not select good food to be eaten by the children.	Unfavorable socioeconomic conditions to maintain a varied diet, poor diet, generating vitamin deficits. The lower the socioeconomic class, the lower the daily consumption of micronutrients. Most families received financial support from the government	Precarious socioeconomic class; food with little variety; low consumption of fruits (5.4%), vegetables (0.5%); consumption of calories above the ideal; suboptimal intake of vitamins; lack of action in nutritional education for families to make better use of the Bolsa Família resource, selecting better foods.

Table 2. Information extracted from selected articles (part b).

Title	Influence of individuals involved with children	Environmental influence	Associated factors
Desnutrição e fatores associados em crianças quilombolas menores de 60 meses em dois municípios do estado do Maranhão, Brasil[22].	NA	High prevalence of malnutrition observed is related to the environmental factors of the families of the evaluated children, which, for the most part, are inserted in lower economic classes D (45.97) and E (39.78) and with lower purchasing power.	Smaller height of the mother; food deprivation; frequent infections (mainly diarrhea); low income and education, informal employment relationships, and difficult access to goods and services.
Condições socioecológicas familiares nos primeiros dois anos de vida de crianças quilombolas no Pará: um estudo de base populacional[23].	NA	Poor basic sanitation; poor garbage collection, which, in general, is buried by 92.1% of the residents; precarious socioeconomic conditions, low education.	Association with H/A deficit (height for age): drinking water from inappropriate sources, inadequate sewage disposal. Aspects related to overweight according to BMI: better infrastructure, such as the presence of an internal toilet.
Fatores Associados ao Déficit Estatural em Crianças Quilombolas Menores de 5 Anos na Região Nordeste do Brasil[25].	In families not served by the FHS (family health strategy), there was a higher prevalence (7.7%; n=35; p=0.075) of low P/A (weight for age). Overweight mothers were more likely to have children with low P/A. In households where the heads had a job, the prevalence of low P/A among children was higher (6.9%, n=45) compared to children of unemployed heads of household (4.5%; n=17). The lack of visits from the CHA (Community Health Agent) also influenced the low P/A. As for low E/A (height for age), the related factors were illiterate mothers, illiterate household heads, and overweight mothers.	Children who lived in households with three rooms or less had a higher prevalence of low (7.1%; n=49; p=0.060), lack of bathroom inside households, lack of running water are also environmental factors that interfered with low results. In homes whose lighting was provided by fuel or other sources, or which did not have lighting, the aforementioned health problem was more prevalent (11.5%; n=7; p=0.072).	As for low P/A: illiterate mothers; households without a bathroom; lack of running water; I did not live in my own home (in the case of the child); not have access to the cistern programs. There was a lower prevalence of low P/A in households where water was treated (5.2%; n=32), and where garbage was collected by the public network (4.4%; n=8). Low W/A was more prevalent among children who had diarrhea episodes in the week preceding the survey (6.5%; n=6). There was also a higher prevalence in households where more than one child <5 years of age lived (7.0%; n=37), or where four or fewer people lived (5.7%; n=35). Regarding H/A, low income was associated with low H/A. A higher prevalence of low E/A was found in households with an employed or retired head (15.7%; n=96), compared to households where the head was unemployed (10.8%; n=38; p=0.034). Families that receive Bolsa Família have a lower percentage of children with low H/A.
Avaliação do consumo alimentar de estudantes da comunidade quilombola Negros do Riacho no município de Currais Novos, no Rio Grande do Norte, Brasil[13].	NA	The snack offered at school (twice a day) where the children spend the whole day may have influenced the results.	Insufficient consumption of micronutrients, mainly calcium, vitamin A, zinc; low consumption of fruits and vegetables.

Table 3. Information extracted from selected articles (part c).

Title	Influence of individuals involved with children	Environmental influence	Associated factors
Comida, cultura e alimentação escolar quilombola[28].	NA	It appears that school menus, despite containing healthy foods, do not contain adequate amounts of fruits, vegetables, and greens. In addition, there is a high supply of savory and sweet cookies in the four regions of the country: North, Northeast, Southeast, and South. The food offered at school can cause countless damages related to the health of quilombola children, such as, for example, noncommunicable chronic diseases.	Low supply of fruits, vegetables, and vegetables on the menus in all regions of the country. High offer of processed foods, especially sausage and sardines, in addition to carbohydrates with low nutritional value.
Nutrição e saúde das crianças das comunidades remanescentes dos quilombos no Estado de Alagoas, Brasil[24].	NA	The vast majority of families are beneficiaries of the Bolsa Família, partially explaining the high prevalence of overweight children, signaling a diet poor in nutrients, but rich in calories, as more than half of the children were anemic (52.7%).	Socioeconomic precariousness; inadequate nutrition; receipt of the family allowance.
Saúde mental materna e estado nutricional do binômio mãe/filho na população quilombola de alagoas[9].	Smaller mothers were associated with children with short stature and malnutrition. Mothers of malnourished children have a lower level of education, smaller height, more children, children with anemia, and families have lower per capita income. Among mothers who had common mental disorder (389), most (60.1%) had anemic children; however, mothers without common mental disorder also had a high number of anemic children (60.5%).	As for chronic malnutrition: income per capita; anemia was related to malnutrition and overweight/obesity. Working outside the home was associated with a higher probability of having malnourished children. A higher number of children was associated with a higher probability of children being malnourished.	The income per capita, height of mother, number of children, education level.
Excesso de peso em estudantes quilombolas e a insegurança alimentar em seus domicílios[27].	There was no statistically significant association between the nutritional status of individuals and the Food Insecurity of quilombola families.	Location of schools; students in urban schools are more likely to be overweight compared to those in rural areas.	Excess weight was associated with the food security of families. There was a high incidence of food insecurity; however, the factors associated with this were not explained in the work.

DISCUSSION

According to the study results, as well as those from several studies[22-25], there is still a continuous neglect of quilombola population. Basic knowledge has not been noticed among these people, such as knowing how to manage in the best possible way the money they receive from the Bolsa Família and the benefits of using healthy foods compared to ultra-processed ones. Furthermore, many of them are unaware of the benefits of the practice of physical activity to maintain a healthy life[17,26].

Studies have shown the correlation between the location of schools and overweight of students. As it is known, the closer to places where ultra-processed foods are consumed, the greater the chances of children consuming them. The prevalence of food insecurity is perceived as being common for studies focusing on the nutritional issue in quilombola populations; however, it is not possible to infer the reasons that lead quilombolas to have a high prevalence of food insecurity[27].

Food insecurity seems to be related to the food offered at school. Since many children are unable to maintain the same diet at home, the school environment becomes the main supplier of food for these children[28]. However, no research has yet been done on this fact.

Cordeiro et al.[27] reviewed that food insecurity was present in 75.2% (n=160) of quilombola families and also highlighted the need for additional studies to understand this phenomenon. Santos-de-Araújo et al.[13] reported that deficiency of micronutrient among families living in quilombola communities was

often related to the consumption of ultra-processed foods; however, the authors did not make any conclusion on aspects related to childhood malnutrition and obesity.

A study found that food insecurity in all Brazilian municipalities was due to a large disparity in food insecurity within the states. In the state of Paraíba, there was a variation of 5.4–22.8% among the municipalities[29]. In a recent study, quilombola populations, especially children, were not investigated, thus showing the vulnerability of this population[30].

Studies that were carried out in quilombola communities in the state of Pará (northern Brazil) investigated the body mass index (BMI) of quilombola children[23], but failed to explain the causes of childhood malnutrition and obesity, as numerous factors are related to overweight and obesity[31], and as a result, few studies have conducted further research on these communities[22,28,32].

This study has limitations that must be addressed. There was a lack of studies on the topic in question, revealing a gap in the literature and hindering the argumentative rationale of this discussion. In addition, environmental influences were not investigated in studies with quilombola children. Therefore, we suggested for the development of future studies.

CONCLUSION

Only six studies describe childhood malnutrition and obesity in quilombola children and possible influences from family members or teachers. Thus, there is a gap in the literature on studies on childhood malnutrition and obesity in quilombola children.

AUTHORS' CONTRIBUTIONS

LPL: Conceptualization, Data curation, Formal Analysis, Investigation, Methodology, Project administration, Resources, Supervision, Validation, Visualization, Writing – original draft, Writing – review & editing. **ESM:** Conceptualization, Data curation, Formal Analysis, Investigation, Methodology, Project administration, Resources, Supervision, Validation, Visualization, Writing – original draft, Writing – review & editing. **FRPQ:** Validation, Visualization, Writing – original draft, Writing – review & editing. **AP-S:** Validation, Visualization, Writing – original draft, Writing – review & editing. **LSS:** Visualization, Writing – original draft, Writing – review & editing. **ESM:** Conceptualization, Data curation, Formal Analysis, Funding acquisition, Investigation, Methodology, Project administration, Resources, Supervision, Validation, Visualization, Writing – original draft, Writing – review & editing.

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REVIEW ARTICLE

https://doi.org/10.1590/1806-9282.20220147

Hepatocellular carcinoma *versus* nonalcoholic fatty liver disease: metabolic, environmental, and genetic association? *De facto*?

Daniel Toman[1,2], Ilker Sengul[3,4], Anton Pelikán[1,2,5], Demet Sengul[6]*, Petr Vavra[1,2], Peter Ihnát[1,2], Jan Roman[1,2], Cuneyt Kayaalp[7]

INTRODUCTION

Hepatocellular carcinoma (HCC) is the most common primary cause of liver cancer and is also considered to be the fourth most frequent cause of cancer and the third most common cause of cancer-related deaths worldwide[1]. The majority of these cases develop due to existing chronic liver conditions such as hepatitis B or C viral infections and alcohol[2]. However, previous shreds of evidence have shown that 15–50% of HCC is presented as idiopathic and could not be explained with any known etiology[3]. However, recent studies suggest that nonalcoholic fatty liver disease (NAFLD) can be a possible risk factor for the development of HCC[4], and it can act through various mechanisms such as insulin resistance, oxidative stress, steatosis, and imbalances in an interplay of adipokine or cytokine. These are propounded as the most important factors responsible for the pathogenesis and progression of NAFLD that could also have a deterministic role in the pathway of liver cancer as it promotes cell growth and DNA damage. Behavioral therapy and several insulin-sensitizing agents have been tried and tested to achieve a better success rate in the management of this condition[5]. This approach was alleged as it could help improve insulin resistance and attenuate the necroinflammation, steatosis, and fibrotic changes in the liver parenchyma. *Unum castigabis centum emendabis* (Rebuke one and correct a hundred). Therefore, an in-depth and detailed understanding of the underlying mechanisms responsible for the mediation of HCC during insulin resistance and identification of its genetic determinants would help in providing actual diagnostic and therapeutic tools of interventions.

METHODS

We have conducted a conventional systematic literature review study to identify the clinical, environmental, and genetic factors responsible for the association between NAFLD and HCC with a special focus on molecular pathogenesis and its application to develop newer diagnostic and therapeutic tools. Search engines such as PubMed, Google Scholar, Scopus, and Science Direct were used to obtain literature regarding e-waste management practices throughout the world. The search strategy included different terms for "Non-Alcoholic Fatty Liver Disease," "Hepatocellular carcinoma," "Genetic Factors," "Environmental factors," "Molecular factors," "Metabolic factors," "Novel Therapy," "Liver cancer," and "Novel diagnostics" as key words.

Inclusion criteria for the case studies, guidelines documents, reports, original and review articles, and other relevant documents retrieved and considered for the review were as follows:

1. Studies prescribing the data in the English language
2. Open access documents and reports available on the journal/websites
3. Studies dealing with a section on clinical, environmental, and genetic factors responsible for the association between NAFLD and HCC or molecular pathogenesis and its implementation to improve newer diagnostic and therapeutic tools.

Pathogenesis of NAFLD

The pathogenesis of NAFLD remains unclear, and understanding the mechanism is arduous. In fact, it is a complex condition

[1]University of Ostrava, Faculty of Medicine, Department of Surgery – Ostrava, Czechia.
[2]University Hospital in Ostrava, Department of Surgery – Ostrava, Czechia.
[3]Giresun University, Faculty of Medicine, Department of Surgery – Giresun, Turkey.
[4]Giresun University, Faculty of Medicine, Department of Endocrine Surgery – Giresun, Turkey.
[5]Tomas Bata University in Zlín, Department of Surgery – Zlín, Czechia.
[6]Giresun University, Faculty of Medicine, Department of Pathology – Giresun, Turkey.
[7]Inonu University, Faculty of Medicine, Department of Surgery, Liver Transplantation Institute – Malatya, Turkey.
*Corresponding author: demet.sengul.52@gmail.com
Conflicts of interest: the authors declare there is no conflicts of interest. Funding: This study was supported by the University Hospital Ostrava in the Czech Republic under grant number MZ ČR – RVO-FNOs/2019.
Received on February 09, 2022. Accepted on February 09, 2022.

that is believed to have multifactorial causation. Two hit hypotheses were frequently used to explain this complex mechanism of NAFLD: steatosis and fibrotic changes. Currently, multiple hit hypotheses are used to explain the mechanism as multiple factors act together in predisposing the person to the mentioned condition, such as the combination of environmental, genetic, and metabolic factors responsible for disturbance in lipid homeostasis and accumulation of excessive triglycerides in the liver. In addition to the above-mentioned factors, insulin resistance is responsible for the disease progression as it may lead to endoplasmic reticulum stress, lipotoxicity, and disturbance in autophagy, which ultimately induce hepatocyte injuries, death, hepatic inflammation, and progressive fibrogenesis[5].

Pathogenesis of HCC in association with NAFLD

Similar to the NAFLD, the occurrence of HCC among NAFLD cases is also a complex and multifactorial phenomenon that depends on the mechanisms described for chronic liver injuries, molecular imbalances associated with dysmetabolism and obesity such as the remodeling of adipocytes, lipotoxicity, adipokines secretion, and insulin resistance[4, 5]. Recent evidence suggest that the gut-liver axis plays an important role in the acceleration of the oncogenesis process among patients with NAFLD. Farnesoid X nuclear receptor has been established to possess significant metabolic effects and plays a significant role in producing histopathologic improvement in NASH that occurs through its pharmacological activation by obeticholic acid. Delineation of these mechanisms, hepatic fibrosis, and oncogenesis in NASH can assist in producing enhanced interventional strategies for the prevention, surveillance, diagnosis, and management of cancer among this population[6]. Hence, we purposed to detail and hypothesize the possible risk factors responsible for HCC in NAFLD. Possible risk factors are demographic factors such as age and gender; metabolic factors such as obesity, excessive insulin, and hepatic iron overload; environmental factors; and genetic factors resulting in advanced stages of fibrotic changes and cirrhosis.

Demographic factors

Age and gender

Hepatocellular carcinoma occurs at higher rates among males around the world irrespective of the etiology. Similar differences are seen in the development of NAFLD. Both age and gender differences are seen in their incidence and severity. NAFLD is most commonly observed in males among the younger age groups, whereas it is observed among the elderly females (>50 years)[7].

Environmental factors concerning metabolic factors

Obesity and type 2 diabetes mellitus

Obesity is one of the most common risk factors for NAFLD and type 2 diabetes mellitus (DM) due to insulin resistance. Asians have an increased risk of developing type 2 DM even with normal or low body mass index (BMI) as retaining a higher rate of central obesity in the absence of generalized obesity. This predisposes them to develop type 2 DM[8]. Association between obesity and NAFLD is depicted through the studies conducted among the patients who had undergone gastric bypass or bariatric surgery with a prevalence of NAFLD ranging from 85% to 98%[9]. A systematic review conducted in Asia, the United States, and Europe showed that the overweight and obese individuals had a significantly higher risk of developing HCC compared to the ones with normal or low BMI[10]. Also, the prevalence of NAFLD among type 2 DM cases is significantly higher, and they are at more risk of developing carcinomas[11].

Underlying pathophysiology

Potential mediators responsible for obesity-linked HCC include dysregulation of anti-inflammatory or pro-inflammatory cytokines, particularly the increased leptin or reduced adiponectin, lipotoxicity, and hyperinsulinemia, which stimulates insulin-like growth factor-1 (IGF-1). First of all, we would like to emphasize the adipocyte remodeling and secretion of cytokines. Obesity is usually characterized by the expansion and remodeling of adipose tissues that lead to a state of chronic inflammation, which is characterized by a different cytokine secretion pattern by the adipocytes. These cytokines include adiponectin and leptin. Other cytokines implicated are tumor necrosis factor-alpha (TNF-α), transforming growth factor-beta (TGF-β), interleukin-6 (IL-6), and interleukin-1beta (IL-1β). TNF-α can induce many pro-oncogenic pathways and obesity by increasing its levels in both malignant and non-malignant tissues[12]. TNF-α and IL-6 were demonstrated to promote diethylnitrosamine-induced HCC in an experimental model of dietary-induced obesity that could be due to the upregulation of extracellular signal-regulated kinases (ERK) and STAT3 pathways[13].

Reduced adiponectin in obesity is responsible for suppressing the angiogenesis of the tumors and inhibits the growth and metastasis of HCC, whereas adiponectin acts through the activation of a tumor suppressor called 5′-adenosine monophosphate-activated protein kinase. It increases apoptosis of cells by regulating mammalian target of rapamycin pathway and c-Jun N-terminal kinase or caspase-3 pathway[14]. Leptin is known to

have potent pro-inflammatory and pro-fibrogenic activities. Its growth-promoting effects act through ERK, STAT3, Janus kinase (JAK), phosphatidylinositol 3-kinase (PI3K), or protein kinase-B (Akt) signaling pathways[13]. This counterpoise between the contrasting effects of adiponectin and leptin plays an important role in the oncogenesis associated with steatosis of the liver.

The liver is at risk of ectopic accumulation of lipids due to various factors, particularly the excess dietary lipids transported through portal veins among obese individuals. Inhibition of phosphatase and tensin homolog (PTEN) expression occurs due to excess collection of unsaturated fatty acids in hepatic cells. PTEN acts as a tumor suppressor and regulates PI3K signaling pathway that is either deleted or mutated in HCC[15].

Obesity causes both systemic and hepatic insulin resistance, which is further worsened by the accumulation of hepatic lipids. Excess insulin for a prolonged period promotes the IGF-binding protein production and increases the IGF-1&2 bioavailability[16]. This stimulates the development of cancer through activation of oncogenic pathways by involving mitogen-activated protein kinase (MAPK), PI3K/Akt, and vascular endothelial growth factor[17]. In addition, sterol regulatory element-binding proteins (an essential component in regulating lipogenesis) within the liver get activated by lipid accumulation in that crucial organ. Of note, in patients with cancer, this protein markedly induces lipogenesis and is linked to poor prognosis[18].

Iron overload

Excessive load of iron in the liver can cause serious insult and augment the risk of developing HCC. It occurs in patients with alcoholic liver disease, hereditary hemochromatosis, post-transplant cases, and HCC patients with a non-cirrhotic liver. Oxidative stress or genetic mutation can lead to necrotic inflammation and carcinogenesis of the liver. Finally, these patients are found to have a more than 200-fold risk of developing HCC[19].

CONCLUSIONS

In-depth understanding about the potential role of genetic predisposition, diet type, gut microbiota, and other environmental and metabolic factors linking the NAFLD and HCC has become crucial. Mostly genetic factors play a significant role in the NAFLD development and progression. The future studies focus on genetic epidemiology requires replication, expression studies, and animal models to understand the molecular role of the genetic variants. The understanding of genetic determinants may lead us to newer diagnostic and therapeutic approaches or interventions, which can prevent or control the progression of NAFLD to liver cancer.

AUTHORS' CONTRIBUTIONS

DT: Conceptualization, Data curation, Formal Analysis, Investigation, Methodology, Project administration, Resources, Software, Validation, Visualization, Writing – original draft. **IS**: Investigation, Methodology, Project administration, Resources, Software, Validation, Visualization, Writing – original draft, Writing – review & editing. **AP**: Conceptualization, Data curation, Formal Analysis, Investigation, Methodology, Project administration, Resources, Software, Validation, Visualization, Writing – original draft. **DS**: Investigation, Methodology, Project administration, Resources, Software, Validation, Visualization, Writing – original draft, Writing – review & editing. **PV**: Conceptualization, Data curation, Formal Analysis, Investigation, Methodology, Project administration, Resources, Software, Validation, Visualization, Writing – original draft. **PI**: Conceptualization, Data curation, Formal Analysis, Investigation, Methodology, Project administration, Resources, Software, Validation, Visualization, Writing – original draft. **JR**: Conceptualization, Data curation, Formal Analysis, Investigation, Methodology, Project administration, Resources, Software, Validation, Visualization, Writing – original draft. **CK**: Validation, Visualization, Writing – review & editing.

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REVIEW ARTICLE

https://doi.org/10.1590/1806-9282.20220165

Clinical prognosis of coronavirus disease 2019 in children and vitamin D levels: a systematic review

Matheus Alves Alvares[1*], Barbara Helena Barbosa Ribas[1], Giulia Baptistella de Miranda[1], Robson Barbosa de Miranda[2], Elisandre Maria Camelo Gomes Natário[1], Isabela Sodré D'Angelo[1], Vera Esteves Vagnozzi Rullo[1]

INTRODUCTION

A novel coronavirus disease 2019 (COVID-19) is a disease caused by the new severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2), which is declared by the World Health Organization (WHO) as a pandemic in December 2019. Since then, the pandemic of COVID-19 has caused more than 4 million deaths worldwide[1] and has been responsible for drastic changes in health systems around the world.

The pediatric population is usually more susceptible to some infectious diseases considering their still developing immune system. However, based on current observations, the susceptibility, frequency of severe cases, and fatalities from COVID-19 appear to be much lower[2,3].

The pathology of COVID-19 involves a complex interaction of the immune system, suppressing the anti-inflammatory response and activating the classical inflammation pathway, which leads to a state of hyperinflammation and cytokine storm that is responsible for the severity of the disease[4]. With the recent findings of the immunomodulatory effect of 25-hydroxyvitamin D [25(OH)D] (i.e., decreased pro-inflammatory cytokines and increased anti-inflammatory cytokines[5]), a possible association between serum vitamin D levels and the clinical course due to COVID-19 has been hypothesized. Thus, some studies demonstrate a relationship between 25(OH)D deficiency severity and mortality from COVID-19[6,7]; however, data on this association in pediatric patients are still lacking.

OBJECTIVE

This study aimed to correlate 25(OH)D levels with the clinical prognosis of pediatric patients diagnosed with COVID-19.

METHODS

This systematic review of retrospective cohort studies evaluated the relationship between pediatric patients with COVID-19 and their serum levels of vitamin D, in the 25(OH)D form. The articles were selected according to the recommendations of the PRISMA[8] (Preferred Reporting Items for Systematic Reviews and Meta-Analysis) statement, which is responsible for organizing the process of writing meta-analyses and systematic reviews. For the selection of articles, a literature search was performed in the primary databases Online Medical Literature Search and Analysis System (MEDLINE) via PubMed, Latin American and Caribbean Literature on Health Sciences (Lilacs) via the Virtual Health Library (VHL), and SciELO.

For MEDLINE, the following descriptors were used: (COVID-19) AND (vitamin D) with the filter Child-birth 18 years; LILACS: COVID-19 AND vitamin D AND children; SciELO: (COVID-19 AND vitamin D) AND (children OR infant), ((COVID-19) AND (vitamin D)) AND (paediatrics).

The inclusion criteria for this review were as follows: healthy pediatric population up to 17 years 11 months and 29 days of age with no medical history, no continuous medication use, and no vitamin D levels related to COVID-19 infection.

Exclusion criteria were non-pediatric patients, literature reviews, and studies evaluating vitamin D dosage in situations not related to COVID-19 infection.

RESULTS

After the search, 56 articles that met the inclusion criteria of this study were selected, of which 44 via MEDLINE, 3 via LILACS, and 9 via SciELO. The searches were conducted from September 30, 2021, to October 9, 2021 (Figure 1).

[1]Centro Universitário Lusíada – Santos (SP), Brazil.
[2]Faculdade de Ciências Médicas da Santa Casa de São Paulo – São Paulo (SP), Brazil.
*Corresponding author: matheusalvares.ep@gmail.com
Conflicts of interest: the authors declare there is no conflicts of interest. Funding: none.
Received on February 06, 2022. Accepted on February 09, 2022.

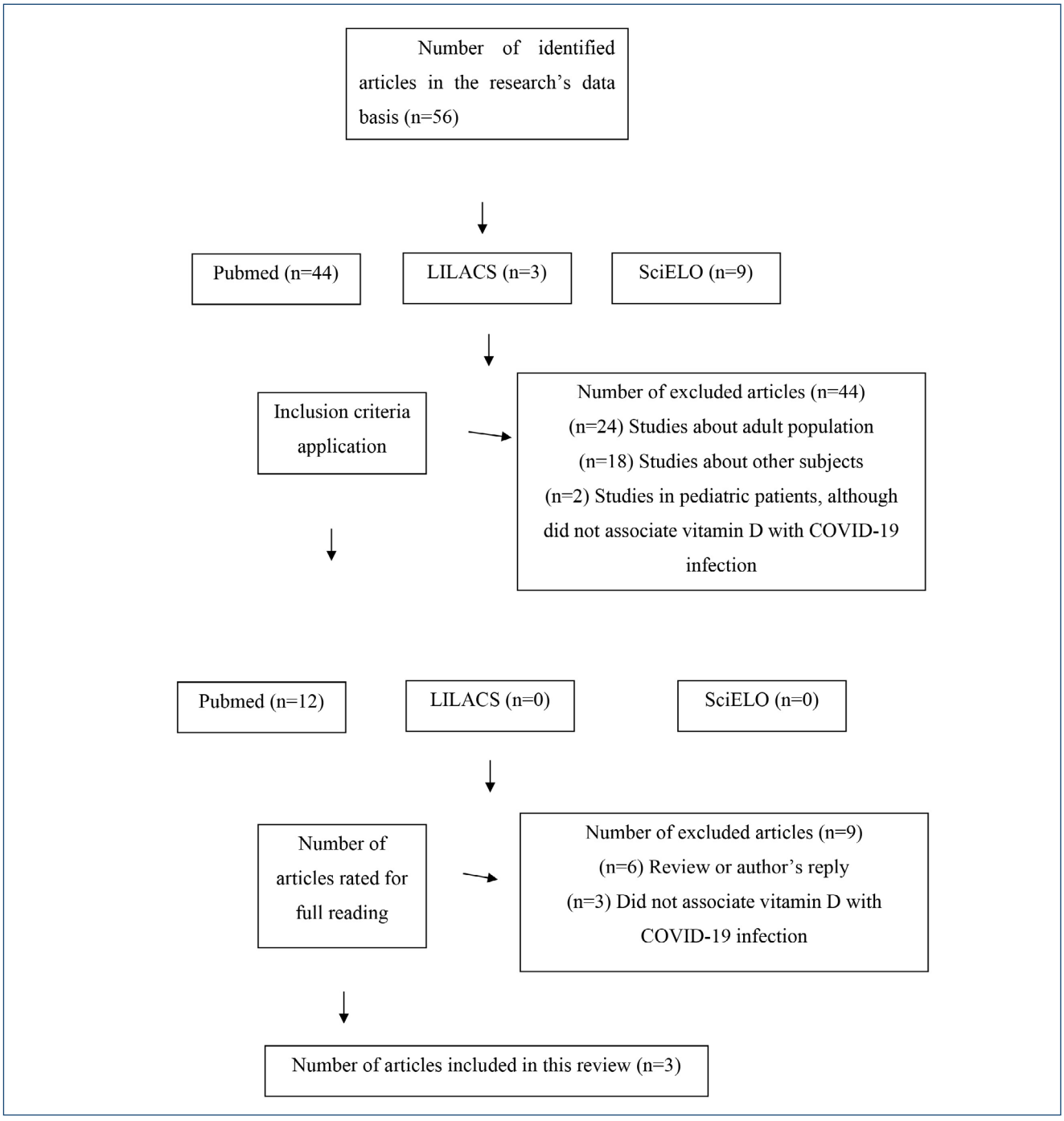

Figure 1. Flowchart of the study inclusion process.

The three selected articles are retrospective cohort studies, whose patients' data were obtained from their medical records. All patients were tested positive for SARS-CoV-2 infection by RT-PCR (polymerase chain reaction) test.

In the study by Alpcan et al.[9], 155 patients were analyzed, of which 75 carried COVID-19 and 80 were from the healthy control group. Patients with metabolic bone disorders and patients with a positive but asymptomatic COVID-19 test were not included.

Bayramoğlu et al.[10] applied the exclusion criteria such as carrying comorbidities and less than 1 year of age and data from 103 patients were obtained for the study. There was only the classification in the 25(OH)D levels as to their sufficiency of all patients

affected by COVID-19. This separation, made according to the clinical course of the patients, allowed the categorization into asymptomatic (n=29), mild (n=40), and moderate to severe (n=34).

Yılmaz and Şen[11] conducted a study on 85 patients and classified them into COVID-19 carriers (40 patients) and healthy controls (45 patients). The patients with COVID-19 were further divided into two groups subsequently in order to discern the 25(OH)D sufficiency levels in each category. Patients less than 1 year and older than 18 years, chronically ill patients, and those with comorbidities were excluded from the study.

Several studies evaluated the 25(OH)D dosages and divided patients according to the sufficiency level in their blood and their clinical courses. Alpcan et al.[9] classified the patients as follows: deficiency <20 ng/dL, insufficiency 21–29 ng/dL, and sufficiency >30 ng/dL; Yılmaz and Şen[11] and Bayramoglu et al.[10] classified the patients as follows: deficiency <12 ng/dL, insufficiency 12–20 ng/dL, and sufficiency >20 ng/dL (Table 1).

Alpcan et al.[9] reported that serum 25(OH)D levels were lower in the group of patients with COVID-19 (21.5±10.0 IU) (p<0.001). Within this group, 12 patients had normal vitamin D levels, 33 patients had deficiency, and 30 patients had insufficiency.

Yılmaz and Şen[11] divided the patients confirmed for SARS-CoV-2 as follows: group 1 as those having 25(OH)D deficiency and insufficiency (n=29, 72.5%) and group 2 as those with normal levels (n=11, 27.5%). In group 1, 18 children were deficient and 11 were insufficient, with a mean 25(OH)D value of 10.83 (4.19–17.69; p<0.001). The overall 25(OH)D levels in COVID-19 patients were 13.14 µg/L (4.19–69.28) (p<0.001).

Bayramoğlu et al.[10] reported that the prevalence of 25(OH) D deficiency was 17.2% in asymptomatic cases, 35.2% in mild cases, and 70.6% in moderate-to-severe cases. In addition, the authors concluded that the level of 25(OH)D deficiency was 16.3 ng/ml (12.6–19.1) in the asymptomatic cases (p=NS), 13.95 ng/ml (10.0–17.2) in mild cases (p<0.001), and 9.95 ng/ml (7.9–12.9) in moderate-to-severe cases (p=0.001) (Table 1).

Regarding the categorization of the clinical picture, different criteria were used in different studies to categorize the patients. Bayramoglu et al.[10], as previously mentioned, divided the patients into asymptomatic, mild, and moderate-to-severe groups.

Yilmaz and Şen[11] expanded and divided the study subjects into asymptomatic, mild, moderate, severe, and critical. The authors reported that the prevalence of vitamin D deficiency in these groups was 10.3%, 58.6%, 24.1%, and 6.9%, respectively (p=0.097) (Table 1).

The categories "asymptomatic" and "mild" are found similar to the study by Bayramoglu et al.[10], as well as the study by Alpcan et al.[9] in relation to patient complaints.

Alpcan et al.[9] classified patients with cough, fever, hypoxemia, and no dyspnea as having only "pneumonia." The authors considered respiratory distress as a picture of tachypnea that requires oxygen therapy. Alpcan et al.[9] did not include patients with low 25(OH)D in such groups.

DISCUSSION

Bayramoglu et al.[10] concluded that the more severe the infection, the higher the 25(OH)D deficiency in the patient and found the prevalence of vitamin D deficiency of 17.2% in the asymptomatic group (p=NS), 35.2% in the mild group (p=NS), and 79.6% in the moderate-to-severe group (p=NS). In contrast, Yılmaz and Şen[11] showed no relationship of the prevalence of 25(OH)D deficiency with a worse disease prognosis, with 10.3% in the asymptomatic group (p<0.097), 58.6% in the mild group (p<0.097), 24.1% in the moderate group (p<0.097), and 6.9% in the severe group (p<0.097). However, Alpcan et al.[9] did not report this prevalence in each group (Table 1).

Table 1. Prevalence of 25(OH) D deficiency in coronavirus disease 2019 and relationship of its levels to the clinical course of the disease.

Author, year	Prevalence of low 25(OH)D levels (<12 ng/dL) according to the clinical course of the disease	Classification of the clinical course of the disease	Vitamin D levels in COVID-19 patients
Alpcan et al, 2021[9]		Asymptomatic Mild Pneumonia	21.510; p<0.001
Bayramoğlu et al., 2021[10]	5 (17.2%); p=NS 14 (35.2%); p=NS 24 (70.6%); p=NS	Asymptomatic Mild Moderate-to-severe	16.3 (12.6–19.1); p=NS 13.95 (10–17.2); p<0.001 9.95 (17.9–12.9); p<0.001
Yilmaz and Şen, 2020[11]	3 (10.3%); p<0.097 17 (58.6%); p<0.097 7 (24.1%); p<0.097 2 (6.9%); p<0.097	Asymptomatic Mild Moderate Severe Critical	13.14 (4.19–69.28); p<0.001

NS, not statistically significant.

This review has some limitations. This study analyzed only few articles. The relationship between the age and serum 25(OH) D levels, as explained in all three studies mentioned previously, showed patients with older ages, i.e., adolescents, had the lowest 25(OH)D levels. Knowing the close relationship between the severity of COVID-19 cases and age, with older ages being considered risk factors, there is a need to compare serum 25(OH) D levels and the severity of clinical course by age groups in future similar studies[10]. Another possible limitation for interpretation of the results is the discrepancy between the values established as sufficient, insufficient, and deficient according to each study (Table 1).

To establish a possible relation of the immunomodulatory action of 25(OH)D, a double-blind interventional study based on empirical vitamin D supplementation in hospitalized patients with COVID-19 could offer answers about its role in the clinical outcome in patients.

Pediatric patients who were supplemented with vitamin D during the COVID-19 pandemic showed reduced risk of developing severe pulmonary forms of the disease[10]; however, there is no retrospective study that correlates correct supplementation (75–125 nmol/L) with outcome in COVID-19 sufferers[7], but there are positive evaluations of the relationship between vitamin D and other respiratory pathogens[11].

Studies on association between vitamin D levels and COVID-19 in children are scarce and therefore further studies on this subject are needed.

CONCLUSION

Through the review of studies, it was not possible to establish a relationship between serum levels of 25(OH)D and clinical prognosis by COVID-19. Since this is a recent theme and still little explored in the literature, more studies are needed to prove a possible cause-and-effect relationship of 25(OH)D levels and severity of the clinical picture.

AUTHORS' CONTRIBUTIONS

MAA: Conceptualization, Formal Analysis, Resources, Software, Supervision, Visualization. **BHBR**: Conceptualization, Data curation, Investigation, Methodology, Project administration, Writing – original draft, Writing – review & editing. **GBM**: Conceptualization, Data curation, Investigation, Project administration, Writing – original draft, Writing – review & editing. **RBM**: Formal Analysis, Validation, Visualization. **EMCGN**: Conceptualization, Investigation. **ISD'A**: Conceptualization, Investigation. **VEVR**: Resources, Software, Supervision, Visualization.

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REVIEW ARTICLE

https://doi.org/10.1590/1806-9282.20220174

Narrative review of Vitex agnus-castus in symptoms in Gynecology

Ceci Mendes[1], Angela Maggio da Fonseca[1], Mayara Souza Alves[1], Luiza Helena Costa Moreira Bayer[1], Eduardo Carvalho de Arruda Veiga[2*], Isabel Cristiana Espósito Sorpreso[1], Edmund Chada Baracat[1], José Maria Soares Júnior[1]

INTRODUCTION

Since ancient times, it is said that women can look different than usual, especially in the phase that precedes menstruation. Hippocratic texts mention tremors, fatigue, and pressure in the head. Romans cite torpor, nausea, and loss of appetite. The name "premenstrual tension" was given by Frank in 1931, based on the set of physical, psychological, and behavioral changes that appear in the period before menstruation and regress with it. In 1953, Greene and Dalton advised using the term "syndrome" instead of tension, as the condition is usually represented by a set of symptoms, with multiple variables and different aspects, depending on the affected people[1].

In 1987, the American Psychiatric Association defined "late luteal phase dysphoric disorder" as a mental disorder[1,2]. This inclusion led to a great deal of discussion, along with several objections, as it represents the evident potential risk of using this diagnosis in criminal charges, in addition to promoting prejudice against the female sex. However, the diagnosis remains recorded in the manuals. At present, this disorder is considered a diagnosis only in very serious cases in which impairment of socialization and usual activity is evident.

Premenstrual syndrome is defined as a set of disorders with somatic, affective, cognitive, and behavioral manifestations that occur in the luteal phase of the menstrual cycle and disappear after menstruation, cyclic, recurrent, and sometimes disabling. One study found that only 3–15% of women have severe symptoms[2].

Due to the day-to-day implications, there is great interest in treating affected women, providing them with greater well-being and friendly coexistence. One of the treatment alternatives is to use the extracts of Vitex agnus-castus.

HISTORIC

In ancient Greece, about two millennia ago, Dioscorides describes Vitex agnus-castus as a medicinal plant. It is also called monk's pepper, chaste tree (or chasteberry in English), northern rosemary, and so on. Its name Vitex agnus–castus was derived from the Latin "chaste lamb". Owing to its ability to reduce sexual desire, the monks used this plant to maintain their vow of chastity[3].

This plant has been traditionally used for centuries to treat various female problems, such as cyclical breast tenderness, menstrual irregularities, and premenstrual tension[4].

CHEMICAL COMPOSITION

Most of the studies were carried out with tinctures or extracts obtained from the fruits containing essential oils, iridoid glycosides, diterpenes, and flavonoids. Essential oils contain limonene, cineole, pinene, and sabinene; primary flavonoids include casticine (Figure 1), orientin, kaempferol, quercetagetin, and isovitexin; diterpenes consist of vitexilactone, rotondifuran, and 7-beta-diacetoxy-13-hydroxy-labda-8,14-diene; and iridoid glycosides include agnosidium (Figure 2) and aucubin (Figure 3). The agnoside is used as a quality marker of extracts. There is no accurate information on the presence of progesterone, 17-hydroxyprogesterone, testosterone, and epitestosterone[4,5].

PHARMACOLOGY

Vitex extract promotes a reduction in prolactinemia. This action results from the binding of components with dopaminergic properties to protein receptors[6]. There is evidence that shows binding to dopamine receptors in the hypothalamus and anterior

[1]Universidade de São Paulo, Faculdade de Medicina – São Paulo (SP), Brazil.
[2]Universidade de São Paulo, Faculdade de Medicina de Ribeirão Preto – São Paulo (SP), Brazil.
*Corresponding author: eduveiga56@gmail.com
Conflicts of interest: the authors declare there is no conflicts of interest. Funding: none.
Received on February 17, 2022. Accepted on February 18, 2022.

pituitary and inhibiting the release of prolactin. There also seem to be other endocrine effects, such as increased progesterone secretion and induction of corpus luteum formation[4].

The estrogenic activity of the ethanol extract was demonstrated in ovariectomized rats by promoting an increase in uterine volume, increasing the dosage of progesterone and estrogens, and also inducing a reduction in LH and prolactin[7].

CLINICAL TRIALS

Premenstrual syndrome

A multicenter study with 1634 patients, observed during three menstrual cycles, using Vitex extract, answered a questionnaire about their psychic symptoms, and attributed to water retention; 93% of the patients reported symptomatic improvement, without significant adverse effects[8].

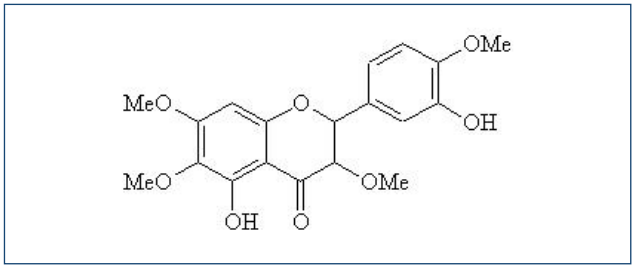

Figure 1. Chemical structure of Casticine[5].

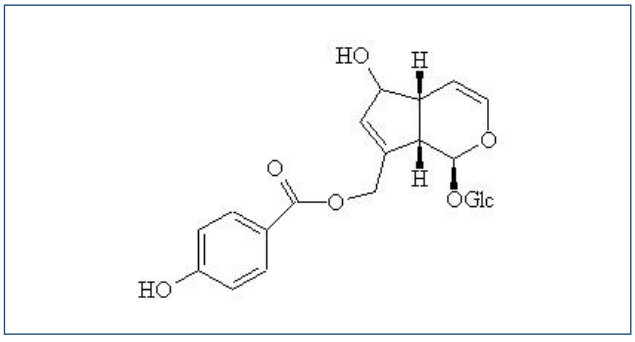

Figure 2. Chemical Structure of Agnosidium[5].

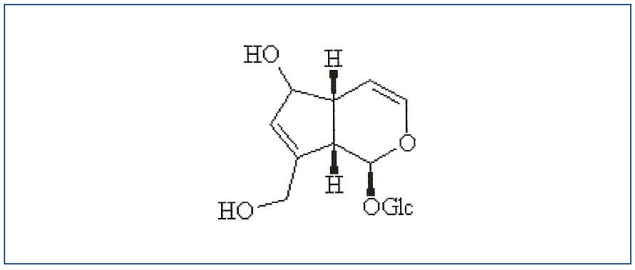

Figure 3. Chemical structure of Aucubin[5].

A study on 170 patients (84 of them with the herbal medicine) during three menstrual cycles compared the efficacy of Vitex agnus-castus with placebo and found an important superiority of the herbal medicine ($p<0.001$), with adverse events without seriousness but similar to the placebo group[9] (Table 1).

With regard to therapeutic options (especially fluoxetine, sertraline, and Vitex), and the above findings, Carr considered the option of using agnus chaste very promising[10].

Comparing the herbal medicine with fluoxetine, a study with 24 patients, during two cycles, did not observe a significant difference between treatments with fluoxetine and monk's pepper, although both improved the psychological and physical symptoms[11].

In a prospective, multicenter study conducted in China, compared with placebo, 202 patients completed 3 months of observation (101 using the extract). The symptom score was significantly lower in patients who used the active drug, leading to the conclusion that this treatment was effective, well-tolerated, and safe[12] (Table 2).

OTHER CLINICAL SITUATIONS

In a review of several studies, the reduction of breast tenderness by reducing prolactinemia is considered an excellent therapeutic option[12].

The immunomodulatory activity of casticin, a flavonoid from Vitex agnus-castus, has been demonstrated in vitro[13].

The effect of a hydrophilic plant extract has also been described in rats to reduce epileptic seizures[14].

The action in fertility regulation has been described for some time. A case of ovarian hyperstimulation attributed to

Table 1. Reduction of symptoms in two therapeutic groups.

Symptoms	Reduction of symptoms (%)	
	Vitex agnus-castus (n=86)	Placebo (n=84)
Headache	-17.8	-5.9
Irritability	-28.9	-18.2
Mood changes	-28.7	-17.6
Changes in breasts	-18.6	-9.4

Significance at $p<0.001$.

Table 2. Therapeutic group scores for moderate-to-severe premenstrual syndrome in Chinese patients.

	Vitex agnus-castus (n=101)	Placebo (n=101)
Previous score	26.17	27.10
Final score	9.92	10.69

Significance at $p<0.01$.

the use of Vitex has been described in a patient undergoing in vitro fertilization treatment[15]. In other circumstances, it was considered an alternative option to assist infertile couples[16]. A double-blind study comparing placebo and nutritional products with various components, including agno chaste, green tea, vitamins, and minerals, demonstrated a very significant increase in progesterone and elevation of basal temperature, regularization of menstrual cycles, and increase in the number of fertilization (p=0.01), without significant adverse effects[17].

In a culture of human neoplastic cells of various types, the extract exerted a cytotoxic action, attributed to the intracellular oxidation activity of the treatment with the extract[18]. Its ability on the biology of prostate cells was also studied, concluding that the extracts may be useful in the treatment of not only prostate cancer but also benign hyperplasia[19]. In colon carcinoma, also in cell culture, treatment with this plant induced apoptosis, suggesting a mechanism of gene activation and proving to be a useful aid in the treatment of this type of cancer[20].

Its possible use in the treatment of problems linked to menopause may be of special interest nowadays. A study in cell culture demonstrates that phytoestrogens contained in the stratum of Vitex agnus-castus can exert actions mediated by estrogen receptors, and apigenin seems to be the most active of these compounds, such as vitexin and penduletin[21]. In vitro studies have also shown that linoleic acid from the fruits of this plant can bind to estrogen receptors and interfere with gene induction, with a protective effect on breast and endometrial cancer, which is desirable in the treatment of climacteric[22]. In rabbits, the action of flavonoids from agnus castus extract in the healing of bone fractures was demonstrated, a fact that may have implications for the treatment of osteoporotic women with fractures[23]. Using a product with extracts from six plants, including Vitex, or placebo, for 3 months (50 patients between 44 and 55 years old), a progressive and marked improvement in climacteric symptoms was observed (47% with the product, 19% with placebo)[24]. Another study in which 93 climacteric women ended 16 weeks using a product combining extracts of Hypericum perforatum and Vitex agnus-castus, or placebo, however, did not show a different effect between the groups, although no important adverse effects were found and tolerability was good[25].

Toxicology

Vitex agnus-castus is quite safe and has no significant toxic effects. The adverse effects cited are mild and reversible. As it is used in the treatment of women with premenstrual syndrome, as well as in the treatment of infertility, that is, women of childbearing age and possibly ovulatory, its use is likely to occur after fertilization. And no harm to the pregnancy or fetus is reported. Its use during lactation to increase milk production has been reported in herbal medicine textbooks, but there are also reports of decreased lactation due to the suppressive action of prolactin. Although there are reports of progesteronic, emmenagogue, and abortion-preventive activity, it is not clear whether or not its use during pregnancy is harmful since the scientific evidence is poor. . Therefore, caution is recommended regarding its use in pregnant or lactating women[4].

Drug interactions

Agno casto should not be used in conjunction with drugs with dopaminergic action, such as bromocriptine and metoclopramide, or any other dopamine agonist. Also, it should not be associated with antipsychotic drugs. Caution is suggested when using hormonal contraceptives or during climacteric hormonal treatment[4].

Adverse reactions

The adverse effects mentioned in the different studies with the plant are of low intensity and reversible. Erythematous rashes, acne, itching, headache, nausea, mild gastrointestinal complaints, fatigue, dry mouth, and menstrual disorders are the most common complaints. Nocturnal seizures occurred in a patient using a combination of herbs, including monk's pepper; however, this effect does not seem to be due to the use of plant[4].

Contraindications

Due to its hypersensitivity reaction, Vitex agnus-castus is also contraindicated in pregnancy and breastfeeding women. Although there is no clinical evidence or reports of hormone interaction, based on theoretical grounds, caution is recommended when using Vitex agnus-castus with hormone therapy.

Indications

The main indications are irregularities of the menstrual cycle such as irregular bleeding, absence of menstruation, and decreased menstrual flow and premenstrual tension, especially if there are symptoms such as breast pain and fluid retention. Other indications include hyperprolactinemia, infertility due to low progesterone levels, or corpus luteum failure. In men, it is useful in cases of sexual frigidity and impotence[5].

Posology

Based on the recommendations of the German Commission E, the recommended daily dose is 40 mg of Vitex agnus-castus, once a day, on an empty stomach.

Overdose

We found no references about overdose.

Prescription information

In cases of infertility, treatment is recommended for 5–7 months[5].

In the case of premenstrual syndrome, the treatment must be carried out for at least 3 months, continuing even after the symptoms are relieved[5].

AUTHORS' CONTRIBUTIONS

CM: Project administration, Data curation, Formal Analysis, Writing – original draft, Writing – review & editing. **AMF:** Project administration, Data curation, Formal Analysis, Writing – review & editing. **MSA:** Project administration, Data curation, Formal Analysis, Writing – original draft, Writing – review & editing. **LHCMB:** Project administration, Data curation, Formal Analysis, Writing – original draft, Writing – review & editing. **ECAV:** Writing – original draft, Writing – review & editing. **ICES:** Writing – original draft, Writing – review & editing. **ECB:** Writing – original draft, Writing – review & editing. **JMSJ:** Project administration, Data curation, Formal Analysis, Writing – review & editing.

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