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Caesarean section scar endometriosis: *quo vadis*?

Demet Sengul[1,a*], Ilker Sengul[2,3,b], José Maria Soares Junior[4,c]

Endometriosis is characterized by the presence of endometrial tissue implants outside the uterine cavity that responds to hormonal stimulation. These implants can be detected in all areas surrounding the uterus, ovaries, posterior cul-de-sac, ligaments of the uterus, pelvic peritoneum, and rectovaginal septum. Endometriosis may be infrequently found in the thorax, gastrointestinal tract, appendix, urinary tract, central nervous system, nose, umbilicus, lower limbs, and cutaneous cellular tissues. Caesarean scar endometriosis, *id est*, the cutaneous endometriosis, is the most common extrapelvic form, *vulgo*, and is located in scars following obstetric and/or gynecologic surgical procedures, such as caesarean delivery, hysterotomy, hysterectomy, episiotomy, ectopic pregnancy, salpingostomy, and tubal ligations, but scarcely in scars following appendicectomy, in the laparoscopic trocar and amniocentesis needle tracts. Diagnosis of surgical scar endometriosis following caesarean section, possessing an incidence of 0.03–0.4%, is not an easy process due to being often mistaken for a suture granuloma, lipoma, abscess, cyst, desmoid tumors, malignancies, incisional hernia, or a strange body[1-5]. Cellular transport theory, coelomic metaplasia theory, and the endometrial tissue reaching the surgical scar through the lymphatic or vascular pathways in order to develop into scar endometriosis afterward are accused and argued in the pathophysiology of the disease, to date[5]. Although mass in a caesarean section scar with symptoms of cyclic pain associated with menstruation is nearly pathognomonic, imaging modalities assist in identifying the condition. In spite of all odds, histopathologic evaluation is the major tool for confirmation[1-4]. Surgical scar endometrioses are known as possessing a potential for the progression of transformation, which rarely transpires for the malignant degeneration, accounting for 0.3–1%[1,6]. Herein, the interval of time from the onset of the benign lesion to the development of malignant form in caesarean section scar endometriosis has been defined as a broad variation, ranging from 3 to 39 years with a mean of 17 years[1,7]. In the upfront surgery setting, in particular, wide surgical excision with a safety margin with or without reconstruction has been recommended for the surgical procedures of endometriosis, *per se,* the gold standard treatment of choice[1,6]. As well as to avoid the possible transformation, some authors recommend a wide excision with at least 10 mm margins in order to prevent the recurrence[6]. Some authors recommended surgical resection with margins at least 5 mm in diameter and depth[8,9]. Although the pathogenesis of endometriosis is not precisely known, immunologic factors, metaplasia, and confounding factors such as diagnosis of endometriosis before the first delivery, breastfeeding, previous surgery, and hormonal contraception are important. Theoretically, pregnancy, *per se*, a state of the altered immune response, and caesarean section could augment the risk of developing endometriosis. Some authors emphasized that the cases with two caesarean sections did not augment the risk of being diagnosed with endometriosis, compared with one caesarean section. In addition, it was stated that those who diagnosed with caesarean scar endometriosis after the first caesarean section are no longer at risk of developing endometriosis for the first time. *Inter alia,* some authors proclaimed that caesarean scar endometriomas are more common after unlabored caesarean sections[10,11]. *In fine, bene diagnosticur, bene curatur. Reddite ergo quae sunt Caesaris, Caesari.*

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AUTHORS' CONTRIBUTIONS

DS: Conceptualization, Supervision, Writing – original draft, Writing – review & editing. **IS:** Conceptualization, Writing – original draft, Writing – review & editing. **JMSJ**: Conceptualization, Writing – editing.

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Use of disease-modifying drugs (tocilizumab, tofacitinib, and baricitinib—a biological or synthetic target specific) in patients hospitalized with COVID-19

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: November 2021.

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

INTRODUCTION

In November 2019, the world was surprised with another pandemic that has spread with great speed, causing enormous loss of life across humanity. The etiologic agent is a virus, called coronavirus, belonging to the Coronaviridae family, whose genetic material is RNA. Being known to cause flu and enteric syndromes since 2003, coronavirus has been associated with severe acute respiratory syndrome (SARS) in Asia and the Middle East respiratory syndrome (MERS) in the Middle East in 2013. Numerous immunobiological drugs with antiviral action and inhibitors of the inflammatory cascade, linked to the physiopathogenesis of acute respiratory syndrome caused by coronaviruses (SARS-CoV-2), have been researched and tested to minimize damage in infected patients.

The benefit of glucocorticoids in critically ill patients supports the concept that an excessive host inflammatory response is responsible for much of the severe disease and death of COVID-19.

The advanced stage of COVID-19 is associated with high levels of C-reactive protein (CRP) and cytokines, including interleukin-1 (IL-1) and IL-6. IL-6 is a pleiotropic pro-inflammatory cytokine produced by several types of cells, including lymphocytes, monocytes, and fibroblasts. SARS-CoV-2 infection induces a dose-dependent production of IL-6 from bronchial epithelial cells. In some patients, this response becomes a non-specific inflammation, a "cytokine storm," involving edema and infiltration of inflammatory cells in the lungs, leading to hypoxia and respiratory failure, being considered an important cause of disease progression and even death of patients with COVID-19. These cases are among the most serious.

The recombinant monoclonal antibody tocilizumab (TCZ) blocks IL-6 receptors and is approved for use in patients with rheumatologic disorders and cytokine release syndrome induced by chimeric T-cell antigen receptor therapy.

Tofacitinib is a potent selective inhibitor of the Janus kinases (JAK) family. In enzymatic assays, tofacitinib inhibits JAK1, JAK2, JAK3, and, to a lesser extent, tyrosine kinase (TyK2). It also has a high degree of selectivity for other kinases in the human genome. In human cells, tofacitinib preferentially inhibits signaling from heterodimeric cytokine receptors associated with JAK3 and/or JAK1, with functional selectivity for cytokine receptors that signal through JAK2 pairs. The inhibition of JAK1 and JAK3 by tofacitinib attenuates the signaling of interleukins (e.g., IL-2, IL-4, IL-6, IL-7, IL-9, IL-15, and IL-21) and interferon types I and II, which results in modulation immune and inflammatory responses, with potential to reduce the damage of SARS-CoV-19.

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Baricitinib is a small molecule reversible JAK1 and JAK2 inhibitor with dual anticytokine and antiviral activity suggested against SARS-CoV-2 infection. It restricts excessive inflammatory signaling and blunts interferon-mediated induction of interferon response genes that include in at least some tissues the viral angiotensin-converting enzyme 2 (ACE2) receptor. Baricitinib inhibits the intracellular signaling pathway of cytokines known to be elevated in severe COVID-19, including IL-2, IL-6, IL-10, interferon-γ, and granulocyte–macrophage colony-stimulating factor, and acts against SARS-CoV-2 through the impairment of AP2-associated protein kinase 1, preventing SARS-CoV-2 cellular entry and infectivity.

OBJECTIVE

The aim of this systematic review was to evaluate the efficacy and safety of treatment with disease-modifying drugs, whether biological (TCZ) or synthetic target specific (tofacitinib and baricitinib), in patients with COVID-19.

METHODS

The clinical question is: What is the impact, on clinical outcomes that matter, of TCZ, tofacitinib, and baricitinib in the treatment of patients hospitalized with COVID-19 compared to conventional treatment?

The eligibility criteria of this study are as follows:

1. Adult patient hospitalized with COVID-19
2. Treatment with TCZ or tofacitinib or baricitinib plus standard therapy compared to conventional therapy with or without placebo
3. Outcomes—death (any cause) or mechanical ventilation (MV) or hospital discharge or adverse events
4. Intermediate outcomes excluded
5. Phase 3 randomized clinical trial
6. No period or language limit
7. Full-text available for access
8. Tracking time: 28 days minimum
9. No history of drug use

The search for evidence was performed in the virtual scientific information databases Medline, Embase, and ClinicalTrials.gov, using the search strategy (COVID OR COV OR CORONAVIRUS OR SARS) AND (tocilizumab OR tofacitinib OR baricitinib) AND random*. Searches in these databases were carried out until the month of September 2021. We imposed no restrictions regarding date of publication, language, or full-text availability.

Two independent researchers selected and extracted the data from the included studies. First, the articles were selected based on the title and abstract. Second, full texts were evaluated to include or exclude the studies; disagreements were resolved by consensus.

The following data were extracted from the studies: author's name and year of publication, population studied, intervention and comparison methods, absolute number of outcome events, and follow-up time.

The measures used to express benefit and harm varied according to outcomes expressed as continuous variables (mean and standard deviation) or expressed as categorical variables (absolute number of events). The results are expressed as mean difference and standard deviation for continuous variables and as absolute risks, risk differences (RD), and the number needed to treat (NNT) or number needed to harm (NNH) for categorical variables. The confidence level used is 95%. If there are common outcomes among the included studies, the results will be expressed through meta-analysis, using the RevMan version 5.4 software[1].

If there is a possibility of performing the meta-analysis, the adopted analysis model varies according to the level of heterogeneity, being fixed for levels of heterogeneity <50% and random when ≥50%.

Randomized clinical trials will have their risk of bias analyzed using the RoB version 2 instrument[2], being considered as very serious, serious, or nonserious. The quality of evidence will be assessed by the GRADE system—Grading of Recommendations Assessment, Development and Evaluation using the GRADEpro software[3], with grading of the quality of evidence as very low, low, moderate, or high.

RESULTS

In the search for evidence, 229, 32, and 72 papers were retrieved in Medline, Embase, and ClinicalTrials.gov, respectively. Of these, meeting the eligibility criteria, 11 studies were selected[4-14], 9 evaluating the use of TCZ[4-12], 1 the use of tofacitinib[13], and 1 the use of baricitinib[14], in the treatment of patients hospitalized with COVID-19, in comparison with conventional therapy [standard care (SC)] with or without placebo (Figure 1).

The results are expressed in the following order and form: (1) TCZ, (2) tofacitinib, and (3) baricitinib, including the synthetic description of the studies included, the risk of bias, and the analysis of their results (also expressed as "forest plots" in the presence of meta-analysis).

TOCILIZUMAB

A total of 6,489 inpatients with moderate/severe COVID-19, who were undergoing therapy with TCZ (n=3,358) compared to conventional treatment with or without placebo (n=3,131), and who were followed to measure the outcomes of death, MV, hospital discharge, and adverse events within 28–30 days of admission were included.

Regarding the risk of bias of the 9 studies included, only 3 of them were double-blind and had evaluator blinding; two had losses >20%; one did not perform sample calculation and analysis by ITT; and two had early interruption, therefore, we considered the overall risk of bias of the studies to be moderate.

The nine studies evaluated the outcome of death from any cause (Figure 2); five MV studies (Figure 3), six hospital discharges (Figure 4), and eight serious adverse events (Figure 5); all outcomes in a follow-up of up to 28–30 days.

Nine studies allowed us to assess the death outcome in 28–30 days, with a total of 6,489 participants, and comparing the TCZ+SC with SC alone, there was no significant difference [absolute risk reduction (RRA)=-0.01; 95%CI -0.04 to 0.03; I^2=60%] (Figure 2). This results in low quality of evidence.

Six studies allowed us to evaluate the outcome of MV in 28–30 days, with a total of 3,062 participants, and comparing TCZ+SC with SC alone, TCZ reduces the risk of MV by 2% (RRA=-0.02, 95%CI -0.04 to -0.00; I^2=0%), requiring

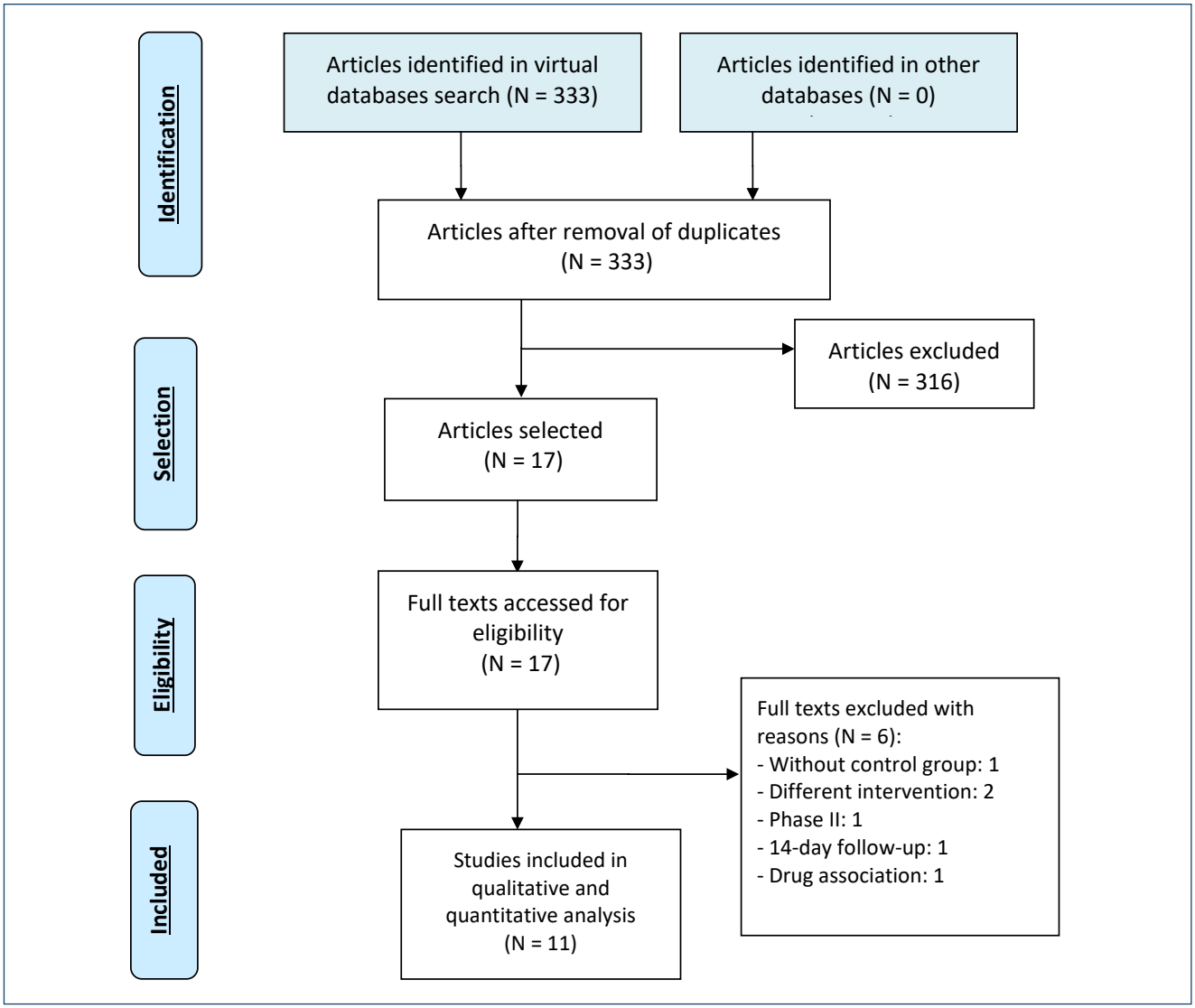

Figure 1. Evidence selection and retrieval diagram. Adapted from: Moher D, Liberati A, Tetzlaff J, Altman DG, The PRISMA Group. Preferred reporting items for systematic reviews and meta-analyses: the PRISMA statement. PLoS Med. 2009;6(7):e1000097. https://doi.org/10.1371/journal.pmed1000097

25 patients to be treated to avoid MV (95%CI 25–1,000) (Figure 3). This results in low quality of evidence.

Six studies allowed us to assess the outcome of hospital discharge within 28 days, with a total of 5,743 participants. Comparing TCZ+SC with SC alone, there was an increase of 6% (95%CI 4–8%) favoring the use of TCZ, being necessary to treat 16 patients (95%CI 12–25) to obtain a hospital discharge during this period (I^2=0%, Figure 4). This results in moderate quality of evidence.

Eight studies allowed evaluating the outcome of serious adverse events, with a total of 2,376 participants. Comparing the TCZ+SC with SC alone, there was no difference between the two approaches (RRA=-0.01, 95%CI -0.02 to 0.01; I^2=0%) (Figure 5). This results in moderate quality of evidence.

TOFACITINIB

A total of 289 patients, aged >18 years, diagnosed with SARS-CoV-19 by polymerase chain reaction (PCR), with radiological image of bronchopneumonia, admitted for <72 h, were included in the study using tofacitinib. Exclusion criteria were noninvasive and invasive ventilation, extracorporeal membrane oxygenation (ECMO), history of thrombosis, immunosuppression, and cancer in current or recent treatment. A total of 144 patients received tofacitinib (10 mg, orally, twice a day for 14 days or until hospital discharge) and 145 received placebo. The primary composite end point was respiratory failure and death, with follow-up up to 28 days. Secondary outcomes were death within 28 days, patients not using MV or ECMO, patients not hospitalized within 14 and 28 days, cure (fever resolution, cough, and no O_2 support), length of hospital stay, and length of stay in the intensive care unit (ICU).

Regarding the risk of bias, assessed using the RoB version 2 tool, it was not blinded, and the outcome was composed (death and respiratory failure); thus, the risk of bias may be considered moderate.

There was an RRA, composite outcome, death, and respiratory failure, in a follow-up of up to 28 days. Also, there was an RRA of 11% (95%CI 1–21%), requiring nine patients to be treated for a benefit. This results in very low quality of evidence.

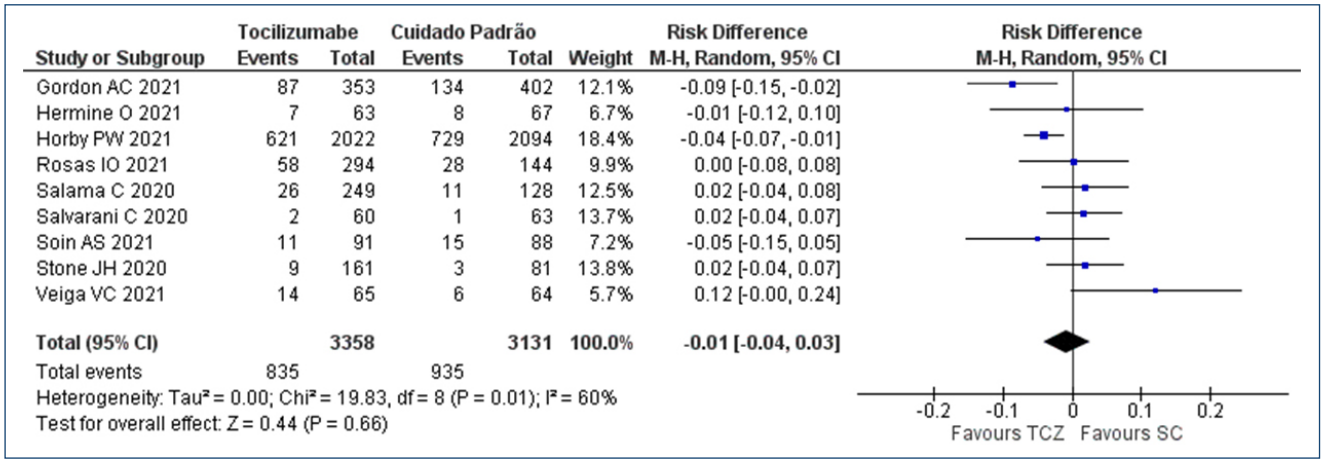

Figure 2. Tocilizumab versus standard care in the incidence of death up to 28 days.

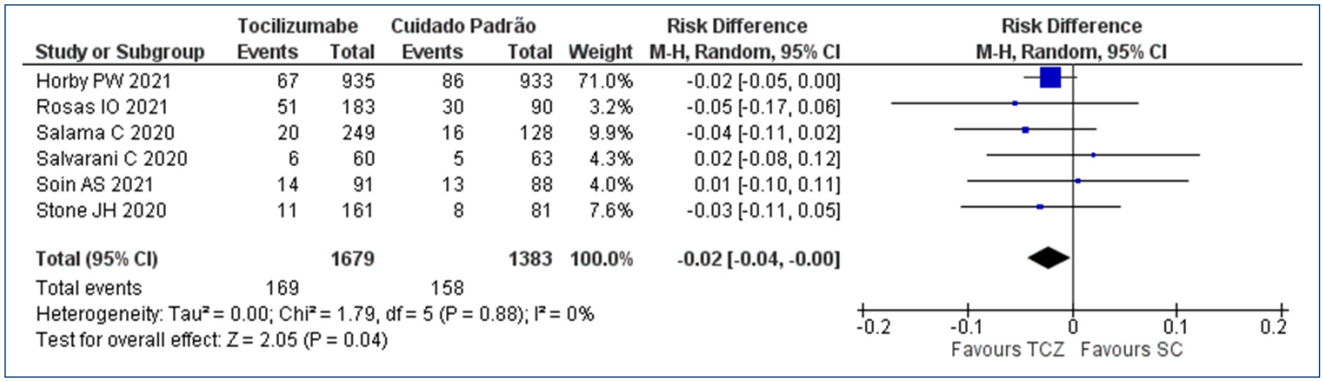

Figure 3. Tocilizumab versus standard care in the incidence of mechanical ventilation up to 28 days.

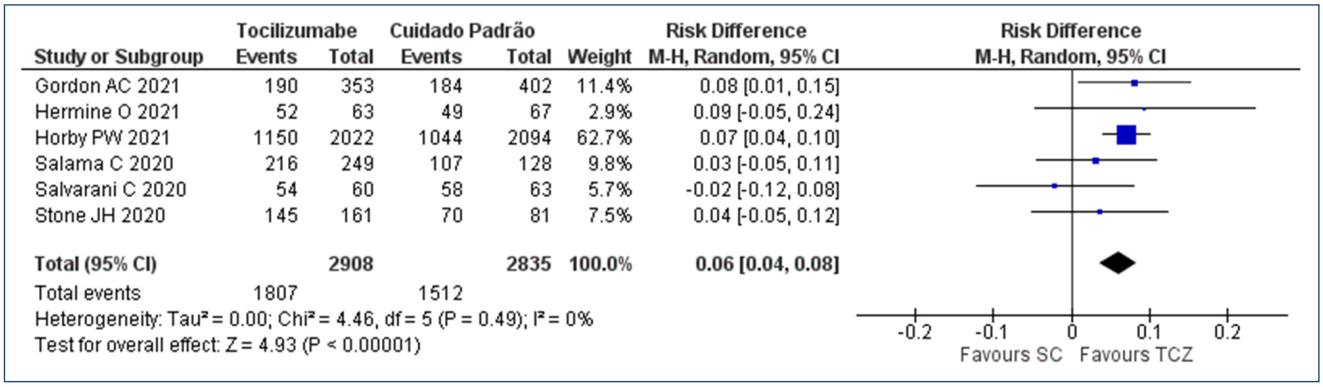

Figure 4. Tocilizumab versus standard care in the incidence of hospital discharge within 28 days.

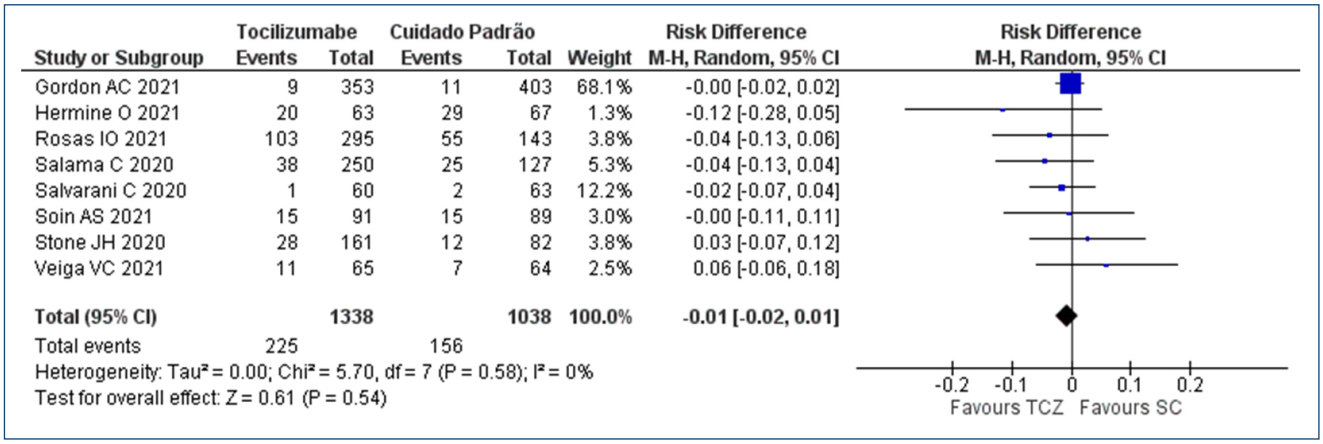

Figure 5. Tocilizumab versus standard care in the incidence of serious adverse events up to 28 days.

Regarding the death within 28 days outcome, there was no significant RRA (3%) (95%CI -7 to 2%). This results in low quality of evidence.

In the evaluation of serious adverse events, there was no difference between the two groups (2%) (95%CI -6 to 10%). This results in low quality of evidence.

BARICITINIB

In this multicenter, randomized, double-blind, placebo-controlled, parallel-group, phase 3 study, eligible participants were at least 18 years of age, were hospitalized with laboratory-confirmed SARS-CoV-2 infection, and had evidence of pneumonia or COVID-19 active and symptomatic. Participants were excluded if, at baseline, they required invasive MV.

Randomization was facilitated by a computer-generated random sequence using a web-interactive response system and was allowed by a study investigator to allocate 1:1 participant to the baricitinib group or the placebo group. Interventions were allocated to identical bottles containing 2 mg baricitinib tablets (total of 4 mg) or matching placebo. Baricitinib tablets or placebo were administered orally (or crushed for administration by nasogastric tube) and administered daily for up to 14 days or until hospital discharge.

The primary composite end point was the proportion of participants who progressed to high-flow oxygen or noninvasive ventilation, invasive MV or ECMO, or death at day 28 in the baricitinib group compared with the placebo group.

Baseline demographics and disease characteristics were similar between study groups. Of the 1,502 participants, 1,248 (83.1%) completed the 28-day treatment period and 254 (16.9%) discontinued treatment during this period, of which 159 (62.6%) died.

There was a 5% reduction in the risk of death, ranging from 2 to 8%, being necessary to treat 20 patients for a benefit, ranging from 12 to 50. There were 62 deaths in 764 patients on

baricitinib (8% risk of death with baricitinib) and 100 deaths in 761 patients in the placebo group (13% risk of death). This results in low quality of evidence.

Regarding adverse events, 334 (45%) of 750 participants in the baricitinib group and 334 (44%) of 752 in the placebo group had at least one treatment-emergent adverse event, and serious adverse events were noted in 110 (15%) participants in the baricitinib group and 135 (18%) in the placebo group. This results in low quality of evidence.

The risk of bias is serious when losses occur due to death in patients who were not submitted to the treatment protocol, but who were included in the mortality outcome. Losses due to death were uneven (unbalanced) between the two groups (7.9% for baricitinib and 12.8% for placebo). In addition, the analysis by intention (for mortality) of treatment was inappropriate as it considered the losses due to death in the risk calculation, as well as the expression of benefit was expressed by hazard ratio (HR) and not by RD (RRA), thus increasing the magnitude of the benefit.

RECOMMENDATION

In patients hospitalized with COVID-19:

- The use of TCZ can reduce the risk of needing MV (2%) and increase the rate of hospital discharge (6%); however, there was no significant RRA of death.
- There is no benefit from using tofacitinib.
- The use of baricitinib can reduce mortality by 5%.

The quality of evidence to support these recommendations is low.

AUTHORS' CONTRIBUTION

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

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Comment on "Limited cardiopulmonary capacity in patients with liver cirrhosis when compared to healthy subjects"

Jundong Wang[1], Zhipeng Li[1*]

Dear editor,

We read an interesting article, written by Nasser et al.[1], entitled "Limited cardiopulmonary capacity in patients with liver cirrhosis when compared to healthy subjects." In this valuable article, the authors found that the cardiopulmonary capacity of patients with liver cirrhosis was lower than that of healthy subjects. Although there is no obvious controversy over authors' findings, we still find some issues in this article that are worth discussing.

The objective of this study, as mentioned in summary, was to compare the cardiopulmonary function of patients with cirrhosis and healthy subjects. However, we combine this objective with that mentioned in the conclusion: "To provide reference for the future research, which is recommended to develop an appropriate physical exercise plan for patients with liver cirrhosis, enhance the patient's cardiopulmonary function, and improve the quality of life." Therefore, we propose to modify the objective in summary to "compare and analyze the cardiopulmonary function of patients with liver cirrhosis and healthy subjects and provide a reference for improving the survival plan of patients with liver cirrhosis."

In the last paragraph of introduction, we find the authors described it in this way: "Patients with liver cirrhosis often lack exercise and have a sedentary lifestyle, which may damage their liver function and further harm their health." Although this conclusion has been confirmed in previous studies[2], the authors missed adding references to support this statement. We suggest adding the corresponding references here.

In the statistics analysis section, the authors paid attention only to age and gender. No statistically significant difference was found for age in this study; this may be due to other demographic characteristics, such as occupation and residence, which may also affect the comparison results. Thus, these differences should also be considered in the pairing analysis. In addition, sample size in this study is relatively small, with only 19 subjects in each group. Therefore, we recommend using absolute numbers instead of relative numbers in the results section. Also, we suggest to enlarge the sample size as much as possible to better corroborate the results of this experiment.

AUTHORS' CONTRIBUTIONS

JW: Formal analysis, Writing – original draft. **ZL:** Conceptualization, Writing – review and editing.

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Froin's syndrome with tuberculosis myelitis and spinal block

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INTRODUCTION

Tuberculosis is a leading cause of infectious disease death worldwide among adults. It has been considered a global public health emergency for the past 25 years[1]. The most severe form is meningitis, which has a high morbimortality, with roughly 50% of patients dead or disabled[2]. An important finding, which can be caused by tuberculosis, is cerebrospinal fluid (CSF) block, with unusual high protein content caudal to it, described as Froin's syndrome.

OBJECTIVE

The aim of this study is to describe a clinical and CSF finding in Froin's syndrome caused by tuberculosis myelitis and a review on Froin's syndrome.

METHODS

The patient data were collected through hospitalization details from September 2016 to September 2018 in an ambulatory consultation.

A short study was done as a systematic review using PubMed with the terms "Froin Syndrome" or "Froin's Syndrome" for etiological identification and CSF analysis. The inclusion criteria were provided information about Froin's syndrome, and exclusion criteria were non-English and earlier than 1950. Also, we did not include abstracts. References from the articles were checked.

RESULTS

A 64-year-old diabetic female patient presented in the emergency department with acute onset of confusion and walking difficulty. Magnetic resonance imaging (MRI) showed a diffusion-weighted hypersignal in the cerebellar vermis, with initial suspicion of stroke. As the patient developed fever, CSF was collected. It showed a lymphocytic pleocytosis. We started acyclovir, cefepime, and vancomycin and then underwent fungal and tuberculosis microbiology tests. The patient worsened her clinical status with lethargy and was admitted to intensive care, where she was placed in mechanical ventilation. The results from repeated MRI revealed hydrocephalus. However, another lumbar puncture was performed with a higher white blood cell (WBC) count, neutrophilic predominance, and an unusual high protein content (Table 1). Since these abnormal proteins increased, neuraxis MRI was performed considering a spinal block (Figure 1). It showed a T2 hypersignal in the cervical spine with CSF block, confirming Froin's syndrome. Anti-tuberculous drugs were added to the scheme with corticoid and external drainage was placed for 5 days where protein chain reaction to mycobacterium was positive. During this, a thorax tomography showed a true-in-bud pattern. All antibiotics were suspended, except for tuberculosis. The patient regained her consciousness and was found with a paraparesis. She had a slow recuperation. Corticoid was withdrawn in a long-time schedule, because she usually had worse leg strength as we lower corticoid doses. After 2 years, she was able to walk with assistance with some degree of spastic paraparesis.

A SHORT SYSTEMATIC REVIEW

There were 14 references matched the search, and their abstracts were reviewed. If there were no abstract, the entire article was reviewed. Two excluded article contained a diagnostic method and non-human cases, respectively. From the remaining 12 papers, one was excluded from the final analysis because it did not have CSF analysis[3]. Two papers were added by searching references section. From these 13 papers, the disease has been described in many conditions with CSF analyses (Table 2).

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Table 2. Articles selected from the systematic review.

		Protein (mg/dL)	White blood cell count (mm³)	Red blood cell count (mm³)
Kleinschmidt-DeMasters B.K. et al. 1998[4]	Necrotizing vasculitis by varicella-zoster virus encephalomyelitis	1,877	1,330	4,430
Mohee K. et al. 2012[5]	CIDP and L2 disc compression	612	2	1
Govindarajan R. and Khan T. 2012[6]	Epidural abscess	3,295	Normal	888
Ljevak J. et al. 2014[7]	Glioblastoma multiforme in the brain and spinal cord	1,700	53	–
Kwon S.-K. and Kim M.-W. 2014[8]	Previous trauma	3,114	50	0
Heckmann J.G. 2015[9]	Alzheimer plus varicella-zoster virus encephalitis	625	321	–
Dancel R. and Shaban M. 2016[10]	Schwannoma	+1,500	1	–
Hale A.T. et al. 2018[11]	Atypical teratoid/rhabdoid tumor	1,250	–	–
Maharjan K. et al. 2018[12]	Tuberculosis epidural abscess	+1,500	–	–
Moscote-Salazar L.R. et al. 2019[13]	Epidural abscess	1,300	25	
Sánchez Carteyron A. et al. 2019[14]	Cerebral glioblastoma multiforme with canal from ventricular stagnation to subarachnoid space	+3,000	–	–
Garispe A. et al. 2019[15]	Trauma and varicella-zoster virus encephalitis and HIV	1,290	63	78
Decramer T. et al. 2019[16]	Trauma	3,800	–	Few

Table 1. Cerebrospinal fluid analysis from the first lumbar puncture (day 1) and the following cerebrospinal fluid analysis.

	First lumbar CSF	Second lumbar CSF	Ventricular external drainage
White blood cell (count/mm³)	178	840	20
Lymphocytes (%)	75	30	65
Glucose (mg/dL)	67	64	58
Protein (mg/dL)	590	2,321	58
Opening pressure (mmH_2O)	200	210	–

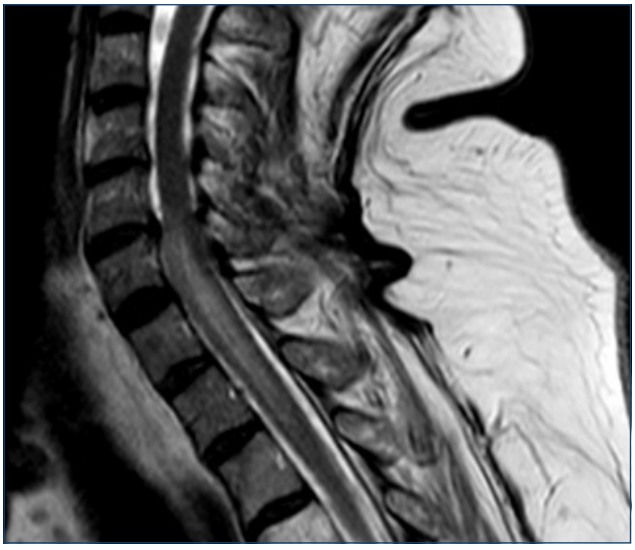

Figure 1. A T2 hypersignal in the cervical spine with cerebrospinal fluid block (Froin's syndrome).

DISCUSSION

Tuberculous meningitis is the most severe form of tuberculosis—nearly 1% of all forms of tuberculosis. Usually, it begins with nonspecific clinical manifestations, such as fatigue, fever, headache, resulting confusion and coma in few weeks[2]. As it progresses, it can have focal brain infarct and hydrocephalus[17]. In this case, the evolution was faster than expected, with acute clinical manifestations and with a rapid evolution to coma. Also, the spine can be affected by tuberculosis, the most known is Pott disease—tuberculosis spondylitis, and with spinal infarction, myelitis, and tuberculoma[18]. In this case, we had a spinal lesion attributed to myelitis, with CSF spinal block leading to Froin's syndrome. It showed a very high protein content caudal to the block and the relatively small increase in the external derivation CSF sample, confirming the spinal block.

Froin's syndrome was described more than 100 years ago. It is the combination of xanthochromia, elevated protein, and hypercoagulated CSF, associated with spinal block[3]. Initially, it was associated with neoplasm; however, it has been described as meningitis, epidural abscess, and trauma. Even only mechanical block can cause it. In our review, different mechanisms have been described. No cases were reported with tuberculosis meningitis and myelitis. Only one case was associated with tuberculosis in Pott disease context[12]. Three cases were associated with varicella-zoster virus encephalitis[4,9,15]. One of them was reported a high protein content with no block[9], which is odd. The pathophysiology is thought to be due to stagnant CSF, causing passive or active diffusive processes resulting in hyperproteinosis

and hypercoagulation[5]. Moreover, one case was reported with a ventricular block[14]. In CSF analysis, there are wide ranges of white blood cells and red blood cells, probably related to etiology. The elevated protein level was found in all cases; as the hallmark of the syndrome, most of the cases were at extreme levels.

Our review has some limitations. We did not include papers before 1950. Also, we do not search from abstracts, which could have more descriptions, since the case reports are prevalently published as abstracts or posters.

Froin's syndrome has been described in seminal works from the beginning of the 20th century. However, nowadays, few reports are exploring the theme. We believe that it should be widespread among clinics and neurologists, because the unique aspects of the syndrome may help to diagnose and manage the diseases properly.

CONCLUSION

Our case had an atypical rapid evolution, but some aspects of tuberculosis meningitis had given clues to diagnosis, such as the hydrocephalus and the abnormal high CSF protein content. But the knowledge of possible Froin's syndrome improved the diagnosis work, with tuberculous myelitis-induced spinal block in a comatose patient.

AUTHORS' CONTRIBUTIONS

CEM: Conceptualization, Project administration, Supervision, Writing – original draft. CEM, RL: Data curation, Formal Analysis, Investigation, Methodology, Writing – review & editing. All authors contributed equally to the manuscript.

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ORIGINAL ARTICLE

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Aesthetic assessment of breast reconstruction in the eyes of plastic surgeons versus nonplastic physicians

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SUMMARY

OBJECTIVE: The aim of this study was to evaluate the perception of the aesthetic result of breast reconstruction surgery from the perspective of plastic surgeons compared with physicians who are not specialists in plastic surgery.

METHODS: Twenty patients who underwent breast reconstruction after mastectomy had their aesthetic results evaluated by 16 plastic surgeons and 16 nonplastic physicians, yielding a total of 620 ratings (320 ratings from plastic surgeons and 320 ratings from other specialists). For all analyses, the level of rejection adopted for the null hypothesis was 5% (p-value <0.05).

RESULTS: Significant differences were observed between the two groups. On average, medical professionals who specialized in plastic surgery always obtained higher scores than other physicians. However, no significant differences were found in the assessment of the aesthetic outcome of breast reconstruction according to the sex of the rating medical professional for any of the assessments considered in this study. A strong positive linear correlation between the time since training in the medical specialty of plastic surgery (r=0.750, p=0.001) and the mean aesthetic outcome score was observed in this study.

CONCLUSION: Plastic surgeons assessed the aesthetic results of breast reconstruction more positively than nonplastic physicians.

KEYWORDS: Breast neoplasms. Reconstructive surgical procedures. Mastectomy.

INTRODUCTION

The evaluation of aesthetic outcomes in the treatment of breast cancer is important because patient satisfaction and oncological outcomes are considered determinants of quality of life[1].

Several instruments are used to measure the aesthetic outcome of breast reconstruction from the medical point of view. The most frequently used subjective method is an assessment performed by one or more observers, typically through photographic records, using scales that compare the treated breast with the untreated breast[2].

Although many questionnaires are used to evaluate outcomes reported by the patients involved in studies on reconstructive and cosmetic breast surgery, only few have been subjected to any formal development or validation, with the exception of the Breast-Related Symptoms Questionnaire[3]. However, this questionnaire is intended only for patients and not for professionals involved in treatment.

Understanding the geometry of anthropometric proportions and its relationship with beauty and identifying the objections regarding the "ideal" aesthetic morphology are essential in defining the goals of breast surgery[4,5].

The assessment of aesthetic outcome in breast cancer surgery is especially relevant because patient satisfaction and oncological outcome are the predominant factors that determine the quality of life[6-8].

This study compared the results of the aesthetic assessment of breast reconstruction from the perspective of plastic surgeons (i.e., physicians who are directly involved in breast reconstruction) versus nonplastic physicians (i.e., physicians who have no experience in breast reconstruction) using an aesthetic assessment scale for healthcare professionals.

METHODS

Standardized photographs of the breast were obtained from a cross-sectional study of 20 patients who underwent reconstruction more than 1 year earlier. Inclusion criteria were as follows: patients with only breast reconstruction and without

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symmetrization, reconstructed patients with symmetrization but without nipple reconstruction, and patients who had already completed the three stages of reconstruction. The study protocol was approved by the Institutional Ethics Committee in Research, and informed consent was obtained.

The photographs were taken by a single researcher at a standardized distance and patient position. A digital camera with a resolution of 12 MP was used. All surgeries were performed by the same multidisciplinary team consisting of a breast surgeon and a plastic surgeon. Breast reconstruction procedures included techniques using autologous flaps and breast prostheses. The photographs were evaluated according to the criteria presented in the modified scale by Garbay et al.[9] (volume of breast, shape of breast, placement of breast, inframammary fold, and breast scars). Then, the findings were classified from 0 to 10, where 0 was the worst and 10 was the best result.

All raters were physicians: 16 plastic surgeons and 16 nonplastic physicians. All ratings of plastic surgeons were certified by the Brazilian Society of Plastic Surgery. None of the raters participated in the patient treatment. Each rater performed, by themselves or by other raters, the assessments independently without accessing the previous assessments.

The demographic and professional variables of the study participants were descriptively analyzed according to sex, age group, medical specialty, and length of time in medical specialty practice. Qualitative variables were described as absolute and relative frequencies, while the quantitative variable related to length of time in practice was described as the mean and 95% confidence interval (95%CI), in addition to minimum and maximum values.

To make comparisons between physicians who specialize in plastic surgery and those who do not, as well as between the professionals according to sex, a test was conducted to detect differences in mean scores corresponding to the final breast aesthetic outcome, which ranged from 0 to 10. These comparisons were performed for each evaluated patient (n=20) and in relation to the mean of all patients. Either Student's t-test (parametric test suitable for normal distribution) or the Mann–Whitney U test (counterpart test for nonparametric distribution) was used, depending on the nature of the variable. The Shapiro–Wilk normality test was used for decision-making. In addition to the values presented in tables, these differences are also presented in boxplots.

Due to the evidence of significant differences in the assessment of physicians according to specialty, the absolute and relative frequencies of the variables, such as breast volume, shape, position, sulcus, and scar, were compared. For these variables, Kendall's W concordance coefficient was estimated to assess interobserver agreement.

The Pearson correlation coefficient (r) and its respective p-value were also estimated to assess the association between length of time in their professional practice (considered the time since the completion of medical specialty training) and the final aesthetic outcome score of breast reconstruction surgery, according to medical specialty. For all analyses, the level of rejection adopted for the null hypothesis was 5% (p-value <0.05).

RESULTS

A total of 32 physicians evaluated the aesthetic outcome of 20 patients undergoing breast reconstruction surgery after mastectomy due to breast cancer, resulting in a total of 620 assessments (320 assessments by plastic surgeons and 320 assessments by nonplastic physicians).

Notably, 53.1% of the raters were women, 59.4% aged between 30 and 40 years of age, and 59.4% had practiced their medical specialty for less than 10 years, with a mean of 9.9 years (95%CI: 6.2–13.7).

Considering all the raters, when observing the aesthetic outcome of the breast reconstruction, a score of 0–10 was assigned. On average, the scores ranged from 3.1 to 9.1, but patients were given a score of 5.9 (95%CI: 5.3–6.5).

On average, the medical professionals who specialized in plastic surgery always obtained higher scores than other physicians; this difference was significant at 95%CI (Table 1).

On average, plastic surgeons gave a score of 7.0 (95%CI: 6.5–7.6, ranging from 5.5 to 9.1), while nonplastic physicians gave a score of 4.8 (95%CI: 4.0–5.6, ranging from 3.1 to 8.5), which represents a mean difference of 2.3 (95%CI: 1.3–3.2).

A high positive linear correlation was also observed between the time since training in the medical specialty of plastic surgery (r=0.750, p-value=0.001) and the mean aesthetic outcome score. In contrast, the same result was not observed for physicians from other specialties (r=0.061, p-value=0.0822).

Regarding breast volume of the 320 assessments performed by plastic surgeons (16 physicians and 20 patients), 43.8% evaluated volume with a marked discrepancy compared with the contralateral side. For nonplastic physicians, 57.8% of the assessments were also scored similar to that above. Regarding shape, 29.7% of plastic surgeons determined that the breast had a natural or symmetrical contour compared with only 11.6% of nonplastic physicians. The assessments of the position, sulcus, and scar of the breast reconstruction were also discrepant, as plastic surgeons obtained higher scores (Table 2).

Table 1. Results of the final aesthetic assessment of patients according to the medical specialty of the physicians who evaluated them.

Patients	Plastic surgeon				Differences*	95%CI or z (p-value)	
	Yes		No				
	Median (SD)		Median (SD)			Superior	Inferior
Patient 1	5.9	(1.5)	2.9	(1.9)	3.0	1.7	4.3
Patient 2**	8.7	(1.1)	6.9	(1.4)	1.8	z=−3.1	(0.001)
Patient 3	6.5	(2.0)	3.6	(1.9)	2.9	1.4	4.4
Patient 4	6.6	(1.7)	3.5	(2.6)	3.2	1.5	4.8
Patient 5**	8.1	(0.8)	6.6	(1.8)	1.5	z=−2.8	(0.006)
Patient 6	7.0	(1.4)	3.9	(2.3)	3.1	1.7	4.5
Patient 7	5.9	(1.3)	3.1	(2.3)	2.9	1.5	4.2
Patient 8	7.3	(1.3)	4.1	(2.2)	3.2	1.8	4.5
Patient 9	6.4	(1.6)	4.3	(2.5)	2.1	0.6	3.6
Patient 10	7.7	(1.5)	6.1	(1.4)	1.6	0.5	2.6
Patient 11**	4.9	(1.7)	2.0	(1.6)	2.9	z=−3.7	(0.001)
Patient 12**	5.9	(1.8)	4.3	(1.6)	1.7	z=−2.6	(0.008)
Patient 13**	6.6	(1.9)	3.9	(1.7)	2.6	z=−3.4	(0.001)
Patient 14	6.8	(1.7)	4.9	(2.2)	1.9	0.4	3.3
Patient 15**	9.4	(0.6)	7.8	(1.3)	1.6	z=−3.4	(0.001)
Patient 16**	8.9	(0.9)	6.6	(1.7)	2.3	z=−3.7	(0.001)
Patient 17	6.3	(2.0)	3.9	(2.2)	2.3	0.8	3.8
Patient 18	6.1	(1.5)	4.8	(2.0)	1.3	0.0	2.5
Patient 19**	8.3	(1.1)	6.3	(1.8)	2.0	z=−3.1	(0.002)
Patient 20	7.2	(1.4)	5.5	(1.8)	1.7	0.5	2.8
Median	7.0	(1.0)	4.8	(1.5)	2.3	1.3	3.2

Note: *All differences were significant. **Significant Shapiro–Wilk normality test (p-value <0.05); thus, the Mann–Whitney U test for comparison of means was adopted.

Regarding the assessment of the aesthetic outcome of breast reconstruction according to the sex of the medical professional, no significant differences were found for any of the assessments in this study. The mean score given by female doctors was 6.0 (95%CI: 5.1–7.0), while the mean score given by male doctors was 5.7 (95%CI: 4.9–6.5) (Table 3).

It was observed that plastic surgeons had higher levels of agreement in three of the five variables analyzed, namely, breast volume, shape, position, sulcus, and scar. Nonplastic surgeons had higher levels of agreement regarding position (W=0.43) and sulcus (W=0.39). The levels of agreement between the specialties were greater than that between sex regarding breast volume and shape.

Among the female doctors, the levels of agreement were higher for the position (W=0.42) and sulcus (W=0.37) variables. This same result was identified for male doctors, but the levels of agreement were higher (W=0.49 and W=0.48, respectively) when compared with the female doctors.

Regardless of sex or medical specialty, the levels of agreement in relation to the position and sulcus are distinct compared with other variables.

DISCUSSION

In this study, we compared assessments by plastic surgeons and nonplastic physicians in the cosmetic outcome of breast reconstruction to observe the differences between the evaluations of plastic surgery specialists and nonspecialists. Since the modified Garbay scale[9] with technical terms aimed at health professionals, nonspecialist physicians would be able to interpret it and, at the same time, would have a "lay" view regarding the results of the reconstruction. The researchers, who were not

Table 2. Results according to variables related to breast volume, shape, position, sulcus, and scar.

Variables	Plastic surgeon			
	Yes		No	%
	n	%	n	
Volume				
Marked discrepancy relative to contralateral side	140	43.8	185	57.8
Mild discrepancy relative to contralateral side	107	33.4	90	28.1
Symmetrical volume	73	22.8	45	14.1
Shape				
Marked contour deformity or shape asymmetry	105	32.8	168	52.5
Mild contour deformity or shape asymmetry	120	37.5	115	35.9
Natural or symmetrical contour	95	29.7	37	11.6
Placement of breast				
Marked displacement	46	14.4	133	41.6
Mild displacement	139	43.4	116	36.3
Symmetrical and aesthetic placement	135	42.2	71	22.2
Inframammary fold*				
Poorly defined/not identified	39	12.2	148	46.5
Defined but with asymmetry	141	44.1	109	34.3
Defined and symmetrical	140	43.8	61	19.2
Breast scars				
Poor (hypertrophy and contracture)	29	9.1	94	29.4
Fair (wide scars and poor color match, but without hypertrophy and contracture)	110	34.4	116	36.3
Good (thin scars and good color match)	181	56.6	110	34.4

Note: *Loss of two data points related to the assessment by non-plastic physicians (n=318).

specialists in plastic surgery, could have an expectation close to that of patients, since they are not acquainted with the results of breast reconstruction.

Significant differences were observed between the two groups. On average, medical professionals who specialized in plastic surgery always obtained higher scores compared with physicians from other specialties.

This is in contrast to the study by Veiga et al.[1], which compared the assessments of two plastic surgeons versus two breast surgeons and found that breast surgeons scored the aesthetic outcome higher than the plastic surgeons.

In the study by Kuroda et al., the aesthetic outcomes of 98 patients who underwent breast reconstruction were evaluated by three different methods: patient self-report, BCCT. core software (Breast Cancer Conservation Treatment. cosmetic results), and assessment of four independent specialists (two breast surgeons and two plastic surgeons) from different institutions. They concluded that the assessments by plastic surgeons and breast surgeons were not in agreement[10].

Wachter et al. compared the assessment of aesthetic outcomes after immediate and late breast reconstruction with implants between 47 patients and 18 professionals (medical students, doctors, and seniors) and observed that the assessments did not differ significantly among the professionals. However, the assessments made by patients were better, whereas the assessments made by the medical professionals were more critical[11].

Patients are typically less critical of the aesthetic outcome than medical professionals, which suggests that patients consider other factors when evaluating the aesthetic outcome[10,12,13].

The assessment of photographic records by one or more specialists is frequently used to evaluate the cosmetic outcome of breast reconstructions, but since aesthetic outcome is a subjective measure, it is difficult to measure the results of breast reconstruction procedures.

Table 3. Results of the final aesthetic assessment, according to the sex of the rating medical professional.

Patients	Plastic surgeon				Differences*	95%CI or z (p-value)	
	Female		Male				
	Median (SD)		Median (SD)			Inferior	Superior
Patient 1	4.3	(2.2)	4.5	(2.5)	−0.2	−1.9	1.5
Patient 2**	8.1	(1.7)	7.6	(1.3)	0.5	z=−1.0	(0.338)
Patient 3	5.8	(2.6)	4.4	(2.1)	1.4	−0.4	3.1
Patient 4	5.4	(3.1)	4.7	(2.3)	0.7	−1.3	2.7
Patient 5**	7.6	(1.2)	7.1	(1.9)	0.4	z=−0.4	(0.711)
Patient 6	5.3	(2.6)	5.8	(2.3)	−0.6	−2.4	1.3
Patient 7	4.6	(2.7)	4.5	(2.0)	0.0	−1.7	1.8
Patient 8	5.9	(2.8)	5.5	(2.0)	0.5	−1.3	2.3
Patient 9	5.3	(2.8)	5.5	(1.8)	−0.2	−2.0	1.5
Patient 10	6.9	(1.7)	6.9	(1.6)	0.1	−1.1	1.3
Patient 11**	3.6	(2.5)	3.3	(1.9)	0.3	z=−0.3	(0.766)
Patient 12**	5.6	(2.0)	4.5	(1.6)	1.1	z=−1.5	(0.132)
Patient 13**	5.4	(2.4)	5.1	(2.1)	0.3	z=−0.4	(0.682)
Patient 14	6.4	(2.4)	5.2	(1.8)	1.2	−0.4	2.7
Patient 15**	8.6	(1.2)	8.6	(1.5)	0.0	z=−0.3	(0.794)
Patient 16**	7.6	(2.0)	7.9	(1.6)	−0.2	z=−0.3	(0.794)
Patient 17	5.6	(2.6)	4.5	(2.0)	1.2	−0.5	2.9
Patient 18	5.9	(1.9)	4.9	(1.7)	0.9	−0.3	2.2
Patient 19**	7.1	(1.9)	7.5	(1.7)	−0.4	z=−0.6	(0.576)
Patient 20	6.1	(2.2)	6.6	(1.2)	−0.5	−1.8	0.8
Median	6.0	(1.9)	5.7	(1.4)	0.3	−0.9	1.6

Note: *None of the differences were significant. **Significant Shapiro–Wilk normality test (p-value <0.05); thus, the Mann–Whitney U test for comparison of means was adopted.

In our study, we observed that the agreement among physicians who specialized in plastic surgery was always higher than among physicians who do not specialized in plastic surgery. This finding suggests that although examination of photographs is a subjective method, when photographic records are assessed by experienced observers, this can become a valid method. However, this type of assessment hinders conclusions when photographs are evaluated by nonspecialists.

In the study by Dikmans et al., in addition to the patients, five plastic surgeons and three mammography nurses evaluated breast reconstruction through photographs. They concluded that the agreement among experienced plastic surgeons was higher than among mammography nurses[13].

Regarding the assessment of the aesthetic outcome of breast reconstruction according to the sex of the rating medical professional, no significant differences were found for any of the assessments considered in this study. These results are in agreement with those of Wachter et al.[11]. However, Veiga et al.[1] observed that female specialists obtained higher scores.

A strong correlation between the time since training in the medical specialty of plastic surgery and the mean aesthetic outcome score may indicate that the experience of plastic surgeons decreases their expectation regarding the outcome, perhaps because they are more accustomed to observe complications and have a more realistic view of the outcome that can be expected after a reconstruction. However, the same result was not observed for physicians from other specialties. Many factors may influence the assessment of aesthetic outcomes, such as age, high body mass index, smoking, tumor size and location, breast size, and adjuvant treatment applied[10,14]. Therefore, the differences between the assessments of the professionals may

be the result of their trained outlook regarding these variables, which can cause limitations in the aesthetic outcome.

CONCLUSION

Plastic surgeons assessed the aesthetics results of breast reconstruction more positively than nonplastic physicians, and the time of experience of plastic surgeons could decrease their expectation regarding the outcome.

ETHICS APPROVAL AND CONSENT TO PARTICIPATE

This study was approved by the ethical committees of the Federal University of Sergipe and was conducted in accordance with the Declaration of Helsinki. All study participants provided informed written consent as set forth in CNS Resolution No. 466/12 and CAAE: 92210218.2.0000.5546.

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AUTHORS' CONTRIBUTIONS

HFFS, CAL: Writing – original draft, Writing – review & editing, Methodology, Formal Analysis, Supervision. HFFS: Conceptualization, Project administration, Resources. HFFS, JLT, RLF, ÉACB, ML, ARM, TCFJ, TO, AASV, CAL: Data curation, Investigation.

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ORIGINAL ARTICLE

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Orthostatic changes in blood pressure and survival in elderly cardiopaths

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SUMMARY

OBJECTIVE: The objective of this study was to analyze the association between orthostatic changes in blood pressure and mortality in elderly cardiopath patients.

METHODS: A cohort of 455 elderly cardiopath patients, monitored at a referral outpatient cardiology clinic in Pernambuco, Brazil, from October 2015 to July 2018. The exposure groups were formed according to their orthostatic changes in blood pressure following the requirements of the Brazilian Guidelines for Hypertension.

RESULTS: Orthostatic hypotension was present in 46 patients (10.1%), 91 had orthostatic hypertension (20%), and 318 had no orthostatic alterations (69.9%). There were 52 deaths during follow-up. The results demonstrated that there was no statistically significant association between orthostatic hypotension and overall mortality (HR 1.30; 95%CI 0.53–3.14; p=0.567) nor between orthostatic hypertension and overall mortality (HR 0.95; 95%CI 0.65–1.39; p=0.34). Survival in relation to the exposure groups presented no statistically significant difference (p=0.504).

CONCLUSION: There was a low frequency of orthostatic hypotension and a mild high frequency of orthostatic hypertension when compared with previous studies, and no association was observed with overall mortality or with the survival time of elderly patients with heart disease.

KEYWORDS: Orthostatic hypotension. Hypertension. Mortality.

INTRODUCTION

Cardiovascular aging is associated with an increased risk of diseases in elderly people, the most common of which are those arising from changes in blood pressure. Arterial stiffening, as well as vascular endothelial dysfunction, leads to an increase in systolic blood pressure and a decrease in diastolic blood pressure[1]. However, autonomic dysfunction, typical of aging, makes it difficult to adapt blood pressure to orthostasis[2], as well as a decrease in the number of sinus node cells and the responses mediated by beta-1 and beta-2 adrenergic receptors[3].

In elderly people, these changes in blood pressure are associated with a progressive cardiovascular risk and target organ damage, consequently increasing morbidity and mortality[4,5], since the control of blood pressure, as well as the maintenance of postural normotension, is more impaired with aging[6].

Orthostatic hypotension (OH) is characterized by a drop in systolic blood pressure of at least 20 mmHg or diastolic blood pressure of at least 10 mmHg, when an individual changes position from lying down to sitting or standing, within an interval of three minutes between measurements, being associated or not with symptoms of cerebral hypoperfusion[5-8]. The prevalence of OH varies from 1.25 to 68%[9,10], with a mean estimate of 30%[11]. OH is associated with risk factors as diabetes mellitus[12], hypertension[13], Parkinson's disease[13], stroke[14], chronic kidney disease (CKD)[15], polypharmacy, and reduction in hepatic clearance, which occurs with aging[3,16].

The orthostatic hypertension (OHY) is also associated with cardiovascular and overall mortality[17-19]. OHY is characterized by an increase of at least 20 mmHg in blood pressure between one and two minutes after an individual has stood up[4].

Thus, the aim of this study was to estimate the association between orthostatic changes (OC) in blood pressure and overall mortality in elderly cardiopath patients.

METHODS

This was a cohort study with a comparison of groups. The sample consisted of 455 elderly patients aged 65 and over, diagnosed with cardiovascular disease, selected consecutively, and treated at the general cardiology outpatient clinic of a referral

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hospital in Pernambuco, Brazil, from October to November 2015 and monitored until July 31, 2018.

Participants were examined on the day of inclusion in the study with a physical examination performed by measuring the blood pressure while lying down, sitting, and standing, with an interval of three minutes between each, together and an interview to collect biological characteristics, life habits, comorbidities, and use of medications. The search for information on deaths was conducted via the Mortality Information System (SIM) throughout the whole study period.

Patients were excluded from the study if they were prevented, for any reason, from assuming the orthostatic position without the help of third parties for five minutes, together with those who had taken cardiovascular medication up to two hours prior to measuring the blood pressure, or presented with uncorrected severe bilateral hearing loss, severe cognitive impairment, and without a legal guardian.

The exposure groups were formed according to their OC in blood pressure following the requirements of the Brazilian Guidelines for Hypertension. OH was defined by a drop in the blood pressure of at least 20 mmHg in systolic pressure or at least 10 mmHg in diastolic pressure after standing for one, three, or five minutes. OHY was defined by an increase in blood pressure of at least 20 mmHg after standing up for two minutes[20].

A descriptive analysis of the characterization and description of the participants was conducted regarding the biological variables, comorbidities, and the medications being taken. The densities of death incidence in 100 person-years and their confidence intervals were estimated according to the condition of the OH and OHY. The associations were analyzed independently. The survival probability was calculated and represented by the Kaplan–Meier curve and the differences between the survival functions were tested according to the condition of the OH and OHY by the Log-Rank test.

In the multivariate analysis, possible confounding factors were analyzed by comparing the groups of patients according to the condition of the OH and OHY, with the biological variables, comorbidities, and medications being taken. The assessment was performed using the chi-squared, Fisher's exact, or Pearson test, and ANOVA was used to compare the mean values. The adjusted measures were estimated by Cox regression analysis. The inclusion criterion for selecting the confounding variables in the adjustment of the hazard ratio (HR) was a significance of up to 20% in the analysis of the comparison of groups according to exposure ($p<0.2$). The level of significance adopted in the analysis of associations was 5% ($p<0.05$).

All patients selected for the study signed the Informed Consent Term and the study is in accordance with that described in resolution no. 466/2012, in addition was approved by the Research in Ethics Committee of the Hospital Complex HUOC/PROCAPE (CAAE: 84801918.4.0000.5192).

RESULTS

A total of 455 patients participated in the study, of which 46 were diagnosed with OH (10.1%), 91 with OHY (20%), and 318 presented with no OC (69.9%). Table 1 describes the biological, lifestyle, and clinical characteristics of the study population. The mean age did not differ between groups (72.7±6.4 years). There was a higher frequency of females, with no difference between the exposure groups. With regard to lifestyle, there was no predominance of either alcohol or illicit drugs use between the groups.

Among the most frequent, arterial hypertension was reported by 94% of patients, and was predominant in all groups. More than half (51%) presented with coronary artery disease (CAD), 53% presented dyslipidemia (DLP), and 35.8% diabetes. With regard to the use of medications, polypharmacy was present in 23.2% of patients (taking four or more medications per day). Almost all patients used antihypertensive drugs (99.87%), where the most commonly used were betablockers (72%) and diuretics (58.9%) (Table 1).

A total of 52 deaths were registered during the 36-month follow-up period, average follow-up time was 24.7 months, with an average of 6 deaths/year for every 100 patients. According to Figure 1, the cumulative probability of death in the first 12 months of follow-up was 4.8% and in 24 months, 10.7%. Survival in relation to the exposure groups presented no statistically significant difference ($p=0.504$).

The mortality rate per year related to the OH group was 6.8 and in patients with OHY the rate was 7.9 deaths per 100 person-years. After estimating the risk of death adjusted by confounding factors, the HR was neither statistically significant for the OH group nor the OHY group (Figure 2).

Diseases of the cardiocirculatory system were responsible for the highest number of deaths in the group with no OC (54.8%) and in the group with OH (42.9%). The deaths of patients in the OHY group were attributed to respiratory system diseases (42.9%).

DISCUSSION

In the present study, in a sample of 455 elderly cardiopath patients monitored on an outpatient basis, aged between 66 and

Table 1. Biological, lifestyle, and clinical characteristics of the elderly patients according to the classification of orthostatic changes.

Characteristics	No OC (n=318) (%)	OH (n=46) (%)	OHY (n=91) (%)	p-value
Age (mean±SD)	72.5±5.9	72.4±8.2	73.7±7.1	0.265
Sex				
Male	150 (47.2)	18 (39.1)	37 (40.7)	0.380
Female	168 (52.8)	28 (60.9)	54 (59.3)	
Alcohol				
Yes	34 (10.7)	3 (6.5)	8 (8.8)	0.626
No	284 (89.3)	43 (93.5)	83 (91.2)	
Illicit drug use				
Yes	3 (0.9)	0 (0)	1 (1.1)	0.789
No	315 (99.1)	46 (100)	90 (98.9)	
Hospitalization in the last 12 months				
Yes	92 (29.2)	10 (21.7)	22 (24.4)	0.439
No	223 (70.8)	36 (78.2)	68 (75.6)	
Comorbidities				
Atrial fibrillation	41 (12.9)	7 (16.2)	18 (20.0)	0.235
Arterial hypertension	297 (93.4)	45 (97.8)	84 (92.3)	0.438
Diabetes mellitus	107 (33.6)	19 (41.3)	36 (39.5)	0.406
Dyslipidemia	175 (55)	18 (39.1)	47 (51.6)	0.127
CAD*	179 (56.3)	19 (41.3)	45 (49.4)	0.114
CKD*	28 (8.8)	6 (13)	6 (6.6)	0.453
Hypothyroidism	15 (4.7)	3 (6.5)	6 (6.6)	0.720
Parkinson's disease	8 (2.5)	1 (2.2)	1 (1.1)	0.719
Stroke	43 (13.5)	4 (8.7)	8 (8.8)	0.360
Cardiac insufficiency	117 (36.8)	13 (28.3)	32 (35.2)	0.526
Previous depression	51 (16)	8 (17.4)	17 (18.7)	0.830
Anemia	21 (6.6)	5 (10.9)	11 (12.1)	0.186
Medication use				
Antihypertensive drugs	318 (100)	46 (100)	90 (98.9)	0.135
Vasodilators	28 (8.9)	6 (13.6)	10 (11)	0.550
Betablockers	231 (72.6)	30 (65.2)	67 (73.6)	0.539
Calcium blockers	99 (31.1)	22 (47.8)	20 (22)	0.008
ACEI* or Ara II*	140 (44)	22 (47.9)	36 (39.6)	0.619
Diuretics	192 (60.4)	24 (52.2)	52 (57.1)	0.532
Antidepressants	21(6.6)	1 (2.2)	8 (8.8)	0.337
Sedatives	49 (15.5)	5 (10.9)	19 (20.9)	0.277
Nitrates	72 (22.6)	7 (15.2)	20 (22)	0.521
Number of classes of medication				
One	25 (7.9)	4 (8.7)	14 (15.4)	0.535
Two	91 (28.8)	13 (28.3)	26 (28.6)	
Three	126 (39.9)	17 (37)	31 (34.1)	
Four or more	74 (23.4)	12 (26.1)	20 (22)	

OC: orthostatic changes; OH: orthostatic hypotension; OHY: orthostatic hypertension; CAD: coronary artery disease; CKD: chronic kidney disease; ACEI: angiotensin-converting enzyme inhibitor; ARA II: angiotensin II receptor antagonists.

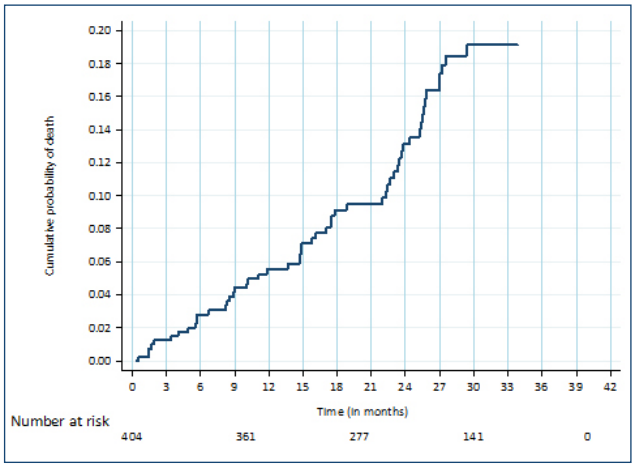

Figure 1. Overall survival curve.

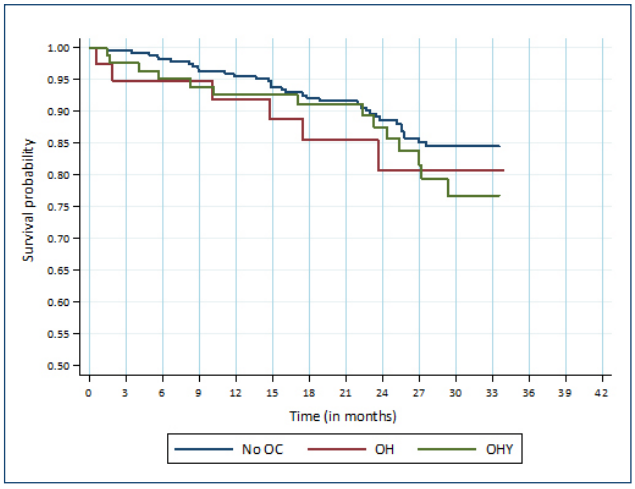

Figure 2. Overall survival related to classification of orthostatic changes.

78 years, the prevalence of OH was 10.1%, similar to studies by Ong et al. (2017)[21] and Freud et al. (2018)[17], which demonstrated a prevalence of 7.8 and 18%, respectively. Both studies assessed OH in elderly people in the same age group as the present study, also monitored on an outpatient basis.

With regard to OH and overall mortality, our results have demonstrated that there was no statistically significant association (HR 1.30; 95%CI 0.53–3.14; p=0.567), thereby corroborating the findings by Szyndler et al.[18], who assessed the impact of OH on cardiovascular and noncardiovascular mortality in 209 octogenarians over a period of 24 months, and also reported no association with mortality. In the studies by Veronese et al.[19] and Freud et al.[17], OH was associated with overall mortality in the univariate analysis. However, after adjusting the multivariate analysis, this association was no longer significant.

According to Freud et al.[17], both in the group of patients aged 75 years and under and in the group aged 75 years and over (which included fragile older adults), no association was reported between OH and overall mortality in the multivariate analysis. A similar result was observed in the study by Veronese et al.[19], who monitored 2,786 older adults for four years, with the same mean age and after adjusting for confounding factors, the association of OH was no longer significant for overall mortality.

However, OH was a risk factor for death related to noncardiovascular diseases. The aforementioned studies have a larger sample size, a longer follow-up time, and a higher prevalence of older people with OH, reinforcing the evidence from the present study of no association between OH and overall mortality.

In our sample, OHY was observed in 20% of the older patients, an above-average prevalence for large studies such as those by Bursztyn et al.[22] and Veronese et al.[19], who assessed elderly patients with OHY monitored on an outpatient basis. The study by Bursztyn et al.[22], a cohort that monitored 1,441 elderly patients, who aged 85–95, for 10 years, reported a prevalence of OHY of only 3 to 4%.

In the present study, there was no increase in OHY-related mortality (HR 0.95; 95%CI 0.65–1.39; p=0.34), a result similar to that reported by Weiss et al.[23], in a prospective cohort of 474 hospitalized older patients, aged between 75 and 87 years, who assessed the association between OHY and mortality.

It should be noted that there are divergences in the literature regarding OHY and its association with mortality. In the study by Veronese et al.[19], in relation to OHY, there was an association both with overall mortality (HR 1.23; 95%CI 1.02–1.39; p=0.03) and with diseases of the cardiovascular system (HR 1.41; 95%CI 1.08–1.74; p=0.02) after adjusting for confounding factors.

Studies related to the association of mortality with OHY have different characteristics, which may explain the different results related to the association with mortality. In the present study, the risk of death in patients with OHY was 1.48 (95%CI 0.8–2.79), with a statistical significance of 20% and a study power equal to 85%. Only 14 deaths were observed in this group, which may have influenced the instability of the risk measure, and consequently a greater inaccuracy of the risk measure (HR). Thus, the study indicates a risk hypothesis, although a longer follow-up period would be necessary, with a greater number of events observed for the cohort of patients with OHY.

CONCLUSIONS

It is concluded that there was a low frequency of OH and a slightly high frequency of OHY and that they were not associated with overall mortality and presented no influence over the survival of the elderly cardiopath patients.

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AUTHORS' CONTRIBUTIONS

LMSMC: Conceptualization, Data curation, Formal Analysis, Writing – original draft.**JVBC:** Data curation, Writing – original draft. **MMBMS:** Data curation, Writing – original draft. **MCAS:** Data curation, Writing – original draft. **ACS:** Data curation, Writing – original draft. **DCO:** Writing – original draft, Writing – review & editing. **DCSF:** Writing – original draft, Writing – review & editing. **URM:** Writing – original draft, Writing – review & editing.

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ORIGINAL ARTICLE

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Burnout syndrome in resident physicians of a Federal University

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SUMMARY

OBJECTIVE: The objective of this study was to determine the frequency of burnout, global, and by dimension, in resident physicians of Federal University of Piauí, and to identify possible factors associated with the presence of the syndrome.

METHOD: This is a cross-sectional, observational, and descriptive study. Population: resident physicians in Federal University of Piauí's medical residency programs (136 individuals). The frequency of burnout was investigated using the Maslach Burnout Inventory. Sociodemographic variables were evaluated through a questionnaire and their associations with the presence of the syndrome were tested.

RESULTS: A total of 67 (49.26%) residents answered the questionnaires. The burnout syndrome frequencies found were global=73.1%; EE=44.8%; DP=64.2%, and PA=47.8%. Statistically significant association was obtained between current year of residency and EE; between having children and PA; between current work routine and DP; and between the use of antidepressant/hypnotic medication and EE. Compared with residency programs, there was a difference in the EE dimension, which was higher among residents in internal medicine residents (88.9%) and pediatrics (83.3%). In the comparative analysis between global burnout levels and all variables evaluated, no associations were found.

CONCLUSION: Burnout syndrome was found in the majority of participating residents. There was an association between sociodemographic variables and the presence of isolated burnout dimensions, but not between sociodemographic variables and global burnout.

KEYWORDS: Burnout. Psychological. Internship and Residency. Epidemiology.

INTRODUCTION

The term burnout was first used by the American psychologist Herbert Freudenberger in 1974, defining it as the state of frustration or fatigue triggered by investment in a particular cause, way of life or relationship that did not live up to expectations[1].

The most commonly used definition for burnout syndrome is the one developed by Maslach and Jackson in 1985. According to it, the syndrome is composed of a triad characterized by emotional exhaustion, depersonalization (negative responses, insensitive, and detached from others), and reduced professional achievement[2].

Burnout syndrome is a serious problem among health care professionals, as it is often associated with the development of anxiety, depression, substance abuse, and suicidal ideation in affected individuals. Patients assisted by professionals with burnout syndrome are more prone to medical errors, which makes the issue even more alarming[3].

It is postulated that resident doctors are even more susceptible to the development of burnout syndrome, since they are subjected to journeys of intense work in which they are demanded both as students in training and as professionals who must already demonstrate great expertise in performed activities[4].

A study with resident physicians of a university hospital in Ceará demonstrated a prevalence of global burnout of 68.7%[5]. No previous studies on the prevalence of this syndrome in resident physicians in Piauí were found.

The present study aimed to determine the prevalence of global burnout and burnout by dimension (emotional exhaustion, depersonalization, and reduced professional fulfillment) in resident doctors of Federal University of Piauí (UFPI) and to identify possible factors associated with the presence of the syndrome.

METHODS

This is a cross-sectional, observational, and descriptive study. Study population consisted of resident physicians from the medical residency linked to UFPI, from different areas and totaling 136 residents.

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The following inclusion criteria were used: resident physicians from UFPI's medical residency programs, who were linked to their respective programs for at least 3 months. Exclusion criteria were: residents who were away from their programs during data collection, notably those who were on maternity leave, leave for medical treatment or under license to provide military service, as well as those who were absent in their respective fields of practice during three visits for data collection. The resident author of this study was also excluded.

Data collection was carried out through a structured interview with the application of two questionnaires. A sociodemographic questionnaire addressed variables such as age, sex, residency program attended, year of residency, marital status, having children, work in other institutions, practice of physical exercise, current use of antidepressants and/or hypnotics, use of alcohol, and use of tobacco. The second questionnaire was the version in Brazilian Portuguese of the Maslach Burnout Inventory (MBI). This is the most commonly used instrument in surveys on burnout; it has 22 questions and covers the three dimensions related to the syndrome: 9 questions about emotional exhaustion (EE); 8 questions about professional achievement (PA); and 5 questions about depersonalization (DP). Answers are on a Likert scale with seven options (never, once a year or less, once a month or less, sometimes a month, once a week, a few times a week, and every day). Burnout syndrome was detected using the cutoff points of high-level exhaustion (≥26), high-level depersonalization (≥9), and low-level professional achievement (≤33). The presence of global burnout was considered high score in the dimensions of emotional exhaustion and/or depersonalization, as previous studies suggested that the achievement dimension reflects a distinct psychopathology[6]. Data collection was performed from May to September 2019. Three attempts of collection were made for each residency program, at their respective training sites, on weekdays and different hours.

Data were submitted to a typing process using Microsoft Excel spreadsheets and later exported and analyzed using software R, version 3.5.1.

Results were presented through percentages of absolute and relative frequencies, as well as through descriptive statistics: average and sample standard deviation, maximum and minimum values; and through a bar graph. To verify the assumption of normality, the Shapiro–Wilk test was adopted. In the bivariate analysis, associations between independent variables and global burnout syndrome and its dimensions were performed using the chi-square test of Pearson or Fisher's exact test. Comparisons between ages according to high burnout or not were performed using the Mann–Whitney U-test, and their values were expressed as median±interquartile range. For all applied tests, the significance level of 5% was adopted.

All participants in the present study signed an Informed Consent Form. This work was approved by the Ethics and Research Committee linked to the University Hospital of Federal University of Piauí, under CAAE 08080819.1.0000.8050, opinion number 3,257,525.

RESULTS

Of the total 136 residents, 67 (49.26%) answered the questionnaires. Among these, 53.7% were women. The average age was 27±3.32 years, ranging from 23 to 45 years. Most were single (70.1%), did not have children (91%), had another stable job besides the residency or performed extra shifts (82.1%), and practiced physical exercise (80.6%). Notably, 22.4% stated that they had been using some antidepressants and/or hypnotic medication. Regarding the consumption of alcoholic beverages, 82.1% affirmed to use it frequently, whereas 17.9% stated that they never used it. Only one resident declared to be a smoker.

The prevalence of global burnout was 73.1%. It was found that 44.8% of residents reached high burnout levels in the EE dimension, 47.8% in the PA dimension, and 64.2% in the DP dimension (Table 1). The frequency of high burnout in at least one dimension was 86.6% and high burnout in all three dimensions was 22.4%, whereas 13.4% did not obtain high levels of burnout in any dimension.

In the comparative analysis between the levels of burnout by dimension and the variables considered, a statistically significant association was obtained between the current year in the residency program and the dimension of emotional exhaustion (p-value=0.028); between having children and the dimension of professional achievement (p-value=0.014); between the current work routine and the dimension of depersonalization (p-value=0.043); and between the use of antidepressant/hypnotic medication and the emotional exhaustion dimension (p-value=0.002; Table 1).

In a comparative analysis between the levels of global burnout and all analyzed variables, no statistically significant associations were found (Table 2).

In Table 3, it is noted that there were no statistically significant differences between the median ages of high and non-high burnout in all three dimensions, as well as in global burnout.

Table 1. Association between observed variables and high burnout by dimension.

Variables	EE		p-value	DP		p-value	PA		p-value
	Yes (%)	No (%)		Yes (%)	No (%)		Yes (%)	No (%)	
Total prevalence	44.8	55.2		64.2	35.3		47.8	52.2	
Gender									
Male	13 (41.9)	18 (58.1)	0.664[a]	21 (67.7)	10 (32.3)	0.573[a]	14 (45.2)	17 (54.8)	0.693[a]
Female	17 (47.2)	19 (52.8)		22 (61.1)	14 (38.9)		18 (50.0)	18 (50.0)	
Year in residency									
1st year	18 (58.1)	13 (41.9)	**0.028[a]**	21 (67.7)	10 (32.3)	0.672[a]	17 (54.8)	14 (45.2)	0.556[a]
2nd year	11 (42.3)	15 (57.7)		15 (58.7)	11 (42.3)		11 (42.3)	15 (57.7)	
3rd year	1 (10.0)	9 (90.0)		7 (70.0)	3 (30.0)		4 (40.0)	6 (60.0)	
Marital status									
Single	21 (44.7)	26 (55.3)	0.611[a]	31 (66.0)	16 (34.0)	0.447[a]	22 (46.8)	25 (53.2)	0.560[a]
Married	9 (50.0)	9 (50.0)		11 (61.1)	7 (38.9)		9 (50.0)	9 (50.0)	
Civil partnership	0 (0.0)	1 (100.0)		0 (0.0)	1 (100.0)		1 (100.0)	0 (0.0)	
Separated	0 (0.0)	1 (100.0)		1 (100.0)	0 (0.0)		0 (0.0)	1 (100.0)	
Have children									
Yes	2 (33.3)	4 (66.7)	0.684[b]	4 (66.7)	2 (33.3)	1[b]	0 (0.0)	6 (100.0)	0.025[b]
No	28 (45.9)	33 (54.1)		39 (63.9)	22 (36.1)		32 (52.5)	29 (47.5)	
Current work routine									
Medical residency only	6 (50.0)	6 (50.0)	0.283[a]	4 (33.3)	8 (66.7)	0.043[a]	7 (58.3)	5 (41.7)	0.160[a]
Stable job besides medical residency	18 (51.4)	17 (48.6)		24 (68.6)	11 (31.4)		19 (54.3)	16 (45.7)	
Sporadic extra shifts besides medical residency	6 (30.0)	14 (70.0)		15 (75.0)	5 (25.0)		6 (30.0)	14 (70.0)	
Frequency of physical exercise									
Never	7 (53.8)	6 (46.2)	0.622[a]	10 (76.9)	3 (23.1)	0.552[a]	6 (46.2)	7 (53.8)	0.996[a]
Once a month to once a week	6 (54.5)	5 (45.5)		6 (54.5)	5 (45.5)		5 (45.5)	6 (54.5)	
2–3 times a week	13 (37.1)	22 (62.9)		23 (65.7)	12 (34.3)		17 (48.6)	18 (51.4)	
Almost everyday	4 (50.0)	4 (50.0)		4 (50.0)	4 (50.0)		4 (50.0)	4 (50.0)	
Use of antidepressant or hypnotic medication									
Yes	12 (80.0)	3 (20.0)	**0.002[a]**	10 (66.7)	5 (33.3)	1[a]	10 (66.7)	5 (33.3)	0.096[a]
No	18 (34.6)	34 (65.4)		33 (63.5)	19 (36.5)		22 (42.3)	30 (57.7)	
Frequency of alcohol consumption									
Never	7 (58.3)	5 (41.7)	0.733[a]	9 (75.0)	3 (25.0)	0.281[a]	7 (58.3)	5 (41.7)	0.565[a]
Once a month or less	10 (41.7)	14 (58.3)		12 (50.0)	12 (50.0)		13 (54.2)	11 (45.8)	
2–4 times a month	10 (40.0)	15 (60.0)		17 (68.0)	8 (32.0)		10 (40.0)	15 (60.0)	
2–3 times a week	3 (50.0)	3 (50.0)		5 (83.3)	1 (16.7)		2 (33.3)	4 (66.7)	
Smoker									
Yes	1 (100.0)	0 (0.0)	0.448[b]	1 (100.0)	0 (0.0)	1[b]	1 (100.0)	0 (0.0)	0.478[b]
No	29 (43.9)	37 (56.1)		42 (63.6)	24 (36.4)		31 (47.0)	35 (53.0)	

Continue...

Table 1. Continuation.

Variables	EE		p-value	DP		p-value	PA		p-value
	Yes (%)	No (%)		Yes (%)	No (%)		Yes (%)	No (%)	
Residency program attended									
General surgery/prerequisite	2 (25.0)	6 (75.0)		5 (62.5)	3 (37.5)		4 (50.0)	4 (50.0)	
Internal medicine	8 (88.9)	1 (11.1)		6 (66.7)	3 (33.3)		5 (55.6)	4 (44.4)	
Dermatology	0 (0)	4 (100)		3 (75.0)	1 (25.0)		1 (25.0)	3 (75.0)	
Obstetrics and gynecology	4 (40.0)	6 (60.0)		6 (60.0)	4 (40.0)		6 (60.0)	4 (40.0)	
Ophthalmology	1 (20.0)	4 (80.0)	0.009[a]	2 (40.0)	3 (60.0)	0.839[a]	0 (0.0)	5 (100.0)	0.468[a]
Orthopedics and traumatology	3 (50.0)	3 (50.0)		5 (83.3)	1 (16.7)		3 (50.0)	3 (50.0)	
Pediatrics	5 (83.3)	1 (16.7)		5 (83.3)	1 (16.7)		4 (66.7)	2 (33.3)	
Psychiatry	1 (12.5)	7 (87.5)		4 (50.0)	4 (50.0)		3 (37.5)	5 (62.5)	
Other	6 (54.5)	5 (45.5)		7 (63.6)	4 (36.4)		6 (54.5)	5 (45.5)	

EE: emotional exhaustion; DP: depersonalization; PA: professional achievement. [a]Pearson's chi-square test. [b]Fisher's exact test.

Table 2. Association between observed variables and global burnout.

Variables	Global burnout		p-value
	Yes (%)	No (%)	
Gender			
Male	24 (77.4)	7 (22.6)	0.463[a]
Female	25 (69.4)	11 (30.6)	
Year in residency			
1st year	25 (80.6)	6 (19.4)	0.420[a]
2nd year	17 (65.4)	9 (34.6)	
3rd year	7 (70.0)	3 (30.0)	
Marital status			
Single	36 (76.6)	11 (23.4)	0.289[a]
Married	12 66.7)	6 (33.3)	
Civil partnership	0 (0.0)	1 (100.0)	
Separated	1 (100.0)	0 (0.0)	
Have children			
Yes	4 (66.7)	2 (33.3)	0.656[b]
No	45 (73.8)	16 (26.2)	
Current work routine			
Medical residency only	6 (50.0)	6 (50.0)	0.126[a]
Stable job besides medical residency	28 (80.0)	7 (20.0)	
Sporadic extra shifts besides medical residency	15 (75.0)	5 (35.0)	
Frequency of physical exercise			
Never	10 (76.9)	3 (23.1)	0.901[a]
Once a month to once a week	8 (72.7)	3 (27.3)	
2–3 times a week	26 (74.3)	9 (25.7)	
Almost everyday	5 (62.5)	3 (37.5)	

Continue...

Table 2. Continuation.

Variables	Global burnout		p-value
	Yes (%)	No (%)	
Use of antidepressant or hypnotic medication			
Yes	12 (80.0)	3 (20.0)	0.742b
No	37 (71.2)	15 (28.8)	
Frequency of alcohol consumption			
Never	10 (83.3)	2 (16.7)	0.238a
Once a month or less	14 (58.3)	10(41.7)	
2–4 times a month	20 (80.0)	5 20.0)	
2–3 times a week	5 (83.3)	1 (16.7)	
Smoker			
Yes	1 (100.0)	0 (0.0)	1b
No	48 (72.7)	18 (27.3)	
Residency program attended			
General surgery/prerequisite	5 (62.5)	3 (37.5)	0.370[a]
Internal medicine	8 (88.9)	1 (11.1	
Dermatology	3 (75.0)	1 (25.0)	
Obstetrics and gynecology	6 (60.0)	4 (40.0)	
Ophthalmology	2 (40.0)	3 (60.0)	
Orthopedics and traumatology	5 (83.3)	1 (16.7)	
Pediatrics	6 (100.0)	0 (0.0)	
Psychiatry	5 (62.5)	3 (37.5)	
Other	9 (81.8)	2 (18.2)	

[a]Pearson's chi-square test. [b]Fisher's exact test.

Table 3. High burnout in three dimensions and global burnout according to the age of residents.

	EE			DP			PA			Global burnout		
	Yes	No	p-value	Yes	No	p-value	Yes	No	p-value	Yes	No	p-value
Age	27±7.8	27±3.0	0.523	27±3.5	27 ±3.3	0.414	27±3.3	28 ±4.0	0.222	27±4.0	28 ±3.5	0.129

EE: emotional exhaustion; DP: depersonalization; PA: professional achievement. Mann–Whitney U-test. Median±interquartile range.

DISCUSSION

The frequency of global burnout in the studied group was 73.1%, demonstrating that this is a very common problem among the participants. The prevalence of burnout in resident physicians is variable in other studies (18–82%), which used different assessment scales and different interpretations, particularly in the definition of global burnout[7]. A study carried out with internal medicine residents at Washington University, which used the same definition of global burnout as our work, demonstrated a prevalence of 76%[6].

However, if we considered the confined definition of global burnout—in which it would be necessary to present high levels in all dimensions—the frequency of the referred syndrome in the participants of this study would be 22.4%. In a study

carried out with resident physicians of a university hospital in Goiás and which adopted such definition, the prevalence of global burnout was 18.05%[8].

In our study, doctors attending the first year of residency exhibited significantly higher levels of emotional exhaustion. In a study carried out in Israel with 78 residents from various areas of activity, burnout scores increased during the first year and decreased after 2 years[9]. Such results can be explained by multiple factors, such as greater number of night shifts during the first year, greater professional insecurity, and lack of adaptation to the work routine.

Participants who had children exhibited significantly lower values in the low professional achievement dimension. In a study with residents from different specialties, residents who had children also had lower burnout rates[10]. Although one could imagine that parenthood would overwhelm these individuals with even more responsibilities, it has proved to be a protective factor against burnout, possibly by bringing more humanization and providing the professional with additional motivation to work.

Participants who had jobs other than medical residency portrayed significantly higher levels of depersonalization. This result differs from that observed by Bond et al.[11] in a study carried out with resident physicians of a university hospital in Porto Alegre, in which there was no association between burnout (global and by dimension) and having another job. However, our results can be explained by the fact that this variable indirectly expresses a greater total workload. Factors such as long working hours and little time for rest and leisure are described as predictors of professional burnout[12].

There was an association between the use of antidepressants and/or hypnotics and a higher frequency of emotional exhaustion. Similar results were obtained in a study conducted with residents in Family and Community Medicine in Portugal[7]. The causal relations between burnout syndrome and depression remain unclear. It is possible that the experience of emotional exhaustion and unsatisfactory functioning may trigger a depressive episode. In contrast, depression can also sensitize the individual and predispose one to develop extreme reactions or stress. In addition, both conditions can occur independently[9].

When comparing the different training programs studied, the levels of emotional exhaustion were significantly higher among residents in internal medicine (88.9%) and pediatrics (83.3%). In a study carried out in Porto Alegre, residents in surgical specialties were less associated with emotional exhaustion and low professional achievement[11]. However, in a 2004 study that compared the burnout rate between different specialties in Michigan medical residency programs, no significant differences were found[10]. It is possible that the observed differences relate to the particularities of the routine in a specific service and cannot be extrapolated to categorize residents of a particular specialty as having a higher risk of developing burnout.

In this study, there was no association between the presence of global burnout or isolated dimensions and the variables: sex, age, marital status, frequency of physical activity, use of alcoholic beverages, and smoking. The link between such variables and burnout syndrome is in fact still obscure, as shown by a systematic review on the topic[1].

A limitation of this study was the large number of residents who did not answer the questionnaires (50.74%). Another limitation refers to the fact that this study is cross-sectional, thus not allowing to determine the causes of the emergence of professional exhaustion. The knowledge of these causes through further studies may allow the development of more effective strategies for preventing the syndrome.

No previous research was found on burnout in resident physicians in the Brazilian state of Piauí. Thus, this study was a pioneer in demonstrating the high frequency of this syndrome in our surroundings. In addition, it carried out extensive research on the association of burnout with sociodemographic variables, which may be important for the elaboration of hypotheses to be tested in future studies that aim to investigate the causes of professional burnout.

CONCLUSION

The frequencies of global burnout and burnout by isolated dimensions (emotional exhaustion, depersonalization, and low professional achievement) were high in the group of residents studied. The emotional exhaustion dimension was associated with being in the first year of medical residency and with using antidepressants and/or hypnotic medication, whereas the depersonalization dimension was associated with having other jobs besides medical residency. In contrast, a lower frequency of burnout in the professional achievement dimension was associated with having children. Furthermore, there was no difference in the presence of global burnout according to sociodemographic characteristics.

AUTHORS' CONTRIBUTIONS

LVS: Conceptualization. LSP: Data curation. LVS: Formal analysis. LSP: Funding acquisition. LSP: Investigation. LVS: Methodology. LVS, LARLR: Project administration. LSP: Resources. LSP, VSA: Software. LVS: Supervision. LVS: Validation. LVS, LARLR: Visualization. LSP: Writing – original draft. LVS, VSA: Writing – review and editing.

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ORIGINAL ARTICLE

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Prevalence of primary dysmenorrhea and associated factors in adult women

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SUMMARY

OBJECTIVE: This study aimed to assess the prevalence and factors associated with primary dysmenorrhea in a sample of adult women.

METHODS: A cross-sectional study was carried out with women aged between 19 and 49 years from a city of northeastern Brazil. Sociodemographic, gynecological, and obstetric variables were assessed by questionnaires and interviews. Dysmenorrhea was measured by self-report, and the Numerical Pain Rating Scale measured the intensity of pain. Statistical analyses included χ^2 test, ANOVA, and logistic regression.

RESULTS: The average age was 33.2±9.1 years and the prevalence of primary dysmenorrhea was 56% for the whole sample. The average duration of symptoms was 2.7±1.8 days and the mean intensity was 6.1±2.6. The previous cesarean section was associated with a higher rate of primary dysmenorrhea (PR=2.33; 95%CI 1.11–4.90) when considering the whole sample. Women who aged 25–39 years and are insufficiently active had higher rates of primary dysmenorrhea (PR=5.24; 95%CI 1.08–27.31).

CONCLUSION: Primary dysmenorrhea has a high prevalence in young adults, adults, and middle-aged women. Cesarean section and being physically inactive was associated with increased rates of dysmenorrhea among adult women.

KEYWORDS: Cross-sectional studies. Dysmenorrhea. Epidemiology. Prevalence. Women's health.

INTRODUCTION

Dysmenorrhea is defined as colic pain in the hypogastrium that occurs during menstruation and other symptoms like sweating, headaches, nausea, vomit, diarrhea, and tremors may occur associated[1]. Dysmenorrhea is classified into primary (menstrual pain without organic disease) or secondary (menstrual pain associated with another preexistent disease, e.g., endometriosis)[1,2].

The prevalence of primary dysmenorrhea (PD) is well studied among teenagers and youngers in different countries and it ranges from 16 to 91%[3,4]. Several risk factors are established in the literature and the casuistic of PD may involve social, demographic, behavioral, gynecological, and reproductive issues[1,4,5].

As the majority of studies about PD were conducted with students and teenagers, the generalization of these evidence for women of all adult age, including middle-aged women, are limited and needs more clarification[4]. Besides that, it is estimated that the prevalence of PD is even higher since many women associate dysmenorrhea as a normal menstrual cycle pain and do not seek medical assistance for this condition[1].

The perception and coping of pain related to PD vary from the women's context. Then, issues related to work, social roles, and women's empowerment can modify these perception among different age groups[6]. This fact reinforces the relevance to know the prevalence of PD and associated factors in the different stages of a woman's adult life and not just in adolescence.

Moreover, PD represents relevant cause of school and work absence, negatively affects academic performance, productivity, daily life activities, and quality of life of these women[4,7]. Then, knowing the prevalence and associated factors in the different ages of woman's life may allow to intervene and minimize the impacts of dysmenorrhea on the lives of these women[8]. Therefore, this study aimed to assess the prevalence and associated factors to PD in adult women (19–49 years of age).

METHODS

A cross-sectional, community-based study was conducted from December 2015 to November 2016, in the municipality

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of Santa Cruz, Rio Grande do Norte, Brazil. The Ethical and Research Committee of Federal University of Rio Grande do Norte approved the research protocol under number CAAE 49237315.9.0000.5568. The study followed the Declaration of Helsinki and all the participants signed the informed consent form.

The sample size was determined using the prevalence of 67.5% of dysmenorrhea, power of 90%, and a nonresponse rate of 5%, resulting in a sample of 195 women. This prevalence was obtained in a previous pilot study with 30 women following the same inclusion criteria (data not shown).

Women were proportionally recruited from among the six services of primary healthcare services of the city. Women were approached for convenience while accompanying a relative or waiting for an appointment for themselves. Previously trained interviewers conducted the interviews in a silent, private place of the health care services.

Women, who aged 19–49 years, with the regular menstrual flow in the last 3 months, and who accepted to participate in the study, were included. Exclusion criteria included women who reported a medical diagnosis of endometriosis, adenomyosis, uterine myoma, or pelvic inflammatory disease; in hormone replacement therapy; or had a history of hysterectomy.

Primary dysmenorrhea was assessed by self-reporting of colic-type pain in the lower abdomen associated with menstruation in the last 3 months[4]. The Numeric Pain Rating Scale (NPRS) assesses the intensity of pain (0–10)[9]. The duration of pain was expressed in days.

Independent variables were obtained by conducting interview and include age (grouped into young adults: 19–24 years, adults: 25–39 years, and middle-aged women: 40–49 years); family income (≤1 minimum wage or more); religion; age of menarche (≤11 years old or ≥12); use of any contraceptive method; menstrual cycle length dichotomized into 28–35 days and (<28 or >35 days); and number of children, cesarean section, and vaginal delivery.

Constipation was determined according to ROMA III criteria[10] and the sexual dysfunction was defined as a score <60 points in the Female Sexual Quotient Questionnaire[11]. The presence and type of urinary incontinence was determined by conducting interview following the recommendations of International Continence Society[12]. The short-form of International Physical Activity Questionnaire (IPAQ) evaluated the level of physical activity, and <600 METs-minute/week indicated insufficiently active women[13].

Data analyzes were conducted by the software SPSS, version 22. The Kolmogorov–Smirnov test confirms the normal distribution of continuous data. We expressed categorical data by absolute and relative frequencies, and continuous data through mean and standard deviations.

Prevalence of dysmenorrhea was calculated for overall and for age groups. ANOVA compared the variance among groups to intensity and duration of pain. Binary logistic regression was performed and the variables with $p<0.20$ were included in the multivariate logistic regression. Statistical significance was defined as $p<0.05$.

RESULTS

Initially, we invited 211 women to participate. Of those, 16 were excluded for having a history of hysterectomy (n=7) or being pregnant (n=9), resulting in 195 women included in the study with a mean age of 33.16±9.06 years old. Sociodemographic and clinical profile is shown in Table 1.

The prevalence of PD was 55.9% in all samples, and 50% in young adults, 55% in adults, and 61% in middle-aged women. Pain intensity and duration of complaints did not differ among groups (Table 2).

The results of univariate and multivariate logistic regression are shown in Table 3. Having at least one cesarean section was associated with 2.33 times risk of having PD among women aged 19–49 years. Among the adult women, who were insufficiently physically active, it was associated with 5.42 times risk of having PD.

DISCUSSION

Primary dysmenorrhea is characterized by uterine hypercontractility provoked by the overproduction of prostaglandins in the endometrium, leading to uterine muscle ischemia, hypoxia, and, subsequently, pain[14]. Although PD is often a gynecological complaint, it is underdiagnosed, undertreated, and even undervalued by women themselves[14]. Our findings show that PS has a high prevalence throughout a woman's adulthood, contradicting evidence that suggests a decrease in pain after pregnancies[3]. However, it was observed that risk factors may differ according to the progression of the life cycle and classical factors involved in physiology of PD were not associated with contraceptive methods, menarche age, and having children[4,14].

In our study, cesarean section was associated with more cases of PD. It is a warning sign because the cesarean is the most common type of operation performed on women, and women who had undergone multiple cesarean sections can progress with cesarean scar defects[15]. The cesarean scar defect

Table 1. Social demographic and clinical profile of sample grouped by age (n=195).

Variables	Women		
	Young adults (n=40)	Adults (n=96)	Middle-aged women (n=59)
	%		
Family income*			
≤1 minimum wage	80.0	79.2	79.7
>1 minimum wage	20.0	20.8	20.3
Profess some religion	77.5	85.4	88.1
Insufficiently physically active	17.5	21.9	13.6
Age of menarche			
≤11 years old	17.5	17.7	22.0
≥12 years old	82.5	82.3	78.0
Use any contraceptive method	60.0	49.5	55.2
Menstrual cycle length (n=172)			
28–35 days	68.6	76.2	71.7
<28 days or >35days	31.4	23.8	28.3
Constipation	37.5	29.2	44.1
Urinary incontinence	15	16.7	30.5
Stress urinary incontinence	7.5	6.3	16.9
Urgency urinary incontinence	2.5	4.2	6.8
Mixed urinary incontinence	5.0	6.3	6.8
Sexual dysfunction	27.5	36.7	40.0
Have children	75.0	82.3	81.4
≥1 Cesarean section (n=146)	70.0	66.7	61.0
≥1 Vaginal delivery (n=146)	67.5	76.0	69.5

*In 2016, the value of a minimum wage in Brazil was R$ 880.00.

Table 2. Comparative analyses of mean intensity and duration of pain during the menstrual cycle among young adult, adult, and middle-aged women (n=109).

	Intensity of pain (NPRS) Mean±SD	Duration of pain (days) Mean±SD
Total sample	6.14±2.55	2.68±1.83
Young adults	6.70±2.58	2.80±1.61
Adults	5.87±2.55	2.40±1.57
Middle-aged womens	6.22±2.56	3.03±2.22
ANOVA (p-value)	0.454	0.265
Young adults×adults (p-value)*	0.433	0.477
Young adults×middle-aged women (p-value)*	0.782	0.895
Adult×middle-aged women (p-value)*	0.798	0.247

*p-value was calculated by the ***post hoc*** Tukey test. NPRS: Numeric Pain Rating Scale.

Table 3. Association of independent variables with dysmenorrhea by age groups.

Variables	All sample (n=195)				Young adults (n=40)		Adults (n=96)		Middle-aged women (n=59)	
	Crude PR (95%CI)	p	Adjusted PR (95%CI)	p	Adjusted PR (95%CI)	p	Adjusted PR (95%CI)	p	Adjusted PR (95%CI)	p
Profess some religion	0.59 (0.26–0.33) ref.	0.200	0.46 (0.17–1.21) ref.	0.116	–	–	–	–	–	–
Yes										
No										
Family income (R$ 880.00)	–	–	–	–	–	–	–	–	0.13 (0.14–1.31) ref.	0.084
≤1 minimum wage										
>1 minimum wage										
Age at menarche	–	–	–	–	–	–	1.18 (0.32–4.35) ref.	0.802	–	–
≤11 years old										
≥12 years old										
Menstrual cycle length	1.66 (0.81–3.41) ref.	0.168	2.05 (0.90–4.64) ref.	0.086	–	–	3.11 (0.87–10.91) ref.	0.076	–	–
menstrual cycle >35 or <28 days										
28–35 days										
Use of the contraceptive method	–	–	–	–	2.68 (0.58–12.31) ref.	0.206	–	–	–	–
Yes										
No										
Urinary incontinence	0.51 (0.25–1.02) ref.	0.058	0.84 (0.33–2.13) ref.	0.709	–	–	0.52 (0.11–2.54) ref.	0.418	–	–
Yes										
No										
Mixed urinary incontinence	0.24 (0.06–0.92) ref.	0.038	0.33 (0.46–2.35) ref.	0.267	–	–	0.15 (0.01–3.97) ref.	0.256	–	–
Yes										
No										
Insufficiently physically active	–	–	–	–	–	–	5.42 (1.08–27.31) ref.	0.040	–	–
Yes										
No										
Sexual dysfunction	0.57 (0.30–1.06) ref.	0.077	0.61 (0.29–1.24) ref.	0.172	–	–	–	–	0.38 (0.09–1.59) ref.	0.185
Yes										
No										
Have children	0.60 (0.29–1.25) ref.	0.174	1.00 (0.38–2.66) ref.	0.997	0.22 (0.04–1.35) ref.	0.102	–	–	–	–
Yes										
No										
Cesarean section	1.99 (1.09–3.62) ref.	0.025	2.33 (1.11–4.90) ref.	0.026	2.94 (0.60–14.64) ref.	0.185	–	–	1.55 (0.32–7.51) ref.	0.587
One or more										
None										
Vaginal delivery					–	–	1.28 (0.39–4.23) ref.	0.683	0.15 (0.02–1.14) ref.	0.066
One or more										
None										

when symptomatic is often related to dysmenorrhea and chronic pelvic pain[16,17]. In this context, the nerve section, inadvertent nerve ligation of fibrous scarring, and myofascial syndrome result in menstrual and chronic pelvic pain[17,18].

Physical inactivity was associated with a higher frequency of PD. The physical activity has positive effects on stress, prostaglandin levels, and blood circulation, resulting in decreased pain and the prevalence of dysmenorrhea[19]. Then, women who do not perform exercise do not receive this benefit of endogenous opioids[20]. Therefore, it is one more motif to encourage women to remain physically active.

Our data are innovative by assessing PD in a sample containing older adults than other studies available in the Brazilian population. Despite this, the generalization of data should be made with caution because our data were collected in a small town, and the prevalence and associated factors to dysmenorrhea in women who live in large cities can be different.

As a limitation of the study, we can mention the use of a convenience sample, the cross-sectional design that prevents the establishment of cause-and-effect relationships, and the collection of data through interviews. For future studies, more robust methodological designs that include clinical assessment are recommended to better establish the relationships found in this study.

CONCLUSION

There was a high prevalence of PD with rates above 50% in adult women of all ages. In this study, only cesarean section and being physically inactive was associated with increased rates of dysmenorrhea among adult women.

AUTHORS' CONTRIBUTIONS

LBS: Conceptualization, Methodology, Formal Analysis, Investigation, Data curation, Writing – original draft, Writing – review & editing. IRB, THMD, CMA, JHD: Conceptualization, Methodology, Formal Analysis, Data curation, Writing – original draft, Writing – review & editing. CWSF: Formal Analysis, Data curation, Writing – original draft, Writing – review & editing. SMAC: Formal Analysis, Data curation, Writing – original draft, Writing – review & editing, Funding acquisition. DD: Conceptualization, Methodology, Formal Analysis, Data curation, Writing – original draft, Writing – review & editing, Project administration, Funding acquisition.

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ORIGINAL ARTICLE

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Nomogram for predicting post-traumatic hydrocephalus after decompressive craniectomy for traumatic brain injury

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SUMMARY

OBJECTIVE: This study aimed to develop and validate a practical nomogram to predict the occurrence of post-traumatic hydrocephalus in patients who have undergone decompressive craniectomy for traumatic brain injury.

METHODS: A total of 516 cases were enrolled and divided into the training (n=364) and validation (n=152) cohorts. Optimal predictors were selected through least absolute shrinkage and selection operator regression analysis of the training cohort then used to develop a nomogram. Receiver operating characteristic, calibration plot, and decision curve analysis, respectively, were used to evaluate the discrimination, fitting performance, and clinical utility of the resulting nomogram in the validation cohort.

RESULTS: Preoperative subarachnoid hemorrhage Fisher grade, type of decompressive craniectomy, transcalvarial herniation volume, subdural hygroma, and functional outcome were all identified as predictors and included in the predicting model. The nomogram exhibited good discrimination in the validation cohort and had an area under the receiver operating characteristic curve of 0.80 (95%CI: 0.72–0.88). The calibration plot demonstrated goodness-of-fit between the nomogram's prediction and actual observation in the validation cohort. Finally, decision curve analysis indicated significant clinical adaptability.

CONCLUSION: The present study developed and validated a model to predict post-traumatic hydrocephalus. The nomogram that had good discrimination, calibration, and clinical practicality can be useful for screening patients at a high risk of post-traumatic hydrocephalus. The nomogram can also be used in clinical practice to develop better therapeutic strategies.

KEYWORDS: Post-traumatic hydrocephalus. Decompressive craniectomy. Traumatic brain injury. Nomogram. Prediction model.

INTRODUCTION

Post-traumatic hydrocephalus (PTH) is one of the most important postoperative complications after decompressive craniectomy (DC) and is a major challenge to both patients with traumatic brain injury (TBI) and surgeons[1]. PTH is among the secondary insults aggravating brain damage and is characterized by impaired secretion, circulation, and malabsorption of the cerebrospinal fluid (CSF), resulting in ventricular dilatation[2]. The specific etiological mechanism of PTH has yet to be fully elucidated, which makes its early diagnosis and treatment difficult. PTH clearly impairs brain metabolism as well as function and often slows down the clinical improvement of patients. The condition also causes adverse outcomes if it is not promptly detected and managed[3]. Current researches have largely focused on exploring the risk factors, hence restricting their clinical application. Consequently, the present study developed and validated a nomogram to assist in predicting the risk of PTH in TBI patients who have undergone DC. The nomogram may therefore contribute to the timely and convenient identification of patients at a high risk of PTH and facilitate earlier clinical intervention.

METHODS

Subjects

The study included a total of 516 individuals out of the 584 TBI patients who had undergone DC between January 2009 and June 2020, at the neurosurgery department of the People's Liberation Army Joint Logistic Support Force 904th Hospital, Wuxi, Jiangsu, China. Later, the dataset was randomly partitioned into the training (364 patients) and validation (152 patients) cohorts in a ratio of 7:3. The study was approved by the ethics committee of the hospital. The following inclusion criteria

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were used: (1) patients presenting with a definite history of craniocerebral trauma, confirmed through computed tomography (CT) scans in all the cases and received treatment according to the guidelines for severe TBI[4]; (2) those aged ≥18 years; and (3) a minimum follow-up duration of 6 months. The following exclusion criteria were used: (1) patients with history of ventriculomegaly, meningitis, or malignancy in the nervous system; (2) those with other serious systemic diseases, including infections, cardiopulmonary failure, or hepatorenal insufficiency; (3) patients who died within 3 days of admission; (4) those with severe multiple injuries affecting cerebral blood perfusion; and (5) patients who were diagnosed with hydrocephalus before injury.

Diagnostic criteria for post-traumatic hydrocephalus

The diagnosis of PTH was done based on a combination of clinical characteristics and positive imaging results. The following characteristics were used: (1) neurological symptoms which included headache and vomiting, nerve deficits, and an altered level of consciousness; (2) the clinical state gradually improved over time but neurological deterioration and disturbance of consciousness worsened again; and (3) the brain CT scan showed progressive ventricular dilation (Evans index >0.3)[5].

Data collection

All the data are highlighted in Table 1. The data consisted of: (1) physiological characteristics including gender and age; (2) chronic conditions including hypertension and diabetes mellitus; (3) preoperative CT findings including the Fisher grade of subarachnoid hemorrhage (SAH), intraventricular hemorrhage (IVH), and midline shifting; (4) postoperative CT findings including type of DC, transcalvarial herniation volume (TCHV), subdural hygroma (SDG), and the craniectomy area. For the collection of postoperative radiological data, there is no fixed time period, but the principle of its maximum extent regardless the delay from surgery. The volume of transcalvarial herniation (TCH) was calculated using a formula previously published by Liao et al.[6] Notably, this formula has the advantages of having a simple principle, few parameters, and ease of implementation. Moreover, SDG was defined as low density, local, and non-lateral restricted regions of subdural CSF accumulation[7]; and (5) other potential factors including open-head injury, cause of head injury, preoperative GCS score, intracranial infection, and functional outcome. The functional outcome of each patient was measured according to the GOS score, 6 months post-discharge[8]. The outcomes were categorized into favorable (GOS 4 and 5) and unfavorable (GOS 1–3) based on the GOS scores[1].

Statistical analysis

Variables that conformed to normal distribution were analyzed using the independent sample t-test and expressed as the meanl distribution were analyzed using the independenting to the GOS score, 6 months post-discharg–Whitney U test and expressed as the median (interquartile range). Classification variables were analyzed using the chi-square test or Fisher exact test, and given as proportions (percentages). Moreover, the least absolute shrinkage and selection operator (LASSO) method was used to identify the optimal features. Following this, the selected features used to develop a regression model. Afterwards, the model was transformed into a nomogram. In addition, the receiver operating characteristic (ROC) curve, calibration plot, and decision curve analysis (DCA), respectively, were used to assess the model. Data analysis was conducted using SPSS (version 26.0; IBM Corporation, Armonk, NY, USA), R (version 3.5.1; http:// www.r-project.org), and Stata (version 14.0; StataCorp, College Station, TX, USA).

RESULTS

Clinical characteristics

The clinical characteristics of patients in the training and validation cohorts are summarized in Table 1. Out of the 364 patients in the training cohort, 98 (26.9%) were diagnosed with PTH and the mean age was 46.6 years. In contrast, 41 (27.0%) out of the 152 patients in the validation cohort were diagnosed with PTH and the mean age was 46.9 years.

Results from feature selection and nomogram construction

Least absolute shrinkage and selection operator regression was performed to screen out the nonzero features from the training cohort. Consequently, the partial likelihood deviance curve with the log (lambda) was plotted. In addition, two dotted vertical lines were drawn at the optimal values by determining the minimum criteria and the 1 standard error (SE) of the minimum criteria (Figure 1A). The number of potential predictors reduced from 16 to 5 (Figure 1B). Thereafter, the above-mentioned 5 unbiased variables, including preoperative SAH Fisher grade, type of DC, TCHV, SDG, and functional outcome, were used to build a model to predict the occurrence of PTH and displayed as a nomogram (Figure 2A). Moreover, it was applied by summing the points determined on the points scale, for each predictor.

Table 1. Demographics and clinical characteristics of study in the training and validation cohorts.

Characteristic	Training cohort		p	Validation cohort		p
	Non-PTH (n=266)	PTH (n=98)		Non-PTH (n=111)	PTH (n=41)	
Gender, n (%)						
Male	184 (69.2)	73 (74.5)	0.323	88 (79.3)	31 (75.6)	0.626
Female	82 (30.8)	25 (25.5)		23(20.7)	10 (24.4)	
Age (year), mean±SD	45.71year))	49.18year))	0.047	47.54year))	45.32year))	0.413
Open-head injury, n (%)						
No	229 (86.1)	83 (84.7)	0.736	96 (86.5)	32 (78.0)	0.205
Yes	37 (13.9)	15 (15.3)		15 (13.5)	9 (22.0)	
Head injury cause, n (%)						
Traffic accident	130 (48.9)	60 (61.2)	0.160	56 (50.5)	19 (46.3)	0.482
Fall down	20 (7.5)	8 (8.2)		10 (9.0)	5 (12.2)	
Slip down	48 (18.0)	12 (12.2)		20(18.0)	11 (26.8)	
Others	68 (25.6)	18 (18.4)		25 (22.5)	6 (14.7)	
Hypertension, n (%)						
No	225 (84.6)	75 (76.5)	0.073	83 (74.8)	34 (82.9)	0.289
Yes	41 (15.4)	23 (23.5)		28 (25.2)	7 (17.1)	
Diabetes mellitus, n (%)						
No	253 (95.1)	91 (92.9)	0.402	107 (96.4)	39 (95.1)	0.661
Yes	13 (4.9)	7 (7.1)		4 (3.6)	2 (4.9)	
Preoperative GCS score, n (%)						
≤8	148 (55.6)	68 (69.4)	0.018	62 (55.9)	29 (70.7)	0.097
>8	118 (44.6)	30 (30.6)		49 (44.1)	12 (29.3)	
Preoperative SAH Fisher grade, n (%)						
1	110 (41.4)	23 (23.5)	<0.001	44 (39.6)	7 (17.1)	0.018
2	85 (32.0)	22 (22.4)		31 (27.9)	12 (29.3)	
3	43 (16.2)	31 (31.6)		21 (18.9)	9 (22.0)	
4	28 (10.5)	22 (22.4)		15 (13.5)	13 (31.6)	
IVH, n (%)						
No	250 (94.0)	85 (86.7)	0.023	107 (96.4)	35 (85.4)	0.024
Yes	16 (6.0)	13 (13.3)		4(3.6)	6 (14.6)	
Midline shifting (cm), n (%)						
<0.5	85 (32.0)	20 (20.4)	0.040	28 (25.2)	9 (22.0)	0.573
0.5–1	113 (42.5)	42 (42.9)		49 (44.2)	22 (53.6)	
>1	68 (25.6)	36 (36.7)		34 (30.6)	10 (24.4)	
Type of DC, n (%)						
Unilateral craniectomy	228 (85.7)	66 (67.3)	<0.001	99 (89.2)	28 (68.3)	0.002
Bilateral craniectomy	38 (14.3)	32 (32.7)		12 (10.8)	13 (31.7)	
Intracranial infection, n (%)						
No	226 (85.0)	68 (69.4)	0.001	90 (81.1)	28 (68.3)	0.093
Yes	40 (15.0)	30 (30.6)		21 (18.9)	13 (31.7)	

Continue...

Table 1. Continuation.

Characteristic	Training cohort		p	Validation cohort		p
	Non-PTH (n=266)	PTH (n=98)		Non-PTH (n=111)	PTH (n=41)	
TCHV (cm^3), median (IQR)	46 (36.0–57.0)	69 (50.0–93.0)	<0.001	49 (33.0–63.0)	69 (48.5–94.5)	<0.001
SDG, n (%)						
No	166 (62.4)	43 (43.9)	<0.001	76 (68.5)	11 (26.8)	<0.001
Ipsilateral	62 (23.3)	15 (15.3)		16 (14.4)	12 (29.3)	
Contralateral	8 (3.0)	4 (4.1)		6 (5.4)	2 (4.9)	
Bilateral	23 (8.7)	21 (21.4)		9 (8.1)	13 (31.7)	
Interhemispheric	7 (2.6)	15 (15.3)		4 (3.6)	3 (7.3)	
Craniectomy area (cm^2), median (IQR)	89.7 (79.9–111.1)	102.2 (88.9–137.1)	<0.001	88.0 (78.5–106.8)	107.1 (89.4–144.0)	<0.001
Functional outcome, n (%)						
Unfavorable	67 (25.2)	62 (63.3)	<0.001	32 (28.8)	21 (51.2)	0.010
Favorable	199 (74.8)	36 (36.7)		79 (71.2)	20 (48.8)	

PTH: post-traumatic hydrocephalus; SD: standard deviation; GCS: Glasgow Coma Scale; SAH: subarachnoid hemorrhage; IVH: intraventricular hemorrhage; DC: decompressive craniectomy; TCHV: transcalvarial herniation volume; SDG: subdural hygroma; IQR: interquartile range.

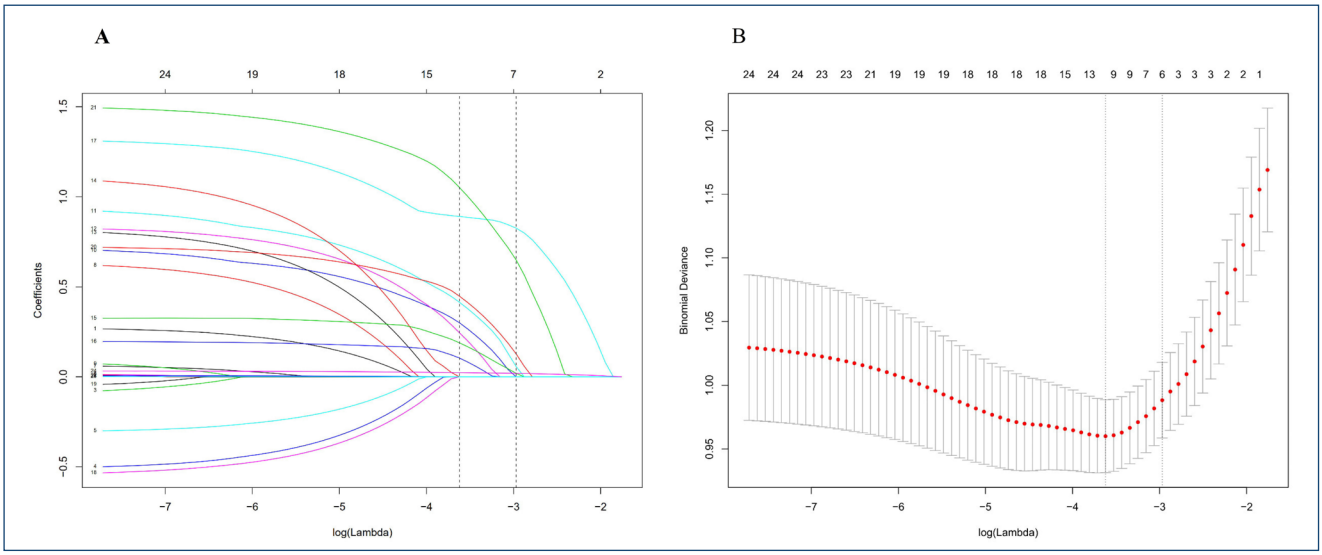

Figure 1. Selection of predictor features in the training cohort using least absolute shrinkage and selection operator regression. (A) The selected optimal parameter (lambda) in the least absolute shrinkage and selection operator model was 10-fold cross-validation based on the minimum criteria. (B) Least absolute shrinkage and selection operator coefficient profiles of the 16 characteristics. Five features with nonzero coefficients were finally obtained. LASSO: least absolute shrinkage and selection operator; SE: standard error.

Validation of the nomogram

The ROC curve for the validation cohort was generated by plotting the true positivity rate (y-axis) against the false positivity rate (x-axis) and bold black solid curve represents the discriminatory ability of the nomogram. In addition, Figure 2B demonstrates that the prediction model had a fairly good discriminatory ability, with an area under the ROC curve of 0.80 (95%CI: 0.72–0.88). Moreover, the calibration curve was generated by plotting the actual diagnosed PTH (y-axis) against the predicted incidence risk (x-axis). The results in Figure 2C show a good fitting degree between prediction and observation.

Furthermore, DCA on the validation cohort showed that the capacity of the nomogram to predict the occurrence of PTH was more beneficial than either the "treat-all" or "treat-none"

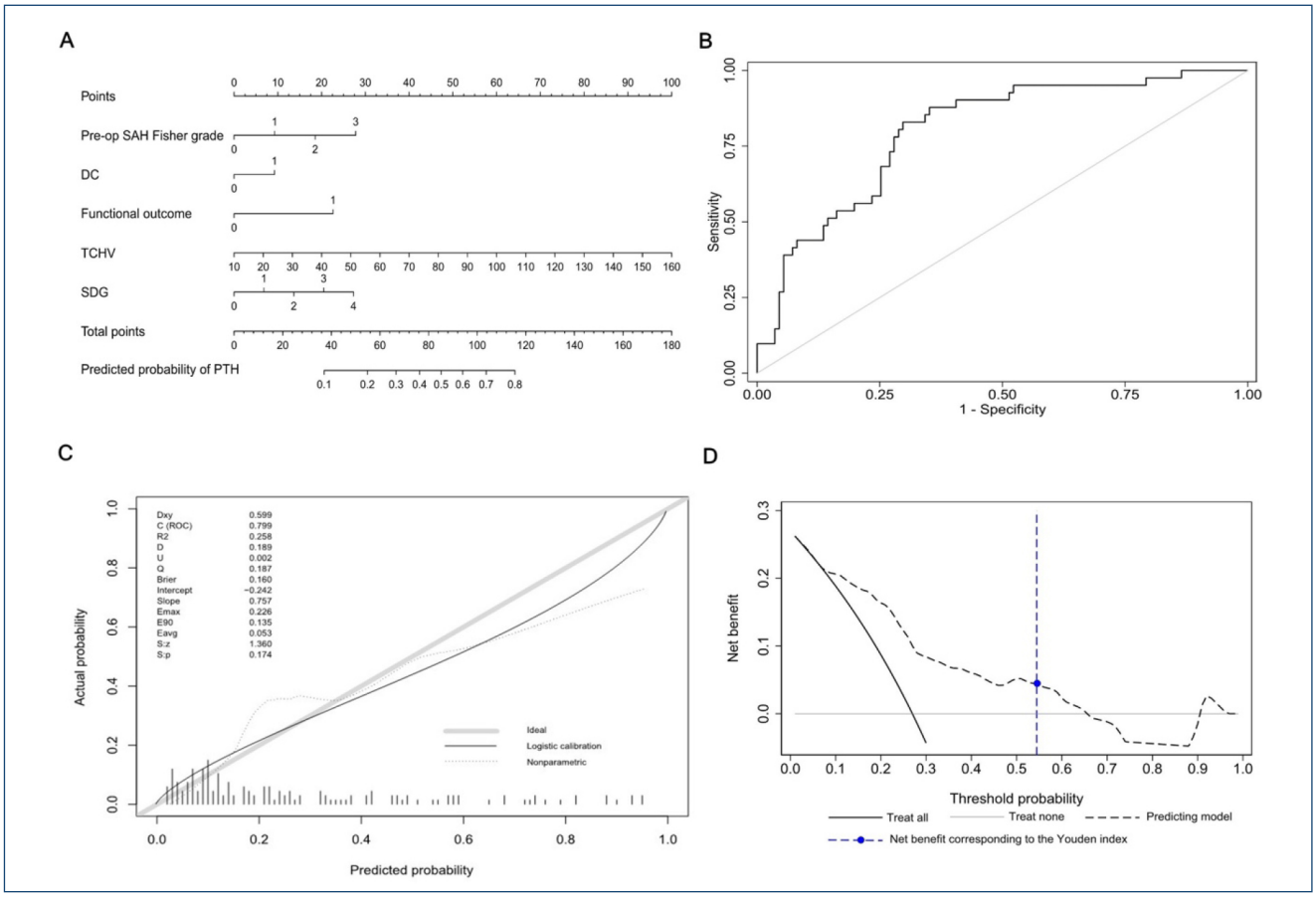

Figure 2. Development and validation of a predictive model for post-traumatic hydrocephalus. (A) A nomogram consisting of the preoperative subarachnoid hemorrhage Fisher grade, type of decompressive craniectomy, transcalvarial herniation volume, subdural hygroma, and functional outcome. Draw a line perpendicular from the corresponding axis of each predictor until it reaches the top line labeled "Points". Sum up the number of points for all predictors then draw a line descending from the axis labeled "Total points" until it intercepts the predicted probability of post-traumatic hydrocephalus axes to determine probabilities of post-traumatic hydrocephalus. For pre-op subarachnoid hemorrhage Fisher grade, 0=Fisher 1 grade, 1=Fisher 2 grade, 2=Fisher 3 grade, 3=Fisher 4 grade. For decompressive craniectomy, 0=unilateral, 1=bilateral. For functional outcome, 0=unfavorable, 1=favorable. For subdural hygroma, 0=no subdural hygroma, 1=ipsilateral, 2=contralateral, 3=bilateral, 4=interhemispheric. (B) A receiver operating characteristic curve to evaluate the discriminating capability of the nomogram. (C) A calibration plot to evaluate the fitting performance of the nomogram. (D) Decision curve analysis to evaluate the clinical utility of the nomogram. SAH: subarachnoid hemorrhage; DC: decompressive craniectomy; TCHV: transcalvarial herniation volume; SDG: subdural hygroma; ROC: receiver operating characteristic; DCA: decision curve analysis.

strategy, with a threshold probability of 8–66% (Figure 2D). Additionally, the DCA results of the model in the validation cohort showed that there was a satisfactory net clinical benefit even under the Youden index (0.532).

DISCUSSION

Although increasing clinical attention has recently been paid to PTH, early, and reliable prediction of PTH using available clinical evidence is challenging. Therefore, it is necessary to develop methods that enable early diagnosis of PTH in order to improve decision-making in clinical practice. In the present study, demographic, clinical, and neuroimaging data from PTH patients were analyzed to examine the association between the putative risk factors. The study used LASSO regression to develop a nomogram for predicting the incidence of PTH. The statistical results herein indicated that the model had a satisfactory goodness-of-fit, robustness, and predictive ability. Therefore, the model could be of great significance in effectively predicting and preventing the progression of PTH. In this study, 16 factors that may have been related to the occurrence of PTH were analyzed through LASSO regression and 5 predictors were finally obtained. The nomogram showed that the weight of all the predictors could be introduced into the model intuitively and visually.

The nomogram showed that PTH was closely related to severity of traumatic SAH. Previous studies reported that the

probability of PTH in patients with severe SAH was significantly higher than that in patients without or mild SAH[9]. One of the many theories proposed to explain the mechanisms underlying the occurrence of hydrocephalus after SAH is that SAH disturbs CSF circulation at the basal cisterns, ventricles, the foramen of Monro, or the extensive subarachnoid space[10,11]. In addition, Chen et al.[3] showed that the Fisher 4 grade is among the strongest radiological factors affecting the occurrence of PTH.

Destruction of the integrity of the cranial cavity was shown to be a major cause of PTH in patients who had undergone DC. It is noteworthy that bilateral DC leads to the outward transmission of pressure pulses in the bilateral cranial cavity, leading to more serious disturbance of CSF circulation and high chances of PTH[12]. Moreover, TCH following DC occurred frequently. Furthermore, a study by Neto et al.[13] similarly suggested that TCHV can act as a predictor of PTH after DC. TCH has a complex pathogenic mechanism, that is, intracranial hypertension caused by various factors leads to a critical reduction in cerebral perfusion, and the brain bulges from the skull defect after DC, leading to the so-called TCH. The drainage of veins and circulation of CSF in herniated brain tissue are blocked, further aggravating both edema in herniated brain tissue and incarceration, thus affecting prognosis and outcomes. From this point of view, it is possible that a large craniectomy area reduces the occurrence of TCH but also causes a series of problems including high infection rates, difficulties in wound healing, and challenges in skull reconstruction[14]. Therefore, the craniectomy area should not be undertaken haphazardly.

The patients who have been in a coma for extended periods of time after operation often experience severe damage to the brain tissue, and the CSF circulation and absorption balance are damaged to a greater extent correspondingly, making it conducive for the development of PTH. In the present study, the results showed that PTH patients had an obviously unfavorable functional outcome, suggesting that they were likely to experience more severe TBI. This was interesting, however since preoperative GCS was not independently associated with PTH, similar to previous studies[15]. It is possible that there was more death of patients with a low preoperative GCS score in the immediate and shot-term postoperative period, thus indirectly decreasing the occurrence of PTH.

Subdural hygroma was shown to be one of the phenomena affecting changes in the dynamics of CSF, and may emerge prior to the occurrence of PTH. Previous studies also suggested that SDG and PTH are essentially caused by disorders in CSF hydrodynamics[9,16]. SDG may represent local damage of CSF homeostasis while PTH indicates a more serious CSF dysfunction. Therefore, patients with SDG have higher chances of developing PTH[16]. The results from the present study indicated that the probability of developing PTH in bilateral SDG and interhemispheric hygroma was significantly higher than that of developing PTH in ipsilateral or contralateral hygroma, corroborating with the findings previously reported by Ki et al.[17] In addition, Kaen et al.[18] similarly showed that interhemispheric hygroma is an important imaging characteristic that predicts the occurrence of PTH.

Receiver operating characteristic curve and calibration plot validated the effectiveness of the model. DCA is a method of evaluating prediction models by calculating the clinical net benefit. The DCA results showed that all the patients benefited from this model, with a threshold probability ranging from 8 to 66%. This further verified the value of the model in practical clinical work.

The study had a number of limitations. First, this was a retrospective study and may therefore have a certain degree of selection and analytical bias. Second, a limited number of patients were recruited from a single institution. Although the prediction model was verified using a validation set, it is necessary to conduct large sample and multicenter studies to prove the feasibility of the nomogram so as to increase the possibility of extensive popularization of the model.

CONCLUSIONS

The present study used demographic, clinical, and neuroimaging indicators to develop a model for assessing the risk of PTH after undergoing DC in TBI patients. The indicators included the SAH Fisher grade, type of DC, TCHV, SDG, and functional outcome. In addition, the ROC curve, calibration plot, and DCA were used to show that the nomogram had a good predictive performance, calibration, and clinical utility. Moreover, the nomogram had the qualities of concise composition with fewer variables and can therefore be used for the identification of individuals at a high risk of PTH so that timely intervention can be implemented.

AUTHORS' CONTRIBUTIONS

Conceptualization: Yuhai Wang (YH), Yinong Xu (YX), JZ (Jianwei Zhuo); Data curation: Yuhai Wang (YH), JZ (Jianwei Zhuo); Formal analysis: JZ (Jianwei Zhuo), Wenwen Zhang (WZ). Funding acquisition: None. Investigation: JZ (Jianwei Zhuo), Wenwen Zhang (WZ), Jilin Sun (JS); Methodology: JZ (Jianwei Zhuo), Wenwen Zhang (WZ), Jilin Sun (JS), Meng Ji (MJ); Project administration: Yuhai Wang (YH), Wenwen Zhang (WZ), Jing Zhang (JZ); Resources: Yuhai Wang (YH); Software: JZ (Jianwei Zhuo), Wenwen Zhang (WZ); Supervision: Yuhai Wang (YH), Yinong Xu (YX), Kai Wang (KW); Validation: Yuhai Wang (YH); Visualization: JZ (Jianwei Zhuo), Wenwen Zhang (WZ), Kai Wang (KW); Writing – original draft: JZ (Jianwei Zhuo), Wenwen Zhang (WZ); Writing – review & editing: Yuhai Wang (YH).

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ORIGINAL ARTICLE

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Correlation analysis of Trial of Org 10172 in acute stroke treatment classification and National Institutes of Health Stroke Scale score in acute cerebral infarction with risk factors

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SUMMARY

OBJECTIVE: The aim of this study was to investigate the correlation between the Trial of Org 10172 in acute stroke treatment classification and the National Institutes of Health Stroke Scale score of acute cerebral infarction as well as acute cerebral infarction's risk factors.

METHODS: The clinical data of 3,996 patients with acute cerebral infarction hospitalized in Hebei Renqiu Kangjixintu Hospital from January 2014 to November 2018 were analyzed retrospectively. According to Trial of Org 10172 in acute stroke treatment, they were divided into five groups: arteriosclerosis, cardio cerebral embolism, arterial occlusion, other causes, and unknown causes. Through questionnaire design, routine physical examination, and physical and chemical analysis of fasting venous blood samples, the risk factors were evaluated, and the correlation between Trial of Org 10172 in acute stroke treatment classification and National Institutes of Health Stroke Scale classification was analyzed using multivariate logistic regression. In addition, the relationship between National Institutes of Health Stroke Scale score and risk factors in different groups was compared, and the correlation between Trial of Org 10172 in acute stroke treatment classification and National Institutes of Health Stroke Scale score was analyzed.

RESULTS: Multivariate logistic regression analysis showed that diabetes, atrial fibrillation or stroke history, age, and education level were related to Trial of Org 10172 in acute stroke treatment classification. In the National Institutes of Health Stroke Scale comparison, the scores of the cardio cerebral embolism group were significantly higher than those of the other four groups, and patients with diabetes, atrial fibrillation, or stroke history had a high share, especially atrial fibrillation (33.06%).

CONCLUSIONS: The nerve function defect is more serious after acute cerebral infarction with cardiogenic cerebral embolism, indicating a poor prognosis.

KEYWORDS: Cerebral infarction. Ischemic stroke. Classification. Risk factors. Cerebrovascular .

INTRODUCTION

Acute cerebral infarction (ACI) is a cerebrovascular disease with high morbidity, disability, and mortality[1] that is affected by various factors. The pathological basis of ACI is the disruption of blood supply in the brain, with ischemia and hypoxia causing ischemic necrosis and cerebral malacia in focal brain tissue[2]. The trial of Org 10172 in acute stroke treatment (TOAST) and the National Institutes of Health Stroke Scale (NIHSS) are currently the most commonly used ACI typing and scoring methods[3]. The TOAST classification denotes five subtypes (LAA, CE, SAO, OE, UE) of ischemic stroke. LAA patients have large-artery atherosclerosis (embolus/thrombosis), CE is the cardioembolism, SAO patients were defined as having small-vessel occlusion, and OE and UE mean a stroke of other determined etiology and a stroke of undetermined etiology respectively, and the specific standard refers to the classification method of You Wenxia et al.[4]

NIHSS can comprehensively evaluate the dysfunction after stroke, with objective evaluation criteria and strong operability. Some scholars[5] found that the predictive ability of NIHSS changes in the prognostic outcome of ACI patients is excellent. The lower the NIHSS score, the better the prognosis of ACI patients. Furthermore, in several studies, such as those conducted by Tan[6] and Wang[7], by dynamically observing NIHSS changes during the hospitalization of patients of each subtype, it was found that patients with CE had the most severe neurological deficits and the worst prognosis; conversely, patients with SAO had the least severe neurological deficits and the best prognosis. In the study conducted by Wang[8], it was also shown that patients with CE had a significantly higher neurological deficit score on admission than other subtypes, a greater proportion of severe cases, a significantly lower rate of neurological improvement at discharge than other subtypes, and the lowest clinical outcome. Moreover, SAO had the lowest neurological deficit score on admission, the mildest disease, the highest rate of neurological improvement at discharge, and the best outcome. In many previous studies, it was suggested that the CE type of cerebral

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infarction has a large lesion area, the lesion affects a wide range of patients, the embolism in the brain is mainly caused by the blockage of large arteries by emboli, and the neuroendocrine changes in the acute phase increase the ventricular load, which makes the construction of collateral circulation more difficult. Therefore, the incidence of poor prognosis is high[9], which has also been confirmed by the autopsy results of patients with ischemic stroke. The SAO type of cerebral infarction is mainly due to luminal changes caused by lipid hyaline degeneration and lumen occlusion in the walls of small arteries and micro-arteries due to long-term hypertension; however, the lesion involvement is small, and the damage is mild[10]. Yuan et al.[11] compared the results of TOAST and NIHSS with the changes in actual clinical symptoms of the patients, and the analysis showed that NIHSS was a good indicator of the prognosis of the patients.

However, the correlation between ACI TOAST and NIHSS score remains unknown recently. Therefore, we conducted this study to investigate the correlation between ACI TOAST and NIHSS, as well as ACI's risk factors.

METHODS

Study subjects

This was a retrospective study. From January 2014 to November 2018, 3,996 patients with ACI TOAST classification who were hospitalized were recruited and divided into five groups based on artery atherosclerosis, cardiac cerebral embolism, SAO, for other reasons, and unknown reasons. This study was conducted in accordance with the Declaration of Helsinki and approved by the ethics committee of our hospital. All participants had signed the informed consent.

Inclusion and exclusion criteria

Inclusion criteria were

1. patients who had been diagnosed with ACI according to the revised diagnostic criteria of the *Chinese Guidelines for the Diagnosis and Treatment of Acute Ischemic Cerebral Stroke 2014*[12] and confirmed by cranial CT or MRI;
2. age was more than 18 years;
3. within seven days of stroke onset; and
4. patients who have signed informed consent.

Exclusion criteria were

1. patients with severe consciousness disorders, psychiatric symptoms, and aphasia;
2. patients who had a hearing impairment and could not cooperate with the examination;
3. patients with hemorrhagic cerebrovascular disease;
4. patients who had the previous history of psychiatric and psychological diseases;
5. patients with combined chronic wasting diseases, malignant tumors, hyperthyroidism, or hematologic diseases; and
6. patients with autoimmune system diseases.

Methods

All the data were investigated by uniformly trained medical personnel in accordance with a uniformly designed questionnaire for eligible patients. The study included a questionnaire, physical examination, laboratory examination, and discharge-related data collection and entry. This study was conducted in accordance with the Declaration of Helsinki and approved by the ethics committee of Renqiu Kangjixintu Hospital.

Questionnaire

This questionnaire included age, gender, and risk factors for vascular diseases, such as the history of hypertension, diabetes, hyperlipidemia, stroke, coronary artery disease, atrial fibrillation, and the use of antiplatelet drugs.

Physical examination

The physical examination included blood pressure, heart rate, height, weight, and waist circumference. For blood pressure and heart rate measurements, all respondents were asked to sit still for 5–10 min before the examination, and then an Omron electronic blood pressure monitor was used to measure the systolic and diastolic blood pressure of the upper extremities of the selected subjects bilaterally. The highest side systolic and diastolic blood pressure was taken from twice examinations for measurement as the final result record.

Laboratory examination

After fasting for 12 h, 6 mL of fasting venous blood specimens were routinely collected from all the participants, and the fibrinogen (FIB) was measured using a Succeeder SF-8000. The fasting plasma glucose (FPG), total cholesterol (TC), triglyceride (TG), low-density lipoprotein cholesterol (LDL-C), high-density lipoprotein cholesterol (HDL-C), lipoprotein a, homocysteine (HCY), uric acid (UA), cystatin C, urea nitrogen, and creatinine were measured using an Olympus 400 fully automated biochemical detector.

TOAST etiological typing

Based on TOAST, ischemic stroke was classified into five types: large artery atherosclerosis (LAA), cardioembolism (CE), small

artery occlusion (SAO), other determined etiologies (OE), and unexplained etiology (UE).

Statistical Methods

All statistical analyses were performed using SPSS version 21.0 (IBM, Chicago, USA). The continuous variables of normal distribution were expressed as mean±standard deviation, the continuous variables of non-normal distribution were expressed as median (interquartile range [IQR]), and the categorical variables were expressed as frequency (percentage [%]). For multiple comparisons, each value was compared using one-way ANOVA following Dunnett's test when each datum conformed to the normal distribution, while the non-normally distributed continuous data were compared using non-parametric tests. The counting data were tested by chi-square test. Multivariate logistic regression was used to determine the independent variable in this study. A value of $p<0.05$ was considered statistically significant.

RESULTS

Baseline characteristics

These participants had been divided into five groups, such as LAA group (3,338 cases), CE group (124 cases), SAO group (489 cases), OE group (24 cases), and UE group (21 cases).

Comparison outcomes among the five groups

The results showed that there were statistically significant differences among the five groups in terms of education, age, history of hypertension, diabetes, hyperlipidemia, history of stroke, atrial fibrillation, coronary artery disease, whether antiplatelet agents were used before the disease, systolic blood pressure, diastolic blood pressure, FPG, UA, and urea nitrogen levels on admission ($p<0.05$). However, there were no statistically significant differences among the five groups in terms of gender, body mass index, smoking, excessive alcohol consumption, whether the peripheral vascular disease was combined, FIB, TG, TC, LDL-C, HDL-C, lipoprotein a, HCY, creatinine, and cystatin C levels on admission ($p>0.05$) (Table 1).

National Institutes of Health Stroke Scale in patients with acute cerebral infarction Trial of Org 10172 in acute stroke treatment on admission

The results showed that the NIHSS on admission were 3.61±3.56 in the LAA group, 5.69±6.14 in the CE group, 2.55±2.06 in the SAO group, 3.54±3.91 in the OE group, and 3.10±3.33 in the UE group. In pairwise comparisons, the difference between the LAA and CE, LAA and SAO, CE and SAO, and SAO and OE was statistically significant ($p<0.05$). However, no statistically significant differences were observed between/among other comparison groups (Table 2).

National Institutes of Health Stroke Scale in patients with acute cerebral infarction Trial of Org 10172 in acute stroke treatment at discharge

The results showed that the NIHSS at discharge were 3.13±3.69 in the LAA group, 4.39±5.82 in the CE group, 2.00±2.03 in the SAO group, 3.21±4.28 in the OE group, and 2.43, 3.21±4 in the UE group. In pairwise comparisons, the difference between the LAA and CE, LAA and SAO, CE and SAO, and SAO and OE was statistically significant ($p<0.05$). However, no statistically significant differences were observed between/among other comparison groups (Table 2).

Analysis of Trial of Org 10172 in acute stroke treatment classification

The results of multivariate logistic regression analysis of TOAST classification are given in Table 3. In multivariate logistic regression analysis, patients with diabetes, atrial fibrillation, or a history of stroke were more likely and had the risk of ACI, besides these factors played a major effect on the TOAST classification (Table 3). There were no episodes of TOAST classification associated with gender. Age and culture degree had a relationship with TOAST classification by the multivariate logistic regression analysis.

DISCUSSION

In this study, according to the TOAST of ACI, LAA cerebral infarction was the most frequent, followed by SAO and CE, while OE and CE caused the least ACI, which is basically consistent with the findings of Han[13] and Jiang[14]. Lei et al.[15] found that the top three were UE, SAO, and CE, while Li et al.[16] found that the top three were LAA, SAO, and CE. The proportion of various subtypes varied in different studies, and the reasons for this may be related to the differences in sample size, geography, examination methods, and many other factors.

In this study, it was found that the patient's education, age, whether combined with hypertension, diabetes mellitus, hyperlipidemia, history of stroke, atrial fibrillation, coronary artery disease, whether antiplatelet drugs were used before the disease,

Table 1. Baseline information of TOAST etiological subgroups of ACI.

Items	LAA (3,338 cases)	CE (124 cases)	SAO (489 cases)	OE(24 cases)	UE (21 cases)	Test statistic value	p-value
Demographic characteristics							
Male [cases (%)]	2,053(61.50)	82(6.13)	318(65.03)	13(54.17)	15(71.43)	4.561	0.335
Junior high school and higher education	889(26.63)	33(26.61)	195(39.880	10(41.67)	14(66.67)	53.978	0.000
Age (years)	65.62±10.88	68.10±12.74	59.84±11.07	52.33±13.38	50.57±16.28	48.658	0.000
Body mass index	24.92±3.63	24.94±3.40	24.92±3.47	25.06±4.41	24.06±3.39	0.310	0.871
Risk factors n (%)							
Hypertension	2,372(71.06)	73(58.87)	321(65.64)	12(50.00)	13(61.90)	18.645	0.001
Diabetes	684(20.49)	15(12.10)	68(13.91)	3(12.50)	2(9.52)	18.294	0.001
Hyperlipidemia	465(13.93)	20(16.13)	40(8.18)	2(8.33)	2(9.52)	13.943	0.007
History of stroke	1,201(35.98)	44(35.48)	94(19.22)	7(29.17)	3(14.29)	57.518	0.000
Atrial fibrillation	45(1.35)	41(33.06)	4(0.82)	0(0.00)	0(0.00)	552.744	0.000
Coronary heart disease	455(13.63)	45(36.29)	38(7.77)	2(8.33)	4(19.05)	69.512	0.000
Smoking	1,608(48.17)	47(37.90)	222(45.40)	13(54.17)	7(33.33)	8.168	0.086
Excessive alcohol consumption	146(4.37)	3(2.42)	28(5.73)	0(0.00)	1(4.76)	4.239	0.375
Antiplatelet drug use	547(16.39)	31(25.00)	48(9.82)	1(4.17)	2(9.53)	25.045	0.000
Peripheral vascular disease	12(0.36)	0(0.00)	2(0.41)	0(0.00)	0(0.00)	0.650	0.957
Systolic blood pressure (mmHg)	164.15±24.18	158.17±25.58	161.92±24.02	151.38±29.23	154.62±26.75	4.808	0.001
Diastolic blood pressure (mmHg)	87.59±13.31	92.84±16.85	90.75±13.39	85.79±15.06	90.14±11.52	10.071	0.000
FIB (g/L)	3,11±1.59	3.07±1.18	2.93±1.21	3.12±0.73	2.82±0.79	1.743	0.138
FPG (mmol/L)	6.22±2.37	5.98±2.02	5.79±1.89	5.21±3.39	5.62±1.85	4.171	0.002
TG (mmol/L)	1.54±1.42	1.35±1.08	1.57±1.29	1.40±0.69	1.37±0.65	0.811	0.518
TC (mmol/L)	4.81±1.15	4.76±1.21	4.71±1.07	4.89±1.04	4.45±1.08	1.495	0.201
LDL-C (mmol/L)	2.72±7.14	2.35±0.80	2.51±5.26	2.42±0.69	2.32±0.67	0.208	0.934
HDL-C (umol/L)	1.18±2.17	1,12±0.30	1.16±0.33	1.03±0.38	1.10±0.26	0.080	0.988
Lipoprotein a (mg/L)	272.38±264.69	272.93±239.08	248.76±366.96	282.20±185.51	357.98±420.77	1.306	0.265
HCY (mmol//L)	20.19±15.27	21.29±15.62	19.58±17.39	17.75±12.99	21.99±15.96	0.552	0.697
UA (umol/L)	334.20±102.12	361.42±112.52	331.65±96.99	316.02±131.41	338.16±104.23	2.462	0.043
Urea nitrogen (mmol//L)	5.71±2.07	6.68±7.36	5.44±1.67	5.45±2.09	5.34±1.27	6.948	0.000
Creatinine (umol/L)	71.56±33.49	76.00±23.99	68.72±33.44	67.90±21.99	63.68±15.47	1.761	0.134
Cystatin C (mg/L)	1.13±6.55	1.06±0.59	0.87±0.43	0.83±0.44	0.84±0.33	0.221	0.927

systolic blood pressure, diastolic blood pressure, FPG, UA, and urea nitrogen levels on admission were factors that were associated with ACI. In addition, the NIHSS scores on admission and at discharge were compared among the five groups after grouping ACI patients according to TOAST. The data showed that the NIHSS scores were the highest in the CE group and the lowest in the SAO group, suggesting that the CE group had more severe neurological deficits and the worst prognosis in this study, which could be explained that the neuroendocrine changes in the brain embolism increase the ventricular

Table 2. Comparison of NIHSS in patients with ACI TOAST.

Groups	LAA	CE	SAO	OE	UE	
NIHSS at admission	3.61S at	5.69S at	2.55S at	3.54S at	3.10S at	
NIHSS at discharge	3.13S at	4.39S at	2.00S at	3.21S at	2.43S at	
	Comparisons	Mean differences (I-J)	Standard error	Sig.	95% Confidence interval	
					Lower bound	Upper bound
NIHSS at admission	LAA V.S. CE	−2.07941	0.32203	0.000	−2.9582	−1.2006
	LAA V.S. SAO	1.06813	0.17050	0.000	0.6028	1.5334
	CE V.S. SAO	3.14754	0.35404	0.000	2.1813	4.1137
	CE V.S. OE	2.15188	0.78525	0.048	0.0089	4.2948
	CE V.S. UE	2.59831	0.83091	0.015	0.3307	4.8659
NIHSS at discharge	LAA V.S. CE	−1.25602	0.33092	0.001	−2.1591	−0.3529
	LAA V.S. SAO	1.13312	0.17522	0.000	0.6549	1.6113
	CE V.S. SAO	2.38914	0.36381	0.000	1.3963	3.3820

Table 3. Multivariate logistic regression analysis of TOAST classification.

	Estimates	Standard error	Wald	Sig.	95%CI	
					Lower bound	Upper bound
Age	-0.029	0.005	28.737	0.000	-0.039	-0.018
Gender						
Male	-0.089	0.119	0.560	0.454	-0.321	0.144
Culture degree						
Junior high school	-0.326	0.121	7.291	0.007	-0.563	-0.089
Risk factors						
Hypertension	0.148	0.116	1.631	0.202	-0.079	0.375
Diabetes	0.525	0.161	10.686	0.001	0.210	0.840
Hyperlipidemia	0.537	0.283	3.605	0.058	-0.017	1.091
Atrial fibrillation	-1.328	0.306	18.813	0.000	-1.928	-0.728
History of stroke	0.464	0.133	12.180	0.000	0.204	0.725
Coronary heart	0.089	0.171	0.272	0.602	-0.246	0.424
Antiplatelet drug use	0.237	0.186	1.638	0.201	-0.126	0.601

load and make the construction of collateral circulation more difficult[9]. However, there was no significant difference in the NIHSS scores between the other three groups. In the baseline information study of different groups, the first three factors related to TOAST classification, atrial fibrillation, stroke history, and diabetes accounted for a very high proportion in group CE, especially atrial fibrillation, accounting for 33.06%, much higher than that in other groups, which was consistent with the results of previous studies, indicating the reliability of the research data. In clinical work, we routinely perform the TOAST of ACI patients to a certain extent to predict their prognosis[17-19].

There were several limitations in this study. Firstly, this trial was not a randomized controlled trial. Secondly, only the NIHSS scores of patients with ACI on admission and at discharge were compared after grouping in this study, and long-term follow-up

was not performed, which may leave a gap in the judgment of long-term prognosis.

CONCLUSIONS

The TOAST classification is effective and reliable, and the related factors include diabetes, atrial fibrillation or stroke history, age, and education level. NIHSS score revealed that neurological impairment after ACI combined with cardiogenic cerebral embolism is more serious, suggesting a poor prognosis. This is consistent with the results of TOAST classification results, and the two have a certain correlation, which is worth further study.

Ethical statement

This study was conducted in accordance with the Declaration of Helsinki and approved by the ethics committee of our hospital. All participants had signed the informed consent.

AUTHORS' CONTRIBUTIONS

HZ: Conceptualization. YQ: Conceptualization. SG: Data curation. KY: Data curation. RJ: Data curation. GZ: Formal Analysis. XY: Formal Analysis, Writing – original draft. JB: Formal Analysis, Writing – original draft. DL: Formal Analysis, Writing – original draft.

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ORIGINAL ARTICLE

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Factors predicting the development of urethral stricture after bipolar transurethral resection of the prostate

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SUMMARY

OBJECTIVE: We aimed to investigate the rate of urethral stricture development, predictor factors, and the reliability following bipolar transurethral resection of the prostate.

METHODS: A total of 124 patients participated in this study. Patient data were retrospectively reviewed. The patients were divided into group 1 (those who developed urethral stricture) and group 2 (those who did not develop urethral stricture). Annual checkups were performed after the postoperative months 1 and 6. The patients were checked by uroflowmetry + post-voiding residue and international index of erectile function. We evaluated the complications that developed during the perioperative period according to the Clavien system.

RESULTS: Urethral stricture developed in 10.5% (13/124) of the patients. It was found that patients who underwent transurethral resection of the prostate for the second time (p=0.007), patients with a preoperative catheter or history of catheter insertion (p=0.009), patients with high preoperative median white blood cell (10^3) counts (p=0.013), and patients with long postoperative catheterization time had a higher rate of urethral stricture after bipolar transurethral resection of the prostate (p=0.046). No grade 4 and grade 5 complications were observed according to the Clavien system in patients.

CONCLUSION: Factors such as second transurethral resection of the prostate surgery, history of preoperative catheter insertion, high postoperative white blood cell count, and long postoperative catheterization time increase the risk of urethral stricture after bipolar transurethral resection of the prostate.

KEYWORDS: Lower urinary tract symptoms. Urethral stricture. Prostate. Urinary tract infections.

INTRODUCTION

In bipolar transurethral resection of the prostate (BTURP), radio frequency energy creates a vapor (plasma) layer containing energy-charged particles around the electrode in a conductive environment, which causes the prostate tissue to be resected easily. In addition, this plasma area prevents the resected tissues from sticking to the electrode. The current from the active electrode passes to the adjacent return electrode without passing through the patient's body, which eliminates the need for diathermy pads. Isotonic 0.9% saline fluid is used as irrigation fluid in the bipolar method[1,2]. There are four different types of bipolar TUR devices developed and actively marketed today: Plasma kinetic technology (Gyrus-PK), AUTOCON II 400 ESU (Karl Storz Endoskope, Tuttlingen, Germany), TURis (Olympus, Tokyo, Japan), and Richard Wolf bipolar device.

There are many studies showing that BTURP is a successful and reliable method[3,4]. Although the rate of developing urethral stricture following BTURP (3.4–12.7%) is not high[11,12], it may cause serious complications such as urinary retention, acontractile bladder, urethral abscess, necrotizing fasciitis, and renal failure. Investigation of factors predicting the development of urethral stricture following BTURP may help prevent serious complications. Many investigators have reported the effect of several factors such as age, operation time, amount of removed prostate tissue, presence of urinary infection, and catheterization time on the development of urethral stricture following BTURP[17-22]. Literature review showed that there is no publication investigating the effect of preoperative white blood cell (WBC) count, having a preoperative catheter or history of preoperative catheter insertion, use of nonsteroidal anti-inflammatory drugs (NSAIDs), history of preoperative prostatitis, secondary surgery history, type of anesthesia applied (i.e., regional or general), and history of postoperative urinary retention on development of urethral stricture. In this study, we have investigated the effect of this and other factors on the development of urethral stricture after BTURP and the rate of urethral stricture development.

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METHODS

Patients who underwent BTURP (Plasmakinetic) between January 2016 and January 2020 and who had no history of preoperative and intraoperative urethral stricture were included in this study. Patient data were collected retrospectively. A total of 128 patients participated in this study. Four of these patients were excluded from the study as they were applied TUR-P for palliative purposes due to prostate cancer. The patients were subjected to preoperative urine culture examination for urinary tract infection (UTI). A bacterial growth of 10^5 colonies/ml in urine culture was considered significant for UTI. The third-generation cephalosporin or quinolone group antibiotics were administered to all preoperative patients for prophylaxis. The patients were discharged on postoperative days 1 and 2. Postoperative checkups were performed with uroflowmetry + post voiding residue (PVR) and international prostate symptom score (IPSS) at month 1, month 6, and then annually. Patients who has Q_{max} < 15 ml/s according to the control uroflowmetry were suspected of urethral stricture, and the definitive diagnosis was made using endoscopy.

The patients were divided into two groups: group 1 (those who developed urethral stricture) and group 2 (those who did not develop urethral stricture). In our study, we investigated the relationship between the development of urethral stricture following BTURP and the presence of a preoperative catheter (indwelling Foley catheter) or a history of catheter (Foley catheter insertion for any reason) insertion, preoperative white blood cell (WBC) (10^3) count, history of diabetes mellitus (DM), postoperative NSAID use, history of preoperative prostatitis (acute bacterial prostatitis), history of secondary BTURP surgery, type of anesthesia applied (i.e., regional or general), the presence of postoperative UTI, smoking, and development of postoperative urinary retention. In addition, we examined the effects of factors such as age, operation duration, prostate weight, amount of prostate tissue resected, and catheterization time, which were previously investigated in the literature, on the development of urethral stricture. We evaluated the complications that developed during the perioperative period according to the Clavien system.

Statistical analyses

Statistical analyses were performed using SPSS version 25 (IBM SPSS Corp., Armonk, NY, USA) software. The suitability of the variables for normal distribution was investigated using Kolmogorov–Smirnov and Shapiro–Wilk analytical methods. Descriptive statistical analyses were performed using the median and interquartile range for non-normally distributed variables. Independent-sample t-test was used for normally distributed independent variables, Mann–Whitney U-test for non-normally distributed independent variables, and chi-square and Fisher's exact tests were used to compare the categorical data. The results were considered statistically significant for cases where the p-value was <0.05 at a 95% confidence interval.

RESULTS

A total of 124 patients participated in this study. Urethral stricture developed in 10.5% (13/124) of the patients. The median age in group 1 and group 2 was 70.76±8.65 and 74.46±8.7 (mean±SD), respectively. There was no statistical difference between the two groups (p=0.148). The number of patients with a preoperative diagnosis of prostatitis was 4 (3.2%), and the number of secondary cases with a permanent catheter was 25 (20.1%).

Notably, 46% (6/13) of urethral strictures developed in the bulbar urethra, 38.5% (5/13) in the membranous urethra, and 16% (2/13) in the bladder neck.

The median preoperative WBC count was 7.30×10^3 (5.87×10^3–8.54×10^3), the median operation time was 60 min (45–65), the median preoperative prostate volume was 57 ml (39–80.75), the median prostate volume resected was 30 ml (17.25–47), and the median postoperative catheterization time was 3.26±1.9 days (median±SD). In the postoperative period, 7 (5.6%) patients developed urinary retention and 11 (8.8%) patients developed UTI. The follow-up period was minimum 10 months and maximum 57 months (Table 1). The catheters were reinserted to patients who developed postoperative urinary retention and were removed after 48 h. It was observed that all of these patients were able to urinate. Perioperative complications were evaluated using the Clavien system. We did not encounter any cases requiring blood transfusion and developing TUR syndrome. Clavien grade 4 and grade 5 complications were not observed in patients.

The demographic and clinical characteristics of patients with or without urethral stricture after BTURP were statistically evaluated. As a result, it was found that urethral stricture following BTURP developed more frequently in second BTURP (p=0.007), history of catheter insertion (p=0.009), those with a high preoperative median WBC count (p=0.013), and those with a long postoperative catheterization period (p=0.046) (Table 2).

In addition, we were not able to investigate the effect of the size and type of the resectoscope (monopolar/bipolar) and the catheter size on the development of urethral stricture as the

Table 1. Demographic characteristics of 124 patients.

Total number of patients	(n=124; 100%)
Mean age (years)±SD	71.15±7.69
Preoperative prostatitis, n (%)	
Yes	4 (3.2)
No	120 (96.8)
Case status, n (%)	
Primary	110 (88.7)
Secondary	14 (11.3)
Preoperative catheter status, n (%)	
Catheter history not available	28 (22.5)
Catheter history available	71 (57.2)
With permanent catheter	25 (20.1)
Median preoperative WBC (10^3) (IQR)	7.30 (5.87–8.54)
Diabetes mellitus, n (%)	
Yes	36 (29)
No	88 (71)
Smoking, n (%)	
Yes	10 (8)
No	114 (92)
Median operation time (min) (IQR)	60 (45–65)
Anesthesia time (min), n (%)	
<60	8 (6.4)
>60	116 (93.6)
Median preoperative prostate volume (ml) (IQR)	57 (39–80.75)
Median removed prostate volume (ml) (IQR)	30 (17.25–47)
Perioperative NSAID use, n (%)	
Yes	106 (85.4)
No	18 (14.6)
Anesthesia type, n (%)	
Regional	63 (50.8)
General	61 (49.2)
Mean postoperative catheterization time (days)±SD	3.26±1.9
Postoperative urethral stricture, n (%)	
Yes	13 (10.5)
No	111 (89.5)
Postoperative retention presence, n (%)	
Yes	7 (5.6)
No	117 (94.4)
Postoperative UTI, n (%)	
Yes	11 (8.8)
No	113 (91.2)

IQR: interquartile range; UTI: urinary tract infection; SD: standard deviation; NSAID: nonsteroidal anti-inflammatory drug; WBC: white blood cell.

Table 2. Factors affecting the development of urethral stricture in patients undergoing bipolar transurethral resection of the prostate: (univariate analysis results).

Total number of patients (n=124; 100%)	No stricture (n=111; 89.5%)	Stricture (n=13; 10.5%)	p*
Mean age±SD	70.76±8.65	74.46±8.7	0.148
Preoperative prostatitis, n (%)			
Yes (n=4)	4 (3.6)	--	0.487
No (n=120)	107 (96.4)	13 (100)	
Case status, n (%)			
Primary (n=110)	102 (91.9)	8 (61.5)	0.007*
Secondary (n=14)	9 (8.1)	5 (38.5)	
Preoperative catheter status, n (%)			
Catheter history not available (n=28)	21 (18.9)	7 (53.8)	0.009*
Catheter history available (n=71)	65 (52.6)	6 (46.2)	
With permanent catheter (n=25)	25 (22.5)	--	
Median preoperative WBC (10^3) (IQR)	6.03 (5.11-7.57)	7.38 (5.91-8)	0.013*
DM presence, n (%)	33 (29.7)	3 (23.1)	0.445
Smoking	--	10 (9)	0.316
Median operation time (min) (IQR)	60 (45-75)	55 (40-62.5)	0.319
Anesthesia time (min), n (%)			
<60 (n=8)	7 (6.3)	1 (7.7)	0.847
>60 (n=116)	104 (93.7)	12 (92.3)	
Median preoperative prostate volume (ml) (IQR)	60 (30-67.5)	46 (40-81)	0.134
Median removed prostate volume (ml) (IQR)	30 (18-50)	20 (10-30)	0.081
Perioperative NSAID, n (%)			
Yes (n=106)	95 (85.6)	11 (84.6)	0.925
No (n=18)	16 (14.4)	2 (15.4)	
Anesthesia type, n (%)			
Regional (n=63)	56 (50.5)	7 (53.8)	0.817
General (n=61)	55 (49.5)	6 (46.2)	
Mean postoperative catheterization time (days)±SD	5.15±1.67	6.23±2.16	0.046*
Postoperative retention presence, n (%)			
Yes (n=7)	6 (5.4)	1 (7.7)	0.549
No (n=117)	105 (94.6)	12 (92.3)	
Postoperative UTI, n (%)			
Yes (n=11)	8 (7.2)	3 (23.1)	0.091
No (n=113)	103 (92.8)	10 (76.9)	

*Chi-square test, Fisher's exact test, independent-sample t-test, Mann–Whitney U-test. IQR: interquartile range; DM: diabetes mellitus; UTI: urinary tract infection; SD: standard deviation; NSAID: nonsteroidal anti-inflammatory drug.

"Storz" brand 26F bipolar resectoscope was used in all patients and a 20F or 22F three-way "Rusch" brand Foley urethral catheter was inserted to all patients at the end of the operation.

We could not find a statistically significant variable in the multivariate logistic regression analysis performed with variables that were found to be significant in the univariate analyses intended to determine independent risk factors affecting the development of postoperative urethral stricture.

DISCUSSION

Although BTURP is a successful method, it also brings about complications such as urethral stricture[3,5]. In this study, it was found that the rate of urethral stricture development following BTURP was 10.5%. Sarier et al. showed in their study that renal transplantation did not increase the risk of urethral stricture and found that the rate of urethral stricture development following BTURP was 8.9–12.5%[21,22]. The rate of stricture following BTURP varies between 2% and 12.7% in different studies[6,7,9]. In this study, the median age of those with and without urethral stricture was similar. In many studies, it has been demonstrated that age does not have a statistically significant effect on the development of urethral stricture[6,7,9].

We found no difference in the stricture risk in 4 (3.5%) patients with preoperative UTI diagnosis compared to those without preoperative UTI. Tan et al.[7] showed that preoperative UTI did not increase the risk of urethral stricture (p=0.717), while Aydemir et al.[10] showed that preoperative UTI increased the risk of urethral stricture.

Tan et al. showed that the risk of urethral stricture did not increase significantly in patients who underwent BTURP for the second time (1/13) (p=1.000). This study revealed that the risk of urethral stricture increased after the second BTURP operation (5/13) (p=0.007). In addition, Tan et al.[7] observed that prolongation of the resection rate (g/min) increased the risk of urethral stricture. In this study, we did not calculate the resection rate separately, but we observed that there was no correlation between the amount of tissue resected and the duration of the operation and the development of urethral stricture. Kumar et al.[9] did not examine the effect of this factor in their study. Komura et al.[11] showed that the risk of urethral stricture increased in prostates over 70 g.

In this study, we found that a long postoperative catheterization time increased the risk of urethral stricture (p=0.045). Contrary to this study, many studies showed that prolongation of postoperative catheterization time did not increase the risk of urethral stricture[7,9-11].

We observed that DM and smoking did not increase the risk of urethral stricture. Kumar et al.[9] also showed in their study that these factors did not increase the risk of urethral stricture.

Some studies argued that the risk of developing urethral stricture is higher with BTURP than with monopolar TURP (MTURP)[12-14,15]. These studies concluded that the high rate of stricture with BTURP is associated with higher energy use, larger diameter of the resectoscope, and longer operation time. Contrary to these studies, there are also studies showing that there is a similar risk of urethral stricture in both methods (monopolar/bipolar)[16,17]. We could not make this comparison as we applied BTURP to all of our patients and we used 26F resectoscope and firm energy (160 W/80 W). In addition, we could not examine the effect of postoperative urethral catheter size on the development of urethral stricture as we inserted a 20F or 22F three-way Foley urethral catheter to all patients.

In this study, we observed that 46% (6/13) of the strictures developed in the bulbar urethra. Komura et al.[11] also showed in their study that urethral stricture mostly developed in the bulbar urethra. In this study, we found that postoperative UTI did not increase the risk of urethral stricture. This could be due to the early diagnosis and treatment of postoperative UTI. As a result, the UTI is short time and the fibroblast activity may not be excessive due to this. Tao et al.[20] showed that postoperative UTI increased the risk of urethral stricture.

Considering the perioperative complications, we did not encounter TUR syndrome or a need for blood transfusion in this study. TUR syndrome and blood transfusion risks were reported in some studies, albeit at a very low rate[18,19].

In the study by Gilfrich et al.[8], this rate was reported to be higher (0.3%). We did not encounter mortality in our patients within the postoperative 30 days.

When we reviewed those studies, we found that the effects of having a history of preoperative catheter insertion or having a permanent catheter, preoperative WBC count, perioperative NSAID use, and the development of urinary retention after postoperative catheter removal on the development of urethral stricture were not investigated. In this study, we found that a history of preoperative catheter insertion or a permanent catheter (p=0.009) and a high preoperative WBC count (p=0.013) increased the risk of urethral stricture. However, we found that the use of perioperative NSAIDs did not affect urethral stricture (p=0.925).

This study has some limitations. The number of patients participated in this study is less. Also, this is a retrospective study. In addition, we could not make energy and larger diameter of

the resectoscope comparison as we applied BTURP to all of our patients and we used 26F resectoscope and firm energy (160 W/80 W). In addition, we could not examine the effect of postoperative urethral catheter size on the development of urethral stricture as we inserted a 20F or 22F three-way Foley urethral catheter to all patients.

CONCLUSION

BTURP is a reliable method. However, second TURP surgery, having a preoperative permanent catheter or catheter insertion history, high preoperative WBC (10^3) count, and long postoperative catheterization time, increase the risk of urethral stenosis after BTURP.

ETHICAL 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. Written informed consent was obtained from all patients who participated in this study.

AUTHORS' CONTRIBUTIONS

FA=Conceptualization, Data curation, Formal analysis, Investigation, Methodology, Project administration, Resources, Software, Validation, Visualization, Writing – original draft, Writing – review & editing; FA & OU=Funding acquisition; OU=Supervision

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ORIGINAL ARTICLE

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Reliability of quantitative sensory testing on myofascial trigger points in the upper trapezius muscle of individuals with chronic neck pain

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SUMMARY

OBJECTIVE: The objective of this study was to measure the intra- and inter-rater reliability of the quantitative sensory testing for measuring the thermal pain threshold on myofascial trigger points in the upper trapezius muscle of individuals with chronic neck pain.

METHODS: Thirty female participants were included, aged between 18 and 45 years and with bilateral myofascial trigger points, active and centrally located in the upper trapezius muscle. Two measurements with quantitative sensory testing were performed by each examiner at an interval of 1 week between them.

RESULTS: We observed substantial reliability for the intra-rater analysis (intraclass correlation coefficient ranging between 0.876 and 0.896) and excellent reliability for the inter-rater analysis (intraclass correlation coefficient ranging between 0.917 and 0.954).

CONCLUSION: The measurement of the thermal pain threshold on myofascial trigger points in individuals with chronic neck pain has acceptable reliability values, supporting the use of the quantitative sensory testing in the research setting and the clinical environment.

KEYWORDS: Myofascial pain syndromes. Reproducibility of results. Pain measurement.

INTRODUCTION

Neck pain is currently the most prevalent musculoskeletal disorders, with an estimated involvement of 50% of the population[1]. Different anatomical structures may be involved in the pathological process of neck pain, such as ligaments, tendons, nerve roots, and, in particular, the myofascial component[2].

Studies show that individuals with musculoskeletal disorders have vascular, metabolic, electromyographic, and thermographic changes[3,4]. In addition, a common clinical sign in patients with neck pain is the presence of myofascial trigger points, especially in the upper trapezius muscle[3].

Regarding the assessment of myofascial pain, Simons et al.[5] presented the method of diagnosing the myofascial trigger points centered on palpation and, in general, this is the most accepted method both in research studies and the clinical practice. However, due to the complexity existing in the evaluation of the painful experience, other methods have been used to complement such assessment, such as algometry, thermography[3], and skin impedance[6].

Within this context, quantitative sensory testing (QST) is another plausible tool to be used in the presence of myofascial trigger points, since it involves a set of methods to assess somatosensory function, including measuring the presence of hyperalgesia and allodynia[7]. It is noteworthy that the myofascial trigger points actively participate in the peripheral and central sensitization processes, as highlighted by important studies[8-10].

Nevertheless, despite the evaluative potential of the QST in patients with myofascial trigger points, for the correct clinical use of this tool, it is necessary to identify the amount of error inherent to the use of the QST in this population. Thus, the aim of this study was to evaluate the intra- and inter-rater reliability of the QST in measuring thermal pain thresholds on myofascial trigger points in the upper trapezius muscle in patients with chronic neck pain. The hypothesis of this study is that the QST has adequate reliability.

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METHODS

Ethical aspects

The project was approved by the Research Ethics Committee of the institution (opinion number 030643/2013), and the data collection was carried out at the Physiotherapeutic Resources Laboratory. The recruitment of volunteers took place in the communities near the university through verbal dissemination, posters, and social media. Once selected, the volunteers were instructed about all the study procedures, objectives, and characteristics, and validated their participation by signing the free and informed consent form.

Study design

This is a reliability study of the QST instrument for measuring the painful response to heat and cold stimuli on myofascial trigger points in women with chronic neck pain, considering different times and different examiners. The researchers responsible for performing the examination were unaware of the participants' pain characteristics (i.e., pain intensity, pressure pain threshold, chronicity, and disability).

Sample

The sample calculation considered a confidence coefficient of 0.95 and confidence interval amplitude for the intraclass correlation coefficient (ICC) of 0.30. In addition, the calculation was performed to detect moderate reliability (ICC=0.75) according to the study conducted by Fleiss[11]. Thus, a minimum sample size of 24 participants was estimated. The processing of the sample calculation was performed based on the study conducted by Bonett[12].

As diagnostic criteria for chronic neck pain, a score of ≥5 on the Neck Disability Index (NDI), a score of ≥3 on the Numeric Pain Rating Scale (NPRS) at rest or during active cervical movement, and the presence of pain for more than 3 months were considered. In addition, the volunteers had bilateral and active myofascial trigger points in the upper trapezius muscle identified according to the diagnostic criteria established by Simons et al.[5] and Gerwin et al.[13], as follows: presence of a tense band in the upper trapezius muscle; presence of a hypersensitive point within the tight band; local twitch in response to palpation of the tight band; and reproduction of referred pain due to compression of 2.5 kg/cm^2 on the trigger point.

The myofascial trigger point was considered active when the participant presented spontaneous pain or reported a familiar pain while performing the compression[5]. Diagnostic criteria were applied by a physical therapist with 8 years of experience in myofascial pain.

Exclusion criteria were: history of cervical trauma; head, face, or cervical surgery; cervical hernia; degenerative spinal diseases; having undergone physical therapy treatment for neck pain in the last 3 months; use of analgesics, anti-inflammatory drugs, or muscle relaxants in the last week; and presence of systemic or autonomic diseases or diagnosis of fibromyalgia.

Assessment procedures

The assessment procedures were carried out as follows: a researcher with experience in measuring the painful experience applied the pain assessment instruments and identified the presence of myofascial trigger points at an initial moment; in a second moment, two other examiners previously trained and familiarized with the use of the QST carried out the evaluations of the thermal pain threshold in two moments at an interval of 1 week between them[14].

Data to fit the participants in the eligibility criteria were initially collected. The NPRS was used to assess pain intensity[15], the NDI was used to assess the neck disability in the presence of pain[16], and the pressure pain threshold assessment was performed using a digital algometer model PTR-300 (Instrutherm, São Paulo, Brazil)[17].

Quantitative sensory testing

The evaluation of the thermal pain threshold was performed using the QST (TSA II Neurosensory Analyzer, Medoc, Ramat Yishai, Israel). The environmental evaluation remained at a controlled temperature of 23°C. For collection, the participant maintained the sitting position and the examiner positioned the equipment electrode over the myofascial trigger points in the upper trapezius muscle. The order of the side to be evaluated was defined by drawing lots before each evaluation.

For collection, three repetitions of the test were performed for each stimulus (hot or cold): the thermal pain threshold with heat had an initial temperature of 32°C and a maximum of 50°C, while the cold had an initial temperature of 32°C and a minimum of 0°C.

The volunteer was initially familiarized with the instrument: a test was performed in the palm region of the hand. During the examination on the trigger point, the volunteer was instructed to interrupt the procedure by pressing a switch whenever the temperature caused her pain, and the temperature value was then recorded. For statistical analysis, the mean of the three repetitions was used.

Statistical analysis

This study was carried out based on the Guidelines for Reporting Reliability and Agreement Studies (GRRAS)[18], and the ICC was

used to determine the intra- and inter-rater reliability of the thermal pain threshold, with its respective 95% confidence interval, standard error of measurement, and minimum detectable difference (MDD). The interpretation of the ICC value was based on the Fleiss study: low reliability (ICC<0.40), moderate (ICC between 0.40 and 0.75), substantial (ICC between 0.75 and 0.90), and excellent (ICC>0.90)[11]. Data processing was performed in the Statistical Package for the Social Sciences, version 17.0 (Chicago, IL, USA).

RESULTS

Forty volunteers were recruited, but 11 were excluded for not reaching the inclusion criteria. The final sample consisted of 29 women, who were right-handed with a mean age of 22.03 years [standard deviation (SD)=3.66] and a mean body mass index of 23.52 kg/m^2 (SD=3.55).

Mean pain intensity was 3.07 points (SD=1.57) at rest and 4.97 points (SD=3.69) after active cervical movement, with mean pain chronicity of 41.00 months (SD=32.36). Mean disability was 10.07 (SD=3.81). The pressure pain thresholds on the left and right myofascial trigger points were 1.77 kg/cm^2 (SD=0.44) and 1.78 kg/cm^2 (SD=0.52), respectively. The thermal pain threshold values of the two evaluators are given in Table 1.

Table 2 presents the intra-rater reliability values of the QST measurement. Substantial reliability was observed, with ICC values between 0.876 and 0.896, SEM between 1.03 and 3.38°C, and MDD between 2.85 and 8.99°C.

The inter-rater reliability values demonstrated excellent reliability, with ICC values between 0.917 and 0.954, SEM between 0.68 and 2.17°C, and MDD between 1.88 and 6.01°C (Table 3).

Table 1. Values of the thermal pain threshold (°C) evaluated using quantitative sensory testing according to the measurements of the two evaluators (n=29).

QST	Examiner 1		Examiner 2	
	Test	Retest	Test	Retest
RUT heat	44.40 (2.99)	45.53 (2.89)	44.29 (2.96)	44.62 (3.13)
RUT cold	18.72 (9.47)	15.39 (10.07)	18.07 (8.86)	17.01 (9.57)
LUT heat	44.07 (3.18)	45.38 (3.19)	43.69 (2.89)	44.45 (3.02)
LUT cold	19.57 (8.89)	15.88 (10.68)	17.49 (9.27)	17.02 (8.78)

Values are shown as mean (standard deviation).

RUT: right upper trapezius; LUT: left upper trapezius.

Table 2. Intra-rater reliability of the measurement of the thermal pain threshold in patients with chronic neck pain (n=29).

QST	ICC	95% CI	SEM (°C)	SEM (%)	MDD (°C)	MDD (%)
RUT heat	0.876	0.740, 0.941	1.04	2.30	2.87	6.38
RUT cold	0.879	0.745, 0.942	3.38	18.50	8.99	51.28
LUT heat	0.896	0.781, 0.950	1.03	2.30	2.85	6.37
LUT cold	0.895	0.779, 0.950	2.91	16.87	8.07	46.75

QST: quantitative sensory testing; RUT: right upper trapezius; LUT: left upper trapezius; ICC: intraclass correlation coefficient; CI: confidence interval; SEM: standard error of measurement; MDD: minimum detectable difference.

Table 3. Inter-rater reliability of the measurement of the thermal pain threshold in patients with chronic neck pain (n=29).

QST	ICC	95% CI	SEM (°C)	SEM (%)	MDD (°C)	MDD (%)
RUT heat	0.948	0.892, 0.975	0.68	1.53	1.88	4.24
RUT cold	0.954	0.904, 0.978	2.09	11.36	5.79	31.49
LUT heat	0.917	0.825, 0.960	0.87	1.99	2.42	5.52
LUT cold	0.943	0.881, 0.973	2.17	11.70	6.01	32.43

QST: quantitative sensory testing; RUT: right upper trapezius; LUT: left upper trapezius; ICC: intraclass correlation coefficient; CI: confidence interval; SEM: standard error of measurement; MDD: minimum detectable difference.

DISCUSSION

The present study showed adequate reliability in the thermal pain threshold on myofascial trigger points in the upper trapezius muscle while considering different times and different examiners. The evaluation of the pain threshold using a heat stimulus showed a smaller amount of error than the evaluation of the pain threshold by the cold stimulus due to the greater variability than the perception of pain with cold. Thus, the thermal pain threshold can be used in the clinical context to assess the somatosensory system as an outcome measure of clinical interventions.

Clinical research on pain is constantly growing due to the emergence of new assessment tools and methods and, in this context, the QST is widely used for the assessment of skin sensation and the sensitive assessment of deep tissues, such as muscles, fascia, ligaments, and viscera[19]. In addition, the QST is able to inform about the functionality of the somatosensory system, quantifying the presence and intensity of sensory phenomena (such as loss or gain of function, hyperalgesia or hypoalgesia, and allodynia), thus contributing to the assessment of various painful conditions[20,21].

With an increase in the clinical use of the QST in different conditions, there is a need for studies to ensure the reliability of this instrument in each specific clinical condition. A systematic review investigating the reliability of thermal QST observed that in 21 studies included, only 5 had high methodological quality. In addition, most studies have been done in healthy patients and in diseases that involve the nervous system, such as neuropathies[22]. The present study was carried out with methodological rigor based on the GRRAS[18]. Another important point of our study is to verify the reliability in a sample not reported yet in published studies, i.e., myofascial pain.

Considering the reliability of the QST in other painful conditions, some studies have investigated orofacial pain[23], knee osteoarthritis[24], and musculoskeletal traumatic injury[25]. Our results found the ICC values similar to the ones in the aforementioned studies, indicating a pattern of error in the measurements performed with the QST, regardless of the population with pain studied.

Pigg et al.[23] evaluated the reliability of the QST to verify the somatosensory function in patients with pain related to the trigeminal nerve. The measurements were made on the skin of the right cheek, the tip of the tongue, and bilaterally on the gingival mucosa of the upper premolar region, and the authors found the ICC values ranging between 0.41 and 0.89 for inter-rater reliability and between 0.43 and 0.87 for intra-rate reliability. Wylde et al.[24] evaluated the test-retest reliability of the thermal pain threshold in patients with knee osteoarthritis and found the ICC values ranging from 0.59 to 0.83.

Middlebrook et al.[25] measured the inter-rater reliability of the QST in the assessment of individuals with traumatic musculoskeletal injury and found the ICC values ranging from 0.57 to 0.94. Our study identified less variation of ICC in the measurements of the thermal pain threshold; however, our sample consisted of patients with chronic pain (>3 months of pain).

The study has limitations that must be considered. Our study included only women due to the higher prevalence of myofascial pain in this gender. In addition, menstrual periods and contraceptive use were not controlled. This is an important limitation since the literature shows variations in the sensation of pain in different phases of the menstrual cycle[26].

CONCLUSION

The measurement of the thermal pain threshold on myofascial trigger points in individuals with chronic neck pain presents acceptable reliability values while considering different times and examiners, which supports the use of this method of assessment for data collection in research and the clinical environment.

AUTHORS' CONTRIBUTIONS

AVDF, RRJG: Conceptualization, Data curation, Formal Analysis, Methodology, Project administration, Writing – review & editing. AKO, MPO, MAB: Conceptualization, Data curation, Formal Analysis, Methodology, Writing – original draft. DBG: Conceptualization, Methodology, Writing – review & editing.

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ORIGINAL ARTICLE

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Relationship between ventricular repolarization parameters and the inducibility of ventricular arrhythmias during electrophysiological study in patients with coronary artery disease

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SUMMARY

OBJECTIVE: Risk stratification of sudden cardiac death in patients with coronary artery disease is of great importance. We evaluated the association between ventricular repolarization and induction of malignant ventricular arrhythmias on electrophysiological study of patients with coronary artery disease.

METHODS AND RESULTS: A total of 177 patients (65±10.1 years, 83.6% male, mean left ventricular ejection fraction [LVEF] 37.5±13.6%) were analyzed. For each 10 ms increment in the QT interval, there was a 7% increase in malignant ventricular arrhythmias inducibility; QT cutoff point of 452 ms had an accuracy of 0.611 for predicting malignant ventricular arrhythmias (p=0.011). Male gender (odds ratio [OR]=4.18, p=0.012), LVEF <35% (OR=2.32, p=0.013), amiodarone use (OR=2.01, p=0.038), and prolonged QT (OR=1.07, p=0.023) were associated with malignant ventricular arrhythmias. In patients with ventricular dysfunction, QT >452 ms was associated with significantly increased risk of malignant ventricular arrhythmias (OR=5.44, p=0.0004). In those with LVEF ³35%, QT dispersion (QTd) was significantly higher in patients with inducible malignant ventricular arrhythmias. QTd >20 ms had 0.638 accuracy and 81.3% negative predictive value in predicting malignant ventricular arrhythmias.

CONCLUSION: QT interval is an independent factor associated with malignant ventricular arrhythmias in patients with coronary artery disease. The combination of ventricular dysfunction and prolonged QT interval is associated with a 5.44-fold increase of malignant ventricular arrhythmias induction. Male gender, amiodarone use, and decreased left ventricular ejection fraction are also associated with increased risk of inducibility of malignant ventricular arrhythmias on the electrophysiological study.

KEYWORDS: Tachycardia, ventricular. Electrocardiography. Coronary artery disease. Death, sudden, cardiac.

INTRODUCTION

Up to 80% of sudden cardiac death (SCD) cases occur in patients with coronary artery disease (CAD). Strategies for the prevention of SCD include the use of antiarrhythmic agents and implantable cardioverter defibrillator (ICD). Left ventricular ejection fraction (LVEF) is the most commonly used parameter for risk stratification of SCD in patients with CAD[1].

Abnormal ventricular repolarization has proven to be a marker of increased risk of malignant ventricular arrhythmias (MVA) and mortality in a variety of settings, including acute CAD, cardiomyopathies, hypertension, and Chagas disease[2].

The aim of this study was to evaluate the association between electrocardiographic (ECG) ventricular repolarization and inducibility of MVA in patients with CAD undergoing electrophysiological study (EPS).

METHODS

This was a cross-sectional study of patients with CAD who underwent EPS in a tertiary hospital. CAD was defined by either history of acute coronary syndrome (ACS) or symptoms of angina and/or dyspnea on exertion associated with significant coronary lesions on cineangiocoronariography or myocardial ischemia on noninvasive examination. Patients with other cardiomyopathies and noninterpretable ECG within 6 months preceding EPS were excluded.

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CardioCalipers[3] was used for ECG measurements. QT interval was measured in lead II using the tangent method; corrected QT interval (QTc) was calculated using Bazett's formula; QT dispersion (QTd) was obtained by the difference between the longest and shortest QT interval among all leads. The interval between the peak and the end of the T wave (Tp-e) was measured in V5 using the tangent method. The Tp-e dispersion (Tp-e d) was calculated by subtracting the longest and shortest Tp-e intervals in all leads; and for Tp-e/QT relationship calculation, both Tp-e and QT were measured on the first beat of V6[3].

EPS was performed as follows: programmed ventricular stimulation at two different sites with two basic cycles and up to three extra-stimuli. Rapid ventricular stimulation (up to 250 ms or until 2:1 ventricular capture) was also performed. Sustained ventricular tachycardia, ventricular flutter, and ventricular fibrillation (VF) were considered MVA, according to current guidelines definitions[4].

Variables were presented by mean, standard deviation, median, and minimum/maximum values; categorical variables were presented by frequencies and percentages. MVA inducibility was compared with ECG parameters considering the model of analysis of variance (ANOVA) with one factor or Kruskal–Wallis nonparametric test.

For univariable analysis of factors associated with MVA induction, Fisher's exact test or chi-square test was used for categorical variables. For those with a quantitative character, we used Student's t-test for independent samples or Mann–Whitney nonparametric test. Normal condition of quantitative variables was assessed by Kolmogorov–Smirnov test.

For multivariable analysis, a logistic regression model was adjusted including variables with statistical significance in the univariable analysis. Wald's test was used to make decisions about the significance of the variables and the estimated association measure was odds ratio (OR) with 95% confidence interval (95% CI). For model validation, Hosmer–Lemeshow test was applied and the value of the area under the receiver operating characteristic (ROC) curve was estimated. A p-value <0.05 indicated statistical significance. Data were analyzed using Stata/SE version 14.1 (Stata Corp., LP, College Station, TX, USA) software.

RESULTS

A total of 182 consecutive patients met the inclusion criteria. Five of them were excluded due to noninterpretable ECG (three), Chagas disease (one), and hypertrophic cardiomyopathy (one).

Mean age was 65±10.1 years, 83.6% were male, and mean LVEF was 37.5±13.6%. The majority of patients (76.8%) had history of ACS and previous aborted SCD occurred in 16.9%. Among the comorbidities, hypertension (89.8%), dyslipidemia (66.7%), and diabetes mellitus (41.2%) stood out. EPS was indicated for assessment of ventricular stability and syncope in 67.8 and 32.2% of cases, respectively (Table 1).

Table 1. Baseline clinical and demographic characteristics.

Variable	Classification	Result
Age (years)		65±10.1 (35–94)
Gender	Male	148 (83.6)
	Female	29 (16.4)
Ejection fraction (%)		37.5 ± 13.6 (18–75)
Ejection fraction (%)	³35	83 (46.9)
	<35	94 (53.1)
Previous ACS	No	41 (23.2)
	Unstable angina	4 (2.3)
	NSTEMI	45 (25.4)
	STEMI	87 (49.2)
Angina	No	151 (85.3)
	CCS 1	5 (2.8)
	CCS 2	15 (8.5)
	CCS 3	5 (2.8)
	CCS 4	1 (0.6)
Intolerance on exertion	No	63 (35.6)
	NYHA I	19 (10.7)
	NYHA II	64 (36.2)
	NYHA III	28 (15.8)
	NYHA IV	3 (1.7)
Aborted SCD	No	147 (83.1)
	Yes	30 (16.9)
Comorbidities		n (%)
Hypertension		159 (89.8)
Dyslipidemia		118 (66.7)
Diabetes mellitus		73 (41.2)
Syncope		56 (31.6)
Chronic kidney disease		34 (19.2)
Stroke or TIA		20 (11.3)
Peripheral artery disease		20 (11.3)
ICD carrier		4 (2.3)
Pacemaker carrier		3 (1.7)
Medications in use		n (%)
Statins		163 (92.1)
Aspirin		159 (89.8)

Continue...

Table 1. Continuation.

Variable	Classification	Result
Beta-blockers		156 (88.1)
ACEi/ARBs		146 (82.5)
Furosemide		87 (49.2)
Amiodarone		73 (41.2)
Spironolactone		60 (33.9)
Nitrates		47 (26.6)
Calcium channel blockers		32 (18.1)
P2Y12 receptor inhibitors		29 (16.4)
Oral anticoagulants		26 (14.7)
Hydralazine		9 (5.1)
Ivabradine		3 (1.7)
Trimetazidine		3 (1.7)
EPS indication		n (%)
Ventricular stability assessment		120 (67.8)
Previous documented ventricular arrhythmias		66 (37.3)
Aborted SCD		30 (17.0)
Sustained VT		17 (9.6)
Nonsustained VT		19 (10.7)
Absence of previous ventricular arrhythmias		54 (30.5)
Syncope		57 (32.2)

ACS: acute coronary syndrome; NSTEMI: non-ST elevation acute myocardial infarction; STEMI: ST elevation acute myocardial infarction; CCS: Canadian Cardiovascular Society; NYHA: New York Heart Association; SCD: sudden cardiac death; TIA: transient ischemic attack; ICD: implantable cardioverter defibrillator; ACEi: angiotensin-converting enzyme inhibitor; ARBs: angiotensin-receptor blockers; EPS: electrophysiological study; VT: ventricular tachycardia.

In univariable analysis, male gender (p=0.03), low LVEF (p=0.01) (especially <35%; p=0.033), and amiodarone use (p=0.032) were associated with higher rates of MVA inducibility. QT interval was significantly longer in MVA induction group (p=0.015).

In multivariable analysis, male gender (OR=4.37, 95% CI 1.1–12.6), LVEF <35% (OR=2.25, 95% CI 1.17–4.35), and QT interval (OR=1.07, 95% CI 1.01–1.12) remained independent risk predictors of MVA. For each 10 ms increase in the QT interval, there was a 7% increase in MVA inducibility.

QT interval of 452 ms was associated with 42.7% sensitivity, 79.4% specificity, 60.4% positive predictive value (PPV), and 65.3% negative predictive value (NPV) for MVA inducibility. Another model of logistic regression was performed using this cutoff point and all variables remained associated with the outcome (Table 2).

History of ACS was not found to be a predictor of MVA. In this subgroup of patients, QT interval remained associated with arrhythmic induction (p=0.013). In individuals without previous coronary events, there was no association between ECG variables and MVA. In patients with previous ACS, QT >432 ms was associated with 55% sensitivity, 68% specificity, 57.9% PPV, and 65.8% NPV for MVA induction.

In individuals with LVEF <35%, none of ECG parameters were related to arrhythmic inducibility on univariable analysis. When LVEF and QT interval variables were evaluated together, prolonged QT (>452 ms) and significant ventricular dysfunction increased the risk of MVA in 5.44-fold (Table 3).

In the subgroup of patients with LVEF ³35%, QTd was significantly higher in those with inducible MVA; such association was not verified in the other studied variables. QTd >20 ms had an accuracy of 0.638 and 81.3% NPV in predicting MVA.

Table 2. Multivariable analysis of parameters associated with malignant ventricular arrhythmias induction on electrophysiological study using the cutoff indicated by the receiver operating characteristic curve.

Variable	Classification	p*	OR*	95%CI
Gender	Female			
	Male	0.012	4.18	1.45–12.05
Amiodarone use	No			
	Yes	0.038	2.01	1.04–3.89
Ejection fraction (%)	³35			
	<35	0.013	2.32	1.20–4.48
QT† (ms)	£452			
	>452	0.004	2.70	1.37–5.36

*Logistic regression model and Wald's test (p<0.05). †Cutoff point indicated by the ROC curve. MVA: ventricular malignant arrhythmias; EPS: electrophysiological study; ROC: receiver operating characteristic; OR: odds ratio; 95% CI: 95% confidence interval.

Table 3. Multivariable analysis of ventricular repolarization parameters in addition to left ventricular ejection fraction associated with ventricular malignant arrhythmias induction.

Variable	p*	OR*	95%CI
LVEF <35%, QT >452 ms	0.0004	5.44	2.13–12.89
LVEF ³35%, QT >452 ms	0.064	2.59	0.95–7.08
LVEF <35%, QT £452 ms	0.12	1.82	0.86–3.86
LVEF ³35%, QT £452 ms† (reference)	–	–	–

*Logistic regression model and Wald's test (p<0.05). †Cutoff point indicated by the receiver operating characteristic curve. MVA: ventricular malignant arrhythmias; LVEF: left ventricular ejection fraction; OR: odds ratio; 95% CI: 95% confidence interval; ROC: receiver operating characteristic.

DISCUSSION

Cardiovascular diseases (CVDs) are responsible for 17 million deaths annually worldwide, 25% of which result from SCD[5]. It is estimated that in the United States, between 300,000 and 350,000 cases of SCD occur annually, accounting for 50% of all deaths from CV etiology[4].

Despite the advances in diagnostic strategies for risk stratification, depressed LVEF remains the best predictor of SCD[6,7]. However, in adults aged >35 years, about two-third of SCD present as the first clinical event in individuals without previously identified heart disease or in patients with heart disease without other risk factors[8].

The role of EPS in the risk stratification of SCD is relevant in the setting of CAD, especially in those with reduced LVEF and nonsustained VT in 24-h Holter monitoring. In these cases, MVA induction has a high PPV[6]. Wilber et al. demonstrated an incidence of SCD of 54% in 2 years in those with induced arrhythmias compared to 6% in the group with noninduced MVA[9]. Similarly, in the Multicenter Unsustained Tachycardia Trial, patients with CAD, LVEF <40%, and inducible MVA had higher rates of all-cause mortality[10].

In this study, longer QT interval was associated with higher risk of MVA induction on EPS. Each 10 ms increase in the QT augmented in 7% the risk of MVA. These findings are in agreement with the data published by Dekker et al.[11], in which patients with prolonged QT had higher rates of CV death. Male gender was also associated with increased risk of MVA, and this finding is consistent with the data published by Schouten et al.[12], who first demonstrated the value of QT in predicting mortality from CVD, especially CAD in men.

QT interval >452 ms had moderate power to estimate MVA induction, similarly to that seen in a multicenter study, in which QT of 430 ms or more was associated with increased CV mortality[13].

The use of amiodarone and LVEF £35% were also related to MVA in the multivariable analysis. While the latter is a well-established predictor of SCD in the context of CAD[1], the former may reflect the presence of ventricular arrhythmias despite drug treatment and, consequently, the greater severity of these patients.

QT prolongation in ACS is associated with spontaneous MVA, increased rates of SCD, and reduced survival in resuscitated patients from out-of-hospital VF. The magnitude of QT increase is related not only to the severity and extent of CAD but also to the depression of myocardial function, reflecting metabolic and electrolytic changes in ischemic tissue, hypoxemia, and autonomic nervous system imbalance[14]. In this study, in patients with previous ACS, QT interval was significantly longer in individuals with MVA. Similar finding was reported in the study by Schwartz and Wolf, in which longer QT was observed in those with acute myocardial infarction (AMI) compared to healthy persons[15]. The cutoff point of 432 ms showed moderate predictive capacity in discriminating MVA induction in those with history of ACS. This finding is in agreement with a case–control study, in which QT >440 ms in patients with previous AMI was associated with increased risk of SCD[15].

Reduced LVEF is the main risk factor for general and sudden mortality in patients with CAD. Values £40% are usually used to identify patients at high risk[1,16,17]. In our study, patients with QT >452 ms and LVEF <35% (p=0.0003) presented higher incidence of inducible MVA. In the multivariable analysis, the combination of both parameters was an independent risk predictor for the outcome. Brendorp et al., in a multicenter trial, showed that individuals with ventricular dysfunction and QT >479 ms had higher all-cause and CV mortality[18]. Similarly, in the study by Padmanabhan et al., patients with systolic dysfunction and QT >450 ms had a mortality rate of 75% in 5 years compared to 52% in the group with QT <450 ms[19].

Finally, QTd <20 ms had 78.6% sensitivity and 81.3% NPV to predict MVA, which denotes discriminatory capacity of patients at lower risk, a finding that is in line with that evidenced previously in a prospective study[20].

Limitations of the study include cross-sectional and observational nature, inclusion of a single center, and use of MVA

induction as a surrogate outcome to mortality. As a future perspective and clinical applicability, we highlight the fact of adding the QT interval as an ECG variable for predicting the risk of MVA in patients with CAD, a noninvasive and easily obtainable marker that adds strength of association, especially in those with LVEF <35% and with previous ACS; additionally, in patients with LVEF ³35%, we highlight the high NPV of QTd, which allows discerning a subgroup of individuals at lower risk.

CONCLUSIONS

QT interval is an independent factor associated with MVA in patients with CAD. The combination of ventricular dysfunction and prolonged QT interval is associated with a 5.44-fold increase of MVA induction. Male gender, amiodarone use, and decreased LVEF are also associated with increased risk of inducibility of MVA on the EPS.

AUTHORS' CONTRIBUTIONS

GDC: Project design, data collection, manuscript writing and review. LVA: Project design, manuscript writing and review. RDL: Manuscript review. MO: Statistical analysis. BMAG, CCP, BOE, RSBL, AVD, and BGM: Data collection and manuscript review. DARM: Project design and manuscript review.

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ORIGINAL ARTICLE

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Do biomarkers have predictive value in the treatment modality of the patients diagnosed with bowel obstruction?

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SUMMARY

OBJECTIVES: This study aimed to investigate the ability of the biomarkers to predict the surgery treatment and mortality in patients above 18 years of age who were hospitalized with the diagnosis of bowel obstruction from the emergency department.

METHODS: This is a 2-year retrospective study. The patients' demographic data, laboratory parameters on admission to emergency department, treatment modalities, and the length of hospital stay were recorded. Patients were divided into two groups: conservative and surgical treatment. Statistical analysis was performed to investigate the value of biomarkers in predicting mortality and the need for surgery. Data were analyzed using IBM SPSS version 22.

RESULTS: A total of 179 patients were included in this study. Of these, 105 (58.7%) patients were treated conservative and 74 (41.3%) were treated operatively. The elevated procalcitonin (PCT) level, C-reactive protein, blood urea nitrogen-to-albumin ratio, and lactate-to-albumin ratio were significantly correlated with surgical treatment, length of hospital stay, and mortality. procalcitonin threshold value of 0.13 ng/mL was able to predict the need for surgical treatment, with a sensitivity of 79% and a specificity of 70.3%. Procalcitonin threshold value of 0.65 ng/mL was able to predict the mortality rate of the patients, with a sensitivity of 92.9% and a specificity of 78.1%.

CONCLUSIONS: Biomarkers, especially procalcitonin, may be useful in bowel obstruction treatment management and may predict mortality.

KEYWORDS: Intestinal obstruction. Emergency. Mortality. Procalcitonin. Surgical procedures, operative.

INTRODUCTION

The rapid increase in the population has led to a large increase in the number of patients admitted to emergency services. Approximately 5–10% of emergency department admissions are due to bowel obstruction[1]. There are two approaches to the treatment of bowel obstruction: conservative and surgical. Patients who fail to improve within 48–72 h with conservative treatment need surgical treatment. In this process, bowel ischemia and necrosis may progress[2,3].

Procalcitonin (PCT) is released from the C cells of the thyroid in healthy individuals. It has been established that the source of increased PCT after bacterial infections is the neuroendocrine cells in the lungs, liver, intestines, and pancreas[4-6]. The half-life of PCT ranges from 18 and 24 h[7]. Plasma levels >0.5 ng/mL are considered pathological[8,9].

C-reactive protein (CRP) was the first acute-phase reactant detected to be susceptible to inflammation and tissue damage. An increased lactate level is an important marker for indicating tissue hypoxia, sepsis, and mortality. Studies show that the CRP/lactate ratio predicts mortality in intestinal obstruction[3,10]. Preoperative low albumin levels are related to extracellular interstitial fluid and may predict mortality[11,12]. Blood urea nitrogen (BUN)/albumin ratio can predict mortality in critically ill patients[13].

In this study, we aimed to investigate the ability of laboratory values (i.e., PCT, CRP/lactate, and BUN/albumin) to predict the need for surgical treatment and mortality in patients diagnosed with bowel obstruction.

METHODS

This study, which was planned retrospectively, included patients who were diagnosed as having ileus in the emergency department of a tertiary care hospital and hospitalized from January 1, 2018 to December 31, 2020. This study obtained the approval from the ethics committee.

Patients

Patients diagnosed with ileus (diagnosis was made by emergency physicians) in the emergency department were included in this

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study. This study consisted of 179 hospitalized patients aged above 18 years with acute abdomen and diagnosed as having ileus. The exclusion criteria were as follows: patients with acute mesenteric ischemia, postoperative early obstruction, cancer diagnoses, patients aged below 18 years, patients who did not accept treatment, those who left the emergency department without permission, and patients referred to another hospital.

Data collection and measurements

Relevant data were collected from the records of the emergency department and the hospital data processing record system. Data analysis included demographic data, laboratory parameters on admission to the emergency department, computed tomography (CT) reports, treatment modalities (conservative or surgical), length of hospital stay (LOS), and mortality. Serum PCT levels were analyzed using chemiluminescence immunoassay (CLIA), and a standard test kit was used. Other biochemical parameters were studied using a Beckman Coulter Chemistry Analyzer AU5800.

We divided the patients into two groups: those who underwent surgery and those hospitalized for conservative treatment with nasogastric decompression. The decision for surgery or conservative treatment was made after consultation with a general surgeon based on the clinical and radiologic findings, the presence of obstruction, and the presence of strangulation, fluid–electrolyte, and acid–base balance. We compared the PCT, CRP, lactate, CRP/albumin, lactate/albumin, and BUN/albumin values in these patients to predict surgical treatment and mortality.

Outcome

The first outcome for this study was in-hospital mortality. The patients were followed up during hospitalization for mortality. The secondary outcomes were the patients' need for surgical treatment and LOS.

Statistical analysis

Data were analyzed using IBM SPSS version 22. Mean, standard deviation, median, minimum–maximum, frequency, and ratio values were used in the descriptive statistics of the data. The χ^2 test was used for the comparison of categorical variables. Student's *t*-test was performed to compare two groups when normally distributed, and Mann-Whitney U test when not normally distributed. A receiver operating characteristics (ROC) curve was used to investigate the accuracy of PCT and other biomarkers in predicting mortality and the need for surgery. The cutoff value was determined using the Youden Index, in which the highest sensitivity and specificity point in the ROC curve was taken. The statistical significance level was set as $p<0.05$.

RESULTS

The total number of patients admitted to the emergency department during the study period (January 1, 2018, to December 31, 2020) was 576,499. Of these, 18,374 patients were hospitalized in the general surgery clinic from emergency department. Of these, 8,841 patients were hospitalized for nontraumatic reasons. Notably, 378 patients included in the study were those who were diagnosed with ileus (diagnosed by emergency medicine physicians) on admission to the emergency department and were hospitalized in the general surgery clinic with this preliminary diagnosis. Overall, 199 patients were excluded from this study: 155 patients had a diagnosis other than ileus (acute appendicitis n=17, acute cholecystitis n=46, acute mesenteric ischemia n=13, acute diverticulitis n=7, strangulated hernia n=15, perforated gallbladder n=5, four gastric perforation n=4, and tumor n=48), 4 patients did not accept hospitalization despite having bowel obstruction, 34 patients had missing file information and laboratory parameters, and 6 patients left the emergency department without permission.

As a result, 179 patients were included in the final analysis; 39.1% (n=70) were female and 60.9% (n=109) were male. The mean age of the patients was 56.5±7.3 years. The distribution, demographic characteristics, and laboratory parameters of the patients according to the treatment they received are presented in Table 1.

The first treatment methods that the patients received after being admitted to the surgery clinic due to ileus were as follows: conservative treatment with nasogastric decompression was performed on 58.7% of the patients (n=105), and surgical treatment was performed on 41.3% (n=74). The mean LOS of the patients who received conservative treatment in hospital was 3.6±2.1 days and that of patients who received surgical treatment was 10.6±8.7. As a result, the LOS of patients who needed surgical treatment was considerably longer than in patients who received conservative treatment ($p<0.001$).

Figure 1 presents the need for surgical treatment of PCT, lactate, CRP/lactate, lactate/albumin, and BUN/albumin values from the laboratory data at the time of hospital admission, as determined using ROC curve analysis. In direct comparisons, PCT showed better overall performance than lactate, CRP/lactate, lactate/albumin, and BUN/albumin, with the area under the ROC curve (AUC) value of 0.798 (95%CI 0.730–0.866). A PCT threshold value of 0.13 ng/mL was able to predict the need for surgical treatment, with a sensitivity of 79% and specificity of 70.3%

Finally, 137 (76.5%) patients were discharged, and 24.5% (n=42) died. ROC analysis was also performed to predict the mortality rate of the patients using PCT, lactate, CRP/lactate,

lactate/albumin, and BUN/albumin values from the laboratory data at the time of hospital admission, as shown in Figure 1. The analysis of this curve is presented in Table 2. PCT showed better results than the other parameters, with an AUC value of 0.921 (95%CI 0.882–0.960; p<0.001). A PCT threshold value of 0.65 ng/mL was able to predict mortality in patients, with a sensitivity of 92.9% and a specificity of 78.1%.

In the analyses for the prediction of mortality, the lactate/albumin ratio (AUC 0.788, 95%CI 0.705–0.872; p<0.001) was higher than the BUN/albumin value (AUC 0.715, 95%CI 0.629–0.802; p<0.001). The lactate/albumin threshold value of 0.075 was able to predict mortality with a sensitivity of 78.6% and a specificity of 63.5%, and the BUN/albumin threshold value was 0.69 with a sensitivity of 88.1% and specificity of 54.7%.

Table 1. Characteristics of the patients according to the requirement of treatment.

	Conservative management (n=74)	Surgical management (n=105)	p-value
Age, years (min–max)	53.4±6.3 (65–87)	57.7±8.3 (65–97)	0.034
Sex, n (%)			
Female	37 (50)	33 (31.4)	0.012
Male	37 (50)	72 (68.6)	
Comorbidity, n (%)			
Hypertension	36 (48.6)	67 (63.8)	0.043
Coronary artery disease	23 (31.1)	52 (49.5)	0.014
Lung disease	19 (25.7)	30 (28.6)	0.669
Kidney insufficiency	11 (14.9)	37 (35.2)	0.002
Diabetes mellitus	16 (21.6)	23 (21.9)	0.964
Congestive heart failure	4 (5.4)	17 (16.2)	0.027
Cerebrovascular disease	10 (13.5)	8 (7.6)	0.197
BT Finding	64 (86.5)	94 (89.5)	0.534
Length of hospital stay (days)	3.6±2.1	10.6±8.7	<0.001
Prognosis			
Survival	69 (93.2)	68 (64.8)	<0.001
Non-survival	5 (6.8)	37 (35.2)	
White blood cell (10^3/µL)	12.1±5.8	12.1±6.1	0.938
Hemoglobin (g/dL)	12.7±2.1	12.5±2.5	0.549
Platelet (10^3/µL)	314.7±140.9	292.9±127.1	0.281
Biochemical Parameters			
Sodium (mmoL/L)	136.8±4.7	135.7±4.9	0.171
Potassium (mmoL/L)	4.5±0.6	4.3±0.8	0.014
Chlorine (mmoL/L)	100.9±5	99.6±6.3	0.140
Calcium (mmoL/L)	9.4±0.8	8.9±0.9	0.002
Blood urea nitrogen (mg/dL)	26.1±14.8	32.0±17.7	0.015
Creatinine (mg/dL)	1.05±0.7	1.6±2.2	0.026
Aspartate transaminase (U/L)	25.1±12.2	37.2±55.5	0.069
Alanine transaminase (U/L)	16.8±10	24.1±33.2	0.067
Albumin (mg/L)	35.6±5.8	31.2±7.6	<0.001
C-reactive protein (mg/L)	8.5±9.8	15.4±13.5	<0.001
Procalcitonin (ng/mL)	2.2±11.1	7.5±15.8	0.009
Lactate (mmoL/L)	2.2±1.1	3.2±2.5	<0.001
Lactate/albumin	0.06±0.03	0.11±0.08	<0.001
BUN/albumin	0.8±0.5	1.1±0.7	<0.001

BUN: blood urea nitrogen.

DISCUSSION

Our study investigated the ability to predict surgery and mortality using laboratory parameters checked at the time of hospital admission in patients who were hospitalized due to ileus from the emergency department. We observed that high PCT values in patients with ileus were greater than other laboratory markers compared to predicting the need for surgical treatment and mortality. We found that the need for surgical treatment increased with PCT values >0.13 ng/mL (sensitivity 79%, specificity 70.3%) and mortality significantly increased at values >0.65 ng/mL (sensitivity 92.9%, specificity 78.1%).

Laboratory parameters affected by inflammatory markers are also expected to increase. These mediators induce the release of PCT from intestinal macrophages and hepatocytes through the portal system[14]. A prospective non-randomized study conducted with 59 patients diagnosed with small bowel obstruction showed that the surgical treatment achieved cut-off value by measuring PCT levels every 6 h. The cutoff value was 0.16 ng/mL at first admission and was >0.27 ng/mL at the 18th hour[15]. In another study of 242 cases that predicted surgical treatment, the authors emphasized that PCT levels in the treatment of ileus could play an essential role in clinical

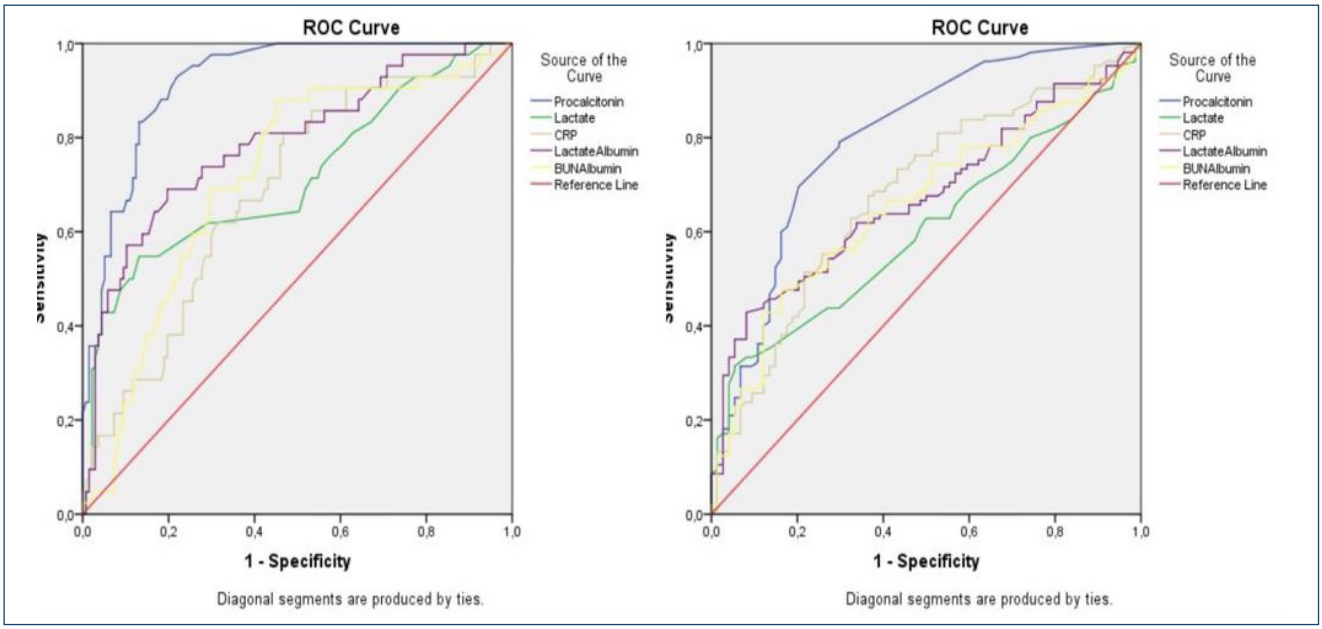

Figure 1. Receiver operating characteristics curves showing comparisons of procalcitonin, lactate, C-reactive protein, lactate/albumin, blood urea nitrogen/albumin values in predicting (A) the need for surgery and (B) hospital mortality.

Table 2. Receiver operating characteristics analysis of procalcitonin, lactate, C-reactive protein, lactate/albumin, and blood urea nitrogen/albumin values for the need of surgery and hospital mortality.

	AUC	SE	(95%CI)	Cutoff	Sensitivity	Specificity	p-value
Surgery need							
PCT	0.798	0.035	0.730–0.866	0.13	79	70.3	<0.001
CRP	0.681	0.040	0.602–0.760	5.9	73.3	56.8	<0.001
Lactate/albumin	0.673	0.040	0.595–0.751	0.07	63.8	60.8	<0.001
BUN/albumin	0.657	0.041	0.577–0.737	0.73	62.9	63.5	<0.001
CRP/lactate	0.615	0.043	0.532–0.699	2.3	69.5	51.4	0.009
Lactate	0.603	0.042	0.522–0.685	2.35	62.9	50	0.019
Hospital mortality							
PCT	0.921	0.020	0.882–0.960	0.65	92.9	78.1	<0.001
Lactate/albumin	0.788	0.042	0.705–0.872	0.075	78.6	63.5	<0.001
BUN/albumin	0.715	0.044	0.629–0.802	0.69	88.1	54.7	<0.001
Lactate	0.713	0.050	0.615–0.811	2.75	61.9	70.8	<0.001
CRP	0.686	0.046	0.597–0.775	8	81	53.3	<0.001

BUN: blood urea nitrogen; CRP: C-reactive protein; PCT: procalcitonin; ROC: receiver operating characteristics.

decision-making in acute bowel obstruction, and they proceeded to surgery with value >1 ng/mL[16].

Our study found that CRP and lactate were also significant in predicting surgical treatment. CRP begins to rise in 3–6 h after inflammation, peaks in 30–60 h[17]. Studies suggested that CRP and lactate levels might help predict strangulation and make early decisions for surgery[18].

Lactate is produced from many tissues, mostly muscle tissue. It has two isomers, L-lactate and D-lactate. D-Lactate is used by human colon bacteria, produced by glycosylase, and its normal serum level is very low. Its elevation is always associated with pathological bowel diseases and strangulation[19].

It was reported that BUN levels increased in critical diseases with high mortality[13,20,21]. Albumin, a negative acute-phase reactant, is a protein that protects plasma osmolarity. The decrease in albumin synthesis due to nutrition and inflammation causes a decrease in serum albumin levels[22]. Our study observed that the ratio of BUN and albumin in patients with intestinal obstruction aged above 18 years was significant in determining LOS and mortality. Especially in patients with impaired intestinal obstruction, increased BUN and decreased albumin values may have an essential place in predicting mortality.

A few studies on PCT and its ability to predict mortality have found different results. In a prospective study of 153 patients who underwent abdominal surgery, no statistically significant relationship was found between PCT and 28-day mortality after surgical treatment[23], but PCT values were associated with 28-day mortality >2.5 ng/mL in 454 patients who underwent surgical treatment in another study[24]. Our study found that PCT value >0.65 ng/mL had a high predictive power for mortality.

The limitations of this study are that it is single-centered and retrospectively arranged study.

CONCLUSION

It is vital to detect intestinal obstruction for emergency surgical decisions and predict whether it will transform into ischemia. PCT, which is measured in the emergency department, can help the surgeon predict mortality as an additional test to physical examinations and radiology in making methods of treatment for patients with intestinal obstruction.

AUTHORS' CONTRIBUTIONS

GKS: Conceptualization, Data curation, Formal Analysis, Writing – original draft, Writing – review & editing. MG: Conceptualization, Data curation, Formal Analysis, Writing – original draft, Writing – review & editing. SA: Conceptualization, Formal Analysis, Writing – original draft, Writing – review & editing. BTF: Formal Analysis, Writing – original draft. AK: Conceptualization, Data curation, Writing – original draft. CI: Conceptualization, Formal Analysis, Writing – original draft, Writing – review & editing. MSS: Conceptualization, Writing – original draft, Writing – review & editing. YS: Conceptualization, Writing – original draft, Writing – review & editing. AS: Conceptualization, Data curation, Writing – review & editing. SS: Conceptualization, Data curation, Formal Analysis, Writing – original draft.

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ORIGINAL ARTICLE

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Evaluation of the cardio-ankle vascular index in COVID-19 patients

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SUMMARY

OBJECTIVE: This study aimed to investigate the relationship and prognostic significance of cardio-ankle vascular index, which is a measure of arterial stiffness that can lead to endothelial dysfunction and poor cardiovascular issues in COVID-19 patients, with COVID-19.

METHODS: The study included 115 patients, of which 65 patients in the case group with Real time reversetranscription-polymerasechainreaction test positive and diagnosed for COVID-19 and 50 volunteers in the control group. Patients with COVID-19 were classified as moderate/severe or mild COVID-19 in the subgroup analysis based on the severity of the disease. We investigated the relationship between cardio-ankle vascular index and COVID-19 by using the VaSera VS-1000 device to automatically measure each patient's cardio-ankle vascular index and ankle-brachial pressure index.

RESULTS: The mean age of participants included in the study was 65.7±10.7 years. Patients and volunteers were statistically similar in terms of age, gender, comorbidities, Charlson comorbidity index scores, and body mass index values (p>0.05). The right-cardio-ankle vascular index value was 9.6±2.4 in the case group and 8.5±1.1 in the control group (p=0.004). The left-cardio-ankle vascular index value was 9.4±2.7 in the case group and 8.5±1.2 in the control group (p=0.01). The right-cardio-ankle vascular index value was 10.8±3.4 in the moderate/severe disease group and 8.8±0.9 in the mild disease group (p=0.008). The left-cardio-ankle vascular index value was 10.7±3.6 in the moderate/severe disease group and 8.5±1.5 in the mild disease group (p<0.001). The right-cardio-ankle vascular index and left-cardio-ankle vascular index values were found to be significantly higher in COVID-19 patients in our study. When receiver operating characteristic analysis was performed to distinguish moderate/severe COVID-19 patients from mild patients, right-cardio-ankle vascular index was area under the curve 0.757 (0.630–0.884), and left-cardio-ankle vascular index was area under the curve 0.782 (0.661–0.902).

CONCLUSION: The right-cardio-ankle vascular index and left-cardio-ankle vascular index values increased in COVID-19 patients in our study, and this was thought to be prognostically significant.

KEYWORDS: COVID-19. Arterial stiffness. Cardio ankle vascular index. Endothelium.

INTRODUCTION

Severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) causes a disease with a high mortality rate and a proclivity for multiple organ failure by wreaking havoc on various organ systems, particularly the lungs, heart, brain, kidney, and vascular system[1]. Endothelial dysfunction is critical in the pathogenesis of the disease. The endothelium, which is located at the key interface between blood and tissues, acts as a portal that operates white blood cells to enter tissues to fight invaders, microbes, or viruses, and to help repair injury and heal wounds[2]. Normal endothelium has a pattern of anticoagulant, antithrombotic, and profibrinolytic properties and has a basis dynamically regulated to maintain a balance between properties supporting and inhibiting thrombus deposition. Furthermore, the endothelial cell has a variety of defense mechanisms reducing local oxidative stress. This balance is disrupted when stimulated by proinflammatory cytokines, bacterial endotoxins, neutrophil extracellular traps (NETs), and similar molecules. NADPH oxidases producing superoxide anions that contribute to oxidative stress are activated[3]. As a result of all of these circumstances, inappropriate or excessive production of cytokines, such as IL-1α and IL-1β, IL-6, and TNF-α, results in a situation named "a cytokine storm." Endothelial damage and associated complications occur as a result. Coronavirus disease 2019 (COVID-19) is a disease with irregular endothelial function, and the severity of the disease is closely related to this endothelial dysfunction[2]. Although COVID-19 is initiated by the impact of pneumocytes and alveolar macrophages, impaired endothelial function contributes to the ongoing destruction of SARS-CoV-2 in the lung. Impaired endothelial barrier function results in protein and fluid accumulation in the alveolar space and impaired blood oxygenation. The resulting cytokine storm causes capillary leakage and exacerbation of the adult respiratory syndrome (ARDS) originated from COVID-19[4,5]. The most serious problems with this

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disease are lung and cardiovascular anomalies[6,7]. Increased arterial stiffness, which is a vascular functional abnormality, has been shown to be an independent risk factor for cardiovascular disease[8]. Both structural and functional abnormalities can cause arterial stiffness[9]. Viral infections can cause functional vascular damage, such as increased arterial stiffness, which is reversible at the beginning of its course[10]. Thrombotic microangiopathy and endothelial dysfunction generalized with pulmonary embolism and venous thromboembolism in patients infected with COVID-19 have been especially demonstrated in autopsy studies[11]. Endothelial dysfunction and associated arterial stiffness may cause adverse cardiovascular issues in COVID-19 patients. This study aimed to measure the functional change in arterial stiffness that may cause endothelial dysfunction and adverse cardiovascular issues in COVID-19 patients and to determine the prognostic significance of this situation.

METHODS

The study was a prospective case-control study conducted at Trabzon Vakfikebir State Hospital from October 2020 to April 2021. The study included a total of 115 participants whose COVID-19 status was known. While the case group included 65 people who tested positive for COVID-19 rtRT-PCR, the control group included 50 people who tested negative for COVID-19 rtRT-PCR and had similar demographic features. COVID-19 patients were divided into two groups based on the severity of the disease. Patients with fever, shortness of breath, or a severe cough were classified as having moderate/severe COVID-19, while those who did not have these symptoms were classified as having mild COVID-19. People with known peripheral artery disease, glomerular filtration rate (eGFR) less than 30 ml/min, or malignancy were not included in the study. Baseline characteristics and clinical histories, values of systolic and diastolic blood pressure, urea, creatinine, eGFR at admission, serum lipid profile, body mass index (BMI), cardio-ankle vascular index (CAVI), and ankle-brachial pressure index (ABPI) examinations of all participants were performed. CAVI and ABPI were measured using the VaSera VS-1000 (Fukuda-Denshi Company Ltd., Tokyo, Japan), which is a portable machine.

The study protocol was designed in accordance with the principles of the Declaration of Helsinki, and the approval (no: 23618724/2021/22) of the ethics committee was obtained.

Statistical analysis

All variables in the study were subjected to descriptive statistical analysis. The Kolmogorov–Smirnov test was used to determine the conformity of data obtained by measures to the normal distribution. Student's t-test was used for data that conform to the normal distribution, and the Mann-Whitney U test was used for data that did not conform to the normal distribution. In the analysis of categorical variables, the chi-square test was used. The data obtained by measurements were expressed as mean±standard deviation. The data obtained by scoring were expressed by numbers (%). The sensitivity and specificity of the statistically significant variables were calculated using the receiver operating characteristic (ROC) curve analysis. $p<0.05$ was accepted as statistically significant.

RESULTS

The study included 65 COVID-19 patients in the case group and 50 volunteers in the control group. Volunteers are people who have tested negative for the COVID-19 rtRT-PCR test and have no other disease symptoms. Patients with COVID-19 were aged 67±12.3 years, and the volunteers were aged 64.5±9.2 years ($p=0.213$). Patients and volunteers were statistically similar in terms of age, gender, comorbidities, Charlson comorbidity index (CMI) scores, and BMI values ($p>0.05$). Systolic blood pressure, one of the hemodynamic parameters, was 127.5±19.8 in the case group and 140.8±24.7 in the control group ($p=0.002$). Both groups had similar diastolic blood pressure ($p=0.174$). The R-CAVI value was 9.62.4 in the case group and 8.51.1 in the control group ($p=0.004$). The L-CAVI value was 9.4±2.7 in the case group and 8.5±1.2 in the control group ($p=0.01$). The R-ABI and L-ABI values in both groups were similar ($p>0.05$). Demographic characteristics, laboratory findings, hemodynamic parameters, and arterial stiffness measurements of patients and volunteers are presented in Table 1.

In our internal evaluation of COVID-19 patients, 25 patients were classified as having moderate/severe disease and were hospitalized, while 40 patients were classified as having mild disease and were treated as outpatients. In the analysis between both groups, gender and age were statistically similar. Hypertension was more common among patients in the moderate/severe disease group ($p=0.004$). The R-CAVI value was 10.8±3.4 in the moderate/severe disease group and 8.8±0.9 in the mild disease group ($p=0.008$). The L-CAVI value was 10.7±3.6 in the moderate/severe disease group and 8.5±1.5 in the mild disease group ($p<0.001$). The R-ABI and L-ABI values in both groups were similar ($p>0.05$). Demographic characteristics, laboratory findings, hemodynamic parameters, and arterial stiffness measurements of the patients in moderate/severe and mild COVID-19 disease groups are presented in Table 2.

Table 1. Analysis of demographic, clinical, and laboratory findings of case and control groups.

	COVID-19 n=65	Control n=50	p-values
Age (years)	66.9±12.3	64.5±9.2	0.213
Gender (female) n (%)	34 (52.3)	19 (38.0)	0.127
BMI (kg/m^2)	27.7±3.6	27.9±3.8	0.804
Systolic BP, mmHg	127.4±19.8	140.8±24.7	0.002
Diastolic BP, mmHg	77.9±11.6	80.6±13.9	0.174
CAD, n (%)	12 (18.5)	17 (34.0)	0.057
Hypertension, n (%)	32 (49.2)	33 (66.0)	0.072
Diabetes mellitus, n (%)	6 (24)	14 (28)	0.926
CMI scores	3.3±1.9	3.6±1.6	0.354
right-cardio-ankle vascular index	9.6±2.4	8.5±1.1	0.004
left-cardio-ankle vascular index	9.4±2.7	8.5±1.2	0.01
right-ankle-brachial index	1.04±0.14	1.04±0.10	0.886
left-ankle-brachial index	1.06±0.26	1.04±0.09	0.984

CAD: coronary artery disease; CMI: Charlson comorbidity index; BMI: body mass index. Bold values are determined as statistically significant.

Table 2. Analysis of demographic, clinical, and laboratory findings of patients according to the severity of COVID-19.

	COVID-19 inpatient n=25	COVID-19 outpatient n=40	p-values
Age	70.7±13.1	64.7±11.2	0.051
Gender (female) n (%)	16 (64)	18 (45)	0.136
BMI (kg/m^2)	28.4±4.1	27.3±3.2	0.226
Systolic BP, mmHg	124.4±20.2	129.4±19.6	0.174
Diastolic BP, mmHg	76.0±8.7	79.1±13.0	0.245
CAD, n (%)	7 (28)	5 (12.5)	0.188
Hypertension, n (%)	18 (72)	14 (35)	0.004
Diabetes mellitus, n (%)	6 (24)	6 (15)	0.363
CMI scores	4.2±2.1	2.8±1.6	0.003
right-cardio-ankle vascular index	10.8±3.4	8.8±0.9	0.008
left-cardio-ankle vascular index	10.7±3.6	8.5±1.5	<0.001
right-ankle-brachial index	1.0±0.16	1.06±0.11	0.162
left-ankle-brachial index	1.06±0.4	1.05±0.1	0.225

CAD: coronary artery disease; CMI: Charlson comorbidity index; BMI: body mass index. Bold values are determined as statistically significant.

When the ROC analysis was performed to distinguish moderate/severe COVID-19 patients from patients with mild disease, AUC 0.757 (0.630–0.884) at cutoff point >8.75 for R-CAVI had 76% sensitivity and 56% specificity, and AUC 0.782 (0.661–0.902) at cutoff point >8.5 for L-CAVI had 88% sensitivity and 58% specificity (Figure 1).

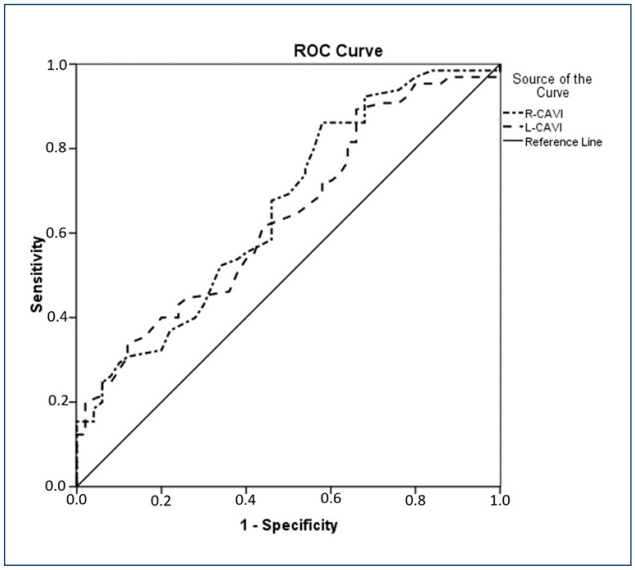

Figure 1. Receiver operating characteristic curve demonstrating the prognostic value of right-cardio-ankle vascular index and left-cardio-ankle vascular index in COVID-19 patients with moderate/severe and mild disease.

DISCUSSION

Under physiological conditions, the endothelium has a structure that prevents mononuclear cell adhesion at the blood–tissue interface. Inflammation caused by allowing white blood cells to enter tissues in order to fight microbial agents and aid in the healing of damaged tissues activates endothelial cells that cause the loss of vascular integrity, allows increased expression of adhesion molecules (such as VCAM-1 and ICAM-1), and allows endothelial cells to participate in the inflammatory response[12]. Increased expression of adhesion molecules stimulates the adhesion and migration of monocytes to the vessel wall, where these

cells further differentiate into macrophages, increasing vasculitis. Continuous endothelial cell activation results in subsequent endothelial dysfunction, which is the first step in atherogenesis and contributes to the development of distinct clinical features that characterize later stages of vascular disease[13]. While coronaviruses are known to cause endothelial dysfunction, it is remarkable that COVID-19 causes endothelial dysfunction in such a short period of time, and this situation is associated with prognosis. Researchers in New York City observed a seven-fold increase in large vessel strokes in patients younger than 50 years old during the 2-week period from March 23 to April 7, 2020, compared with a 2-week period over the previous 12 years[14]This study aimed to assess the functional change in arterial stiffness, which is commonly associated with endothelial dysfunction in COVID-19 patients, and to determine the prognostic significance of this condition. The presence of nitric oxide primarily regulates arterial stiffness, and CAVI, an indicator of arterial stiffness, somehow measures endothelial cell function[15]. In our study, R-CAVI and L-CAVI values were found to be significantly higher in the analysis between the case and control groups, as well as between moderate/severe patients and mild patients, and the level of endothelial dysfunction was associated with the clinical status of the patients. The AUC value was determined by ROC curve analysis to be 0.757 for R-CAVI and 0.782 for L-CAVI, and the area under the quite high curve was located. The high sensitivity rates at the determined cutoff points also demonstrate the usefulness of the CAVI measurements.

CONCLUSIONS

The findings of the study lead us to believe that both R-CAVI and L-CAVI values can be used as prognostic indicators in COVID-19 patients. Given the global impact of the pandemic, well-designed large-scale clinical studies are required to convert this knowledge into clinical practice.

AUTHORS' CONTRIBUTIONS

EA: Conceptualization, Writing – original draft, Writing – review & editing. AK: Data curation, Formal Analysis, Writing – review & editing. GY: Data curation, Formal Analysis, Writing – original draft, Writing – review & editing.

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ORIGINAL ARTICLE

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When to remove the drainage catheter in patients with percutaneous cholecystostomy?

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SUMMARY

OBJECTIVE: The treatment for patients with acute calculous cholecystitis who have high surgical risk with percutaneous cholecystostomy instead of surgery is an appropriate alternative choice. The aim of this study was to examine the promising percutaneous cholecystostomy intervention to share our experiences about the duration of catheter that has yet to be determined.

METHODS: A total of 163 patients diagnosed with acute calculous cholecystitis and treated with percutaneous cholecystostomy between January 2011 and July 2020 were reviewed retrospectively. The Tokyo Guidelines 2018 were used to diagnose and grade patients with acute cholecystitis.

RESULTS: The mean age was 71.81±12.81 years. According to the Tokyo grading, 143 patients had grade 2 and 20 patients had grade 3 disease. The mean duration of catheter was 39.12±37 (1–270) days. Minimal bile leakage into the peritoneum was noted in 3 (1.8%) patients during the procedure. The rate of complications during follow-up of the patients who underwent percutaneous cholecystostomy was 6.9% (n=11), and the most common complication was catheter dislocation. Cholecystectomy was performed in 33.1% (n=54) of the patients at follow-up. Post-cholecystectomy complication rate was 12.9%. At the follow-up, the rate of recurrent acute cholecystitis episodes was 5.5%, while the mortality rate was 1.8%. The length of follow-up was five years.

CONCLUSIONS: The rate of recurrence was significantly higher among the patients with catheter for <21 days. We recommend that the duration of catheter should be minimum 21 days in patients undergoing percutaneous cholecystostomy.

KEYWORDS: Acute cholecystitis. Cholecystostomy.

INTRODUCTION

Acute cholecystitis is one of the most common diseases in surgical clinics in developed countries[1]. According to the Tokyo Guidelines 2018 (TG18), percutaneous cholecystostomy (PC) can be performed in a selected group of grade 2 and three patients who are considered not being able to handle the high-risk surgery. However, the eligible patient selection for PC and the subsequent management of these patients in the clinic have not been clearly defined[2]. Patients with multiple comorbidities, late presentation to healthcare facility after the onset of symptoms, and unresponsive to antibiotic therapy are the candidates for PC[3]. Patients with high-grade disease according to the TG18 severity rating are associated with prolonged hospital stays and more common complications[4]. Surgical treatments tried to be minimized every passing day[5]. Our aim was to analyze the clinical follow-up of patients undergoing PC to determine the safe timing that can be recommended for the removal of the catheter by the algorithms to be created, thereby contributing to the development of treatment algorithms.

METHODS

This retrospective cohort study was conducted at the Haydarpasa Numune Training and Research Hospital, Istanbul, which is a tertiary care referral center. A total of 163 patients diagnosed with acute calculous cholecystitis and treated with PC between January 2011 and July 2020 were included. Upon the ethics committee approval (N°. HNEAH-KAEK 2021/KK/5), the hospital database was used to review the patients who had an entry for the "PC" procedure. The Tokyo Criteria were used for the diagnosis of acute cholecystitis[4]. Inclusion criteria were as follows:

- Patients with grades 2–3 acute cholecystitis according to the TG18 criteria,
- Patients with acute cholecystitis presenting to the hospital more than 72 h after the onset of symptoms and/or not clinically responding to intravenous (IV) antibiotic therapy within 48–72 h.
- Exclusion criteria were as follows:
- Patients undergoing PC for biliary drainage due to reasons such as malignancy and bile duct strictures.
- Patients with acute acalculous cholecystitis.

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Routine abdominal ultrasonography was performed in all patients. PC was performed by an experienced radiologist under local anesthesia, using the Seldinger technique under ultrasound guidance by a transhepatic or transperitoneal approach. A culture antibiogram was tested using the bile samples collected from each patient as a routine during PC. Stasis enzymes, bilirubin, white blood cell (WBC) and C-reactive protein (CRP) values before PC, and WBC and CRP values at discharge after PC were recorded for all the patients. The time from the onset of symptoms (days), comorbidities, American Society of Anesthesiologists (ASA) scores, names of microorganisms in case of growth in the culture, the timing of drainage tube removal, the technique for tube placement, the presence/absence of recurrent acute calculous cholecystitis episodes (recurrence) after PC at the follow-up, the presence/absence of cholecystectomy, and complications were recorded. The length of follow-up was five years.

The IBM SPSS Statistics version 22 (IBM SPSS, Turkey) software package was used for the statistical analyses of the study data. The normality of the parameters was tested using the Shapiro-Wilk test. In addition to the descriptive statistical methods (mean, standard deviation, and frequency), the Mann-Whitney U test was used to compare quantitative data and non-normally distributed parameters between two groups. A $p<0.05$ was considered statistically significant.

Table 1. Distribution of general characteristics.

		Mean±SD	Min–Max
Age (years)		71.81±12.81	32–96
Length of hospital stay (median)		10.64±7.45 (8)	1–44
Duration of complaints (days) (median)		3±1.09 (3)	1–10
The day of hospital stay for PC		2.52±2.26 (2)	0–17
Duration of catheter (n=160)		39.12±37 (30)	1–270
Timing of cholecystectomy (n=54)		72.33±61.61 (55.5)	7–365
		n	%
Sex	Male	100	61.3
	Female	63	38.7
ASA	2	20	12.3
	3	37	22.7
	4	106	65
Tokyo grading	2	143	87.7
	3	20	12.3
Comorbidities	No	10	6.1
	Yes	153	93.9

ASA: American Society of Anesthesiologists; PC: percutaneous cholecystostomy; SD: standard deviation.

RESULTS

The mean length of hospital stay was 10.64±7.45 days, and the mean time from the onset of complaints to presentation to healthcare facility was 3±1.09 days. Of a total of 163 patients, 61.3% were males. The mean age was 71.81 years. There was at least one comorbidity, and mostly multiple comorbidities, in 153 of the patients. PC was performed by a transhepatic approach in 111 (68.1%) patients and by a transperitoneal approach in the remaining patients. The most commonly used one was 8F (71.8%) catheters in the procedure. General characteristics and comorbidities of the patients are presented in Table 1.

The most frequently administered IV antibiotic was ceftriaxone+metronidazole with a rate of 45.4%. Antibiotic changes were made in 29 patients. A growth rate of 40.5% (n=66) was detected in the culture performed during the procedure, and the most common microorganism was *Escherichia coli* with a rate of 43.9% (n=29). In patients with recurrence, the duration of IV antibiotic use before the procedure was statistically significantly shorter than those without any recurrent episodes ($p=0.030$ and $p<0.05$, respectively).

According to TG18, 143 patients had grade 2 disease and 20 patients had grade 3 disease. The ASA score was 3 or 4 in 143 patients and two in 20 patients. Cholecystectomy was performed in 54 (33.1%) patients at follow-up, and the mean time from PC to cholecystectomy was 72.33±61.61 days. Post-cholecystectomy complication rate was 12.9%. Wound site infection was the most common complication (4/7). Two patients had postoperative bile leakage and were treated with Endoscopic Retrograde Cholangio-Pancreatography (ERCP). One patient was re-operated for intra-abdominal abscess. The perioperative duodenal injury that occurred in two patients was repaired primarily.

The PC is technically 100% successful. Minimal bile leakage into the peritoneum was noted in 3 (1.8%) patients during the procedure. The rate of catheterization-related complications during follow-up of the patients was 6.9% (n=11); catheter revision was performed for the catheter dislocation in seven patients.

The timing of percutaneous cholecystostomy tube (PCT=percutaneous drainage tube) removal was 39.12±37 days, and three patients with failed recording of the exact catheter removal time were not included in the calculation. In our study, recurrent acute calculous cholecystitis at follow-up was considered recurrence and the recurrence rate was found to be 5.5% (9/163) (Table 2).

Table 2. Relationship between recurrence (acute cholecystitis episode) and parameters.

	Recurrence Absent	Recurrence Present	p-value
Duration of catheter			
<21	36 (23.4)	6 (66.7)	0.004
≥21	118 (76.6)	3 (33.3)	
Duration of catheter			
<100	143 (92.9)	9 (100)	0.406
≥100	11 (7.1)	0 (0)	
Duration of catheter			
<7	9 (5.8)	0 (0)	0.456
≥7	145 (94.2)	9 (100)	
Tokyo grading			
2	134 (87)	9 (100)	0.248
3	20 (13)	0 (0)	
Preoperative WBC (cells/μL)			
<18000	104 (67.5)	5 (55.6)	0.458
≥18000	50 (32.5)	4 (44.4)	
Antibiotic resistance			
No	127 (82.5)	7 (77.8)	0.721
Yes	27 (17.5)	2 (22.2)	
Positive growth culture			
No	90 (58.4)	7 (77.8)	0.251
Yes	64 (41.6)	2 (22.2)	

WBC: White blood cells. Bold values denote statistical significance at p<0.05.

There were no significant differences between cases with and without recurrences regarding CRP, duration of hospital stay, and WBC counts. The duration of PCT was statistically significantly shorter in patients with recurrent episodes than in those without any recurrent episodes (p=0.014). When the effect of catheter duration on recurrence was examined for 7, 21, and 100 days, there was a significant effect on recurrence only for the duration of <21 days (p=0.004) (Tables 2 and 3).

The mortality rate was 1.8% and the mortality was calculated for the postoperative 60 days. All three patients who died were at very high risk, had grade 3 disease, had an ASA score of 4, and were directly admitted to intensive care unit upon presentation to the hospital.

Table 3. Comparison of duration of antibiotic use and duration of catheter between patients with and without recurrence.

	Recurrence		p-value
	No	Yes	
	Mean±SD (median)	Mean±SD (median)	
Pre-PC duration of intravenous antibiotic use (days)	2.71±2.31 (2)	1.56±1.33 (1)	0.030*
Post-PC duration of intravenous antibiotic use (days)	7.62±5.05 (6)	6.22±3.15 (6)	0.562
Duration of catheter (days)	39.12±37 (30)	21.89±16.8 (16)	0.014*

PC: percutaneous cholecystostomy; SD: standard deviation. *Mann-Whitney U test, p<0.05. Bold values denote statistical significance at p<0.05.

DISCUSSION

The main treatment of patients with grade 1 acute cholecystitis is early laparoscopic cholecystectomy[6]. When patients with acute cholecystitis are treated conservatively, gallbladder and bile duct complications may develop in only 30%[7]. We believe that PC is the most important weapon in nonsurgical treatment instead of cholecystectomy in selected grades 2 and three patients.

The most common microorganism was *E. coli*, and the growth rates were found to be consistent with the literature (growth rate of 29–54% in the literature)[6,8]. There was no significant difference in recurrence between patients with and without growth in their cultures. Despite the significantly shorter duration of preoperative IV antibiotic use in patients with recurrence than those without recurrence, there was growth in the bile cultures of only two (22.2%) patients with recurrence, and *Enterococcus faecium* was isolated in both. We believe that further research with more recurrence cases is required to better understand or confirm this relationship.

In the study by Wise et al., the timing for the catheter tract formation was determined as 20 days[9]. Studies on the timing of tube removal in patients undergoing PC could not establish a clear relationship[10,11]. Bhatt et al.[12] analyzed 145 patients and found no significant relationship between the duration of catheter and recurrent episodes. In this study, however, there was a significant number of patients with acute calculous cholecystitis and acalculous cholecystitis (n=47), and the mean duration of catheter was relatively long (mean: 57 days, 30–86 days) due to the presence of these patients and short durations of catheter could not be fully evaluated[12].

For patients with very high mortality and morbidity, some studies suggest permanent follow-up upon PC without cholecystectomy or follow-up with PCT until cholecystectomy[13,14,15]. Accordingly, our study also performed PCT immediately before or during cholecystectomy in 22 of 54 patients undergoing cholecystectomy. Regardless of cholecystectomy, the catheter remained for a long time in some patients, exceeding 100 days in 11 patients. All of these patients had multiple morbidities, had a high ASA score, did not accept surgery, or were planned to be followed up by the clinician without surgery due to the risks, and none of them had recurrence. Of course, living with a tube for a long time will negatively affect the quality of life.

The study by Bundy et al. on 324 patients reported similar culture growth rates (39.5%) to our study, while the mean duration of catheter was 89 days, and recurrence was not evaluated. The mortality rate was higher compared to our study (6.8%). However, this study included patients with acalculous cholecystitis and calculated long-term mortality[16].

While Hsieh et al. found that PCT remained for >2 weeks and high CRP levels were associated with early recurrence, our study showed that early PCT removal have a significant relationship with recurrence, but no significant relationship between high CRP levels and recurrence. This study recommended the removal of the PC tube immediately after recovery from acute illness. Although recurrence rates were similar to our study, the said study calculated recurrence for a two-month period. Furthermore, since the mean duration of catheter was relatively short, it did not provide information on long-term outcomes. (Recurrence was observed in 11/126 patients, the duration of catheter was 16.6±14.00)[17]. Another cohort study found the timing of <7 days for catheter removal to be associated with recurrent episodes, whereas our study could not establish such relationship[18].

Loozen et al. reported that the rate of recurrent episodes was 22%, whereas other studies report rates ranging from 3% to 47%. In our study, the rate was 5.5%. This difference is attributed to the different acute episode definition made by each study. While some studies recorded every gallstone-related complication as an acute episode, most studies, like our study, recorded acute calculous cholecystitis episode as an episode[19].

One of the three non-surviving patients died one day after PCT placement. It is controversial whether there is a true mortality rate for PC, as PC was performed after this patient developed permanent septic shock[20]. We believe that it was too late to administer PC to the patient.

Due to its retrospective design, the benefits of our study are limited. PC is a promising method considering the CHOCOLATE[21] trial, which found no difference in mortality rates and showed a lower rate of major complications in PC when compared the outcomes of high-risk acute cholecystitis patients treated with either laparoscopic cholecystectomy or PC.

CONCLUSIONS

Approximately two-thirds of the recurrent episodes were observed in patients who underwent PCT before 21 days. There was a significant correlation between the timing of <21 days for catheter removal and experiencing a recurrent episode of acute cholecystitis.

AUTHORS' CONTRIBUTIONS

SAK: Conceptualization, Data curation, Writing – original draft, Writing – review & editing. MT: Conceptualization, Data curation, Writing – review & editing.

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ORIGINAL ARTICLE

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Comparison of C-reactive protein and C-reactive protein-to-albumin ratio in predicting mortality among geriatric coronavirus disease 2019 patients

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SUMMARY

OBJECTIVE: The aim of this study was to evaluate and compare C-reactive protein and C-reactive protein-to-albumin ratio performances in predicting mortality of geriatric patients who visited the emergency department.

METHODS: The data of patients with COVID-19 and aged 65 years and above, who visited emergency department during the study period, were retrospectively analyzed. The data were obtained from an electronic-based hospital information system. The area under the receiver operating characteristic curve and the area under the curve were used to assess each cutoff value discriminatory for predicting mortality.

RESULTS: The mean age of the population included in this study was 76 (71–82) years, while 52.7% were males. The sensitivity, specificity, and area under the curve values for C-reactive protein in terms of mortality were calculated as 71.01, 52.34, and 0.635%, respectively, while the sensitivity, specificity, and area under the curve values for C-reactive protein-to-albumin ratio were calculated as 75.74, 47.66, and 0.645%, respectively ($p<0.001$). In the pairwise comparison for the receiver operating characteristic curves of C-reactive protein and C-reactive protein-to-albumin ratio, no statistically significant difference was found.

CONCLUSIONS: Geriatric patients are the "most vulnerable" patient group against the COVID-19. In this study, both C-reactive protein and C-reactive protein-to-albumin ratio were found to be successful in predicting mortality for geriatric COVID-19 patients.

KEYWORDS: Albumins. COVID-19. C-reactive protein. Geriatrics. Mortality.

INTRODUCTION

It has been more than a year and a half since the first case was emerged in Wuhan (China), in December 2019[1]. The novel coronavirus, the severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2), caused an epidemic described as coronavirus disease 2019 (COVID-19)[2]. The spectrum of COVID-19 ranges from possibly asymptomatic patients to acute respiratory distress syndrome, which leads to severe progressive pneumonia and death[3,4].

There is obvious evidence that geriatric patients have a higher risk of mortality from COVID-19[5]. Elderly individuals are more susceptible to the outcomes of SARS-CoV-2 infection than younger people due to weaker immune systems, comorbidities, and the presence of underlying conditions[6,7]. Therefore, early identification of patients who will require critical care is vital for the geriatric patient population.

It has been understood that the C-reactive protein (CRP) level is associated with inflammation, and its concentration in the blood is not influenced by age, gender, or physical condition[8]. The CRP is a well-known index of serious pulmonary infections, and it has been reported to be positively correlated with severity in COVID-19 disease[9]. Albumin is an important component of serum proteins and is an indicator of systemic inflammation[10]. Low albumin is shown to have the poor nutritional status and liver and kidney dysfunction. It is further accepted as an independent indicator of poor survival in critically ill patients[11]. Low albumin levels in COVID-19 patients were found to be associated with a poor prognosis[12]. In a recent study, the ratio of these two inflammatory markers to each other was reported to be associated with mortality in CRP-to-albumin ratio (CAR) and COVID-19 patients[13].

The aim of this study was to examine the relationship between CAR and mortality at the time of admission in patients with COVID-19 who visited the emergency department (ED).

METHODS

This single-center, retrospective, and observational study was carried out in the ED of a tertiary care teaching hospital between

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February 1, 2021, and April 1, 2021. The institutional review board approved the analysis and issued a waiver of consent (Ethics Committee ruling number: 2021/514/200/28, dated: April 28, 2021). During the two-month period assigned for this study, CRP and albumin tests were requested at the time of admission to the ED, and the patients who were aged 65 years and above and hospitalized were included in this study. The diagnosis of COVID-19 was determined according to the World Health Organization (WHO) guidelines. This study included only patients who had positive results in the reverse transcriptase polymerase chain reaction (RT-PCR) test of nasal and pharyngeal swab samples[14]. Patients with negative RT-PCR test results, patients with deficient CRP and/or albumin values, patients transferred from another hospital, patients who died or were discharged from the ED, and patients aged below 65 years were excluded from this study.

The following data were collected from each patient scanning the hospital-based electronic data recording system: age, gender, PCR test results, comorbidities [chronic obstructive pulmonary disease (COPD), coronary artery disease (CAD), hypertension (HT), diabetes mellitus (DM), congestive heart failure (CHF), atrial fibrillation (AF), chronic neurological disease (CND), and chronic renal failure (CRF)], and laboratory results [complete blood count (CBC), CRP, and albumin levels]. If an eligible patient was admitted more than once during the study period, only the most initial visit was included in the analysis. The most abnormal values were registered in patients who had more than one laboratory test in the ED. CAR (mg/g) values were calculated by dividing the CRP (mg/L) value by the albumin (g/L) value. The study data were registered into an Excel database (Microsoft Inc., Richmond, WA, USA) and analyzed by the first researcher. After data analysis, other researchers performed quality improvement feedback. The primary study outcome was the patient's mortality, and the survival follow-up was assessed 28 days after admission.

Statistical analysis

Statistical analysis was performed using IBM SPSS Statistics version 26.0 and MedCalc Statistical Software version 19.0.6. The Mann-Whitney U test was used for continuous data analysis, and the chi-square test was used for categorical data analysis. The continuous data were reported as median and interquartile range (IQR). The categorical data were presented as frequency and percentage (Tables 1 and 2). A $p<0.05$ was considered statistically significant.

Receiver operating characteristic (ROC) analysis was performed using the DeLong method to evaluate the prognostic performance of CRP and CAR[15]. The area under the curve (AUC) was calculated to evaluate the prognostic performance of the CRP and CAR parameters. The Youden's J index (YJI) analysis was used to calculate the sensitivity, specificity, positive predictive value (PPV), negative predictive value (NPV), and the threshold value at the highest AUC[16].

RESULTS

This study was conducted using data from a total of 404 patients, of which 191 were women and 213 were men. There were 235 patients in the survivor group and 169 patients in the non-survivor group. The median age of the population included in this study was 76 (71-–82) years, with a minimum age of 65 and a maximum age of 102. The median age was 75 (70–81) years for the survivor group and 78 (72–84) years for the non-survivor group.

When the impacts of the chronic diseases on the COVID-19 prognosis were examined, a significant difference was found between the groups for DM, CHF, and CRF, while no significant difference was found between the groups for COPD, HT, CAD, AF, and CND (Table 1). When the impacts of laboratory parameters on the COVID-19 prognosis were analyzed, a significant difference was found between the groups for white blood cells (WBCs), neutrophils, lymphocytes, CRP, albumin, and CAR, while no significant difference was found between the groups for hemoglobin and platelets.

The predictive values of the CRP and the CAR in terms of in-hospital mortality were analyzed by ROC analysis. The sensitivity, specificity, PPV, NPV, AUC, and YJI values of the CRP were calculated as 71.01, 52.34, 51.7, 71.5, 0.635, and 0.23%, respectively ($p<0.001$), in terms of in-hospital mortality (Figure 1 and Table 2). The sensitivity, specificity, PPV, NPV, AUC, and YJI values of the CAR were calculated as 75.74, 47.66, 51.0, 73.2, 0.645, and 0.23%, respectively, in terms of in-hospital mortality.

When the ROC curves of the CRP and the CAR were compared, the difference between AUCs was calculated as 0.0104, and the p-value was 0.056. No statistically significant difference was found in the pairwise comparison of the ROC curves.

DISCUSSION

In this study, geriatric COVID-19 patients who were admitted to the ED were examined in two groups as survivor and non-survivor. It was concluded that the mortality group had significantly higher CAR and CRP values at the time of admission. However, no significant difference was found between CRP and CAR.

Depending on the increase in human life span, changes occur in many physiological systems of geriatric individuals. The immune system may be suppressed due to aging. This can further be defined by the reduction in T cells and T-cell receptors produced in the thymus. These changes increase the risk of infections and cause an increase in mortality rates of elderly individuals[17]. This weak situation that appears with aging has additionally shown its impact on the COVID-19 epidemic period. For instance, Italy had an overall mortality rate of 12.6% due to the epidemic. Furthermore, the mortality rate was found to increase significantly with age: it increased to <1% in patients below 50 years of age, 2.6% in the fifth decade, 9.8% in the sixth decade, 24.2% in the seventh decade, and 29.0% in the eighth decade[5].

The COVID-19 epidemic had a significant impact on geriatric individuals, and advanced age was reported to be an independent risk factor for the disease[18]. Therefore, early risk prediction tools in ED admissions of geriatric patients have been an important research topic in the literature. The inflammatory reaction plays a significant role in the pathophysiology of

Table 1. Demographic and comorbidity data of the study population.

	Category	Survivor (n=235)		Nonsurvivor (n=169)		Total	Significance
		n	%	n	%	n	p-value
Gender	Female	124	64.9	67	35.1	191	0.009
	Male	111	52.1	102	47.9	213	
COPD	No	212	58.2	152	41.8	364	0.928
	Yes	23	57.5	17	42.5	40	
DM	No	152	54.3	128	45.7	280	0.017
	Yes	83	66.9	41	33.1	124	
HT	No	129	54.7	107	45.3	236	0.090
	Yes	106	63.1	62	36.9	168	
CHF	No	216	60.2	143	39.8	359	0.021
	Yes	19	42.2	26	57.8	45	
CAD	No	198	56.9	150	43.1	348	0.196
	Yes	37	66.1	19	33.9	56	
AF	No	229	58	166	42	395	0.740*
	Yes	6	66.7	3	33.3	9	
CRF	No	224	60.2	148	39.8	372	0.004
	Yes	11	34.4	21	65.6	32	
CND	No	230	58.1	166	41.9	396	>0.999*
	Yes	5	62.5	3	37.5	8	
		Survivor		Nonsurvivor		Total	
		Median	IQR	Median	IQR	Median	IQR
Age		75	70–81	78	72–84	76	71–82	0.002

COPD: chronic obstructive pulmonary disease; DM: diabetes mellitus; HT: hypertension; CHF: congestive heart failure; CAD: coronary artery disease; AF: atrial fibrillation; CRF: chronic renal failure; CND: chronic neurological disease. *Fisher's exact test.

Table 2. Predictive performance of C-reactive protein and C-reactive protein-to-albumin ratio in terms of severity in COVID-19 patients.

	Sensitivity (95%CI)	Specificity (95%CI)	PPV (95%CI)	NPV (95%CI)	AUC (95%CI)	YJI (95%CI)	Criterion of YJI	p-value*
CAR	75.74 (68.6–82.0)	47.66 (41.1–54.3)	51.0 (47.3–54.7)	73.2 (67.0–78.6)	0.645 (0.596–0.692)	0.23 (0.14–0.31)	>1.54	<0.001
CRP (mg/L)	71.01 (63.5–77.7)	52.34 (45.7–58.9)	51.7 (47.6–55.8)	71.5 (65.8–76.6)	0.635 (0.586–0.682)	0.23 (0.14–0.32)	>62.3	<0.001

CI: confidence interval; PPV: positive predictive value; NPV: negative predictive value; AUC: area under the curve; YJI: Youden's J index; CAR: C-reactive protein-to-albumin ratio; CRP: C-reactive protein. *In the pairwise comparison of the Receiver operating characteristic curves of C-reactive protein and C-reactive protein-to-albumin ratio, p=0.056.

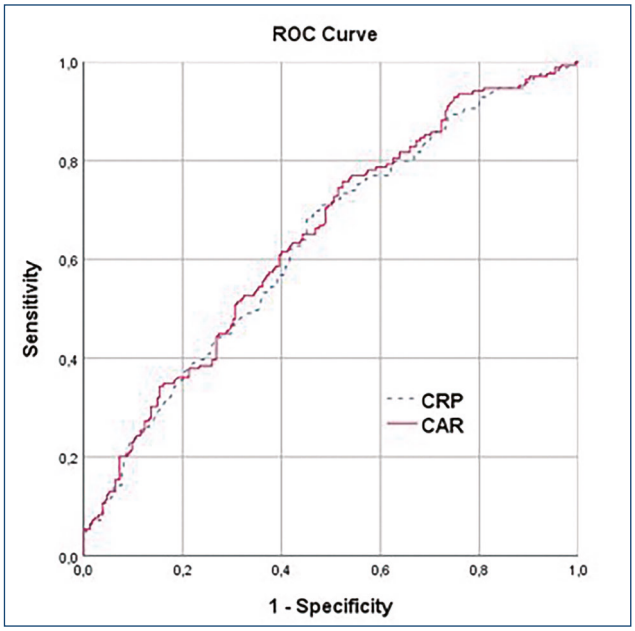

Figure 1. CRP: C-reactive protein; CAR: C-reactive protein-to-albumin ratio. Receiver operating characteristic curves of C-reactive protein and C-reactive protein-to-albumin ratio for mortality prediction in COVID-19 patients.

COVID-19[19]. Therefore, inflammatory markers such as CRP have been studied as prognostic indicators of COVID-19[20]. It has been shown that albumin, which is expected to decrease in inflammatory conditions, also decreases in severe COVID-19 patients[21]. El-Shabrawy et al. examined the importance of biomarkers in predicting the prognosis of COVID-19 in their study. In this study, a total of 116 patients were studied in two groups as severe and nonsevere, and it was concluded that a high CAR value could be used as an independent marker during the prediction of 30-day mortality in COVID-19 patients[13]. In the light of this information, the results of our study were found to be in line with the literature.

In this study, the relationship between patients' comorbidities and their mortality was also examined. A significant correlation was found among DM, CHF, CRF, and mortality. These outcomes are not unexpected. One of the most common comorbidities in geriatric individuals with COVID-19 infection is DM[22]. In a meta-analysis, the prevalence of diabetes in hospitalized patients was 9.7%. In a large-scale worldwide observational study including 169 hospitals and approximately 9000 patients from three continents, CHF was found to be an independent predictor of in-hospital mortality[23]. The mortality rate associated with pneumonia in patients with CRF appears to be 14–16 times higher than that in the general population[24]. In a meta-analysis including 1389 COVID-19 patients, a significant association was found between the CRF and severe COVID-19[25].

As with any retrospective study, this study has some limitations. First, our sample size was small, thus limiting the potential of our analysis. In addition, we conducted the study at a single institution; therefore, the findings may not be representative of the general population of COVID-19 patients aged ≥65 years. Conclusively, the study focused on patient mortality. Accordingly, we cannot predict other related outcomes for the geriatric population, such as patients' persistent oxygen demand or requirement for transfer to a care center.

CONCLUSIONS

Geriatric patients are the patient group with the highest risk of poor outcome for COVID-19. This study demonstrated that the CRP and CAR geriatric patient population had good predictive performance in predicting mortality.

AUTHOR CONTRIBUTIONS

EY: Conceptualization, Data curation, Supervision. FD: Conceptualization, Formal Analysis, Writing – original draft, Writing – review & editing. RA: Conceptualization, Formal Analysis, Writing – original draft, Writing – review & editing.

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ORIGINAL ARTICLE

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Effects of artichoke leaf extract on hepatic ischemia-reperfusion injury

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SUMMARY

OBJECTIVE: The aim of this study was to evaluate the hepatoprotective effect and mechanism of action of artichoke leaf extract in hepatic ischemia/reperfusion injury.

METHODS: Rats were divided into three groups such as sham, control, and artichoke leaf extract groups. Antioxidant enzyme activities and biochemical parameters were examined from the tissue and serum obtained from the subjects. Histopathological findings were scored semiquantitatively.

RESULTS: Statistically, the antioxidant activity was highest in the artichoke leaf extract group, the difference in biochemical parameters and C-reactive protein was significant compared with the control group, and the histopathological positive effects were found to be significantly higher.

CONCLUSIONS: As a result, artichoke leaf extract had a hepatoprotective effect and that this effect was related to the antioxidant and anti-inflammatory effects of artichoke.

KEYWORDS: Liver. Ischemia-reperfusion. Artichoke. Hepatoprotective. Antioxidant.

INTRODUCTION

Liver ischemia/reperfusion (I/R) injury develops due to hypoperfusion that occurs during trauma and surgery of the liver and due to macrophage activation, that occurs after reperfusion. Excessive amounts of reactive oxygen species (ROS) released as a result of the stimulation of macrophages bind to cellular macromolecules (including DNA, proteins, and lipids), causing tissue damage and cell death[1,2].

Despite many experimental studies in the literature, it can be seen that an effective pharmacological strategy against I/R injury has not yet been developed. To create an effective treatment method in this area, there is ongoing research into natural agents rich in flavonoids, anthocyanins, and other phenolic compounds that effectively treat I/R[3]. Many studies have shown that artichoke leaf extract (ALE), rich in phenolic compounds and caffeic acid derivatives, provides a hepatoprotective effect by significantly preventing oxidative damage in hepatocyte membranes. It has been reported in many studies in the literature that ALE exhibits both nephroprotective and hepatoprotective properties in paracetamol and cadmium-induced toxicity[4-7].

Although various studies show the hepatoprotective effect of ALE, there is no study evaluating its efficacy in hepatic I/R injury. Therefore, this study aimed to assess whether or not ALE has a hepatoprotective effect in hepatic I/R injury and the mechanisms of this effect.

METHODS

This study was carried out by following the principles of the National Laboratory Animal Use and Care Directive, with the approval of the Animal Ethics Committee of Selçuk University Experimental Medicine Research Center. A total of 30 adult male Wistar albino rats, each weighing 300±25 g, were included in this study. No rats were given parenteral or enteral antibiotics throughout the experiment. The rats were randomly separated into three groups of 10 rats in each. All the rats were intramuscularly anesthetized with 50-mg/kg ketamine hydrochloride (Ketalar®; Parke-Davis, Istanbul, Turkey) and 10-mg/kg xylazine (Rompun®; Bayer, Istanbul, Turkey). Ischemia was created by clamping the hepatic artery and portal vein for 60 min,

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and then liver tissue and blood samples were taken at the 90th minute of reperfusion.

Group I (sham group): Laparotomy and hepatic pedicle mobilization were performed on the rats, and liver tissue and blood samples were taken at the end of 90 min.

Group II (control group): I/R model was performed without any medication.

Group III (artichoke extract group): The rats in this group were given ALE at a 300-mg/kg dose via orogastric tube 2 h before the operation.

The dose of artichoke extract was planned to be 300 mg/kg, with reference to the information obtained from scanning many articles in the literature. The extract was generally administered as oral gavage in these studies[8,9].

Artichoke leaf extract preparation

The ALE used in this study was prepared at the Faculty of Engineering and Natural Sciences, Department of Chemical Engineering, Ankara Yıldırım Beyazıt University. Artichoke leaves were cut into small slices and dried in an oven at 103°C until a constant weight is obtained. The dried artichoke leaves were ground into powder and placed in a test tube, then 10% (v/v) aqueous acetonitrile solution was added to stabilize the extract. Aqueous methanol solution (70%) was added at 70°C, then the mixture was mixed in an ultrasonic bath and kept at 70°C in a water bath for 10 min. The test tube was brought to room temperature, centrifuged at 3500 rpm for 10 min, and the supernatant was then transferred to another container.

Determination of total phenolic/flavonoid antioxidant amounts

The obtained extract was diluted 100-fold with deionized water. Notably, 1 mL of diluted extract, 5 mL of Folin–Ciocalteu reagent, and 4 mL of sodium carbonate solution were put into a plastic tube and mixing in intermediate steps was done accordingly. Resulting solution was analyzed with UV–vis spectrophotometer, and absorbance values at 765 nm were recorded. Calibration curve was generated using the absorbance values at 765 nm, and calibration equation was found. Absorbance values at 765 nm were used to calculate the total polyphenol content of the sample by the calibration equation. For the total phenolic amount of ALE as gallic acid equivalent (GAE), the total flavonoid amount was calculated using quercetin equivalent (QE) as the standard.

Biochemical evaluations

At the end of the experiment, liver tissue and blood samples were obtained from the rats. Tissues were washed with cold distilled water and physiological serum, and blood was removed and frozen in liquid nitrogen in a sterile manner. The samples were taken to the Research Laboratory of the Biochemistry Department of the Faculty of Science. Serum was obtained by centrifuging the blood at 10,000 rpm for five min at 4°C. Frozen tissues were minced on ice, and homogenization was performed in a Potter-Elvehjem glass Teflon homogenizer placed on ice. The resulting homogenate was centrifuged to remove cellular debris, and the supernatant was separated from the pellet by filtering through a double layer of sterile gauze and centrifuged again. Finally, the supernatant from the obtained fraction was poured off, and 0.5 times the initial tissue weight of cold suspension buffer (2 mM EDTA, pH 7.5; 10% glycerin) was added to the pellet, homogenized by hand, and stored at -80°C until the assay.

The activity measurement of the catalase (CAT), superoxide dismutase (SOD), and glutathione peroxidase (GPx) enzymes was determined using the spectrophotometric method of Aebi[8], Marklund and Marklund[9], and Paglia and Valentine[10], respectively. Aspartate aminotransferase (AST) and alanine aminotransferase (ALT) activities were determined spectrophotometrically using Reitman and Frankel's method[11].Lactate dehydrogenase (LDH) measurement was made with the spectrophotometric method optimized by Wroblewski and LaDue[12]. In addition, total bilirubin (TBIL), direct bilirubin (DBIL), alkaline phosphatase (ALP), C-reactive protein (CRP), creatine kinase (CK), total protein (TPROT), and albumin (ALB) levels were measured using appropriate methods.

Measurement of gene and protein expressions

The determination of ALB, fibrinogen, and prothrombin amounts of microsomal fractions obtained from tissues was made with Lowry et al.'s method using BSA (bovine serum albumin) as a standard[13]. The obtained proteins were evaluated with the western blot method following vertical electrophoresis and sodium dodecyl sulfate polyacrylamide gel electrophoresis (SDS-PAGE).

To determine the effects of the studied plant components on the gene expression levels of the enzymes, RNA isolation from the tissues obtained was performed using the RNA TRIZOL method[14]. In this study, ALB, fibrinogen, and prothrombin RNA were isolated. The complementary DNA (cDNA) synthesis from the obtained RNAs was performed using the iScript™ cDNA Synthesis Kit. Quantitative real-time polymerase chain reaction (qRT-PCR) studies were performed using the CFX-Connect Real-Time PCR system (Bio-Rad, USA). Changes in gene expressions were detected by calculating the ratio of

specific gene messenger RNA (mRNA) expressions to mRNA expression of housekeeping genes ($2^{-\Delta\Delta Ct}$). The primers used were designed using Primer 3 software and their specificity was checked by the National Center for Biotechnology Information.

Histopathological assessments

After the liver tissues were fixed in 10% formalin solution for 24 h, standard dehydration procedures were applied and then the samples were blocked in paraffin. A 4-µm thickness section was cut from the blocks, prepared, and stained with hematoxylin and eosin. These prepared tissue samples were examined under an OLYMPUS BX51TF model light microscope. The histopathological findings of the liver were scored semiquantitatively from 0–4 by evaluating sinusoidal congestion, hepatocyte necrosis, and liver cell vacuolization with the modified Suzuki score[15].

Statistical analysis

Biochemical data were analyzed using the Statistical Package for Social Sciences (SPSS) version 23.0 for Windows software (SPSS Inc., Chicago, IL, USA). All variables were found to be normally distributed with respect to the mean. Therefore, the data were presented as mean±standard deviation (SD) values. A $p<0.05$ was considered statistically significant.

Statistical analysis of the pathological scores was performed using R 3.6.0 software (https://www.r-poject.org). The data were reported as number (n) and percentage (%). A chi-square test was conducted to examine the association between histopathological scores and study groups. Since the proportion of cells with the expected value <5 was more than 20%, p-values were calculated with Monte Carlo simulation. After the χ^2 test, the two-proportion Z test with Bonferroni adjustment was used for multiple comparisons. A $p<0.05$ was considered statistically significant.

RESULTS

Determination of total phenolic/flavonoid antioxidant amounts

For the total phenolic amount of ALE as GAE, the total flavonoid amount was calculated using QE as the standard. The total phenolic and flavonoid amount was found to be 38.03±0.95 µg GAE/mg and 18.11±0.26 µg QE/mg, respectively.

Biochemical analysis results

The results of the biochemical analyses are given in Tables 1 and 2. According to these results, the CRP values in the control group were found to be statistically significantly higher than those in the sham and artichoke groups ($p<0.05$). No significant difference was observed between the sham and artichoke groups in CRP values ($p>0.05$). Similarly, ALT, AST, LDH, ALP, and CK values were significantly higher in the control group than those in the sham and artichoke groups ($p<0.05$). The values of all these parameters were higher in the artichoke group than those in the sham group. A statistically significant difference was observed between the sham and artichoke groups in all the other parameters, except for CK ($p<0.05$). No significant difference was determined between the groups regarding the TPROT, ALB, TBIL, and DBIL values ($p>0.05$).

Antioxidant enzyme activities

In evaluating the results of SOD, CAT, and GPx, which are the parameters used to assess antioxidant enzyme activities, antioxidant activity in the artichoke group was statistically significantly higher than that in the other two groups ($p<0.05$). In contrast, no statistically significant difference was found between the SOD and CAT values of the sham and control groups ($p>0.05$).

When ALB, fibrinogen, and prothrombin protein expressions and ALB, fibrinogen, and prothrombin gene expressions

Table 1. Average values of biochemical parameters.

GROUPS	CRP	ALT	AST	LDH	ALP
GROUP 1 (SHAM)	0.16±0.07[a]	181.22±14.48[a,b]	181.77±48.82[a,b]	1667.77±144.98[a,b]	64.55±10.36[a,b]
GROUP 2 (CONTROL)	0.33±0.13[c]	511.52±28.64[c]	800.80±68.89[c]	4239.12±186.88[c]	280.12±71.45[c]
GROUP 3 (ARTICHOKE)	0.18±0.05	224.10±21.28	567.03±54.68	2379.60±114.34	±28.66

CRP: C-reactive protein; ALT: alanine aminotransferase; AST: aspartate aminotransferase; ALP: alkaline phosphatase. [a]Statistically significant difference between Group 1 *versus* Group 2. [b]Statistically significant difference between Group 1 *versus* Group 3. [c]Statistically significant difference between Group 2 *versus* Group 3.

were evaluated, it was observed that there was no statistically significant difference between the groups (p>0.05).

Histopathological results

The comparisons of the histopathological scores of the study groups are shown in Table 3. A statistically significant association was determined between the sinusoidal congestion and the study groups (p=0.017). The proportion of minimal sinusoidal congestion was higher in the sham (n=6, 60%) and perioperative artichoke extract (n=4, 40%) groups compared with the control group (n=0, 0%). The proportion of severe sinusoidal congestion was higher in the control group (n=6, 60% *versus* n=1, 10% and n=6, 60% *versus* n=1, 10%). A statistically significant association was determined between necrosis and the study groups (p=0.011). Necrosis was absent at a higher rate in the sham (n=10, 100%) and perioperative artichoke extract (n=9, 90%) groups compared with the control group (n=4, 40%), and the proportion of single-cell necrosis was higher in the control group (n=6, 60% vs. n=0, 0% and n=6, 60% *versus* n=1, 10%). No significant difference was determined between the groups regarding the rates of vacuolization (p>0.999). The histopathological images of the groups are given in Figures 1–3.

DISCUSSION

I/R injury, which occurs due to hypoperfusion in the liver, causes irreversible adverse effects in many tissues and organs other than the liver. Many factors such as anaerobic metabolism, oxidative stress and ROS secretion, mitochondrial damage, and cytokines play a role in regulating hepatic I/R processes[16]. Although many studies have been conducted on the application of agents with protective effects to prevent hepatic

Table 2. Average values of biochemical parameters according to groups.

GROUPS	CK	TPROT	ALBUMIN	TBIL	DBIL
GROUP 1 (SHAM)	2095.22±122.68[a]	70.97±8.45	35.65±2.39	0.17±0.04	0.11±0.04
GROUP 2 (CONTROL)	5843.00±186.22[b]	67.58±3.95	34.00±2.52	0.27±0.09	0.16±0.09
GROUP 3 (ARTICHOKE)	2791.10±100.58	66.31±5.71	33.73±2.32	0.18±0.07	0.16±0.06

CK: creatine kinase; DBIL: direct bilirubin; TBIL: total bilirubin; TPROT: total protein. [a]Statistically significant difference between Group 1 *versus* Group 2. [b]Statistically significant difference between Group 2 *versus* Group 3.

Table 3. Comparisons of the histopathological scores of the study groups.

	Group 1 (Sham)	Group 2 (Control)	Group 3 (ArtExt)	p-value
Histopathological scores				
Sinusoidal congestion				0.017
None (n=1)	1 (10)	0 (0)	0 (0)	
Minimal (n=10)	6 (60)[a]	0 (0)[b]	4 (40)[a]	
Mild (n=3)	1 (10)	1 (10)	1 (10)	
Moderate (n=8)	1 (10)	3 (30)	4 (40)	
Severe (n=8)	1 (10)[a]	6 (60)[b]	1 (10)[a]	
Necrosis				0.011
None (n=23)	10 (100)[a]	4 (40)[b]	9 (90)[a]	
Single-cell necrosis (n=7)	0 (0)[a]	6 (60)[b]	1 (10)[a]	
Vacuolization				>0.999
None (n=38)	10 (100)	9 (90)	10 (100)	
Minimal (n=2)	0 (0)	1 (10)	0 (0)	

ArtExt: artichoke extract. Data are shown as number (n) and percentage (%). The p-value was calculated using χ^2 test with Monte Carlo simulation, followed by *post hoc* test with Bonferroni adjustment for proportion test. Different superscript letters in each row indicate a statistically significant difference between groups.

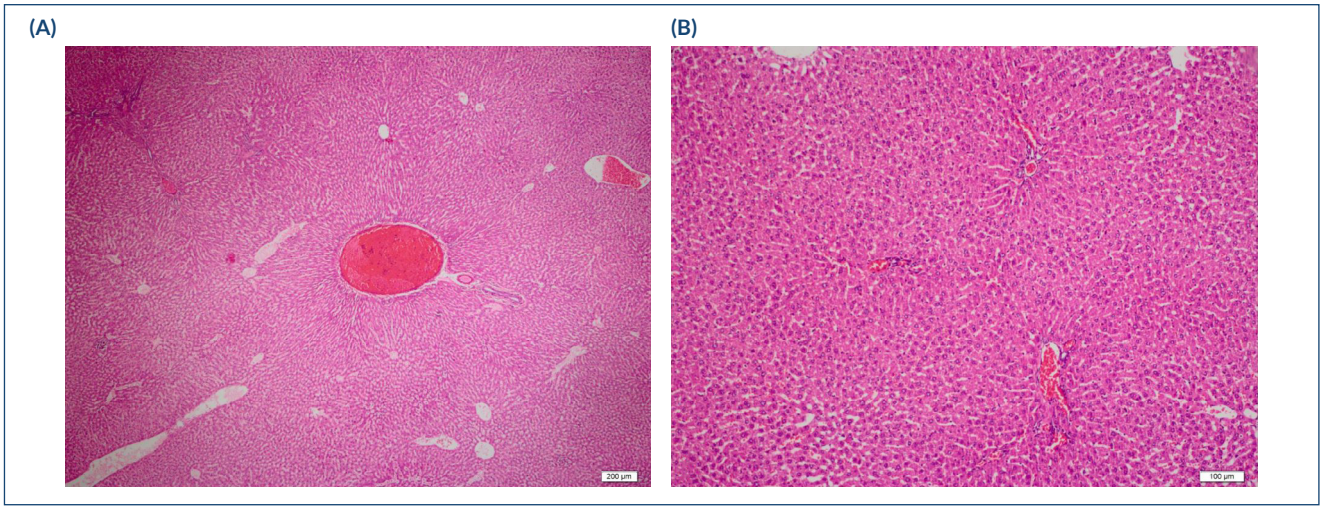

Figure 1. **(A, B)** Portal area and central vein observed in the liver tissue of Sham group. Portal areas and lobules are in a regular structure, with no inflammation or sinusoidal congestion (Hematoxylin and Eosine, 40×, 100×).

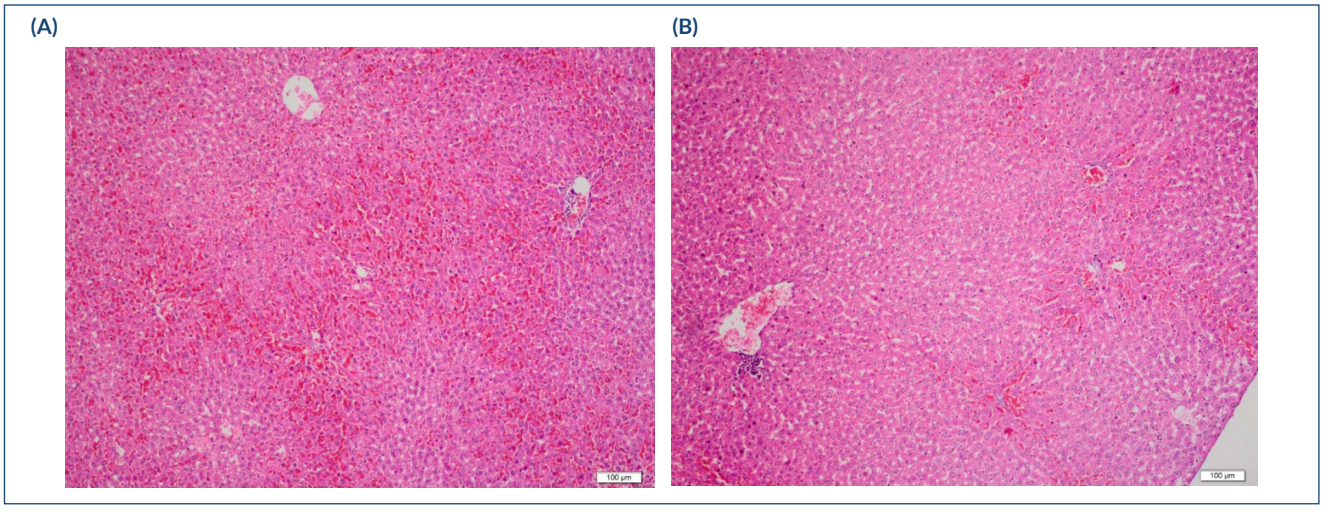

Figure 2. **(A, B)** In the liver tissue of Group 2, mononuclear inflammatory cells and prominent sinusoidal congestion are observed in hepatocytes around the central vein (Hematoxylin and Eosine, 100×).

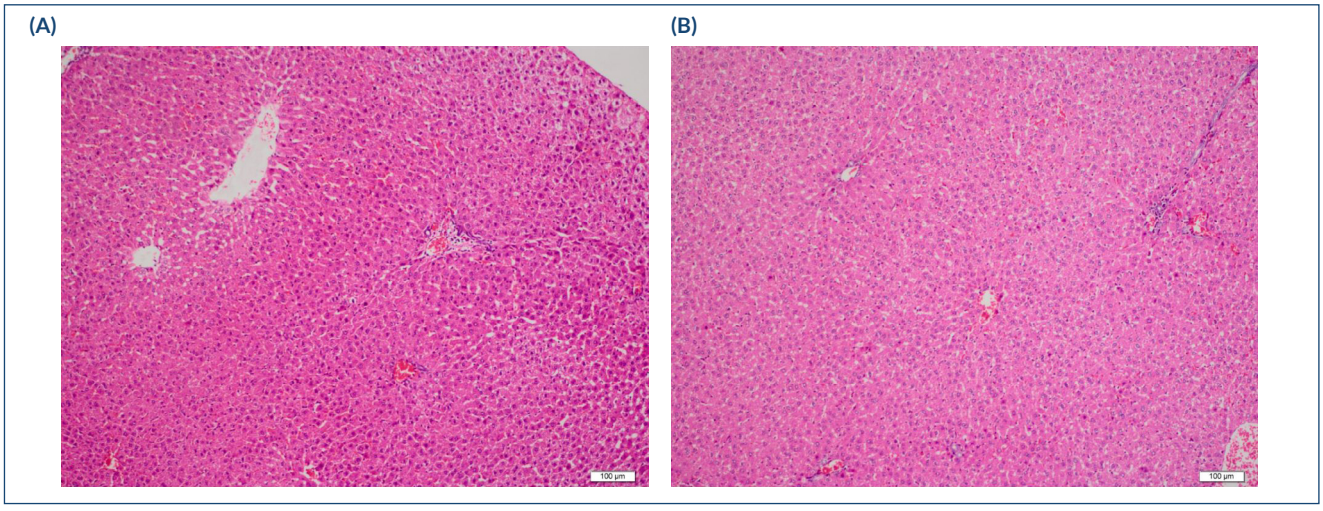

Figure 3. **(A, B)** Group 3 showing sparse mononuclear inflammatory cells and findings of mild sinusoidal congestion (Hematoxylin and Eosine, 100×).

I/R injury in experimental studies, there are no studies evaluating the efficacy of ALE[17-19].

Artichoke is a native plant of the Mediterranean basin, which is known worldwide for its medicinal properties, including hypoglycemic, cholesterol lowering, anti-atherosclerotic, hepatoprotective, prebiotic and probiotic, choleretic (ALE might increase secretion in perfused rat liver and liver cell cultures), antimicrobial, antifungal, immunomodulatory, and anticarcinogenic effects. However, it is accepted that the positive impact of artichoke on health is mainly related to its antioxidant and anti-inflammatory effects[20].

By helping to remove ROS, ALE prevents lipid peroxidation in cell membranes and significantly prevents oxidative damage[20]. In this study, with the use of ALE during I/R injury, a statistically significant improvement was observed in the ALT, AST, LDH, ALP, and CK values in plasma, which had increased as a result of membrane damage, and this was considered the hepatoprotective effect of ALE against I/R injury.

More than 80% of many proteins synthesized by the liver, such as coagulation factors, ALB, thyroid-binding globulin, and complement proteins, pass into the systemic circulation[21]. When the effects of liver I/R injury on blood protein levels and protein and gene expressions were evaluated in this study, there was no statistically significant difference between the sham, control, and artichoke treatment groups ($p>0.05$). Although I/R injury is severe trauma to the liver, no difference between the groups was interpreted as the damage not being of a long-term duration to affect blood protein levels.

Mard et al. showed that Kupffer cell swelling, vasoconstriction, leukocyte infiltration, platelet aggregation, sinusoidal congestion, and central vein enlargement induce injury after hepatic I/R[22]. In this study, sinusoidal congestion and necrosis were statistically significantly higher in the control group in the histopathological examination ($p<0.05$). In the light of these results, ALE can be considered to have histopathologically positive effects on liver I/R injury.

To evaluate the antioxidant activity, the antioxidant enzymes' activity (SOD, CAT, and GPx) was measured. Antioxidant activity was seen to be the highest in the artichoke group, and this difference was statistically significant when compared with the other groups ($p<0.05$).

In the evaluations made to explain the source of the hepatoprotective effect of ALE shown biochemically and histopathologically, the total phenolic and flavonoid amount of ALE was found to be 38.03±0.95 µg GAE/mg and 18.11±0.26 µg QE/mg, respectively. Therefore, on the basis of these results, the antioxidant effect of ALE used in this study was attributed to the phenolics and flavonoids it contained.

A previous study demonstrated that *Cynara scolymus* extract also has anti-inflammatory properties[23]. In this study, CRP, one of the indicators of inflammation, was statistically significantly higher in the control group than that in the sham and artichoke groups.

CONCLUSION

In the light of the results of this study, the prepared artichoke extract can be considered to have a hepatoprotective effect against the I/R injury associated with the antioxidant and anti-inflammatory effects of the artichoke.

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AUTHORS' CONTRIBUTIONS

SC: Conceptualization, Writing – original draft, Writing – review & editing. **KK:** Conceptualization, Data curation, Formal Analysis. **SK:** Project administration, Formal Analysis. **SH:** Project administration, Formal Analysis. **BÇ:** Data curation, Formal Analysis, Writing – review & editing. **IB:** Data curation, Formal Analysis, Writing – original draft. **FS:** Data curation. **PC:** Formal Analysis. **HGB:** Formal Analysis. **MŞ:** Writing – review & editing.

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ORIGINAL ARTICLE

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Hemogram index parameters in the evaluation of male breast cancer and inflammatory response: a case-control study

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SUMMARY

OBJECTIVE: Our aim was to investigate the hemogram index parameters and their clinical significance in the evaluation of the inflammatory response of patients with male breast cancer, who are rarely observed in the literature.

METHODS: In total, 22 (n=22) healthy male and 28 (n=28) male breast cancer patients without synchronous/metachronous tumors were included in this study. They were grouped as the healthy male control group (Group 1) and the male breast cancer patient group (Group 2). The male breast cancer was divided into two subgroups, namely, early stage [(stage: 0/I/II) (Group 2A)] and late stage [(stage: III/IV) (Group 2B)], and their hemogram index parameters were compared.

RESULTS: A significant (p>0.05) increase was observed in neutrophil/lymphocyte ratio (NLR) and·platelet/lymphocyte ratio (PLR) values in the late stage (Group 2B: stage III/IV) compared to the early stage (Group 2A: stage 0/I/II) and healthy control (Group 1) groups.

CONCLUSIONS: In male breast cancer patients, neutrophil/lymphocyte ratio and platelet/lymphocyte ratio values were significantly higher as the stage of cancer increased. These readily available simple tests can be used to evaluate the host's inflammatory response in male breast cancer.

KEYWORDS: Male breast cancer. Neutrophil. Platelet. Lymphocyte. Monocyte.

INTRODUCTION

Male breast cancer (MBC) is a rare disease accounting for approximately 0.5% of all cancer cases in the United States and 0.8% in Turkey[1,2]. Increasing evidence has recently shown that not only the tumor characteristics but also the inflammatory response of the host are effective in the development, progression, and prognosis of neoplastic diseases, including female breast cancers (FBCs)[3]. Although liquid biopsies (such as circulating tumor cells, circulating DNA, circulating miRNA, circulating lncRNA, and exosome) have been developed in the evaluation of treatment response and prognosis in patients with breast cancer, their use is limited due to their high cost[4,5].

In this study, we aimed to investigate the low-cost hemogram index parameters (HIPs) and their clinical importance in the evaluation of the inflammatory response of MBC patients, who are rarely seen in the literature.

METHODS

Ethical approval

Local ethics committee approval (dated: August 13, 2021, decision no.: 2902) was obtained.

Selection of patients

Within the scope of the study, the files of 34 MBC patients with code C50 who stayed in the hospital between March 1, 2006, and March 1, 2020, were reviewed retrospectively.

Notably, 28 (n=28) primary MBC patients without synchronous/metachronous tumors were included in this study. The control group consisted of 22 (n=22) healthy men over the age of 18 years who had normal breast examination and breast ultrasonography results, had normal HIP values, and were matched with MBC patient groups in terms of age and gender.

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A total of six patients with synchronous/metachronous tumors were excluded from this study. Five of the MBC patients who were excluded from this study were in the early stage, and one was metastatic. The patients' estrogen receptor (ER) and progesterone receptor (PR) were positive. Human epidermal growth factor receptor 2 (HER2) was positive in a patient with early-stage MBC. The histopathological examination revealed invasive ductal cancer (IDC) in five patients and invasive papillary cancer in one patient.

Hemogram index parameters and study design

The patients' HIP [absolute leukocyte count, i.e., white blood cells (WBC), absolute neutrophil count (ANC), absolute lymphocyte count (ALC), absolute monocyte count (AMC), absolute platelet count (APC), absolute neutrophil count/absolute lymphocyte count ratio (NLR), absolute neutrophil count/absolute monocyte count ratio (NMR), absolute platelet count/absolute lymphocyte count ratio (PLR), absolute lymphocyte count/absolute monocyte count ratio (LMR), mean platelet volume (MPV), and red blood cell distribution width (RDW)] values, histopathological data, and disease staging were recorded at the time of diagnosis. The groups were divided into two groups, namely, the healthy control group (Group 1) and the MBC group (Group 2). MBC patients were divided into subgroups as Group 2A (stage 0/I/II) and Group 2B (stage III/IV), and their HIP values were compared by the XN 9000® (Sysmex, Kobe, Japan) device[5-7].

Statistical Methods

Mean, standard deviation, median, minimum–maximum value frequency, and percentage were used for descriptive statistics. The distribution of variables was checked with the Kolmogorov–Smirnov test. The independent samples *t* test and Mann-Whitney U test were used for the comparison of quantitative data. The χ^2 test was used for the comparison of qualitative data. The SPSS software version 27.0 was used for statistical analyses.

RESULTS

The most common symptom at admission in the MBC patients included in this study was a mass with 89.3%. Of the patients, 85.8% underwent surgery. Of the patients undergoing surgery, 64.3% underwent mastectomy + axillary lymph node dissection (MRM or modified radical mastectomy), 17.9% underwent mastectomy + sentinel lymph node biopsy (MSLNB), 3.6% underwent palliative mastectomy (PM), and 14.2% underwent diagnostic tru-cut biopsy (Bx). In the histological examination, 64.3% were grade (G) 2, and lymphovascular invasion (LVI) was positive in 53.6%. The most common histological type was IDC. Of the patients, 92.9% had ER+, 78.6% PR+, 71.4% HER2– tumors, and 50% were in stages III and IV at the time of diagnosis (Table 1).

The mean age of Group 1 (control) and Group 2 (MBC) were 61.0±8.3 and 60.6±10.6 years, respectively. The mean age of Group 2A (stage: 0/I/II) and Group 2B (stage: III/IV) were 63.1±11.5 and 60.1±13.9 years, respectively. No significant difference ($p>0.05$) was found between the main groups and subgroups in terms of age and gender distribution of the patients. When comparing the HIPs, no significant difference ($p>0.05$) was observed in the values of WBC, ANC, ALC, AMC, APC, RDW, PDW, and MPV (Tables 2 and 3).

When comparing the healthy control group (Group 1) and the MBC group, no significant difference ($p>0.05$) was observed between the HIP values. NLR and PLR values increased significantly ($p>0.05$) in the late (Group 2B: stage III/IV) disease stage compared to the early stage (Group 2A: stage 0/I/II) and healthy control (Group 1) groups. Although the LMR value was significantly lower ($p<0.05$) in the late-stage (Group 2B: stage III/IV) patients compared to the healthy control group (Group 1), there was a noticeable decrease (Group 2A: 4.29±1.67 *versus* Group 2B: 2.75±1.53), which had no significant relationship ($p>0.05$) with disease staging. There was no significant difference ($p>0.05$) between the healthy control group (Group 1) and the early-stage (Group 2A: 0/I/II) patients group (Table 3).

DISCUSSION

The incidence of MBC represents less than 1% of breast cancers worldwide[1,2,8]. A mass in the breast, observed in 75–81% of patients, is the most common symptom. MBC patients are at later stages (stage III/IV) compared to FBC patients at the time of the diagnosis[9,10]. The incidence of stage III/IV cancer at admission is >60% in Africa, <40% in North America and Western European countries, and between 40% and 60% in Eastern Europe and South America. The reasons for admission at later stages are reported to be race, low socioeconomic status, lack of awareness about the disease, and uncertainties in the characterization of high-risk patients for screening in the literature[8,11-17]. In our study, the most common symptom was a breast mass, and 50% of them were at late stages at the time of diagnosis. Our results were better than the data available in the African literature and worse than those in developed countries.

Table 1. Distribution of clinicopathological data of male breast cancer patients

		n	%
Symptoms	Mass	25	89.3
	Mass and ulcerated	3	10.7
Surgery or diagnosis	MRM	18	64.3
	Mastectomy+SLNB	5	17.9
	Palliative mastectomy	1	3.6
	Biopsy	4	14.2
Histological type	DCIS	1	3.6
	IDC	21	74.0
	Mix type	5	17.8
	Special type	1	3.6
Tumor size category	pTis	1	3.6
	pT1	8	28.6
	pT2	9	32.1
	pT3	0	0.0
	pT4	10	35.7
Nodal category (N)	pN0	10	35.7
	pN1	10	35.7
	pN2	6	21.4
	pN3	2	7.2
Nodal status	Yes	18	64.3
	No	10	35.7
Metastasis (M)	M1	6	21.4
	M0	22	78.6
Stage	Stage 0	1	3.6
	Stage I	5	17.8
	Stage II	8	28.6
	Stage III	8	28.6
	Stage IV	6	21.4
Grade (G)	G1	0	0.0
	G2	18	64.3
	G3	6	21.4
	Missing	4	14.3
ER status	ER<1	1	3.6
	ER≥1	26	92.8
	Missing	1	3.6
PR status	PR<1	5	17.8
	PR≥1	22	78.6
	Missing	1	3.6
HER2 status	Yes	4	14.3
	No	20	71.4
	Missing	4	14.3
Lymphovascular invasion	Yes	15	53.6
	No	4	14.3
	Missing	9	32.1

MRM: modified radical mastectomy; SLNB: sentinel lymph node biopsy; DCIS: ductal carcinoma in situ; IDC: invasive ductal cancer; T: tumor size; N: nodal category; M: metastasis; ER: estrogen receptor; PR: progesterone receptor; HER 2: human epithelial growth factor receptor-2.

There is a need for regional studies to reveal the reasons for the late admission of patients.

In the African literature, 61.5–88.9% and 46.5% of patients in developed countries have axillary lymph node metastases at the time of diagnosis[11,12,14]. Although breast-conserving surgery and SLNB are alternative options in the treatment of early-stage (stage 0/I/II) MBC, MRM is still the standard surgical treatment method in recent days[11,14,18,19]. In locally advanced (stage III) MBC, staged surgical mastectomy can be performed after preoperative systemic chemotherapy (10). Patients with metastatic (stage IV) MBC are younger (≤65 years old), those with T1 tumors or those who have undergone surgical mastectomy have better survival rates than those who have not undergone a surgical intervention[20]. According to the immunohistochemical evaluation of the patients, 83–96% had ER+, 81–96% had PR+, and 10.6–35.1% were HER2 positive, and the most common histological type was IDC, which was observed in 80–90% of the patients[13,15,17]. More than half of these patients had LVI, and the predominant histological grade was G2[8-13,15,17]. In terms of histopathological evaluation and surgical treatment, our results are in accordance with the literature.

In breast cancers, males and females have similar prognostic factors. The main prognostic factors associated with disease-related survival are as follows: G, stage, hormone receptor status, tumor size, and lymph node status[21]. Recent studies on FBC have shown that patient-related inflammatory factors play a role in tumor initiation, formation, development, recurrence, metastasis, and treatment response. High NLR, PLR, and low LMR are reported as prognostic factors associated with survival[3,22,23]. In the study by Sun et al. comparing HIP values of healthy and FBC patients, MPV, RDW, NLR, and PLR values were found higher in FBC patients[6]. In a similar study, Rana et al. observed a decrease in the mean lymphocyte count as the stage of FBC patients increased[7]. In their study conducted on patients with metastatic FBC, Lee et al. reported that overall survival was shorter in patients with low ALC[24]. This is related to the decrease in the number of CD8+ T lymphocytes, which is the basic mechanism of tumor immunity, or the suppression of T-lymphocyte activity by neutrophils, which develop secondary to the increase in interleukin-8 secreted from the tumor. In addition, tumor angiogenesis and stroma formation are supported by the effect of vascular endothelial growth factor secreted from platelets[6,23]. It is reported that these easily accessible parameters may be useful in the management of FBC patients. However, due to the lack of studies on MBC and HIP in the literature, our knowledge is based on the data of WBC patients.

Table 2. Comparison of hemogram index parameters between control group and breast cancers.

	Group 1 (control)			Group 2 (stage 0/I/II/III/IV)			p-value
	Median	Mean±SD/n (%)		Median	Mean±SD/n (%)		
Male		22	100		28	100	1.000[x2]
Age	59.5	61.0±8.3		60.0	60.6±10.6		0.399[m]
WBC (×10⁹/L)	7.50	7.65±1.42		7.08	8.08±2.63		0.953[m]
Neutrophil (×10⁹/L)	4.28	4.45±0.79		4.29	4.89±2.58		0.845[m]
Lymphocyte (×10⁹/L)	2.38	2.37±0.89		2.15	2.07±0.57		0.115[t]
Monocyte (×10⁹/L)	0.57	0.59±0.19		0.60	0.89±1.02		0.551[m]
Platelet (×10⁹/L)	234.0	238.4±64.0		225.5	246.4±86.0		0.718[t]
RDW	13.3	14.0±1.8		13.9	14.1±1.2		0.197[m]
PDW	16.0	21.2±14.4		15.7	19.6±13.1		0.314[m]
MPV (fL)	8.90	9.31±1.81		9.40	9.34±1.33		0.660[t]
NLR	1.95	2.39±2.18		2.19	2.72±2.26		0.423[m]
PLR	101.2	103.7±45.1		108.9	127.5±53.8		0.123[m]
LMR	4.02	4.54±2.35		3.54	3.52±1.76		0.171[t]

SD: Standard deviation; WBC: white blood cells (×109/L); RDW: red blood cell distribution width (%); PDW: platelet distribution width (%); MPV: mean platelet volume (fL); NLR: neutrophil-to-lymphocyte ratio; PLR: platelet-to-lymphocyte ratio; LMR: lymphocyte-to-monocyte ratio.[t]t test; [m]Mann–Whitney U test; [x2]χ^2 (Fisher's exact test).

Table 3. Comparison of hemogram index parameters between control group and subgroup breast cancers.

	Group 1 (control)			Group 2A (stage 0/I/II)			Group 2B (stage III/IV)			p
	Median	Mean±SD/n (%)		Median	Mean±SD/n (%)		Median	Mean±SD/n (%)		
Male		22	100		14	100		14	100	1.000[x2]
Age	59.5	61.0±8.3		67.0	63.1±11.5		63.5	60.1±13.9		0.757[A]
WBC (×10⁹/L)	7.50	7.65±1.42		6.80	7.43±2.10		8.18	8.73±3.01		0.354[K]
Neutrophil (×10⁹/L)	4.28	4.45±0.79		3.73	4.14±2.12		4.75	5.63±2.85		0.298[K]
Lymphocyte (×10⁹/L)	2.38	2.37±0.89		2.25	2.30±0.47		1.96	1.84±0.57		0.890[A]
Monocyte (×10⁹/L)	0.57	0.59±0.19		0.52	0.79±1.01		0.67	0.98±1.06		0.204[K]
Platelet (×10⁹/L)	234.0	238.4±64.0		220.5	240.7±103.3		228.5	252.1±67.9		0.870[A]
RDW (%)	13.3	14.0±1.8		13.8	13.8±0.9		14.0	14.4±1.4		0.157[K]
PDW (%)	16.0	21.2±14.4		14.5	15.8±8.8		16.2	23.4±15.7		0.196[K]
MPV (fL)	8.90	9.31±1.81		9.40	9.66±1.15		9.25	9.02±1.47		0.554[A]
NLR	1.95	2.39±2.18*		1.48	1.84±0.93*		2.78	3.59±2.84		0.034[K]
PLR	101.2	103.7±45.1*		97.5	105.6±38.9*		131.0	149.4±58.9		0.023[K]
LMR	4.02	4.54±2.35*		4.36	4.29±1.67		2.49	2.75±1.53		0.030[A]

SD: Standard deviation; WBC: white blood cells (×109/L); RDW: red blood cell distribution width (%); PDW: platelet distribution width (%); MPV: mean platelet volume (fL); NLR: neutrophil-to-lymphocyte ratio; PLR: platelet-to-lymphocyte ratio; LMR: lymphocyte-to-monocyte ratio. Bold values denote statistical significance at p<0.05. [A]Analysis of variance; [K]Kruskal–Wallis (Mann–Whitney U test); [x2]χ^2 (Fisher's test); *Difference with Group 2B (stage III/IV).

In the literature, the only up-to-date publication on MBC patients and HIP belongs to Huszno et al., who reported that high PLR, NLR, and MLR values are associated with low overall survival in MBC patients[25]. In our study, as the MBC patients' disease stage increased, their NLR and PLR values also increased significantly (p<0.05) while a noticeable but nonsignificant (p>0.05) decrease was observed in LMR mean values (Group 2A: 4.29±1.67 *versus* Group 2B:

2.75±1.53). There was no significant (p>0.05) difference between the healthy control group and the MBC group. This was because it was affected by MBC patients at the early stage (Group 2A: 0/I/II). Our results are in accordance with the existing literature.

The main limitation to our study is that a survival study could not be conducted due to its retrospective design, the rarity of MBC patients, and its limited sample size. However, we believed that our results would provide some perspectives for prospective larger-scale studies.

CONCLUSION

As the disease stage increased in MBC, NLR and PLR values also increased significantly higher. These readily available simple tests can be used to evaluate the host's inflammatory response to MBC.

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AUTHORS' CONTRIBUTION

FD: Conceptualization, Methodology, Writing – original draft, Writing – review & editing. HÖ: Conceptualization, Formal Analysis, Investigation, Writing – review & editing. KU: Conceptualization, Formal Analysis, Investigation, Writing – review & editing. SBH: Methodology, Formal Analysis, Investigation, Writing – review & editing. BO: Formal Analysis, Methodology, Writing – review & editing. ŞÇ: Methodology, Formal Analysis, Investigation, Writing – review & editing. EF: Formal Analysis, Investigation, Writing – review & editing. SS: Methodology, Writing – original draft, Writing – review & editing.

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ORIGINAL ARTICLE

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Oral dydrogesterone in frozen-thawed embryo transfer cycles

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SUMMARY

OBJECTIVE: The aim of this study was to compare the use of micronized vaginal progesterone and oral dydrogesterone in the endometrial preparation for frozen–thawed embryo transfer.

METHODS: This was a randomized, controlled, open, two-armed clinical trial, with women undergoing frozen–thawed embryo transfer along with hormone replacement therapy for endometrial preparation, between September 2019 and February 2021. A total of 73 patients were randomly selected and orally administered 40 mg/day dydrogesterone (dydrogesterone group, n=36) or 800 mg/day micronized vaginal progesterone (micronized vaginal progesterone group, n=37), after endometrial preparation with transdermal estradiol. The main outcome was a viable ongoing pregnancy with 12 weeks of gestation as evaluated by ultrasound.

RESULTS: The reproductive outcomes in frozen–thawed embryo transfer cycles were similar, with pregnancy rates in the dydrogesterone and micronized vaginal progesterone treatment groups being, respectively, 33.3 and 32.4% at 12 weeks pregnancy (confidence interval= -22.4–20.6, p=0.196).

CONCLUSIONS: The use of oral dydrogesterone may be a more patient-friendly approach to endometrial preparation in frozen–thawed embryo transfer cycles, avoiding undesirable side effects and discomfort resulting from vaginal administration, while also providing similar reproductive results.

KEYWORDS: Dydrogesterone. Embryo transfer. Progesterone. Fertilization in vitro. Infertility.

INTRODUCTION

More efficient cryopreservation strategies, such as the development of the vitrification technique and positive results pertaining to their safety, have progressively increased the use of frozen–thawed embryo transfer (FET) over the past decade[1]. Using a protocol with an antagonist and triggering the final follicular maturation with an agonist, followed by a "freeze-all" strategy and embryo transfer in a subsequent cycle, is an effective option for preventing the ovarian hyperstimulation syndrome (OHS) and leads to high rates of live births[2,3]. Other advantages and the applicability of FET are multiple pregnancy risk prevention by the elective transfer of one or a few fresh embryos, thereby allowing for the cryopreservation surpluses and carrying out a preimplantation genetic study[4].

Several different protocols are available for endometrial preparation. Still, there is no consensus on the most effective procedure for preparing the endometrium before FET in normo-ovulatory patients[1]. The methods of endometrial preparation for FET can be divided into natural and medicated (artificial) cycles. During the natural cycle, participants were only monitored, without receiving any pharmacological intervention before ovulation. In contrast, in the medicated cycle, estrogen was administered to achieve endometrial proliferation and suppression of follicular growth, and progesterone is administered to mimic the luteal phase[5].

Progesterone can be administered via oral, vaginal, rectal, subcutaneous, or intramuscular routes. All these forms of administration appear to have similar efficacy[6]. However, the vaginal route is the standard of treatment at most *in vitro* fertilization (IVF) centers. One explanation for this is that the vaginal route does not involve the first hepatic passage and also provides higher and sustained serum concentrations than does the oral route. Nevertheless, all forms of progesterone administration can have side effects, such as discharge and bleeding by the vaginal route; and daily intramuscular administration can lead to pain at the injection site[6].

In view of the side effects and difficulty involved in parenteral and vaginal administration, the oral route would be an option for luteal phase support and to prepare endometrium for the transfer of thawed embryos. Since micronized progesterone does not have good intestinal absorption, dydrogesterone (DYD) appears to be a better option. It is a retro-steroid with good oral bioavailability and high selectivity for progesterone

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receptors. It can be used at lower oral doses to mimic the luteal phase due to its better bioavailability and the progestogenic activity of its metabolites[7]. The use of this medication is considered safe during pregnancy[8].

Data from prospective studies on the support for the luteal phase in IVF with fresh embryo transfer have shown that oral DYD is as effective as micronized vaginal progesterone (MVP), with better patient satisfaction rates[9,10]. Safety results were similar between both groups[11].

However, the vast majority of studies have been carried out with IVF cycles using fresh embryo transfer, whereas those using frozen embryos remain scarce. For this reason, we were interested in comparing MVP and oral DYD in the endometrial preparation for the transfer of frozen–thawed embryos.

METHODS

This was a randomized, controlled, parallel, open clinical trial, with two groups of women undergoing FET along with hormone replacement therapy for endometrial preparation, at the Assisted Reproduction Service at Hospital Pérola Byington, in partnership with the Faculty of Medical Sciences at Santa Casa de São Paulo, conducted between September 2019 and February 2021.

Patients' characteristics such as age, body mass index (BMI), as calculated by the formula weight/height² (kg/m²) and categorized based on the criteria defined by World Health Organization, referral for assisted reproduction techniques, endometrial thickness after 10–12 days of estrogen use, number of embryos transferred, embryonic stage and quality, biochemical pregnancy (positive β-human chorionic gonadotropin hormone [HCG] test), clinical pregnancy (visualization of the fetal heartbeat by ultrasound at six weeks of gestational age), and pregnancy at 12 weeks of gestation were routinely input into the electronic medical records in our database.

The patients were randomly divided into two groups: one group used oral DYD, whereas the other used MVP (Figure 1).

Inclusion criteria

Women undergoing embryo cryopreservation and FET due to the risk of OHS, surplus embryos following failed pregnancy after the fresh transfer, the absence of transfer due to an inappropriate endometrium, or patients who underwent preimplantation genetic diagnosis were included in this study.

Exclusion criteria

Women with an endometrium smaller than 7 mm after endometrial preparation with estrogen, history of recurrent miscarriages (history of ≥3 spontaneous miscarriages), severe male factor, uterine diseases, and the presence of hydrosalpinx and those who had a dominant follicle even after estrogen administration were excluded from the study.

Endometrial preparation protocol

Estradiol administration was initiated transdermally (Oestrogel® Besins Healthcare, Belgium) at a 6 mg/day dose on the second day of the menstrual cycle. After 10–12 days of estrogen therapy, a blood sample was collected, and a transvaginal ultrasound was performed to assess the estradiol, *luteinizing hormone* (LH), progesterone levels, and endometrial thickness. If the thickness of the endometrium was <7 mm, estrogen therapy was extended for another five days, and the dose increased to 8 mg/day. When a 7-mm thick, triple-line endometrium was observed, accompanied by serum progesterone concentrations <1.5 ng/mL, we started administering MVP 800 mg/day (Utrogestan® 200 mg, Besins Healthcare) in one of the groups; in the other group, 40 mg/day (Duphaston®

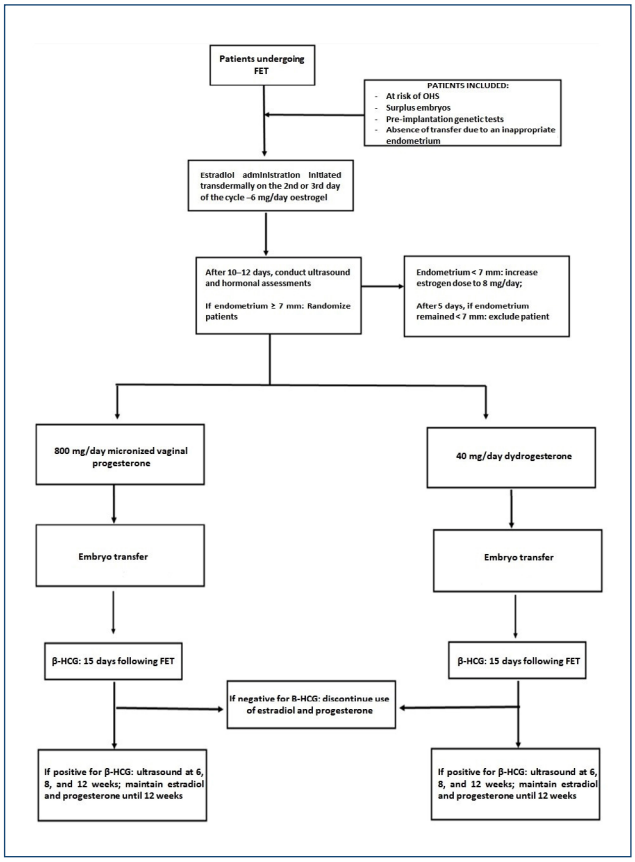

Figure 1. FET: frozen–thawed embryo transfer; OHS: ovarian hyperstimulation syndrome; β-HCG: human chorionic gonadotropin hormone; US: ultrasound. Research protocol flowchart.

10 mg; Abbott BV, Netherlands) DYD was given orally while maintaining estradiol administration. Embryo transfer was performed after progesterone administration on day three for day three embryos and on day five for blastocysts.

Supplementation with estrogen and progestogen was continued at the same dose until the pregnancy test, performed 15 days after embryo transfer. This support was continued up to 10–12 weeks in viable pregnancies. Ultrasonography was performed during the sixth, eighth, and twelfth weeks of amenorrhea.

Embryo transfer

Embryos were obtained from fertilization *in vitro* cycles or intracytoplasmic sperm injection, vitrified, and heated on day three or at the blastocyst stage. All embryo transfers were performed with ultrasound guidance. The number of embryos transferred, their stage, and their quality were recorded. If at least one good-quality embryo was transferred, quality was classified as Q+. The criteria for Q+ quality was the same as those for day three embryos: 6–10 cells with less than 20% fragmentation according to the Holte classification[12]; whereas for blastocysts, expanded to hatched blastocysts with internal cell mass and trophectoderm A or B quality (from 4B upward) according to the Garden classification[13].

Sample size calculation and statistical analysis

For calculating the sample size, the comparison of proportions was considered; the reference values were those from LOTUS I[10]. A difference of 0.281 was adopted, with a significance level of 5%, and a test power of 80%. In this case, we found n=36 per group.

For the bivariate analysis, a proportion comparison was performed using the normal approximation method with a significance level=0.05; 95% confidence intervals (CIs) were constructed for proportion differences.

The computer software used for conducting the statistical analysis was Statistical Package for the Social Sciences (SPSS) version 13.0 for Windows.

RESULTS

Initially, a total of 111 cycles of patients who were to undergo FET with hormone replacement therapy for endometrial preparation was randomized into one of the treatment groups. In general, 65.8% (73/111) reached the end of the study after exclusion criteria were applied, 37 of whom were in the MVP group and 36 in the DYD group.

The patients' characteristics were similar between the two treatment groups and are summarized in Table 1. The patients' age ranged from 23–40 years, with a mean of 33.2 years (±4.4): in the DYD group, it was 34.1 (±4.4) years, and in the MVP group, it was 32.3 (±4.3) years.

Most patients did not have comorbidities. In relation to BMI, 64.4% of them had a BMI lower than 30 kg/m², with an average of 25.8 kg/m² (overweight). Hypothyroidism, with appropriate treatment, was described in 8.1% (n=3) of the individuals in the MVP group versus 11.4% (n=4) in the DYD group.

The number of embryos transferred was also similar between the two treatment groups. There was a greater number of embryos that were transferred in the blastocyst stage as compared to D3. In most cycles (73.6%), at least one good-quality (Q+) embryo was transferred; this was similar in the two groups (77.1% in the VP group and 70.3% in the DYD group).

The reproductive outcomes in FET cycles were similar to the two progesterone supplementation methods (oral DYD vs. vaginal progesterone), as demonstrated by the pregnancy rate at 12 weeks of gestation (Table 2). Pregnancy rates in the DYD and MVP treatment groups were respectively: biochemistry 38.9 and 37.8% (p=0.189, 95%CI -23.4–21.2), clinical 33.3 and 35.1% (p=0.192, 95%CI -20.0–23.6), and 12 weeks pregnancy 33.3 and 32.4% (p=0.196, 95%CI -22.4–20.6). The rate of pregnancy loss in the first trimester was similar in the groups, with two cases having been observed in each group.

DISCUSSION

This study demonstrated that the reproductive outcomes in FET cycles were similar to the two methods of progesterone supplementation (oral DYD versus vaginal progesterone) with regard to the study's primary objective, which is the rate of ongoing pregnancies, and its secondary objectives, which are the biochemical and clinical pregnancy rates. Accordingly, we can provide supporting evidence for the use of oral DYD in FET, similar to the results already established in the literature for fresh embryo transfer.

Several studies have shown oral DYD as an alternative to MVP to support the luteal phase in IVF cycles when using fresh embryo transfer[6,9,11,14-16]. Among these, the randomized, double-blind, multicenter phase III clinical trial (LOTUS I) for luteal phase support has notably demonstrated that oral DYD is as effective as MVP, as determined by pregnancy rates at 12 weeks of gestation[10].

Table 1. Patients' characteristics and treatment results.

	Oral DYD (36)	MVP (37)	Total (n=73)
Mean age, years (SD)	34.1 (4.4)	32.3 (4.3)	33.2 (4.4)
Age, n (%)			
<35 years	17 (43.5)	22 (56.4)	39 (53.4)
≥35 years	19 (55.8)	15 (44.1)	34 (46.6)
Mean BMI, kg/m^2 (SD)	25.2 (5.0)	26.5 (5.7)	25.8 (5.3)
Mean endometrial thickness on the day progesterone was administered (mm)	9.0 (1.7)	9.2 (1.6)	9.1 (1.7)
Embryonic stage, n (%)			
D3	14 (38.9)	16 (43.2)	30 (41.1)
Blastocyst	22 (61.1)	21 (56.8)	43 (58.9)
Number of embryos transferred, n (%)			
1	17 (47.2)	16 (43.2)	33 (45.2)
2	16 (44.4)	19 (51.4)	35 (47.9)
>2	3 (8.3)	2 (5.4)	5 (6.8)
Embryonic quality, n (%)			
Q+	27 (77.1)	26 (70.3)	53 (73.6)
Q−	8 (22.9)	11 (29.7)	19 (26.4)

DYD: dydrogesterone; MVP: micronized vaginal progesterone; SD: standard deviation; BMI: body mass index.

Table 2. Pregnancy rates after treatment in the two study groups.

Pregnancy	% (n/N)		Difference inpregnancy rate (Oral DYD – MVP)	95%CI
	Oral DYD	MVP		
Pregnancy rate				
Biochemical pregnancy, n (%)	38.9 (14/36)	37.8 (14/37)	1.1	-23.4–21.2
Clinical pregnancy, n (%)	33.3 (12/36)	35.1 (13/37)	1.8	-20.0–23.6
Pregnancy at 12 weeks, n (%)	33.3 (12/36)	32.4 (12/37)	0.9	-22.4–20.6

Clinical pregnancy: six weeks of gestational age; DYD: dydrogesterone; MVP: micronized vaginal progesterone; CI: confidence interval. Biochemical pregnancy: positive β-human chorionic gonadotropin hormone test two weeks after embryo transfer.

It is important to highlight the relevance of our results since several randomized clinical trials are showing that the oral DYD is an alternative to MVP to support the luteal phase when using fresh embryo transfer. Nevertheless, there is a lack of studies comparing the efficacy of these two types of progestogens in FET cycles, which would probably be the most effective way to assess the two types of treatment, since the corpus luteum would not secrete progesterone in these cases.

Our findings are also supported by ample evidence from a meta-analysis comparing oral DYD with MVP for supporting the luteal phase in women undergoing IVF with the transfer of fresh and/or frozen-thawed embryos, showing similar reproductive outcomes with the two progestogens[17]. However, this study did not take into account the clinical heterogeneity that may exist due to the main endocrinological differences between both IVF protocols in cycles with either fresh embryo transfer or FET[11,18]. To reduce this bias, in our study, we only evaluated FET cycles and excluded patients who had a dominant follicle after estrogen administration.

Our findings with FET cycles are corroborated by the results described by Rashidi et al.[19], who conducted a randomized, controlled, single-blind study with 180 women undergoing FET. They were recruited and allocated into three groups (i.e., Group A was given 50 mg of intramuscular progesterone twice daily; Group B: 20 mg oral DYD twice daily;

Group C: 400 mg MVP twice daily). Their results showed that oral DYD is as effective as intramuscular and vaginal progesterone. However[19], they did not evaluate either ovulation or luteinization that can occur in 5% of cycles, which is one of the limitations considered by the authors.

We observed similar rates of ongoing pregnancies in the two research groups, and no patient discontinued treatment due to side effects or intolerance to the progestogens used. The 40 mg DYD dose (the highest dose safely used in other studies) was chosen based on data disclosed in the literature and on recommendations from IVF specialists[11,19].

Nonetheless, this study has some limitations. The analysis of the results was originally performed to consider the rate of ongoing pregnancies, but the rate of live births may be of greater clinical interest. The findings of this research are strengthened by the selection of an appropriate sample size comprising 73 randomized individuals, the fact that both treatment arms are well balanced, and the use of broad eligibility criteria. Yet, with a larger sample size, we could have obtained more robust evidence. Therefore, there is a need for further work comparing the effectiveness of these two types of progestogens in FET cycles in a larger group.

CONCLUSIONS

The use of oral DYD may be a more patient-friendly approach to endometrial preparation in FET cycles, avoiding undesirable side effects and discomfort resulting from vaginal administration, while providing similar reproductive results.

AUTHORS' CONTRIBUTIONS

LCGMM: Conceptualization, Data curation, Formal Analysis, Writing – original draft, Writing – review & editing. **MCN:** Conceptualization, Data curation, Formal Analysis, Writing – original draft, Writing – review & editing. **AD:** Conceptualization, Data curation, Formal Analysis, Writing – original draft, Writing – review & editing. **ARR:** Data curation, Formal Analysis. **SMRRL:** Conceptualization, Data curation, Formal Analysis, Writing – original draft, Writing – review & editing.

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REVIEW ARTICLE

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Helminthiasis: a review of articles

Gilson de Abreu Viza Junior[1*]

SUMMARY

Helminthiasis is an infectious disease caused by intestinal parasites that affect people. They cause abdominal pain, nausea and vomiting, heartburn, diarrhea, gastric ulcerative lesions, and colonization by *Helicobacter pylori*. This review of articles was carried out in June 2021. The following databases were used: SciELO (CrossRef), Directory of Open Access Journals (DOAJ), Scopus (Elsevier), Materials Science and Engineering Database, andScieELO Public Health from 1967 to 2012. The descriptor used was "helminthiasis." The electronic search returned 20 articles; 19 were excluded after analyzing the titles and abstracts for not covering the topic addressed. At this stage of the study, one eligible article remained, which was included in the review. This review strengthens the understanding of the potential use of vermifuge for the development of therapies for helminthiasis.

KEYWORDS: Helminthiasis. Ascaris lumbricoides. Trichuris trichiura. Ancylostoma duodenale. Necator americanus.

INTRODUCTION

Helminthiasis is an infectious disease caused by intestinal parasites that affect people and are usually caused by *Ascaris lumbricoides*, *Trichuris trichiura*, and hookworms, such as *Ancylostoma duodenale* and *Necator americanus*[2]. Distributed all over the world, it affects men and animals. These parasites occur in Asia, Europe, Africa, and the Americas. Considered a third world country disease and neglected, by lack of basic sanitation, climate change, international travel, migration flows, resistance to chemotherapy if treated ineffectively tend to evolve to chronicity and incurability[3,4]. They cause abdominal pain, nausea and vomiting, heartburn, diarrhea, and gastric ulcerative lesions, and colonization by *Helicobacter pylori*. Complementary endoscopic examinations are very useful in diagnostic confirmation[3]; however, there are faster and less honorable ways to identify the infection.

According to experts, parasitosis is the most widespread disease in the human and animal population. Human pathogenesis appears to be related to the parasite strain, host immune resistance, and acquired infection form[1].

With the use of chemotherapy for organ and bone marrow transplantation, and, with the onset of acquired immunodeficiency syndrome, the incidence of opportunistic infection by parasites has increased[3].

Neutrophils

Neutrophils are the most abundant white cell circulation population and the main cell type in acute inflammatory reactions. Neutrophils circulate as a spherical cell approximately 12–15 µm in diameter with numerous membranous projections. The core is segmented into three to five connected lobes (Figure 2-1A). Because of their nuclear morphology, neutrophils are also called polymorphonuclear leukocytes (PMNs). The cytoplasm contains two types of membrane-bound granules. Most of these granules, called specific granules, are full of enzymes such as lysosome, collagenase, and elastase. These granules do not contain strong colors with acid or basic dyes (hematoxylin and eosin, respectively), with neutrophils distinct from two other types of leukocyte strain circulation with cytoplasmic granules, called basophils and eosinophils[6].

The greatest function of neutrophils is phagocyte microbes, especially opsonized microbes, and necrotic cell products destroy these phagolysosomes. In addition, neutrophils produce fatty contents and antimicrobial substances that kill extracellular microbes and can also damage healthy tissues[6].

An effective treatment against parasitosis is vermifuge during the acute and chronic phases of the disease.

The medicines used are:

- Albendazole;
- Mebendazole.

MATERIALS AND METHODS

This review of articles was carried out in June 2021. The following databases were used: SciELO (CrossRef), Directory of Open Access Journals (DOAJ), Scopus (Elsevier), Materials

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Science and Engineering Database, and ScieELO Public Health from 1967 to 2012. The descriptor used was: "Helminthiasis".

Table 1 shows the eligibility criteria for the studies, defined in the search process.

The selection of studies was performed by the independent researcher (Viza Jr, G. de A.), including the analysis of titles and abstracts and reading of the full texts. Disagreements were resolved by rereading. The extraction and systematization of the results were performed using Microsoft Excel® and Microsoft Word® software. The results were organized in order to meet the following objective: the review of Helminthiasis articles.

RESULTS AND DISCUSSION

The electronic search returned 20 articles; 19 were excluded after analyzing the titles and abstracts for not covering the topic addressed. At this stage of the study, one eligible article remained, which was included in the review (Figure 1).

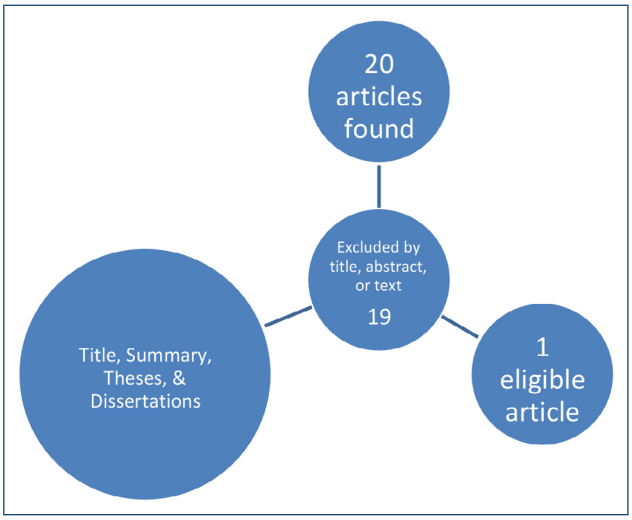

Figure 1. Diagram of the selected articles.

PASSIVE IMMUNIZATION

Passive immunization is achieved by transferring antibodies produced from the animal or human to the child. This type of immunity produces a quick and efficient protection, which, however, is temporary, lasting on average a few weeks or months.

Passive immunization can be defined as the administration of antibodies to a recipient, with the aim of providing immediate protection against a microbial agent, a toxic substance, or a cell[7].

Natural passive immunity is the most common type of passive immunity, characterized by the passage of antibodies from the mother to the fetus through the placenta.

Premature newborns, especially those considered extremely premature, have invariably low maternal immunoglobulin (IgG) levels, reaching the levels of only 100 mg/dL in the first month of life[5].

Passive immunization is generally indicated in cases of:

- Congenital and acquired immunodeficiencies;
- Susceptible individuals exposed to certain diseases;
- When the weather does not allow adequate protection through active immunization alone;
- Certain diseases, whether the administered antibody can suppress the action of a toxin (i.e., botulism, diphtheria, tetanus) or the inflammatory response (Kawasaki disease).

Table 1. Inclusion and exclusion criteria adopted in this review.

Inclusion	Exclusion
Helminthiasis studies Parasitology Worm Articles in Portuguese, English and Spanish from 1967 to 2012	Theses, dissertations, technical reports, exclusive cell studies, reviews, book chapters, editorials, letters to the editor and newspaper articles

With the advancement of scientific techniques and in the field of immunology, several types of products are currently used in passive immunization:

- Standard IgG, available in intramuscular and intravenous form (IVIG);
- Hyperimmune IgG (specific);
- Animal serums and antitoxins;
- Monoclonal antibodies.

Monoclonal Antibodies (mAbs): These are antibodies produced by a single clone of a parental B lymphocyte and are, therefore, identical with respect to their physicochemical and biological properties.

These mAbs can be generated in the laboratory to recognize and bind to an antigen of interest, thus enabling passive immunization.

This procedure was first described, in an article published in the journal Nature by scientists César Milstein and Georges Köhler in 1975. For this feat, both shared the Nobel Prize for Medicine in 1984 with the Dane Niels Kaj Jerne (Figure 2).

Passive immunization is not always effective, and the duration varies from 1 to 6 weeks. Side effects exist in all forms of administration, and precautions must be taken especially when using the products of animal origin.

Source: http://www.gettyimages.com/

Figure 2. César Milstein and Georges Köhler receiving the Nobel Prize.

Active immunization: A protein or a polysaccharide that is not produced by an individual and enters your body via the parental (non-digestive) route, even if they do not harm you, is recognized as antigens that will produce a protein capable of inactivating and/or destroying the invader (antibody).

Lymphocytes, a type of white blood cell, and plasmocytes, a defense present in the connective tissue, produce antibodies that will fight the antigens.

By recognizing the antigen and producing the antibodies, the body builds an immunological memory in the form of "memory cells," which will recognize and coordinate the production of specific antibodies against the specific antigens. The organism keeps the way in its immunological memory the way to prevent a new invasion by the same pathogenic agent.

This mechanism can be classified as active immunization when the body produces its own antibodies. It is a slow but long-lasting process that can sometimes last a lifetime.

Active immunity can be defined as the protection provided by antigenic stimulation of the immune system with the development of a humoral (antibody production) and cellular response. This stimulation can occur by natural infection or by using a vaccine.

"Vaccination is the deliberate exposure, by injection, ingestion, or inhalation of a nontoxic product that stimulates the individual to produce antibodies"[8].

Active natural immunization: Every organism at birth is exposed to several host microorganisms and has to control a microbial invasion in a short period of time. The immune system takes some time to become functional, and the full development of immune capacity depends on antigenic stimulation.

Organisms are susceptible to infections within the first few weeks of life. Antibodies and possibly maternally acquired T cells (passive immunity) are essential in the first week of life.

The diverse range of T-cell receptors (TCR) and the production of cytokines are limited in the neonate, due to little exposure to foreign antigens. As the organism comes into contact with agents that are foreign to its natural microbiota, it starts to develop an immune response that will, in the future, serve as protection against those same agents. This process is called active natural immunization.

LIMITATIONS

This review proposes an analysis of Helminthiasis cases, but a limitation must be considered. Our sampling frame was based on a specific number of databases. Thus, some articles may not be retrieved due to the limitations applied in the search, as well as limitations in the algorithms adopted in the search interface of each database.

These aspects directly affect the sensitivity and specificity of the research strategy, which may have helped to identify important articles. As a strategy to minimize, all articles that are not limited to database or keywords were screened.

FINAL CONSIDERATIONS

This review strengthens the understanding of the potential use of vermifuge for the development of therapies for Helminthiasis.

ACKNOWLEDGMENTS

Thanks to God and my family.

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REVIEW ARTICLE

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Full and empty nest syndromes in women in the climacteric period

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INTRODUCTION

The empty nest syndrome (ENS) was cited as menopausal symptoms related to mood changes and characterized when the last or only child leaves the parental home, as well as in case of death of spouses/partners[1]. Others describe the ENS as a presence of loneliness, aggravated by emotional and psychosocial symptoms, depressive mood, and emotional lability prevalent in the climacteric period[1-3].

The social changes and family configuration bring a new way of experiencing and dealing with the symptoms of menopause[4,5]. The phenomenon known as "Full Nest Syndrome" (FNS) is a recent term in the literature characterized as a change in family coexistence, with the permanence of adult children in their parents' house[4]. It denotes a change in the role of women in the family nucleus regarding socioeconomic attributions, educational, and reproductive autonomy.

Both syndromes can be identified in women's health care in the climacteric period. Factors associated with the presence of ENS and FNS should have a differential investigation and analysis instead of being automatically attributed to menopause, as they have different definitions and approaches in health care. Besides, the authors highlighted the scarcity of studies on the theme and the impact of these two syndromes on mood symptoms during the climacteric period[5-7].

Thus, analyzing the psychosocial factors of FNS and ENS reveals, through the scientific literature, the specificities of each syndrome, which can contribute to a better quality of care and different and effective intervention actions. The purpose of this review was to analyze, through a systematic review, factors related to FNS and ENS in the climacteric period.

METHODS

This is a systematic review based on PRISMA[8] performed by the Climacteric Sector of the Gynecology Division of the Hospital das Clínicas at Medicine School of the São Paulo University (HC/FMUSP), registered in PROSPERO in February 2019 (ID number: CRD42019121218).

Research strategy

This review was based on a systematic research conducted on January 2020 using PubMed, Web of Science, Embase, and PsycINFO databases and followed the PICO (P=Population, I=Intervention, C=comparison, and O=outcome) strategy, in order to obtain the keywords at Medical Subject Headings (MeSH) and Embase subject headings (Emtree) – empty nest, full nest, menopause, climacteric, premenopause, and postmenopause (Appendix 1).

Inclusion criteria

Studies published in English were selected if they met the following criteria:

(1) studies related to women in the climacteric period and
(2) that approach FNS and ENS.

There was no restriction on sample size or publication date.

Exclusion criteria

The articles were excluded if:

(1) they were not data-based (i.e., books, theoretical articles, or minor revisions),
(2) had population not clearly identified in the climacteric period, and

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(3) superficially addressed the FNS and ENS, describing only the prevalence of the syndromes, without characterizing the symptoms.

Search strategy

Three stages were used to select the articles. The first stage was to screen all titles; the second stage was to exclude articles using the abstract; and the third stage was to analyze the entire text, searching for eligible manuscripts. All stages were based on the selection criteria explained above.

To increase the reliability of the analysis and minimize possible biases, all the search and selection phases were independently reviewed by two researchers (ACGA and MSA) who, after reading all articles, entered a consensus to establish which articles met the inclusion criteria. In cases in which there was disagreement over the selection of studies among the investigators, a third reviewer (LTSZ) was consulted.

Assessment of study quality

Two reviewers independently assessed the risk of bias of each included study and discussed their assessments to achieve consensus. Score disagreements were resolved by consensus, and a final agreed-upon rating was assigned to each study.

Since both quantitative and qualitative studies were considered in this study, appropriate tools were used for each one.

For quantitative studies, the Newcastle-Ottawa Scale (NOS) adapted for cross-sectional studies was used to assess the quality of research[9,10]. The NOS has a "star system" in which a study is judged on three dimensions, namely, selection (five stars), comparability (two stars), and outcomes (three stars), indicating the quality of the study. The range of stars in the NOS comprises 0–10 stars.

For qualitative studies, the consolidated criteria for reporting qualitative research (CORE-Q) was used to assess the quality of research[11]. The CORE-Q is a 32-item checklist for interviews and focus groups by three domains, namely, "research and reflexivity team" (8 items), "of the study" (15 items), and "analysis and findings" (9 items). The nonavailability information needed to answer CORE-Q questions was filled in as no information in the article.

RESULTS

The search of the databases resulted in 102 papers. Duplicate articles were excluded using the Microsoft Excel "Duplicates" tool and manually, totalizing 39 articles. After screening for title and abstract, 29 articles were excluded as they were not related to the theme and 7 articles were not available for free. The 26 remaining articles were read in their entirety, and 18 articles did not meet the inclusion criteria; thus, 8 articles were selected to compose this systematic review (Figure 1).

In Table 1, eight eligible articles are presented and classified according to the score obtained in the NOS and COREQ application. The articles that made a qualitative analysis of the data were classified as moderate according to the COREQ evaluation, obtaining a score between 16 and 19 out of a total of 32 points[12-15]. The articles that made a quantitative analysis of the data were classified with 7–9 out of 10 stars[16-19].

Also, in Table 1, the aim of this study, sample, and main results related to ENS and/or FNS are presented. Eight articles were published between 1984 and 2013 and were related to the ENS and women in the climacteric period. Only one article covered both FNS and ENS[17]. The studies were conducted in Mexico, Japan, Malaysia, USA, Uruguay, and Australia, and the number of participants included varied from 40 to 386, totalizing 1525 women in the climacteric period[12-19].

The study design of the articles was cross-sectional, with only one article being a longitudinal study with a follow-up of 8 years[12-16,18,19].

In Table 2, we presented the events and situations that trigger the ENS and/or FNS and changes related to the syndromes. Two articles did not mention any changes related to ENS and/or FNS[18,19].

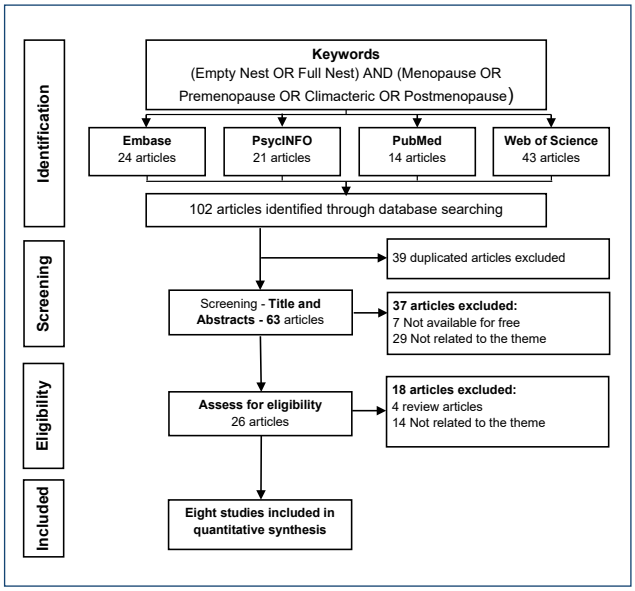

Figure 1. Literature review citation selection flowchart (Adapted from Moher et al.[8]).

Table 1. Summary of the articles selected by systematic review related to Empty and Full Nest Syndrome.

Author, year Local	Aim of study	Population	Main results related to empty/full nest syndrome	Quality
Black et al.[12]; 1984. Maryland, USA.	To study the psychological well-being of graduated women in their middle years.	232 women, ages between 46–61 years, who had graduated from a large mideastern university between 1943–1952. 39% had reached the empty nest stage	Overall, the ENS didn't seem a universal problem to these women, since most of them reported being happy in mid-life (especially those with high schooling level and those who were working). Many women with ENS felt free to explore other activities. However, the syndrome was triggering for those who already had other issues.	COREQ: 17/32 Moderate
Huerta et al.[16]; 1995. Mexico.	To study the association of symptoms with attitudes toward sexuality, life-style, family functioning, and follicle-stimulating hormone (FSH) levels in perimenopausal women.	222 women with mean age of 47.7 years. The majority were overweight (mean BMI of 29.9), from urban origin (76.6%) and had a low schooling level for themselves (3.2 years), partner and parents. As in concern with their occupation, 76.6% were housewives, 11.3% were workers and 5.9% had a commerce. 76.1% were married or part of a free union, 12.2% were widows, 9.5% were unmarried and 2.2% were divorced. The mean number of children was 8; the mean age of the oldest son was 25.8 years and the mean age of the youngest son was 12.1 years.	The ENS was a constant complaint among perimenopausal women.	NOS: 8/10
Defey et al.[13]; 1996. Montevideo, Uruguay.	To define women's perception of themselves and their health care needs in this period of life.	78 women between the ages of 45–60 years.	The ENS was more described by women who had kept a high emotional dependency with their children. Among the positive feelings that emerged after the children's departure, it was observed a greater sense of independency; on the other hand, negative feelings included mostly loneliness.	COREQ: 16/32 Moderate
Dare et al.[14]; 2011. Perth, Australia.	To report how contemporary women experience physiological and psychosocial midlife transitions.	40 Australian women, ages between 45–55. 12 women had dependent children living at home (30%), one had dependent children not living at home (2.5%) and 6 had young adult children still living at home (15%). 17 women were empty nesters (42.5%) and four never had children. With regard with the participants occupation: three were unemployed, three were students, four were self-employed, 15 were professional and 12 were admin/paraprofessional.	Most women in the study didn't described the ENS as an issue. Many of them coped well with their children leaving. They viewed their children's departure as an opportunity to dedicate themselves to other activities, of their own interest, beyond motherhood. The relationship between mother and child in the past may be related to the way the women face ENS. Those who felt positive changes with the ENS reported that they were often repressed by society, as this was not the "correct" reaction to this event. This reinforces the relationship between the ENS and social/cultural factors.	COREQ: 19/32 Moderate

Continue...

Table 1. Continuation.

Author, year Local	Aim of study	Population	Main results related to empty/full nest syndrome	Quality
Dennerstein et al.[17]; 2002. Melbourne, Australia.	To document changes in household composition in this contemporary sample of mid-aged Australian-born women over an 8-year period of follow-up, and to determine effects on women's quality of life of children leaving and returning home.	381 Australian born women aged between 45 and 55 years, followed for eight years. 35% of them had more than 12 years of education, 82% were living with a partner and 35% were in full-time employment. These women were not taking hormone therapy or oral contraceptive pills, and they had experienced menses in the previous three months. During the study, the percentage of households with children decreased from 83–45%.	The children's departure, which created an empty nest environment, didn't affected negatively the quality of these women's lives. There wasn't increase on the depression rates, or other negative symptoms. Also, there wasn't any adverse effects on the frequency of sexual activities or on the relationship with their partners. There was an improvement of happiness and a reduction in the number of daily hassles with the child leaving home. Women who had a more positive vision about this transition phase were the most benefited.	NOS: 9/10
Takamatsu et al.[18]; 2004. Tokyo, Japan.	To extract psychosocial factors from Japanese cases of menopausal disorders in which the patients exhibited the impact of psychiatric elements and required counseling.	97 Japanese women, mean age 61.3±4.5 years, who had received counseling for the treatment of undefined complaints between 1993–1998. Among these patients, 36 consisted of women in a premenopausal status, 61 in postmenopausal status, 36 were undergoing natural menopause, and 25 patients had undergone bilateral ovariectomy. 91 subjects were married, five were unmarried and one was divorced. 32 women had jobs and 62 women had a least one child. 11.3% reported ENS.	The ENS was a relatively rare topic among the studied population; postmenopausal women and patients who had undergone bilateral ovariectomy were the ones who most experienced the syndrome.	NOS: 7/10
García-Campos et al.[19]; 2009. Leon, México.	To study the possible interaction of care of grandchildren with women's symptoms at postmenopause.	386 postmenopausal women, aged 55–75 years. They had previous regular menses and their last menstrual cycle occurred over 12 years before. The mean age was 63 years; the mean age at menopause was 47.7 years; seven of them reported consume of alcohol and 35 smoked daily. They had a mean of five children and 13 grandchildren. Most of them had low schooling and were obese or overweight.	Factors such as having children/grandchildren, active participation in the care of grandchildren and low schooling are positively related with the ENS.	NOS: 7/10
Wong et al.[15]; 2012. Klang Valley, Malaysia.	To address the following issues: **(A)** women's understanding about midlife crisis, experiences, helpseeking, coping strategies, and needs, and **(B)** the correlates of midlife crisis and sociocultural influences.	89 women over 45 years of age, from three main ethnic groups (Malays, Chinese, and Indians). Most participants were married (89.9%), were housewives (61.8%), had secondary school or higher education (64.0%), and had an average monthly household family income less than RM 2,000 (50%). 64 participants were po-stmenopausal, 20 were premenopausal and five were perimenopausal.	The ENS was a theme frequently repeated as something related with midlife crises. Some women reported having a social network as essential to minimize the syndrome's symptoms. Since women with negative thoughts about aging experienced more symptoms, health professionals most encourage strategies that focus on the acceptation of this process, in a positive way.	COREQ: 18/32 Moderate

Table 2. Trigger and changes related to Empty and Full Nest Syndrome.

Author, year	Trigger related to the empty/full nest syndrome	Changes related to:	
		Empty Nest Syndrome (ENS)	Full Nest Syndrome (FNS)
Black et al.[12]; 1984.	More than the fact the child had left home, what triggered the symptoms were the motives who led them to leaving. For example, one woman thought that her daughter had got married too soon.	These women could, now, dedicate more time and energy to themselves. Usually, when the event was traumatic, it was more related with how the children left than with the actual departure. In women with other issues, the ENS works as a trigger to initiate depressive symptoms.	Not mentioned.
Huerta et al.[16]; 1995[a].	Children leaving home.	Familiar communication decreases the chances of developing the ENS. Negative changes included an unwillingness to live and suicide thoughts. Diminished affectivity and diminished communication with a partner are factors that can contribute to the ENS.	Not mentioned.
Defey et al.[13]; 1996.	Women who had perceived their children as appendix of themselves were the ones who had more symptoms of the ENS with the children's departure.	Feeling of abandonment and, in some women, intensification of marital conflicts that had remained unnoticed. On the other hand, positive changes included an urgency for independency, an opportunity to be alone with the partner and a better communication with their own children (since there weren't daily conflicts anymore).	Not mentioned.
Dare et al.[14]; 2011.	The syndrome had greater impact on those women who weren't prepared for their children's departure. Besides, women more emotionally dependent with their children had more negative changes when they left.	Positive changes included greater sense of freedom, and acknowledgment of this period as an exciting and potential one. Furthermore, several women expressed pride about the fact that their children were growing independently. Only two women demonstrated negative changes related with the ENS. However, they also had negative feelings towards other subjects, and this was intensified with the children's departure.	Not mentioned.
Dennerstein et al.[17]; 2002.	Women who were already concerned about their children's departure, even before the beginning of the event, had less positive mood changes and more negative mood changes than those who had not been worried. Furthermore, children's return home might have triggered negative symptoms in those women who had not been concerned with their departure.	In the first year after the children had left home, there was decline in the negative mood scores, increase in the positive mood scores, improvement on the well-being and reduction on daily hassles.	With the children returning home, there was a tendency of decline in the frequency of sexual activities. Besides, women who had experienced a positive change on the mood with the departure of children were more likely to experience the opposite with their return.
Takamatsu et al.[18]; 2004	The ENS was more described by the postmenopausal patients. It was also more related with ovariectomized women in comparison with those undergoing natural menopause.	Not mentioned.	Not mentioned.
García-Campos et al.[19]; 2009.	The empty nest score was lower in women without children or grandchildren. High schooling was also related with lower scores on the ENS. Finally, participation in the care of grandchildren was more associated with the ENS.	Not mentioned.	Not mentioned.
Wong et al.[15]; 2012.	Participants who had negative thoughts toward aging aspects, such as a possible occurrence of the ENS, were more likely to experience the symptoms.	Half of the women described the children's departure as a good change, since now they had more free time to pursue their own interests. The other half felt very depressive, cried daily, felt lonely and extremely sad.	Not mentioned.

DISCUSSION

This systematic review makes it possible to orientate and distinguish factors related to FNS and ENS in the climacteric period.

Among the triggering factors of the ENS, the authors highlighted the dependent relationship between mothers and children and the anticipated concern about their children's departure[13-15,17].

Wong et al. conducted a survey with three ethnic groups (i.e., Malaysian, Indian, and Chinese) and found that half of the women reported feeling sadness, emptiness, depression, and extreme loneliness[15]. The ENS was a theme frequently repeated as something related to midlife crises.

We can observe these same reports in the three other articles related to ENS, in which women whose children left home presented some emotional lability, as well as family conflicts, financial problems, physical changes, and decrease in social life[12,13,16]. These characteristics are associated with the climacteric period, and these factors aggravate the feeling of loneliness and abandonment.

Huerta et al. demonstrated that diminished affectivity and communication with a partner are factors that can contribute to the ENS[16]. Negative changes included an unwillingness to live and suicidal thoughts. Good familiar communication decreased the chances of developing the ENS.

Garcia-Campos analyzed the relationship between taking care of grandchildren and the ENS[19]. They discovered that the higher frequency of meeting with, and helping in the care of, grandchildren correlates with scores of losses of sexual interest and was more associated with ENS.

The study by Polisseni et al. corroborates this finding as the authors pointed out that the family configuration in which there are children leaving home, grandchildren being born, and/or retirement facilitates the appearance of affective deprivation, feeling of uselessness, and fear of aging alone, the factors associated with ENS and their repercussions[6]. They estimated that one-third of women in the climacteric period will have at least one depressive episode and reported that hormonal and social changes corroborate concurrently in this period[20].

The most common mood symptoms in this review in ENS were melancholy and sadness. Mitchell and Lovegreen described the presence of these feelings in the family configuration in which worried parents, with a greater sense of guilt, consider immature and nonautonomous children aggravating or causing the ENS[7]. In contrast, parents who feel that their children are self-sufficient have greater ease and tranquility in experiencing this social change. The authors also affirmed that women in the climacteric period with active social life present a lower appearance of feelings of sadness and melancholy after the children leave home.

Takamatsu et al. analyzed the psychosocial landscape of women in coping with menopausal symptoms, and what psychological issues were triggered[18]. Their difficult situations included problems with their husbands, children leaving home, anxiety, problems at work, difficulties with their mothers-in-law, and ENS in the postmenopausal period. Premenopausal anxiety was related to job reorganization or life difficulties, problems with coworkers, difficult relationship with husbands, and divorce were the issues more frequently present.

Wong et al., Takamatsu, et al., Defey et al., and Garcia-Campos et al. investigated the ENS and found that depressive symptoms and lack of perspective of life improved with therapeutic or social groups[13,15,18,19].

The therapeutic and social groups emphasize the resumption of some activities, which were abandoned due to the birth of the children, as a practice to be encouraged in the follow-up of women in the climacteric period[15,18,21-23]. In addition, Chen et al. reinforced that outdoor activities are the key point to reduce depressive symptoms, and those who are athletes, who participate in groups of conversation, or who have intense social interaction feel less need to be with their children daily and have less feeling of solitude[24].

Dennerstein et al. conducted an 8-year follow-up study with 381 Australian women aged between 45 and 55 years to determine the effects on women's quality of life after children leave and return home[17]. They encountered that the children's departure, which created an empty nest environment, did not affect negatively the quality of these women's lives. Moreover, there was not an increase in the depression rates or other negative symptoms and no adverse effects on the frequency of sexual activities or on the relationship with their partners.

In the studies developed by Defey et al., Dare, and Wong et al., positive changes were also reported with children leaving home[13-15]. They reported that the women experienced an opportunity to be alone with the partner and a better communication with their own children (since there were no daily conflicts anymore); there was also a decline in the negative mood scores, increase in the positive mood scores, improvement on the well-being, and more free time to pursue their own interests.

The study conducted by Dennerstein et al. was the only study that addressed the FNS and found that when children return home, there was a tendency of decline in the frequency of sexual activities[17]. Besides, women who had

experienced a positive change in the mood with the departure of children were more likely to experience the opposite with their return.

The FNS, contextualized by Rambo et al., has factors related to the permanence of the young adult in parents' house, "kangaroo generation", the increase of schooling time, difficult insertion in the labor market, and economic dependence[4]. Silveira and Wagner and Vieira and Rava reported about the children of the "kangaroo generation" and their parents and found that the main factor associated with the emergence of this context in FNS is the lack of professional perspective of the child or the lack of job opportunity and maintenance of financial independence[25,26].

In addition, the children also seek salaries commensurate with their qualifications and specializations, not content with the first job that offers them independence. All these contexts corroborate with the appearance of the FNS.

Unfortunately, in our systematic review, few authors reported details on the socioeconomic level of the children or dependents of their participants or cases. Thus, we emphasized the importance of encouraging studies with quality criteria about the topic FNS.

Weber et al. explained that indulgent parents are responsive but not demanding, i.e., they have respect for their children and at the same time do not stimulate the autonomous development of the child because they are always performing tasks for them[27]. As a result, children grow up with a sense of dependence on their parents and mistakenly believe that they will not be able to develop on their own. It is the role of the parents to stimulate this autonomy at an early age, always demonstrating that they will be around to help in difficult times.

Garcia-Campos, Defey et al., Takamatsu et al., and Wong et al. mentioned triggering factors related to biological, familial, social, and, more rarely, financial aspects[13,15,18,19]. The economic factor is present regarding the appearance of the two syndromes. In FNS, women are in a phase of life that should be directed toward their biopsychosocial changes, as well as rest, and they are faced with their children without financial autonomy. In contrast, in the ENS, the woman shows fragility after the independence of her loved ones.

Factors that trigger changes are present in the lives of these women. This aspect was evidenced in the results presented in several studies, highlighting the positive factors related to women's autonomy, time available to themselves, and family life[12-15,17,19].

The negative symptoms (i.e., sadness, anxiety, and fear) were mainly related to somatic changes, highlighting body changes, issues related to attractiveness, and work performance as main triggers[12-19]. In addition, Garcia-Campos et al. reported that the responsibility to take care of grandchildren, divorce, and lack of social interaction were associated with loss of sexual interest and couple conflicts[19]. All these triggering factors should be considered by health professionals who assist women during the climacteric period and late postmenopausal period since these aspects interfere in several dimensions and aspects in the life and health of women.

A limiting factor for this study was the lack of specific health descriptors for these subjects. In addition, the literature presents a shortage of clinical research focused on the new context of the family nucleus related to FNS.

The use of the CORE-Q checklist and NOS in this study brings the importance of systematizing work processes in qualitative and quantitative research that should follow methodological quality criteria, in order to allow evaluation and analysis to elucidate nonbiophysical and fundamental aspects in clinical practice.

The novelty of this review is that the emergence of FNS and ENS during the climacteric period presents the socioeconomic context as the main trigger, associated with the biological and cultural specificities of each woman.

The emotional conflict present in both syndromes is a factor that points to the financial dependence of the children and the permanence of the children in the parents' home, or even the internal conflict that occurs in the woman, often related to her financial dependence.

We propose a discussion about how both syndromes should have a multi-professional approach. In relation to FNS, the proposal of multi-professional and intersectoral intervention as social support should include the family, stimulating the autonomy and independence of the children.

The negative changes associated with ENS and FNS were depressive mood, depression, lack of time for self-care, and lack of sexual interest and attractiveness. In contrast, the main positive aspects were the feeling of autonomy and familiar coexistence. All these data are noticed during the care of women in the climacteric period and in the postmenopausal period of life, being fundamentally structured within the FNS and ENS.

Therefore, regarding the ENS, the focus of health care intervention should be on the women, stimulating their autonomy and reducing possible psychological dependencies that make them want their children always close by.

CONCLUSIONS

The factors related to the ENS demonstrated in the review were the woman's condition of having children and financial

dependence, whereas the low socioeconomic level stood out in the FNS. The trigger of symptoms related to the ENS and FNS was mainly related to body changes caused by hypoestrogenism and social aspects. The negative changes associated with ENS and FNS were depressed mood, depression, lack of time for self-care, and lack of sexual interest and attractiveness. In contrast, the main positive aspects were the feeling of autonomy and familiar coexistence.

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AUTHORS' CONTRIBUTIONS

ACGA: Conceptualization, Data curation, Investigation, Project administration, Visualization, Writing – review & editing. **MSA:** Conceptualization, Data curation, Investigation, Project administration, Visualization, Writing – review & editing. **LTSZ:** Methodology, Validation, Visualization, Writing – review & editing. **SVS:** Methodology, Validation, Visualization, Writing – review & editing. **PRSN:** Data curation, Formal analysis, Methodology, Supervision, Writing – review & editing. **ECB:** Conceptualization, Project administration, Supervision, and Visualization. **JMSJ:** Formal Analysis, Project administration, Writing – review & editing. **ICES:** Conceptualization, Data curation, Methodology, Project administration, Supervision, Validation, Visualization

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Appendix 1. Research strategy.

Base	Query	Number of articles
Pubmed	("Menopause"[Mesh] OR "Menopause, Premature"[Mesh] OR "Postmenopause"[Mesh] OR "Premenopause"[Mesh] OR "Climacteric"[Mesh]) AND (Empty nest OR Full nest)	14
Embase	('menopause and climacterium'/exp OR 'menopause'/exp OR 'climacterium'/exp OR 'postmenopause'/exp OR 'premenopause'/exp) AND ('empty nest' OR 'full nest')	24
Web of Science	(TÓPICO: (*menopaus*) OR TÓPICO: (climacteri*)) AND (TÓPICO: (Full nest) OR TÓPICO: (Empty nest))	43
PsycInfo	((IndexTermsFilt: ("Menopause")) OR (Any Field: (climacteric)) OR (Any Field: (*menopaus*))) AND ((Any Field: (Full Nest)) OR (Any Field: (Empty nest)))	21

COMMENTARY

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Comment on "Prevalence of arterial hypertension and associated factors: a population-based study"

Zi Wei Chen[1], Chenchen Pan[1*]

Dear Editor,

We are more than glad to read the high-quality article entitled "Prevalence of arterial hypertension and associated factors: a population-based study," published by Layann[1] and his research group[1]. They found that some factors, such as older, brown, sedentary, and overweight, are significantly associated with hypertension. However, as far as I am concerned, there are some questions that should be discussed further in the study.

First of all, the authors have not confirmed the discharge and inclusion criteria, and the source of the sample is still controversial. They should clarify the definition of overweight and obesity, as well as marital status. In addition, we do not know the start time and end time of the study.

As proposed in this study, the percentage of single subjects is lower than that of married or divorced subjects. The reason is failure to explain further in this study. The relationship between single subjects and divorced subjects, and whether hypertension is psychological or physiological need to be explained in detail. The authors also mentioned that hypertension has nothing to do with school. Two problems need to be explored in this case. First, the school will inherit the psychological pressure. Second, whether single or divorced, their psychological problems have the same effect. Therefore, the result is whether hypertension is related to single or divorced has nothing to do with school; this contradicts the result. Whether the study pressure degree of school is a comparative experiment is not described in detail. The definition of overweight or obesity should be offered in this study. The authors found that hypertension is related to education level. There is no specific concept of education level, regarding comprehensive education level or education level of a certain kind of knowledge.

We are still in doubt whether the contradiction between skin color and hypertension-related complex conclusions mentioned in this article is due to the sample being too small or not representative, and therefore the authors should describe further in detail. In this study, the definition of sitting was not clear. In our views, strictly speaking, sitting was sedentary, not exercising, which is just long. Sedentary exercise is exercise after or before a long life.

Finally, the study discusses only adults, but not young children. The reason behind this should also be briefly explained. In addition to age, what makes children less prone to such diseases should be explained in order to guide the role of promoting adult prevention and reduction of such diseases.

AUTHORS' CONTRIBUTIONS

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

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https://doi.org/10.1590/1806-9282.67.02.20200535ERRATUM

In the manuscript "Transcutaneous Electric Nerve Stimulation on ischemic rest pain in inpatients: randomised trial", DOI: 10.1590/1806-9282.67.02.20200535, published in the Rev Assoc Med Bras. 2021;67(2):213-217, on page 213:

Where it reads:

Jorge Machado

It should read:

Carla Jorge Machado

Summary:

Where it reads:

METHODS: In patients ^{3}18 years old, with chronic limb-threatening ischemia and rest pain ^{3}3 in the Visual Analogue Scale, without diabetic neuropathy were randomly assigned to 1) Transcutaneous Electric Nerve Stimulation (100 Hz, 200 μs) or 2) sham intervention, both during one or two 20 min treatment sessions.

It should read:

METHODS: In patients ≥18 years old, with chronic limb-threatening ischemia and rest pain ≥3 in the Visual Analogue Scale, without diabetic neuropathy were randomly assigned to 1) Transcutaneous Electric Nerve Stimulation (100 Hz, 200 μs) or 2) sham intervention, both during one or two 20 min treatment sessions.