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Journal of The Brazilian Medical Association

Is pornography associated with sexual dysfunction?

Ana Larissa Marques Perissini¹ , Luis Cesar Fava Spessoto² , Fernando Nestor Facio Júnior^{2*} 

The consumption of digital pornography for the purpose of sexual excitation is a phenomenon that grows every year in countries with unrestricted access to the Internet due to its easy access and anonymity¹. In a world that has become more digital during the coronavirus disease 2019 (COVID-19) pandemic, contact with different types of virtual sexual contents has enabled individuals in isolation to maintain their sexual practices, popularizing a modality that had already been growing among adults and adolescents in recent years and alerting society about how this new sexual standard is being molded². The ease, diversity, and level of excitation that can be achieved with online pornography indicates that it may operate as a supernatural stimulus, leading the Internet to become the most important means of the dissemination of pornographic content¹.

The consumption of pornography *per se* is not a disease but can become one when sexual excitation achieved through the online material becomes dominant over experiences with real sexuality and it takes on the characteristics of dependence³. There are several unresolved issues regarding the nature and magnitude of these effects, but pornography may fit the structure of addiction, considering the similar mechanisms as those found with chemical compounds, triggering potential effects on health, especially sexual dysfunctions, with strong evidence of a reduction in sexual satisfaction¹. Impulsivity in sexual behavior, classified as compulsive sexual behavior disorder in the *Diagnostic and Statistical Manual of Mental Disorders*, 5th edition (DSM-5) and *International Classification of Diseases*,

11th Revision (ICD-11), is a characteristic often highlighted in the problematic use of pornography⁴, including among individuals with complaints of sexual dysfunction.

A low desire for sex with one's partner has become a common observation in clinical practice, as men seek help due to excessive sexual behavior and use pornography combined with masturbation. Studies offer evidence of an increase in sexual difficulties among young men in recent years⁵. The most common diagnosis is erectile dysfunction of a psychogenic nature, low prevalence of an organic origin, anorgasmia, and premature ejaculation, generally associated with depressive symptoms, increased anxiety, stress, and a lack of motivation⁴.

Emotional symptoms, behavioral problems, misinformation about sex, difficulties in affective relations, and an unhealthy lifestyle are common among a large part of consumers of online pornography and hinder the evaluation of the true cause of sexual dysfunction⁵. As a phenomenon of contemporary society with little research on the effects of the consumption of digital pornography, further studies are needed to elucidate this issue.

AUTHORS' CONTRIBUTION

ALMP: Conceptualization, Formal analysis, Supervision, Validation, Writing – original draft, Writing – review & editing. **LCFS:** Conceptualization, Formal analysis, Validation, Writing – original draft, Writing – review & editing. **FNFJ:** Conceptualization, Formal analysis, Validation, Writing – original draft, Writing – review & editing

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Hepatosplenic shear wave elastography for prediction of esophageal varices in cirrhosis: a promising future?

Ana Cristina Santos de Paula Pessoa^{1*} , Carlos Antonio Bruno da Silva¹ 

The liver is the largest solid organ of the human body, corresponding to 1/34 of total body weight. It has several metabolic functions, including processing, storing, and redistributing biomolecules such as glucose, amino acids, and fatty acids. In addition, the liver acts in immunological processes and the metabolism and elimination of drugs and hormones; it also has valuable regenerative capacity. Due to its importance, acute or chronic hepatic lesions may cause several diseases¹.

Cirrhosis is defined as the final stage of chronic liver disease (CLD). It results from constant and progressive aggression to the liver and is characterized by fibrosis, with the conversion of the normal liver architecture into regenerative nodules and subsequent distortion of the organ lobular and vascular architecture. There are several etiologies, such as steatohepatitis, viral hepatitis, excessive alcohol consumption, obstruction of the circulation through the suprahepatic veins and inferior vena cava, metabolic and autoimmune liver diseases, and structural changes of the bile ducts. As the condition progresses, liver failure (LF) and portal hypertension (PH) might occur²⁻⁴. Of the numerous causes that lead cirrhotic patients to emergency services, variceal upper digestive hemorrhage (VUDH), spontaneous bacterial peritonitis (SBP), hepatic encephalopathy (HE), ascites, pleural effusion, and LF are the most common ones. These complications occur due to PH and/or LF and may be a natural progression of the disease or result from decompensation by a precipitating factor, such as bleeding, infection, alcohol and/or drug abuse, dehydration, or constipation².

Variceal digestive hemorrhage is an important cause of mortality in patients with PH. Studies show that up to 60 and 30% of patients with decompensated and compensated cirrhosis,

respectively, present with esophageal varices (EV) at the time of diagnosis. All patients with cirrhosis should undergo evaluation for EV, i.e., an esophagogastroduodenoscopy (EGD). However, besides being an invasive procedure, EGD is costly since it requires sophisticated equipment, sedation, and trained staff^{5,6}. As such, several noninvasive methods for EV diagnosis have been proposed, including the platelet/spleen ratio. Similarly, elastography has successfully measured liver and spleen stiffness. Initially, the transient technique (FibroScan[®]) was studied before the investigation of acoustic radiation force impulse (ARFI) and shear wave elastography (SWE)⁷.

Some studies on liver and spleen elastography show the satisfactory identification of varices. However, this method evaluates only the mechanical properties of the liver or spleen and does not provide information on the hemodynamics related to the development of varices. Several studies corroborate the correlation between increased liver stiffness and the presence of large varices⁸.

Ultrasound elastography is a noninvasive method for the diagnosis of tissue stiffness which is determined by measuring the propagation speed of ultrasound waves through the organ. The software is coupled with the multidisciplinary ultrasound equipment, and ARFI is applied to the region of interest, usually segments V and VIII, with the transducer positioned between intercostal spaces. As for the spleen, the inferior pole is the region of interest during the examination, with a positioning technique similar to the one used for the liver. Standardization allows more accurate measurement, reducing interobserver variation and increasing reproducibility. The more stiffened the organ due to fibrosis progression, the higher the

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wave propagation speed. The result is determined by the pressure measured in kPa (kilopascal), while the speed is measured in meters per second (m/s)⁹⁻¹¹.

Kim et al.¹² conducted a study in South Korea with 103 patients to evaluate the diagnostic performance of SWE in predicting the presence of EV, including high-risk EV, in patients with compensated cirrhosis, besides comparing it with other nonspecific predictors and the presence of splenomegaly. The authors concluded that hepatic stiffness measured by SWE is an effective noninvasive diagnostic tool to predict the presence of EV and proved to be more accurate than the platelet/spleen ratio, especially in patients without splenomegaly. They also described SWE as the only effective independent factor for predicting high-risk EV.

In Egypt, Hashim et al.⁶ performed SWE in 100 patients with cirrhosis due to hepatitis C through the measurement of the liver (LS) and spleen (SS) stiffness. The same patients underwent upper digestive endoscopy to evaluate for EV. The authors reported a significant difference in LS and SS between patients with and without varices ($p < 0.001$). LS measurement at the 16.2 kPa cutoff and SS measurement at the 42.7 kPa cutoff by elastography predicted the presence of varices with 89.8 and 94.9% sensitivity, respectively, and 57.6 and 87.9% specificity, respectively. Cutoff points of 19.6 for LS and 51.5 kPa for SS predicted a high risk for EV with 77.5 and 85% sensitivity, and 63.4 and 84.6% specificity, respectively. Results showed that elastography was more sensitive and specific in identifying the presence and risk of EV for SS than LS.

In Rome, Gibiino et al.¹³ conducted a systematic review with studies measuring spleen stiffness by elastography to evaluate adults with hepatic and non-hepatic PH. The results were organized using transient elastography and shear wave elastography. Almost 20 studies were included, wherein elastographic techniques were compared with the measurement of the hepatic venous pressure gradient, which is the gold standard for the diagnosis of PH. In general, spleen stiffness measurement showed good diagnostic accuracy for clinically significant PH in CLD, with reliable cutoff values for severe PH in some cases. The authors concluded that spleen elastography can be an accurate noninvasive tool to assess the presence of PH. However, the technical differences available for evaluation and the various cutoff values may still limit its use in clinical practice.

In Egypt, Dwidar et al.¹⁴ studied 120 patients with CLD undergoing SWE and endoscopy and correlated the data of organ stiffness with the presence of varices; the authors found that liver measurement was better than spleen measurement in predicting varices with cutoff values of 10.3 and 18.25 kPa, respectively. However, spleen measurement was superior in grading varices, presenting cutoff values of 19.62 and 14.21 kPa for

grade II varices and 28.75 and 15.6 kPa for grade III varices. They concluded that hepatosplenic elastography can be considered a noninvasive choice for varix screening, leaving digestive endoscopy for patients requiring intervention.

In Bucharest, Fierbinteanu-Braticevici et al.⁷ analyzed 135 patients with cirrhosis using clinical examination, laboratory tests, abdominal ultrasound, LS and SS evaluation, and upper digestive endoscopy. For endoscopy, the patients were classified into three groups: no evidence of EV, small-caliber varices, and varices requiring treatment. Patients with EV of any degree had significantly higher mean SS values than those with no EV (3.37 m/s versus 2.79 m/s, $p < 0.001$), similarly patients with varices requiring treatment had significantly greater mean SS values than those who did not need treatment (3.96 m/s versus 2.93 m/s, $p < 0.001$). Elastographic spleen measurement was proved to be an excellent method for predicting patients with varices requiring treatment.

Patients without splenomegaly are difficult to assess using SWE. Procopet et al.¹⁵ reported failure in up to 40% of those examined. This problem is minimized with adequate training, examiner experience, and innovative technology, even if these come from different manufacturers^{13,15}.

In São Paulo, Ramos⁵ conducted a study evaluating the accuracy of elastography techniques (FibroScan[®] and ARFI) in predicting EV and their risk of bleeding in patients with non-cirrhotic portal hypertension. Splenic elastography by FibroScan[®] with a cutoff point of 65.1 kPa showed an accuracy of 0.62 (95%CI 0.46–0.78; $p = 0.121$) for the presence of varices. In the prediction of varices at a high risk of bleeding, the best cutoff point was 40.05 kPa, which showed an accuracy of 0.63 (95%CI 0.52–0.76; $p = 0.016$). Splenic ARFI elastography with a cutoff point of 2.67 m/s showed an accuracy of 0.64 (95%CI 0.50–0.78; $p = 0.065$) for the presence of varices. For those with a high risk of bleeding with this method, the cutoff point was 3.17 m/s, with an accuracy of 0.61 (95%CI 0.51–0.71; $p = 0.033$). The author concluded that splenic elastography methods showed moderate accuracy and high positive predictive value in diagnosing the presence of varices. When splenic elastography by FibroScan was associated with platelet/spleen ratio, a moderate accuracy with high specificity was evidenced to predict varices with high risk of bleeding. The same author indicated an overlap of values between patients with and without EV, which may limit the application of this method in clinical practice.

This study concluded that hepatosplenic SWE is a safe, low-cost, noninvasive, and easily reproducible method for EV prediction. It may be exceedingly useful in the screening and follow-up of cirrhotic patients, allowing for the avoidance of serial digestive endoscopies. However, this requires further studies to validate an appropriate cutoff point.

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ACSSPP: Conceptualization, Data curation, Formal analysis, Investigation, Methodology, Project administration, Resources, Software, Supervision, Validation, Visualization, Writing – original

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

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Ketofol: is it the best sedoanalgesic for pediatric procedures outside the operating room?

Eduardo Mekitarian Filho^{1*} 

To the Editor,

It was with great interest that I read the article by Hayes JA et al.¹, entitled “Safety and efficacy of the combination of propofol and ketamine for procedural sedation/anesthesia in the pediatric population: a systematic review and meta-analysis” in the present issue of *Anesthesia & Analgesia*.

In fact, the need of pediatric procedures has increased in the past years, due to more availability and knowledge of adverse events from sedatives and other diseases. It would obviously be presumed that the emergency pediatrician had to be trained well to perform safe sedation, since an anesthesiologist cannot be free all the time. After the “death” of chloral hydrate, this situation required major concerns. Propofol, a high extremely effective hypnotic agent, with or without the sedative midazolam, had been used in place of other potential gravity drugs. Ketamine, a unique sedative and analgesic, also has been used safely in fast procedures that require sedation and analgesia. The combination of these two drugs, also referred to as “ketofol,” has gained many advantages in reducing the doses and adverse events of one of them alone. Propofol is a very short-acting agent that provides no analgesia. It can cause adverse events such as hypotension and bradycardia if large doses are administered, and its use is prohibited by the Food and Drug Administration (FDA) for intensive care units (ICU) for more than 24 h, although several articles reported a much longer time with no side effects². Ketamine, an N-methyl-D-aspartate acid (NMDA) receptor antagonist, produces a dissociated state with minimal risk of airway compromise or apnea if administered slowly, and stable or elevated hemodynamic (blood pressure and heart rate) parameters, antagonizing possible effects of propofol, but may cause nausea, vomiting, and *delirium* during the recovery phase, which is very rare.

El Mourad et al.³ studied the effects of ketofol, propofol, and dexmedetomidine (DEX) for transesophageal echocardiography (TEE). The time onset and offset of sedation, duration of TEE

procedure, and the need for rescue propofol were significantly less in the propofol and ketamine groups compared with the group using DEX. Rao et al.⁴ found that, compared with placebo, midazolam, and opioids, DEX significantly decreased the incidence of post-anesthesia emergency agitation or *delirium* in pediatric patients. However, DEX did not exhibit this superiority compared with propofol and ketamine. The significant difference was not exhibited compared with propofol (or pentobarbital) [OR (odds ratio) 0.56, 95%CI (confidence interval) 0.15–2.14, p=0.39], ketamine [OR 0.43, 95%CI 0.19–1.00, p=0.05], clonidine [OR 0.54, 95%CI 0.20–1.45, p=0.22], chloral hydrate [OR 0.98, 95%CI 0.26–3.78, p=0.98], melatonin [OR 1.0, 95%CI 0.13–7.72, p=1.00], and ketofol [OR 0.55, 95%CI 0.16–1.93, p=0.35].

Rayes et al.¹ found that other combination of drugs (e.g., chloral hydrate and fentanyl), compared with ketofol (administered either together or in separate *bolus*), had no statistical difference in providing tachycardia (OR 1.27; 95%CI 0.89–1.8) but was safer in the bradycardia group, with a tendency of protection (OR 0.61, 95%CI 0.38–0.98). Light hypotension without the need for intervention was also more associated with ketofol (OR 0.52; 95%CI 0.37–0.73). Because of these reasons, it is important to administer ketofol for painful and sedative-requiring procedures.

Stevic et al.⁴ studied 203 patients aged one month to 15 years who received sedation for laser therapy, using either combined ketamine and fentanyl or ketofol alone. Tachycardia was recorded in a significantly higher number of patients who received ketamine as the anesthetic agent (35.9 *versus* 3%). Hypertension was also significantly more frequent in patients who received ketamine in comparison with patients who received ketofol (25.2 *versus* 3%). Laryngospasm, a dangerous but rare adverse event for ketamine, was not observed in both the examined groups. There was no statistically significant difference between groups in satisfaction of parents and doctors.

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Apnea and respiratory depression occurred significantly more frequent in ketofol than in ketamine group (12 *versus* 0.97% and 13 *versus* 0%).

Gulec et al.⁵ randomized 60 children for elective circumcision and compared the effects of a mixture of ketamine alone or ketofol. A difference in the initial pulse rate was observed ($p>0.050$). Initial diastolic blood pressure and subsequent serial measurements of 5, 10, 15, and 20 minutes; systolic blood pressure; diastolic blood pressure; and pulse rate in ketamine group were significantly higher ($p<0.050$). A difference of the initial pulse rate was observed ($p>0.050$). Initial diastolic blood pressure and subsequent serial measurements of 5, 10, 15, and 20 minutes; systolic blood pressure; diastolic blood pressure; and pulse rate in ketamine group were significantly

higher ($p<0.050$). They concluded that ketofol provides better sedation quality and hemodynamic than that provided by ketamine alone in pediatric circumcision operations. The authors did not observe significant complications during sedation in these two groups. Therefore, ketofol appears to be an effective and safe sedation method for circumcision operation.

In conclusion, even with a few articles mentioned in this study, ketofol has a short pathway to become the best pediatric procedure sedative outside the operating room, with data from Hayes et al.¹ being confirmed by other good-quality articles. This article is extremely well-written and clear and concludes that using propofol with ketamine is safe, since you have in your hands appropriate resuscitation tools and are prepared to conduct the side effects, albeit rare, when you need to do this.

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

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SUMMARY

OBJECTIVE: To verify the association between metabolic syndrome and its components, and intake of antioxidant nutrients in adolescents.

METHODS: This is a cross-sectional study of the data of 327 adolescents in a high school in Teresina, Piauí, Brazil, pertaining to their socioeconomic background, anthropometric measurements, dietary intake (selenium; copper; zinc; vitamins A, C, and E), hemodynamics, and biochemical tests. The criteria for diagnosing metabolic syndrome in adolescents were applied. Binary logistic regression was used to verify the association between metabolic syndrome and its components, and intake of antioxidants. The level of significance was established at $p < 0.05$.

RESULTS: Prevalence of metabolic syndrome was 7.0%, with a significant association between body mass index and blood pressure. Lower tertiles of copper and vitamins A and E intake were associated with high triglyceride and glycemic levels. The association with vitamins A and E remained after adjustment.

CONCLUSIONS: A significant association between lower vitamins A and E intake and metabolic syndrome components (altered triglycerides and glycemic levels) was found. Besides further studies on this issue, the need for health interventions was found, which ensures the appropriate intake of antioxidant nutrients during adolescence.

KEYWORDS: Adolescents. Metabolic syndrome. Antioxidant nutrients.

INTRODUCTION

Metabolic syndrome (MS) is characterized by a set of cardiometabolic changes that elevate the cardiovascular risk in an individual. MS has become a public health challenge, given that the rapid increase in obesity and sedentary lifestyles of children and adolescents can lead to future problems¹. The prevalence of MS is rising among adolescents, and so it has become essential to identify and examine the risk factors, such as physical

inactivity, smoking, and improper eating habits, which predispose adolescents to MS and thus enable early interventions².

Adolescents are more susceptible to unhealthy eating habits, such as the intake of excessive high calorie food and insufficient vegetables³. Moreover, the intake of poor diet leads to the development of chronic noncommunicable diseases (NCDs) associated with dyslipidemia and high blood pressure levels. Therefore, it is important to monitor the food intake of this

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group, including their intake of antioxidant nutrients that are found in fruits, vegetables, and leafy greens⁴.

The frequent intake of antioxidants provides effective protection against organic oxidative processes, the imbalance of which can lead to several NCDs. Antioxidants such as vitamins A and C, which can be found in fruits and vegetables, can maintain the balance between free radical formation and antioxidant defenses. Conversely, the insufficient intake of these micronutrients can lead to an imbalance in antioxidant defenses, which is common in situations such as MS and overweight⁵.

Given the rising global prevalence of MS in adolescence, the importance of consuming antioxidants and the lack of studies on the relationship between MS and intake of antioxidants in adolescents, this study analyzes the association between MS (and its components) and intake of antioxidants in adolescents. The hypothesis of this study was that lower intake of antioxidant nutrients was associated with MS and its components in adolescents.

METHODS

Study Characteristics and Ethical Aspects

For this cross-sectional study, the data of adolescents aged between 14 and 19 years enrolled in public and private high schools in Teresina, Piauí, Brazil were used. Data were obtained from the base research project *Saúde na escola: diagnóstico situacional do ensino médio* (translation: School-based health: a situational diagnosis of high school) conducted by the Federal University of Piauí (UFPI), and pertained to students in the first semester of 2016.

The project was approved by the UFPI Research Ethics Committee (Decision No. 1.495.975) under Resolutions 196/96 and 466/2012 of the National Health Council. The adolescents and their parents and/or legal guardians signed the informed consent form for minors.

Sampling Procedures

First, a total of 169 high schools in Teresina were selected. Then, the schools were organized by the type of administration (public/private), geographical areas of city, and size (small: up to 115 students, medium: 116–215 students, large: over 215 students). Both schools, a public and a private, were randomly drawn for each size and geographical area, to obtain a total of 24 institutions, corresponding to 12 schools for each type of administration.

The adolescents were selected through a proportionate stratified sampling method based on the following order: school size, grade level, sex, and age. To calculate the minimum sample,

the Epi Info 6.04d software (Centers for Disease Control and Prevention, Atlanta, USA) was used and 40,136 high school students from the 2014 School Census were chosen. A 95% confidence interval (CI), 17.1% prevalence of overweight⁶, 5% precision, 1.4 design effect, and 5% significance level were adopted⁷. Thus, the minimum sample required was 316 adolescents. Considering the possible loss of cases, an additional 10% of students from each school were randomly drawn to obtain a sample of 348 adolescents.

Socioeconomic and Demographic Variables

The following socioeconomic and demographic variables: sex, maternal education (≤ 8 years and > 8 years of schooling), and family income (< 2 and ≥ 2 minimum wages) were observed. These data were obtained through a semistructured questionnaire, which was tested prior to the study.

Food Intake Assessment

Information on the adolescents' food intake from a 24-h food record (R24h) based on the "multiple pass method" were collected. A second R24h to 40% of the population after an interval of 2 months to correct any intrapersonal variability was applied⁸.

Nutwin software, version 1.6.0.7, of the Federal University of São Paulo, Department of Health Informatics, was used to calculate the amount of micronutrients: zinc (Zn); copper (Cu); selenium (Se); and vitamins A, C, and E. These amounts using the Multiple Source Method software, version 1.0.1 (The German Institute of Human Nutrition Potsdam-Rehbrücke, Department of Epidemiology, Nuthetal, Brandenburg, Germany) were adjusted to determine the usual intake.

Blood Collection and Determining Markers of Lipid Metabolism and Glycemia

Of note, 5 mL of venous blood was collected from the adolescents in the morning, after a 12-h fast, and then placed the blood samples in pre-labeled vacuette[®] tubes. high-density lipoprotein cholesterol (HDL-C), triglyceride (TG), and glycemic concentrations were determined using the enzymatic colorimetric method (BioSystems 310 Model, Curitiba, Paraná, Brazil) with Labtest[®] kits.

Anthropometric Assessment

The recommendations of Cameron⁹ and Jelliffe and Jelliffe¹⁰ were followed to collect the anthropometric data. The adolescents were weighed on a portable electronic scale (SECA[®], model 803, Hamburg, Germany) to a precision of 100 g. Their

heights were measured using a stadiometer (SECA®, messband 206 model, Hamburg, Germany) to a precision of 0.1 cm and these measurements were repeated three times and the mean was calculated.

Body mass index (BMI) of the participants was calculated by the ratio of body weight (kg) to height (m) squared. To classify their nutritional status, the BMI-for-age index, expressed as z-scores, was adopted according to the curves provided by the World Health Organization (WHO)¹¹.

The waist circumference (WC) of the participants was measured at the midpoint between the last rib and iliac crest¹² using an inelastic measuring tape (SECA®, 201 model, Hamburg, Germany) to a precision of 0.1 cm and this procedure was repeated three times and the mean was calculated.

Blood Pressure

The procedures of the 7th Brazilian Guideline of Arterial Hypertension¹³ was adopted by applying a calibrated aneroid sphygmomanometer (Durashock Welch Allyn-Tycos®, model DS-44, New York, USA) and the appropriate cuff size. The average of two measurements, the initial measurement and another measurement after 5 min of rest, were taken. If the difference between the systolic blood pressure and diastolic blood pressure was greater than 5 mmHg, the measurements were repeated two times and mean value was calculated.

Diagnosing Metabolic Syndrome

The following cutoff points were employed for the diagnosis of MS: WC ≥90th percentile, blood pressure ≥90th percentile, HDL-C ≤45 mg/dL, TG ≥90 mg/dL, and fasting blood glucose ≥100 mg/dL¹⁴⁻¹⁶. An adolescent had to have three or more of the aforementioned conditions to be diagnosed for MS¹⁴.

Statistical Analysis

The data in Excel® were organized and exported to the SPSS program (for Windows® version 20.0) for statistical analysis. A bivariate analysis to verify the association between the variables using the 2 × 2 chi-squared test with a 95%CI was used. The results are presented in Figures 1 and 2.

To consider the post-stratification weighting factor and verify the odds ratio (OR) between the dependent and explanatory variables, the variance estimation was used, and the nutrients were expressed as tertiles. The third tertile (highest intake of nutrients) was used as reference for our analyses.

The adjusted binary logistic regression for robust variance as well as adjusted and non-adjusted analyses was used. Variables with a p-value below 0.20 in crude analysis were included in the multivariate analysis calculations. To control the potential confounding factors, these variables were adjusted for sex, age, maternal education, family income, physical activity, and alcohol intake. The level of significance was set at p<0.05.

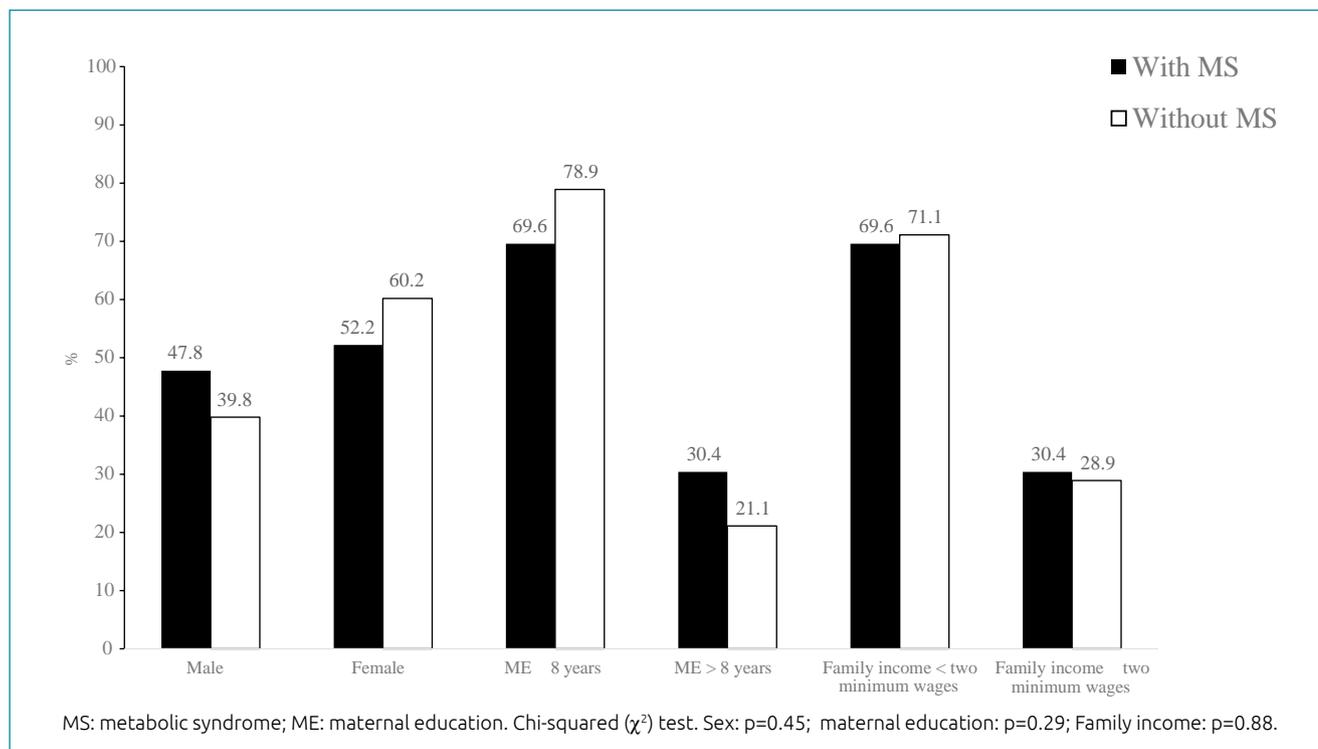


Figure 1. Socioeconomic characteristics according to the presence or absence of metabolic syndrome.

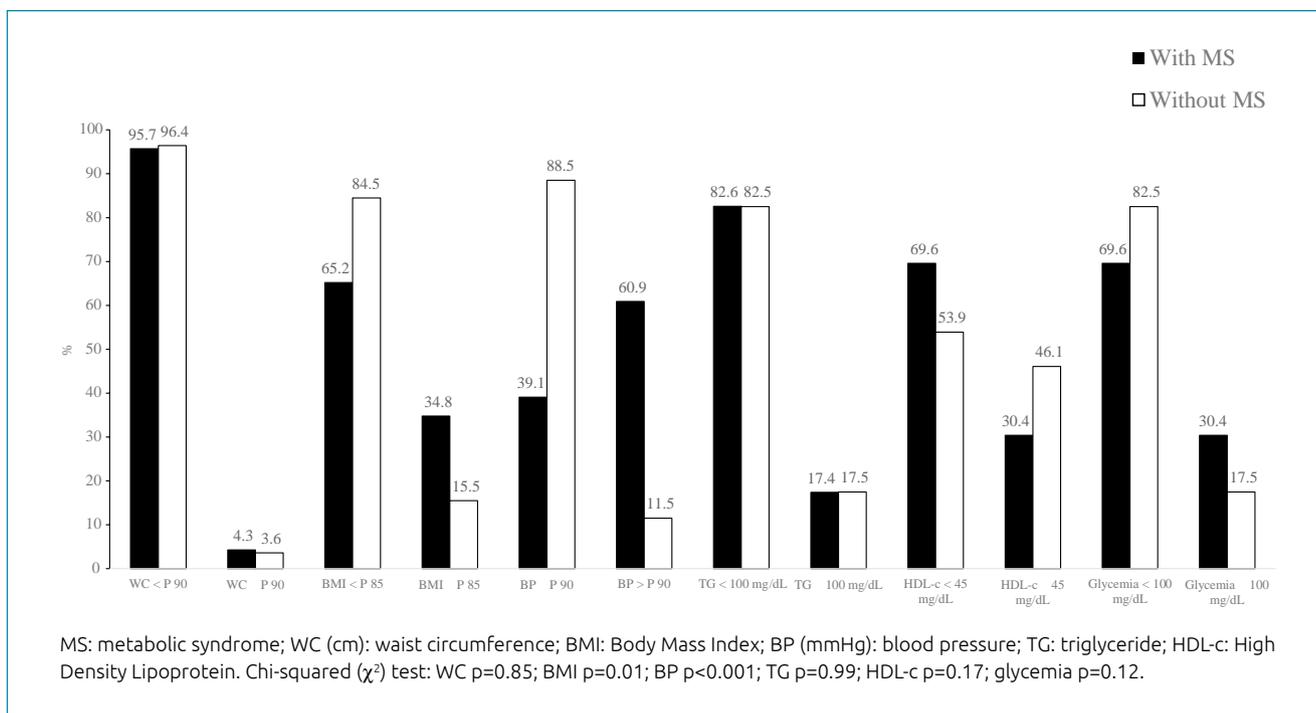


Figure 2. Nutritional, pressoric and biochemical characteristics according to the presence or absence of metabolic syndrome.

RESULTS

The final sample included 327 adolescents; 21 participants did not complete the questionnaire or were excluded due to blood hemolysis.

Figures 1 and 2 show the characteristics of the population by socioeconomic, nutritional, blood pressure, and biochemical variables based on MS. The MS prevalence rate was 7%, indicating a statistically significant association between BMI and blood pressure.

Table 1 shows the association between antioxidant intake stratified by tertiles and MS and its components. The lowest tertile of intake of Cu (OR: 2.06, 95%CI: 1.01–4.23), vitamin A (OR: 2.42, 95%CI: 1.07–5.44), and vitamin E (OR: 2.56, 95%CI: 1.04–6.33) had a significant association with high TG concentration. Moreover, a lower intake of vitamins A (OR: 3.59, 95%CI: 1.59–8.13) and E (OR: 2.45, 95%CI: 1.03–5.84) was associated with altered glycemia.

Table 2 shows the results after adjusting the variables for sex, age, maternal education, income, physical activity, and alcohol intake. Antioxidant vitamins A and E maintained their association with high TG concentrations (OR: 9.23, 95%CI: 2.41–35.39 and OR: 4.89, 95%CI: 1.40–17.04, respectively), indicating risk. A lower intake of these vitamins was also linked with altered glycemia (OR: 3.65, 95%CI: 1.26–10.55 and OR: 4.25, 95%CI: 1.17–15.49, respectively).

DISCUSSION

This study found an association between the components of MS and lower intake of antioxidants, which can influence the overall health of adolescents and increase their risk of developing NCDs. Our main findings indicate that lower tertiles of intake of vitamins A and E increased the adolescents' risk of alteration in TG and glycemic concentrations.

This study also indicated a higher MS prevalence compared with the Study of Cardiovascular Risks in Adolescents (ERICA). However, ERICA used different diagnostic criteria¹⁷. Conversely, a Piauí study of adolescents from private schools showed an MS prevalence of around 3%¹⁸, which is lower than the finding of this study. The MS prevalence detected in our study is comparable with the worldwide prevalence among children and adolescents, which ranges from 1 to 23%¹.

BMI and blood pressure were analyzed as risk markers linked to MS. A previous study using this same sample of adolescents associated overweight and high WC with the risk of altered TG, a component of MS¹⁹. These associations confirm the importance of monitoring the nutrition of adolescents and support early intervention, specifying the adolescence as a potential period for developing many risk factors for NCDs²⁰.

The results before and after adjusting the variables for the intake of antioxidant nutrients revealed an association between lower tertiles of intake of vitamins A and E and high

Table 1. Risk analysis between consumption of antioxidant nutrients and metabolic syndrome components (n=327).

| Variables | HDL-C ≤40 mg/dL | TG ≥110 mg/dL | Glycemia ≥110 mg/dL | BP ≥90th percentile | MS |
|------------------|--------------------------|--------------------------|--------------------------|--------------------------|--------------------------|
| | OR (95%CI) p |
| Zn | | | | | |
| 3rd tertile | 1 | 1 | 1 | 1 | 1 |
| 2nd tertile | 0.93 (0.56–1.53) 0.77 | 2.84 (1.45–5.56) 0.02 | 1.00 (0.52–1.90) 1.00 | 0.80 (0.39–1.65) 0.55 | 1.17 (0.46–2.96) 0.74 |
| 1st tertile | 1.02 (1.58–1.79) 0.94 | 1.56 (0.69–3.50) 0.28 | 1.07 (0.52–2.19) 0.86 | 1.17 (0.55–2.48) 0.68 | 2.17 (0.59–7.94) 0.23 |
| Cu | | | | | |
| 3rd tertile | 1 | 1 | 1 | 1 | 1 |
| 2nd tertile | 0.94 (0.55–1.61) 0.83 | 1.37 (0.64–2.92) 0.41 | 0.78 (0.38–1.61) 0.50 | 1.27 (0.59–2.72) 0.54 | 0.67 (0.25–1.84) 0.44 |
| 1st tertile | 0.80 (0.47–1.36) 0.40 | 2.06 (1.01–4.23) 0.04 | 1.29 (0.66–2.50) 0.45 | 1.37 (0.64–2.91) 0.41 | 1.15 (0.37–3.56) 0.80 |
| Se | | | | | |
| 3rd tertile | 1 | 1 | 1 | 1 | 1 |
| 2nd tertile | 0.72 (0.42–1.24) 0.23 | 0.37 (0.16–0.85) 0.01 | 0.97 (0.47–2.03) 0.94 | 0.93 (0.41–2.12) 0.87 | 0.46 (0.14–1.56) 0.20 |
| 1st tertile | 1.22 (0.63–2.37) 0.56 | 1.22 (0.63–2.37) 0.56 | 1.45 (0.72–2.95) 0.29 | 2.05 (0.97–4.30) 0.05 | 1.23 (0.46–3.23) 0.67 |
| Vitamin A | | | | | |
| 3rd tertile | 1 | 1 | 1 | 1 | 1 |
| 2nd tertile | 1.09 (0.63–1.89) 0.76 | 2.65 (1.19–5.90) 0.01 | 2.34 (1.00–5.45) 0.04 | 0.85 (0.41–1.75) 0.66 | 0.90 (0.33–2.43) 0.83 |
| 1st tertile | 1.15 (0.66–2.00) 0.62 | 2.42 (1.07–5.44) 0.03 | 3.59 (1.59–8.13) 0.01 | 0.53 (0.24–1.19) 0.12 | 1.63 (0.52–5.18) 0.40 |
| Vitamin C | | | | | |
| 3rd tertile | 1 | 1 | 1 | 1 | 1 |
| 2nd tertile | 0.71 (0.40–1.26) 0.24 | 1.17 (0.55–2.45) 0.68 | 0.39 (0.18–0.86) 0.02 | 0.69 (0.32–1.51) 0.36 | 0.75 (0.24–2.31) 0.61 |
| 1st tertile | 0.72 (0.42–1.24) 0.24 | 1.12 (0.54–2.32) 0.75 | 0.63 (0.32–1.25) 0.18 | 0.76 (0.36–1.58) 0.67 | 1.34 (0.48–3.77) 0.57 |
| Vitamin E | | | | | |
| 3rd tertile | 1 | 1 | 1 | 1 | 1 |
| 2nd tertile | 1.12 (0.68–1.85) 0.65 | 1.69 (0.84–3.43) 0.14 | 1.26 (0.63–2.51) 0.51 | 1.01 (0.51–2.00) 0.98 | 1.49 (0.55–4.07) 0.43 |
| 1st tertile | 1.71 (0.79–3.66) 0.16 | 2.56 (1.04–6.33) 0.03 | 2.45 (1.03–5.84) 0.04 | 0.94 (0.34–2.61) 0.91 | 1.28 (0.31–5.41) 0.73 |

MS: metabolic syndrome; HDL-C: high density lipoprotein cholesterol; TG: triglyceride; BP: blood pressure; Zn: zinc; Cu: copper; Se: selenium; OR: odds ratio; 95%CI: 95% confidence interval.

Table 2. Adjusted risk analysis between consumption of antioxidant nutrients and metabolic syndrome components (n=327).

| Variables | HDL-C ≤40 mg/dL | TG ≥110 mg/dL | Glycemia ≥110 mg/dL | BP ≥90th percentile | MS |
|-------------|--------------------------|---------------------------|---------------------------|--------------------------|-----------------|
| | OR (95%CI) p | OR (95%CI) p | OR (95%CI) p | OR (95%CI) p | OR (95%CI) p |
| Zn | | | | | |
| 3rd tertile | 1 | 1 | 1 | 1 | 1 |
| 2nd tertile | – | 2.01 (0.88–4.59) 0.09 | – | – | – |
| 1st tertile | – | – | – | – | – |
| Cu | | | | | |
| 3rd tertile | 1 | 1 | 1 | 1 | 1 |
| 2nd tertile | – | – | – | – | – |
| 1st tertile | – | 1.93 (0.77–4.87) 0.16 | – | – | – |
| Se | | | | | |
| 3rd tertile | 1 | 1 | 1 | 1 | 1 |
| 2nd tertile | – | 0.28 (0.08–0.87) 0.03 | – | – | – |
| 1st tertile | – | – | – | 1.12 (0.37–3.39) 0.84 | – |
| Vitamin A | | | | | |
| 3rd tertile | 1 | 1 | 1 | 1 | 1 |
| 2nd tertile | – | 5.64 (1.62–19.66) 0.00 | 2.45 (0.83–7.18) 0.10 | – | – |
| 1st tertile | – | 9.23 (2.41–35.39) 0.01 | 3.65 (1.26–10.55) 0.01 | 0.48 (0.16–1.42) 0.48 | – |
| Vitamin C | | | | | |
| 3rd tertile | 1 | 1 | 1 | 1 | 1 |
| 2nd tertile | – | – | 1.07 (0.35–3.25) 0.90 | – | – |
| 1st tertile | – | – | 1.85 (0.73–4.73) 0.19 | – | – |
| Vitamin E | | | | | |
| 3rd tertile | 1 | 1 | 1 | 1 | 1 |
| 2nd tertile | – | 1.52 (0.59–3.94) 0.38 | – | – | – |
| 1st tertile | 1.76 (0.60–5.19) 0.30 | 4.89 (1.40–17.04) 0.01 | 4.25 (1.17–15.49) 0.03 | – | – |

MS: metabolic syndrome; HDL-C: high density lipoprotein cholesterol; TG: triglyceride; BP: blood pressure; Zn: zinc; Cu: copper; Se: selenium; OR: odds ratio; 95%CI: 95% confidence interval. Analyses adjusted for sex, age, maternal education, family income, physical activity, and alcohol consumption.

TG and glycemic concentrations, indicating risk. A study of adolescents showed the association between serum vitamin A, which expresses the food intake or metabolic mobilization of the vitamin, and dyslipidemia²¹, thus confirming our findings. Retinoic acid, an active form of vitamin A, stimulates lipolysis and oxidation of fatty acid and reduces TG content, demonstrating its relationship with lipids in the body²².

However, vitamin E can improve the action of insulin because it is involved in gene expression associated with glucose and lipid metabolism and can influence both dyslipidemia and glycemic changes. A preliminary study has shown that a lower incidence of NCDs corresponds to a higher intake of this nutrient²³. In addition, vitamin A at the cellular level improves insulin signaling and induces important gene expression for glucose metabolism²², thus corroborating our findings.

Low serum levels of fat-soluble micronutrients (vitamins A, D, E and carotenoids) have been associated with MS. The optimal levels of these antioxidants in the body can help prevent MS through their antioxidant and anti-inflammatory properties, which are vital to hormone regulation and/or lipid metabolism, besides acting as glucose homeostasis sensors²⁴.

Studies assessing the association between antioxidant vitamins and MS in adolescents are scarce. Park et al.²⁵ found that the intake of total vitamins A and C is inversely associated with MS in Korean women. In this study, no significant association between the intake of antioxidant micronutrients and MS was observed, probably due to the low incidence of MS. However, our findings indicate that the intake of antioxidant micronutrients was associated with isolated components of MS. Further investigations, especially studies with a longitudinal design, need to consider the factors that predispose adolescents to MS and examine how the intake of antioxidants can help promote the health of this population.

This study has some limitations. As this is a cross-sectional study, the findings are limited to the level of association, and the cause and effect interpretations are not possible. Therefore,

the longitudinal studies for a better understanding of this issue are suggested. Other limitations arise from the use of R24h, such as the variance in the intake of nutrients and its over- or under-reporting of ingestion. In this study, these errors were reduced through intrapersonal variability adjustments.

These results are relevant because the sample used is representative of public and private high school students in the municipality of Teresina, Piauí. Furthermore, these results clarify the relationship between the intake of antioxidants and MS during adolescence, and demonstrate the need for effective health intervention strategies such as including the sources of antioxidant nutrients in adolescents' diet.

CONCLUSIONS

This study could find no association between MS and the tertiles of the intake of antioxidant nutrients. However, the association between lower tertiles of the intake of vitamins A and E and altered MS components (TG and glycemia), which indicates risk, was observed. These findings can help shed light on the relationship between the intake of antioxidant nutrients and MS during adolescence and can lead to further health interventions and future studies.

AUTHORS' CONTRIBUTION

CCB: Formal analysis, Investigation, Methodology, Writing – original draft, Writing – review & editing. **LMN:** Conceptualization, Data curation, Formal analysis, Investigation, Methodology, Visualization, Writing – review & editing. **LCRSL:** Formal analysis, Investigation, Methodology, Visualization, Writing – original draft, Writing – review & editing. **BGMR:** Investigation, Visualization, Writing – original draft, Writing – review & editing. **VC:** Supervision, Visualization, Writing – review & editing. **KMGF:** Conceptualization, Formal analysis, Methodology, Supervision, Visualization, Writing – review & editing.

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Fake news: the impact of the internet on population health

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SUMMARY

OBJECTIVE: The aim of this study was to evaluate the search for health information on the Internet and to determine the frequency and main means of spreading fake health news.

METHODS: A descriptive cross-sectional study was conducted through the virtual distribution of questionnaires on social media platforms in 2019 by using the snowball technique. The questionnaire collected information regarding sociodemographics, means used to clarify doubts about health, implementation of information obtained through the Internet, receipt of fake news, and means of transmission of fake news. Quantitative variables are described as means and standard deviations, and categorical variables are described as frequencies and percentages. The chi-square and Fisher's exact tests were used.

RESULTS: Out of 1,195 respondents, 53% had followed Internet guidance without consulting a health professional, especially young people and individuals with low education levels ($p < 0.05$). The resources most used to answer questions about health were a physician (78%) and Google (51%), and searches using the latter were more predominant among younger age groups ($p < 0.05$). A large part of the sample (89.4%) had received fake news, and the main means of receipt were Facebook and WhatsApp.

CONCLUSIONS: The Internet was the second most commonly used means to search for health information. A significant portion of the population adopts actions based on this information. The frequency of broadcasting fake news through this digital medium is high.

KEYWORDS: Internet. Social media. Online access to information. Misinformation.

INTRODUCTION

The Internet has democratized access to health information, increasing the autonomy of patients in their relationship with healthcare professionals. Known by some as the “Dr. Google” phenomenon, the online search for symptoms, diagnoses, and treatments by patients has caused fear due to the various misinformation that accompanies such searches¹.

In this scenario, fake news is a cause for concern. *Fake news* is defined as intentionally false information that is similar to credible news but with the intent to manipulate the recipient

and draw attention to its content^{2,3} by misinforming and/or obtaining advantages over certain populations³.

Fake news usually has a wide reach, especially when propagated over the Internet. People usually give in to the emotional or political appeals coming from negative news². Negative news arouses greater interest than does optimistic news, and therefore, such news stories are shared quickly⁴. To induce greater credibility, these stories usually involve health professionals or institutions⁵.

According to PSafe (2018), a cybersecurity company, in its fifth Digital Security Report, health was the second most frequent target of fake news, accounting for 41.6% of all fake

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news². Currently, there is an epidemic of fake news in Brazil, directly impacting public health, and this epidemic has motivated actions to combat disinformation. The Brazilian Ministry of Health has dedicated an exclusive page to this topic, *Saúde sem Fake News* (saude.gov.br/fakenews), which encourages people to send images or texts they have received via WhatsApp so that the information can be checked. Subsequently, the news is classified as true or false and posted on the page.

Given this scenario, the aim of this study was to evaluate the search for health information on the Internet by the population and to determine the frequency of receiving fake health news and main means by which fake news is propagated.

METHODS

This was a descriptive cross-sectional observational study. This study was approved by the Research Ethics Committee of the Universidade Positivo in 2019 (Opinion 3,496,815).

The data collection was performed in 2019 through the virtual distribution of questionnaires (Google Forms) on social media platforms. Brazilians who were older than 18 years and who agreed to participate in the study were included. The questionnaire collected information about sociodemographics, means to clarify doubts about health, implementation of information obtained through the Internet, receipt of fake news, and means of fake news transmission. Duplicate questionnaires were excluded. To reduce the risk of incomplete electronic forms, all fields were marked as “mandatory questions.” The participants were informed that the data would be kept confidential.

To distribute the questionnaires, nonprobabilistic sampling (snowball technique) was used, a methodology that consists of the individuals selected by the researchers to propagate the questionnaire to their acquaintances, gradually increasing the sample size. To ensure sample diversity, the questionnaires were sent to people of different ages and with different professions. These participants were invited to spread the questionnaire among their groups with people of a similar profile, and so on, forming reference chains for the data collection.

The quantitative variables are presented as means and standard deviations, and the categorical variables are presented as frequencies and percentages. Statistical analyses were performed using the Statistical Package for the Social Sciences version 20.0® (SPSS Inc., Chicago, IL, USA) using the chi-square test and Fisher's exact test. The significance level was set at $p < 0.05$.

RESULTS

A total of 1,195 questionnaires were answered, of which 815 (68.2%) were answered by women. The median age of

the respondents was 35 years (minimum 18 and maximum 83 years). The young adult population was predominant, that is, 706 (59.1%) individuals; 370 (30.9%) were between the ages of 40 and 60 years, and 119 (10%) were older than 60 years. Regarding origin, 935 (78.2%) respondents were from Paraná, and 260 (21.8%) were from other states.

Regarding education, 282 (23.6%) respondents had complete or incomplete elementary or high school education, and 913 (76.4%) had complete or incomplete higher education. Of the total, 235 (19.7%) respondents were students, 176 (14.7%) were health professionals, and 750 (62.8%) were professionals from other areas.

The majority, 929 (77.7%), stated that they go to the physician to clarify doubts about health, 609 (51%) stated that they consult Google, 219 (18.3%) stated that they resort to friends, 167 (14%) stated that they seek information in Basic Health Units, and 104 (8.7%) stated that they look for information on government websites. It was possible to include more than one source of information in the responses. The younger the age group, the greater was the use of Google. In turn, physicians were more sought after by older individuals ($p < 0.05$) (Figure 1).

To answer health questions, women sought the opinion of physicians more than did men (79.8 versus 73.4%, $p = 0.017$), while men used Google more than women (56.8 versus 48.2%, $p = 0.006$). People with higher education levels sought the opinion of physicians more ($p < 0.001$). There was no positive association between education level and seeking health information on social networks and Google ($p = 0.734$ and $p = 0.454$, respectively).

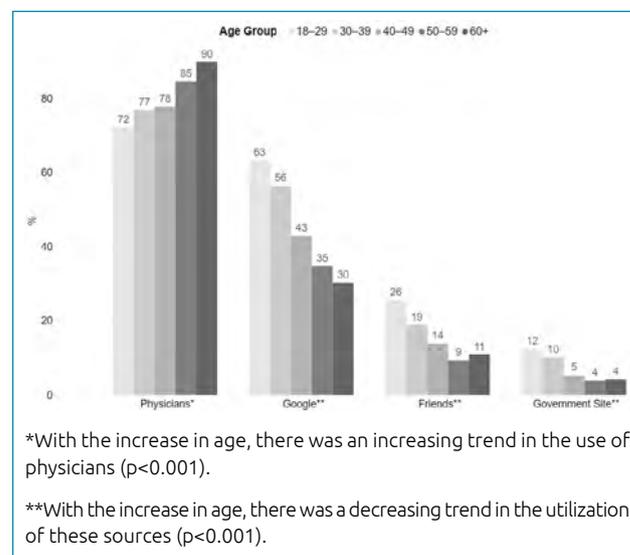


Figure 1. Distribution of health information search sources by age group ($n = 1,195$).

Of the total participants, 638 (53.4%) had followed health guidance from social networks without consulting a professional in the field, and 190 (15.9%) had not followed any medical guidance because of the social network content. Regarding health-related behaviors, young people were more influenced by news found on the Internet (Figure 2).

Individuals with an education that did not exceed the high school level followed information obtained on the Internet without consulting a professional more often than did individuals with higher education ($p=0.029$).

The majority of the respondents, 888 (74.3%), claimed to verify the sources of health news received. Health professionals claimed to verify these sources more than did other professionals (83.1 versus 72.9%, $p<0.001$), and people with higher education claimed to verify these sources more than did those with a lower level of education (77.7 versus 63.5%, $p<0.001$).

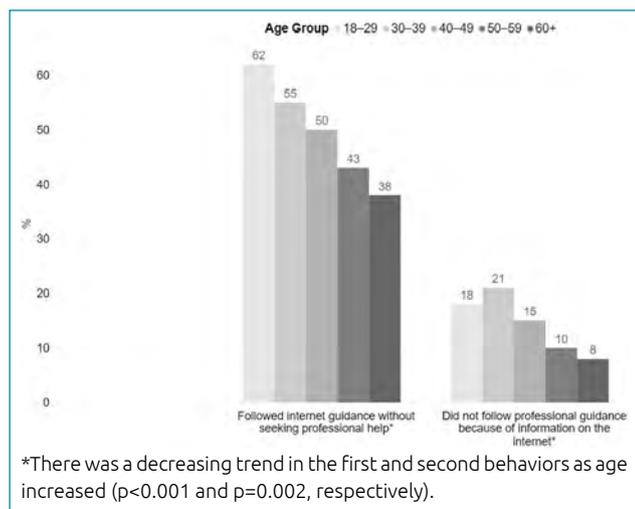


Figure 2. Actions taken by the population regarding health information obtained through the Internet by age group ($n=1,195$).

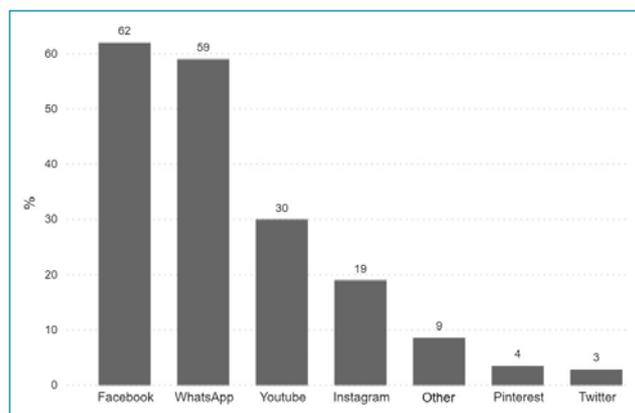


Figure 3. Percentage distribution of the source of fake news by social media platform ($n=1,069$).

Most of the respondents, 1,069 (89.4%), received some fake news about health. The main routes of receipt are shown in Figure 3. Facebook was the main source for younger respondents ($p=0.015$), and WhatsApp was the main source for older respondents ($p=0.005$).

Only 9 (0.7%) respondents had never heard about “fake news,” while 1,081 (90.5%) were unaware of the *Saúde sem Fake News* tool. Health professionals showed greater knowledge of this resource than did other professionals (16.4 versus 8.1%, $p=0.0017$).

DISCUSSION

Physicians were the source most consulted among the respondents to answer questions about health. Women reported contacting a physician to answer their questions more frequently than did men, a finding that is consistent with the Brazilian reality, where health services are more commonly used by women. This is due, among other factors, to the various socio-cultural and institutional barriers that hinder men from seeking health services⁶.

However, the Internet is an important vehicle for health information and has been increasingly used. In this study, there was a worrying trend among young people regarding a reduction in the use of physicians as sources of health information and a significant increase in Google searches. This could be explained by the higher occurrence of chronic diseases in the elderly population and consequently more frequent medical follow-ups. In addition, this portion of the population has greater difficulty finding this information on the Internet⁷. The behavior of young people, in turn, is probably due to greater contact with technology, leading to greater confidence in using online tools. This finding suggests that with the aging of this population, the search for information on the Internet will tend to increase and will become frequent even among future elderly individuals.

The data show that the greater the use of the Internet, the lower is the inclination to seek a physician and the higher are self-medication levels⁷. This is consistent with what was found in this study, as among those who reported having followed Internet guidance without consulting a health professional, the majority were young people.

People with a lower level of education also more frequently followed guidance obtained on the Internet without consulting health professionals. This can be explained by the lower access to health services by this portion of the population⁸.

If reliable sources are used, the search for health information on the Internet may have benefits, such as a greater understanding by the patient about the treatment and prevention

of diseases⁹. However, it can lead to increased self-diagnoses, leading to erroneous conclusions and impairment in the physician–patient relationship¹⁰. It can also cause anxiety, increased medicalization, instrumentalization, and overdiagnosis among patients¹⁰. Also concerning is the increase in self-medication, its various side effects, and its interference with prescribed treatments⁹.

The percentage of respondents who had received proven fake health news was high (89.4%). In Brazil, the impact of fake news can be observed in the low adherence to vaccination campaigns, as occurred from 2016 to 2018 with the yellow fever and measles vaccines, which lead to new outbreaks of these diseases⁵, and during the COVID-19 pandemic in 2020/21, when several ineffective treatments were disseminated³. In addition, fears caused by false information can lead to reduced adherence to treatment and scientifically proven diagnostic methods¹¹.

PSafe (2018) reported that the three main platforms for the dissemination of fake news are WhatsApp, Internet browsers, and Facebook. In agreement with these data, the most frequent means of the dissemination of fake health news found in this study were Facebook and WhatsApp; these platforms are easy to access and facilitate the creation and sharing of content, in addition to being the most currently accessed media platforms^{2,11}. The lack of monitoring of what is posted and limited media education among users also facilitates the dissemination of fake news¹¹.

Given that the Internet has become one of the main resources for searching health information and that fake news is increasingly present on the Internet, it is essential to develop strategies for the safe use of these technologies. Coordinated actions among health professionals, governments, fact-checkers, and social media platforms are necessary¹².

The Ministry of Health adopted an important action in the fight against fake news by creating *Saúde sem Fake News* in 2018. However, our study showed that only 9.5% of participants and only 16.4% of health professionals knew about this channel.

Investment in media education and awareness campaigns about fake news is extremely important. Another suggestion is to reduce the priority of sites that are sources of fake news by search engines, leading to less views of these publications¹³.

As fake news feeds on the distrust of people regarding medicine and science, it is important to strengthen the physician–patient relationship. For this, professionals must use language accessible to the population, be open to clarify doubts, and provide their patients with reliable sources to search for health information on the Internet^{5,9}.

One of the limitations of this study is that the sample was not completely representative of the Brazilian population. There was a predominance of respondents with higher education. Due to this, it is possible that this study underestimated the influence of the Internet on the health of the population because people with less education were those who most followed information from the Internet.

CONCLUSIONS

Young people mostly used the Internet to learn about health. A large proportion of the population implements advice found on the Internet without consulting a physician (53.4%), especially people with low education levels and young people, and this behavior can have harmful consequences on health.

The percentage of people who had received fake health news, mainly through Facebook and WhatsApp, was quite high (89.4%). Faced with this increasingly worrying scenario, it is necessary to invest in the dissemination and implementation of services and measures to combat fake news.

AUTHORS' CONTRIBUTIONS

ETZ, GPMW, IKB: Project conceptualization, Methodology, Data curation, Formal analysis, Investigation, Writing – original draft, Writing – review & editing. **LHK, DP:** Project conceptualization, Methodology, Data curation. **EMCPM:** Project conceptualization, Methodology, Project administration, Supervision, Validation.

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Clinical evolution of a severe asthmatics group in the use of immunobiological therapy in a Brazilian Public Hospital

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SUMMARY

OBJECTIVE: A small portion of the asthmatic population (3.6%) has severe asthma (SA), presenting high morbimortality rates and demanding more financial resources than other asthmatic populations. The use of immunobiological therapy is an effective tool in controlling symptoms, decreasing the number of exacerbations, and reducing the use of systemic corticosteroids in these patients. In Brazil, epidemiological data regarding this asthmatic population using immunobiologicals and their evolution are scarce.

METHODS: This is an observational, analytical, cross-sectional, and retrospective study. The sample consisted of adult patients with SA in follow-up at the pulmonology service of the Complexo Hospital de Clínicas of the Federal University of Paraná, from January 2011 to August 2019. The analyzed variables were as follows: the number of exacerbations that required hospitalization in the previous year, forced expiratory volume in one second (FEV1), and asthma control test (ACT) scores before and after the start of immunobiological therapy.

RESULTS: We studied 20 patients with SA using omalizumab or mepolizumab. We observed an increase in the mean ACT score of 4.8 points, a nonsignificant reduction in the number of exacerbations that required hospitalization, and a slight improvement in the FEV1. Regarding the patients using chronic systemic corticosteroid therapy, 14.2% (n=1) of patients had the medication discontinued and 57% (n=4) of patients had the dose reduced by half.

CONCLUSION: The use of omalizumab and mepolizumab as additional therapy in SA provided a significant improvement in the ACT and allowed the dose reduction of systemic corticosteroids, without significant improvement in FEV1 and in the frequency of severe exacerbations.

KEYWORDS: Asthma. Omalizumab. Mepolizumab.

INTRODUCTION

Asthma is a highly prevalent chronic disease, currently affecting approximately 339 million people worldwide and 20 million Brazilians¹⁻³. Of note, 3–10% of asthmatics have severe asthma (SA), consuming six times more resources than those who have mild and moderate asthma, accounting for 50–60% of the total costs of asthma treatment^{4,6}.

According to a Dutch population study, only 3.6% of asthmatics have SA⁷, which, according to the criteria of the 2014 ATS/ERS document⁴, is defined as asthma that remains symptomatic and with exacerbations even with high doses of inhaled corticosteroids, along with the association of one or more therapeutic classes after excluding the main noncontrol factors⁶.

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SA imposes great suffering on these patients who remain symptomatic, exacerbating and losing lung function, even after diagnostic confirmation, treatment of associated comorbidities, adherence and drug compliance, correct technique for using inhaler devices, and the use of high glucocorticoid doses associated with other therapeutic options^{6,8,9}. Moreover, these patients suffer from the side effects of medications, have a high mortality rate, and have profound negative consequences in their psychological, physical, and social dimensions¹⁰.

New therapeutic options have emerged in recent years for this specific group of asthmatics, such as omalizumab, commercialized in Brazil since 2004, which is a recombinant humanized monoclonal antibody anti-immunoglobulin E (IgE) that acts in the inflammatory process of allergic asthma, improving the quality of life, decreasing the number of exacerbations, and reducing the need for using systemic corticosteroids^{11,12}.

In 2017, mepolizumab, which is a humanized monoclonal anti-interleukin 5 (anti-IL5) antibody that acts by reducing the number of systemic eosinophils in severe eosinophilic asthmatics, was approved for commercialization in our country¹³. The consequent decrease in the eosinophilic inflammation of the airways has a positive impact not only on increasing the quality of life and lung function but also on decreasing exacerbations and the use of oral corticosteroids¹⁴.

Despite being already used for treating SA and suggested as a therapeutic option in step 5 of the asthma treatment in the Global Initiative for Asthma (GINA) document of 2019², studies that evaluate the effectiveness of these medications in “real life” are scarce and thus necessary.

Through an observational and retrospective study, we assessed 20 patients with SA who were treated with omalizumab and mepolizumab from January 2011 to August 2019 at the asthma outpatient clinic of the Complexo Hospital de Clínicas of the Federal University of Paraná (CHC-UFPR).

METHODS

The asthma outpatient clinic at the Complexo Hospital de Clínicas of the Federal University of Paraná (CHC-UFPR) was created in 2002 and is a reference for the treatment of this disease in the State of Paraná, Brazil. A total of 1,071 patients diagnosed with asthma are accompanied at this outpatient clinic, and 32 of them have SA (Table 1); however, only 22 patients were eligible to use immunobiologicals (omalizumab or mepolizumab), according to the criteria shown in Tables 2 and 3.

Inclusion criteria were as follows: patients aged above 18 years; patients with a minimum follow-up period of 6 months; patients diagnosed with SA that remained uncontrolled in spite of the optimized therapy in steps 4 or 5 of the GINA; and

patients who needed systemic corticosteroids for more than 50% of the days of the year⁴.

Uncontrolled asthma criteria (Table 2) consisted of the asthma control test (ACT) score lower than 20 points, as well as one or more exacerbations of asthma in the previous year⁴, in addition to fulfilling the necessary criteria for the use of omalizumab or mepolizumab (Tables 3 and 4)^{15,16}.

Two patients were excluded from this study: one for having started omalizumab in another service and the other for having less than 12 weeks of the use of mepolizumab.

We analyzed the pre-bronchodilator forced expiratory volume in one second (FEV1) percentage predicted, the scores in the ACT, the number of severe exacerbations that required hospitalization in the previous year, and the use of systemic corticosteroids before and 1 year after initiating omalizumab.

Since the use of mepolizumab is recently studied in our service, we took into consideration the period of 12 weeks of the use of this medication for the analysis of variables.

The results of quantitative variables were described as mean, standard deviation, median, and minimum and maximum values. Categorical variables were described by frequency and percentage.

Student's *t*-test for paired samples or the nonparametric Wilcoxon test were used to compare both assessments (before and after the use of the immunobiological) in relation to quantitative variables. The normality condition was analyzed by using the Kolmogorov-Smirnov test. *p* values <0.05 indicated statistical significance. The data were analyzed using the computer program Stata/SE v.14.1. StataCorpLP, USA.

This study was approved by the Research Ethics Committee of CHC-UFPR, approval number 03076918.0.0000.0096.

RESULTS

From all the 1,071 asthmatics, we evaluated 20 patients who had SA and who were using immunobiologicals in the period ranging from January 2011 to August 2019. The majority were females, consisting of 15 (75%) patients, and in 7 patients (35%), the onset of asthma occurred in their childhood. Only two patients (10%) had a history of low smoking load (≤ 5 pack-years) and more than 15 years of smoking cessation (Table 1).

Regarding comorbidities, 11 patients had (55%) allergic rhinitis and 9 (45%) patients had gastroesophageal reflux disease (GERD); the mean body mass index (BMI) was 29.8 (± 5), and nine patients (45%) were obese (BMI ≥ 30) (Table 1).

In addition to treating comorbidities, both the therapeutic adherence and the correct use of the inhaler device were also routinely checked when possible.

Table 1. Basic characteristics of patients.

| Variable | Valid n | Classification | Result* |
|---|---------|----------------|----------------------|
| Age (years) | 20 | | 49.2±11.7 (29–72) |
| Body mass index (kg/m ²) | 20 | | 29.8±5.0 (21.2–39.7) |
| SpO ₂ | 20 | | 95.5±2.2 (91–99) |
| Eosinophils (number) | 20 | | 369±271 (0–1062) |
| Eosinophils (%) | 20 | | 4.2±2.6 (0–10) |
| Total immunoglobulin E | 20 | | 472±340 (50–1244) |
| Asthma in childhood | 20 | No | 13 (65) |
| | | Yes | 7 (35) |
| Osteoporosis | 20 | No | 17 (85) |
| | | Yes | 3 (15) |
| Diabetes | 20 | No | 18 (90) |
| | | Yes | 2 (10) |
| High blood pressure | 20 | No | 14 (70) |
| | | Yes | 6 (30) |
| Rhinitis | 20 | No | 9 (45) |
| | | Yes | 11 (55) |
| Gastroesophageal reflux disease | 20 | No | 11 (55) |
| | | Yes | 9 (45) |
| Smoking load (pack years) | 20 | 0 | 18 (90) |
| | | 3 | 1 (50) |
| | | 5 | 1 (50) |
| Active smoker | 20 | No | 20 (100) |
| | | Yes | 0 (0) |
| Cessation (years) | 20 | 0 | 18 (90) |
| | | 17 | 1 (50) |
| | | 20 | 1 (50) |
| Use of long acting muscarinic antagonist | 20 | No | 8 (40) |
| | | Yes | 12 (60) |
| Use of leukotriene inhibitor | 20 | No | 16 (80) |
| | | Yes | 4 (20) |
| Use of systemic corticosteroid before the use of immunobiological therapy | 20 | No | 13 (65) |
| | | Yes | 7 (35) |
| Prednisone dose | 7 | 5 | 1 (14.3) |
| | | 10 | 1 (14.3) |
| | | 20 | 1 (14.3) |
| | | 30 | 1 (14.3) |
| | | 40 | 2 (28.6) |
| | | 60 | 1 (14.3) |
| Use of systemic corticosteroid after the use of immunobiological therapy | 20 | No | 14 (70) |
| | | Yes | 6 (30) |
| Prednisone dose | 6 | 5 | 2 (33.3) |
| | | 10 | 2 (33.3) |
| | | 20 | 1 (16.7) |
| | | 60 | 1 (16.7) |
| Use of omalizumab | 20 | No | 3 (15) |
| | | Yes | 17 (85) |
| Use of mepolizumab | 20 | No | 17 (85) |
| | | Yes | 3 (15) |

*Described by mean±standard deviation (minimum–maximum) or by frequency (percentage).

Table 2. Criteria to define severe asthma (SA).

| SA (use of >800 µg/day of inhaled budesonide or equivalent): |
|--|
| ✓ In regular use of long-acting beta-2-agonist |
| ✓ ACT <20 points |
| ✓ At least one exacerbation requiring hospitalization in the previous year or need for using systemic corticosteroid for more than 50% of the days of the year |

Table 3. Eligibility criteria for the use of omalizumab.

| |
|--|
| ✓ Adults over 18 years old, with adherence to the treatment, with a follow-up period longer than one year, and diagnosed with SA |
| ✓ Allergic asthma, diagnosed by allergic skin test |
| ✓ Weight between 30 and 150 kg |
| ✓ Total serum IgE between 30 and 1,500 IU/mL |

Table 4. Eligibility criteria for the use of mepolizumab.

| |
|---|
| ✓ Adults above 18 years old, with adherence to the treatment, with a follow-up period longer than 1 year, and diagnosed with SA |
| ✓ Serum eosinophil count ≥150 cells/mm ³ in the screening, or eosinophils ≥300 cells/mm ³ in previous 12 months |

All patients were regularly using high-dose inhaled corticosteroids (>800 µg budesonide per day, or equivalent) and long-acting beta-2-agonist; 12 patients (60%) were on regular use of long-acting antimuscarinic, 16 (80%) patients were using a leukotriene inhibitor, and 7 (35%) patients were using systemic corticosteroids, of which 71.5% of patients were on 20 mg of prednisone/day or more (Table 1).

Seventeen patients (85%) were eligible for using omalizumab (Table 3); however, 3 (17%) of them had the drug discontinued after one year of follow-up due to therapeutic failure. The dose was prescribed according to the label indication in the medication package insert, taking into consideration the body weight and serum IgE at the beginning of the treatment. In case of more than 10% of the change in the patient’s body weight, the dose was adjusted accordingly.

The analyzed data of two patients were incomplete, missing FEV1 for the first patient and ACT score for the second.

Three patients (15%) were eligible to use mepolizumab, according to the criteria described in Table 4. In this case, the variables were assessed at the beginning and after 12 weeks of using this medication.

The mean pre-bronchodilator FEV1 percentage predicted was 47.3% (27.3–129%), and the mean number of exacerbations requiring hospitalization in the previous year was 1.8 (0–5). The mean ACT before the intervention was 10.5 (4.2–17).

After the use of immunobiologicals, we observed a slight increase in the absolute FEV1 and in the percentage predicted, but without statistical significance (p=0.111).

The mean number of severe exacerbations requiring hospitalization dropped from 1.8 to 1.1, a decrease of 0.7, however, with p value=0.191.

The ACT score presented the most significant change among all the analyzed variables, with a mean increase of 4.8 points (5.8–18) and with the value of p=0.001, as shown in Figure 1. Initially, seven patients were chronically using systemic corticosteroids; for one patient, we were able to discontinue the use of prednisone, and for four others, the medication was half dosed (Table 5).

DISCUSSION

Studies regarding omalizumab and mepolizumab for the treatment of SA show, as outcomes, decrease in the number of exacerbations, as well as improvement in quality of life, decrease in symptoms, reduction in the dosage, or discontinuing of chronic use of systemic corticosteroids. The results regarding the improvement in lung function are still controversial, and there is no compelling evidence that the use of immunobiologicals results in a significant increase in lung function¹³⁻¹⁶.

In our study, we observed significant improvement in asthma control with the use of immunobiologicals, with a mean increase of 4.8 points in the ACT score (Figure 1). There was a nonsignificant reduction in the number of severe exacerbations

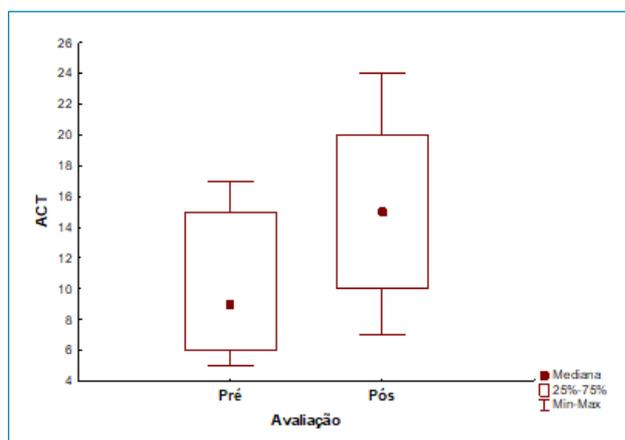


Figure 1. Evolution of the asthma control test before and after the use of immunobiological therapy.

Table 5. Evaluation of variables: number of severe exacerbations in the previous year, forced expiratory volume in one second, and asthma control test score before and after the use of immunobiological therapy.

| Variable | Evaluation | n | Mean | Standard deviation | Median | Minimum | Maximum | p* |
|---|------------|----|------|--------------------|--------|---------|---------|-------|
| Number of severe exacerbations in the previous year (requiring hospitalization) | Before | 20 | 1.8 | 1.7 | 1 | 0 | 5 | 0.191 |
| | After | 20 | 1.1 | 1.4 | 0.5 | 0 | 5 | |
| | Difference | 20 | -0.7 | 2.2 | -0.5 | -5 | 3 | |
| FEV1 (N°) | Before | 19 | 1.3 | 1.3 | 0.4 | 0.6 | 2.5 | 0.093 |
| | After | 19 | 1.5 | 1.3 | 0.5 | 0.8 | 3.8 | |
| | Difference | 19 | 0.2 | 0 | -0.5 | 0.5 | 1.8 | |
| FEV1 (%) | Before | 19 | 47.3 | 46 | 15 | 16.4 | 88 | 0.111 |
| | After | 19 | 54.6 | 46 | 16 | 27.3 | 129 | |
| | Difference | 19 | 7.3 | 1 | -14 | 19 | 62 | |
| ACT | Before | 19 | 10.5 | 9 | 5 | 4.2 | 17 | 0.001 |
| | After | 19 | 15.3 | 15 | 7 | 5.5 | 24 | |
| | Difference | 19 | 4.8 | 3 | -2 | 5.8 | 18 | |

*Student's *t*-test for paired samples or nonparametric Wilcoxon test, $p < 0.05$. FEV1: forced expiratory volume in one second; ACT: asthma control test.

(requiring hospitalization) and a reduction in the total dose of systemic corticosteroids. We did not observe a significant increase in FEV1. These findings have already been shown in other Brazilian studies that used omalizumab to treat SA, whose main results were the improvement of symptoms and of quality of life^{17,18}.

It is worth noting that, although small, the group of patients with SA in this study share similar characteristics (Table 1) with the large cohorts of severe asthmatics (TENOR II and U BIOPRED), having a predominance of females, high BMI scores, and low FEV1^{10,19}.

The unavailability of endotype biomarkers²⁰, such as FeNo²¹, periostin²², and sputum eosinophils²³, for patients with SA in this study may have influenced our results regarding therapeutic effectiveness, since a better understanding of the inflammatory pathway of asthma influences the decision of using not only the immunobiologicals but also its choice.

Due to the high cost of immunobiologicals, creating a regional database for longitudinal studies regarding this small group of asthmatics is necessary in order to provide more evidence of cost-effectiveness and long-term safety²⁴.

CONCLUSION

With an adequate indication, the use of omalizumab and mepolizumab in the study population provided a significant improvement in asthma control, as measured by the ACT; however, there was no significant change in the frequency of

exacerbations with the need for hospitalization, as well as no significant change in FEV1.

AUTHORS' CONTRIBUTIONS

LMR: Conceptualization, Data curation, Formal analysis, Investigation Methodology, Project administration, Resources, Software, Supervision, Validation, Visualization, Writing – original draft, Writing – review & editing. **RSMS:** Conceptualization, Data curation, Formal analysis, Investigation Methodology, Resources, Software, Validation, Visualization, Writing – original draft, Writing – review & editing. **DD:** Conceptualization, Data curation, Formal analysis, Investigation Methodology, Resources, Software, Validation, Visualization, Writing – original draft, Writing – review & editing. **JS:** Conceptualization, Data curation, Formal analysis, Investigation Methodology, Resources, Software, Validation, Visualization, Writing – original draft, Writing – review & editing. **GLL:** Conceptualization, Data curation, Formal analysis, Investigation Methodology, Resources, Software, Validation, Visualization, Writing – original draft, Writing – review & editing. **MFRQF:** Conceptualization, Data curation, Formal analysis, Investigation Methodology, Resources, Software, Validation, Visualization, Writing – original draft, Writing – review & editing. **FMC:** Conceptualization, Data curation, Formal analysis, Investigation Methodology, Visualization, Writing – original draft, Writing – review & editing.

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Epidemiological analysis of hysterectomies performed at the public health system in the largest Brazilian city

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SUMMARY

OBJECTIVE: To analyze the public data of hysterectomies performed in the only health system in the city of São Paulo between 2008 and 2018.

METHODS: The following public health system data were extracted and analyzed: age, technique, number of surgeries, mortality during hospitalization, length of stay in the establishment (days), and amounts paid by the public network.

RESULTS: A total of 20,119 procedures were analyzed. The most prevalent procedure was total hysterectomy (43.2%), followed by vaginal hysterectomy (26.7%), subtotal hysterectomy (24.3%), and laparoscopic hysterectomy (5.8%). Early discharge (hospital stay of up to 1 day) was more prevalent in cases of vaginal hysterectomy (39%). We observed a marked downward trend in the number of total hysterectomies. Total hysterectomy was the most expensive procedure; no significant difference was noted in the cost of vaginal versus laparoscopic hysterectomy. We noticed a trend of rising costs over the years. The most frequent hospital admission code was that of leiomyoma of the uterus in cases of total, subtotal, and laparoscopic hysterectomy.

CONCLUSION: Despite the decrease in the number of hysterectomies over the 11-year study period in São Paulo, it remains in high demand mainly for the treatment of uterine leiomyomatosis. Laparoscopic hysterectomy has been gaining ground and showed a slightly upward trend with a shorter hospital stay. Laparoscopic and vaginal hysterectomy required less financial support from the health system than open surgery.

KEYWORDS: Big data. Database. Hysterectomy. Public health.

INTRODUCTION

Hysterectomy, the surgical removal of the uterus, is among the most prevalent gynecological surgeries worldwide¹. Most hysterectomies (70%) are performed for the treatment of benign diseases such as abnormal uterine bleeding, symptomatic uterine fibroids, adenomyosis, and uterine prolapse². In benign diseases, surgery is considered after clinical treatment failure occurs³.

Hysterectomy can be performed through abdominal, vaginal, laparoscopic, or robot-assisted routes³ and can be total (if the uterus is entirely removed) or subtotal (if the cervix is

preserved)⁴. Multiple variables influence the choice of the benign hysterectomy surgical route according to the surgeon's technical skills and the patient's condition, such as uterine volume, parity, presence of extrauterine pelvic diseases, and history of previous pelvic surgery.

Although hysterectomy is frequently performed, few studies in Brazil have analyzed its epidemiological data from a single large city. Thus, this study aimed to describe the epidemiological aspects of hysterectomies performed between 2008 and 2018 in the city of São Paulo using publicly available data from the Brazilian Public Health System (SUS).

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METHODS

The study analyzed data accessible on the TabNet platform belonging to the DATASUS system⁵, which provides information on the procedures performed in hospitals at the SUS. The platform has 22 selections for rows, 16 for columns, and 8 for content, providing 2,816 possible formatting combinations separated by monthly periods. The study was conducted at Albert Einstein Israelite Hospital and approved by the institution's research ethics committee.

Data referring to hysterectomies were selected from January 2008 to December 2018 from the TabNet app of the Municipal Health Department of São Paulo. A total of four procedures were analyzed and coded using the SIGTAP codes (SUS Procedures Table, Medicines, and OPM Table Management System): total hysterectomy (04.09.06.013-5), subtotal hysterectomy (04.09.06.012-7), laparoscopic hysterectomy (04.09.06.015-1), and vaginal hysterectomy (04.09.06.010-0).

Data including number of surgeries, age group, mortality during hospitalization, length of hospital stay, and amount paid were analyzed. Four groups were formed to verify the association between procedure type and age: less than 20 years, 20–39 years, 40–59 years, and 60 years or older. Patients were classified according to the International Classification of Diseases, 10th revision (ICD-10) codes reported at the time of hospital admission.

The results were collected using software to access the site content and turn it into web scraping codes. After collection and treatment, the data were organized and grouped in a spreadsheet within Microsoft Office Excel 2016® (v. 16.0.4456.1003, Redmond, WA, USA).

The data were described as absolute and relative frequencies. Comparisons by procedure type were made using the chi-square test⁶. The evolution of procedures and costs over the years were evaluated by generalized estimating equation (GEE) models using the negative binomial and gamma distributions, both with a logarithmic link function⁷. A significance level of 5% was considered, and the analyses were performed using statistical packages R⁸ and SPSS v26.0⁹.

RESULTS

The search determined that 20,119 procedures were performed between January 2008 and December 2018, with total hysterectomy as the most prevalent (43.2%), followed by vaginal hysterectomy (26.7%), subtotal hysterectomy (24.3%), and video-laparoscopic hysterectomy (5.8%). The analysis of procedural data by age group showed the highest prevalence was in the 40–49 years, corresponding to 54.1% of the procedures.

The results indicated significant differences in hysterectomy types among the age groups, with vaginal hysterectomy being the most frequent surgical route among patients over 60 years of age (82.7%) and total hysterectomy (41–48%) being the most common in the other age groups. The difference was statistically significant ($p < 0.001$).

The relationship between procedure type and length of hospital stay was also statistically significant ($p < 0.001$). Figure 1 shows the distribution of length of stay among the procedure types as percentages. For all procedures, the most frequent hospital length of stay was 2–3 days, while the highest prevalence of early discharge (on the same day or just 1 day after surgery) occurred in the video-laparoscopic hysterectomy group (5.08%).

The death rate for hysterectomies was 1.19 per 1,000 procedures. There were no deaths in the video-laparoscopic surgery group. Mortality was more prevalent in the subtotal (2.25 per 1,000) and total (1.38 per 1,000) hysterectomy groups ($p = 0.012$).

Figure 2 shows that during the study period, there was a marked decrease in the number of total hysterectomies performed and a less accentuated decrease in the number of vaginal hysterectomies performed. The graph also shows a subtle increase in use of the laparoscopic approach. The annual change in the number of procedures was estimated using GEE models that considered the negative binomial distribution and used the year as a covariate to analyze how the numbers changed over time. The estimated mean ratio (MR) indicated a downward trend in the number of vaginal (MR=0.883; $p < 0.001$), subtotal (MR=0.961; $p = 0.053$), and total (MR=0.883; $p < 0.001$)

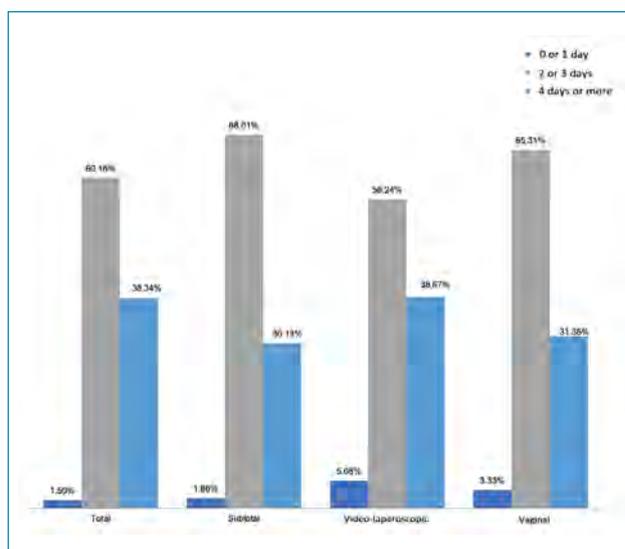


Figure 1. Length of hospital stay in days classified by procedure type.

hysterectomies versus an upward trend in the number of video-laparoscopic hysterectomies (MR=1.070; $p=0.158$).

The costs of the procedures and their behaviors over the years were also analyzed (Figure 3). The most expensive procedures were total hysterectomies; no significant difference was noted in the costs of vaginal versus laparoscopic hysterectomies. In addition, the data showed a trend of rising costs over the years. However, in 2016, there was an atypical decrease in costs, especially for total hysterectomy. There was a significant cost increase over the years compared with 2008, with the exception of vaginal hysterectomy ($p>0.05$).

During the survey, the ICD codes from the hospital admission for hysterectomies were also considered. The most frequent ICD code was uterine leiomyoma for total, subtotal, and laparoscopic hysterectomy, reaching 86, 89, and 78%, respectively. In vaginal hysterectomies, the most prevalent ICD was pelvic organ prolapse (54.7%). Other diseases were also documented, such as endometriosis, pelvic varices, and abnormal uterine bleeding; however, their incidence did not reach 5% of cases.

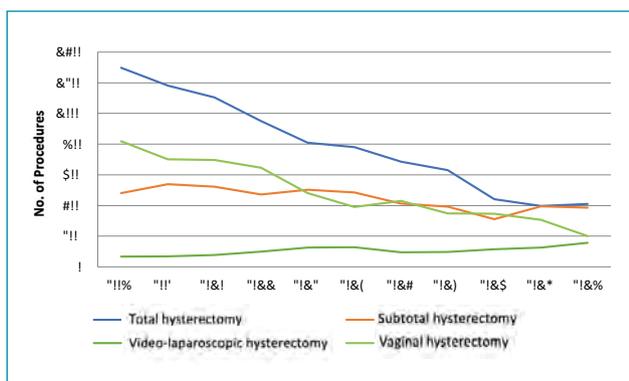


Figure 2. Number of procedures analyzed, 2008–2018.

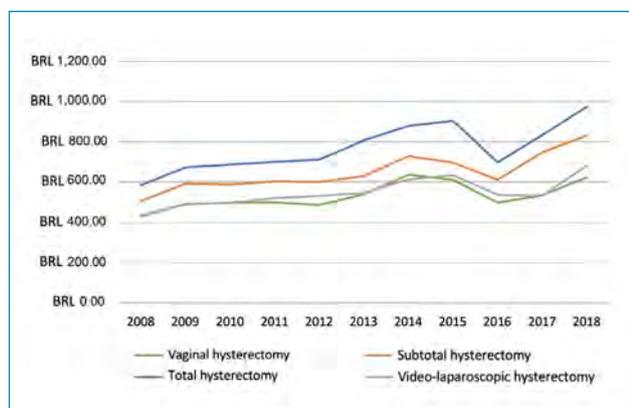


Figure 3. Values transferred by SUS (Brazilian public health system) per procedure for all hospitals analyzed, 2008–2018.

DISCUSSION

The increase in procedures performed between 2008 and 2018 indicated a marked downward trend in the number of total hysterectomies. This trend was reported by other studies, including in Brazil, in which data on hospitalizations for hysterectomies between 2008 and 2017, available at DATASUS, for the five regions of Brazil were analyzed, totaling 1,004,668 hysterectomies during that period. This period also presented a decreasing number of hysterectomies (16%), with the Southeast region showing the greatest downward trend¹⁰. This decrease was probably due to patients' access to less invasive or nonsurgical treatments, such as the use of the levonorgestrel intrauterine device and surgical hysteroscopy. These data show a positive perspective that the reduction of surgeries may be due to successful clinical control of gynecological symptoms.

The increasing trend of video-laparoscopic hysterectomies demonstrates a beneficial technological transition. Despite the upward trend, the total value in São Paulo remained low as laparoscopic devices are more commonly available in private hospitals and the number of gynecologists skilled at this procedure type is small. A cohort study conducted in the United States that analyzed 264,758 women undergoing hysterectomy for benign diseases showed a prevalence of 40% for laparoscopic hysterectomies; 46% of the patients were discharged on the same day¹¹.

Hysterectomy was the most commonly performed in the 40–49 years age group, corresponding to 54.1% of the procedures. However, vaginal hysterectomy was the most common surgical route in patients aged 60 years or above (82.7%). These data were corroborated by those of different studies that also observed a predominance of surgeries performed in women aged 40–49 years¹². This predominance may have been caused by the high prevalence of uterine leiomyoma in women in this age group¹³.

The length of stay can be a measure of health care efficiency¹⁴. The most frequent hospital length of stay for all procedures was 2–3 days, and early discharge (hospital stay up to 1 day) was more prevalent in vaginal hysterectomies (39%). The literature corroborates these data, showing that a prolonged hospital stay is less common after minimally invasive and vaginal hysterectomies. An American study that identified 157,589 women undergoing benign hysterectomy from 2006 to 2015 indicated that intraoperative factors were the most important contributors to length of stay in laparoscopic and abdominal hysterectomy, while demographic factors such as age and ethnicity dominated in vaginal hysterectomy¹⁵.

The overall mortality rate in this study was 1.19 per 1,000 procedures, being more prevalent in subtotal (2.25 per 1,000) and total (1.38 per 1,000) hysterectomies. In the literature,

the described overall mortality rate of hysterectomy for benign diseases is about 0.4 per 1,000 cases¹⁶. The mortality rate analyzed in the present study refers only to data collected during hospitalization; our use of anonymous information prevented the identification of deaths after hospital discharge.

The present study has some limitations because the comparison in the literature included in-hospital and out-of-hospital mortality data. Another limitation is the fact that 673 patients (3.34%) had malignant diseases. There are some SITGAP-specific codes for oncologic hysterectomies; however, they were not used to describe the surgery performed, causing study selection bias.

The monetary value provided by the SUS for total hysterectomies was higher than those for laparoscopic and vaginal procedures with a tendency for increasing costs over the years. Results similar to the current cost analysis studies indicate that vaginal hysterectomy is the most cost-effective route and laparoscopic hysterectomy can be cost-effective compared with open surgery¹⁷. The length of hospital stay, use of disposable surgical devices, and length of operating room stay are the main determinants of hospital costs¹⁸. One of the limitations of this study is the fact that the SUS has a remuneration table for procedures that usually do not reflect the real cost. Therefore, the monetary analysis was based only on the financial volume provided by the SUS and does not necessarily indicate the full hospital expenses. Additional limitations are the scarcity of information about reoperation and the analysis of patient mortality rates after hospitalization. These are secondary limitations due to the anonymity of the data available in a government information database.

Finally, uterine leiomyoma was the most frequent ICD code for the procedures (proportion higher than 75%), with the exception of vaginal hysterectomies, for which pelvic organ prolapse was more common (54.7%). The literature corroborates this finding, presenting uterine myomatosis as the main indication for hysterectomy. However, pelvic organ prolapse

predominates as the indication for hysterectomy in postmenopausal women, with vaginal hysterectomy as the most commonly chosen surgical route¹⁹.

CONCLUSIONS

Conducting studies that trace epidemiological profiles of diseases and the analysis of trends in a particular type of procedure, costs, length of stay, among others, are important from the perspective of public health planning and resource allocation.

The present study demonstrated a decrease in the number of hysterectomies over time, possibly related to the increasing effective use of clinical methods to control symptoms. In addition, considering the surgical procedures analyzed, laparoscopic hysterectomy has been gaining ground and showed a slight upward trend and shorter hospital stay in addition to lower cost than total hysterectomy.

New analyses must be conducted to trace the epidemiological profile of and treatment methods for gynecological diseases to provide tools for the management and planning of public and private health care resources in Brazil.

AUTHORS' CONTRIBUTIONS

CFA: Conceptualization, Data curation, Formal analysis, Funding acquisition, Investigation, Methodology, Project administration, Resources, Software, Supervision, Validation, Visualization, Writing—original draft, Writing—review & editing. **DBC:** Conceptualization, Data curation, Formal analysis, Funding acquisition, Investigation, Methodology, Project administration, Resources, Software, Supervision, Validation, Visualization, Writing—original draft, Writing—review & editing. **SP:** Conceptualization, Data curation, Formal analysis, Funding acquisition, Investigation, Methodology, Project administration, Resources, Software, Supervision, Validation, Visualization, Writing—original draft, Writing—review & editing.

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Impact of the COVID-19 pandemic on the development of burnout syndrome in frontline physicians: prevalence and associated factors

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SUMMARY

OBJECTIVE: To evaluate the prevalence of burnout syndrome (BS) in physicians working during the COVID-19 pandemic in Paraíba and to investigate the association between BS and the sociodemographic and labor variables of these professionals.

METHODS: This was a cross-sectional study including physicians who were active during the pandemic in Paraíba, whether they were on the front line (group 1) or not (group 2). Sociodemographic and labor variables were collected, and the Maslach Burnout Inventory-Human Services Survey (MBI-HSS) questionnaire was applied.

RESULTS: A total of 126 physicians were included, including 82 who were on the front line. Among the professionals with results compatible with BS, 85.5% were in group 1, compared with 14.5% in group 2, and this difference was statistically significant. At the 5% level, the variables associated with BS were age (24–33 years), not having children, working on the front line, working in the COVID-19 ICU, being on duty, and having contracted COVID-19.

CONCLUSIONS: This case series found a positive association between the development of BS and medical action on the front line of the COVID-19 pandemic in Paraíba.

KEYWORDS: Coronavirus. Burnout. Health professional. Factor analysis statistical. Chi-square test.

INTRODUCTION

According to World Health Organization (WHO) data, as of May 2021, COVID-19 has affected more than 200 countries, resulting in approximately 159 million cases and approximately 3 million deaths¹. In Brazil, this number has been increasing considerably, with more than 15 million

cases and approximately 428,000 deaths from the disease reported as of May 2021².

Infection with the new coronavirus, SARS-CoV-2, which causes a severe acute respiratory syndrome known as COVID-19, may be asymptomatic or can cause problems ranging from mild respiratory tract symptoms to sepsis and multiple organ

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failure, which is life-threatening; thus, it has led to a significant increase in hospitalizations³.

The increase in the number of cases and their evolution has caused an overload of health systems, especially in Brazil. As a result of this workload, many health professionals may experience burnout, fatigue, and stress, among other risk factors for physical and mental illness³.

Burnout syndrome (BS) or burnout is a possible effect of chronic exposure to occupational stress and affects health professionals, particularly those working in hospitals⁴. It is believed that with the overload of health services, many professionals may have developed the disorder, with impacts on both the life of professionals and the care they provide.

The present study aimed to evaluate the prevalence of BS in physicians working during the COVID-19 pandemic in Paraíba and to verify its association with the sociodemographic and labor variables of these professionals.

METHODS

This was a cross-sectional study that included physicians of both sexes who worked during the COVID-19 pandemic in Paraíba, either on the front line (group 1) or off it (group 2). The physicians were recruited by e-mail and/or telephone in November 2020. The sample was obtained from the medical departments of reference hospitals for COVID-19 (group 1) and nonreference hospitals (group 2). Those who did not meet the inclusion criteria or did not adequately complete the data collection instrument were excluded.

The study was approved by the research ethics committee under no. 4,354,660 and followed the standards for research in humans.

A questionnaire was administered via Google Forms to obtain free and informed consent, collect sociodemographic and labor information, and administer the Maslach Burnout Inventory-Human Services Survey (MBI-HSS) questionnaire version validated for Portuguese⁵. The MBI-HSS consists of 22 items that reflect 3 dimensions: emotional exhaustion (EE; 9 items), depersonalization (DP; 5 items), and reduced personal achievement (rPA; 8 items)⁶.

The data were analyzed using R[®] software. To test the fit of the three-factor structure of the MBI-HSS, confirmatory factor analysis (CFA) was performed using the maximum likelihood method. The prevalence of BS was calculated, and the chi-square test was performed to investigate the association between the explanatory variables and the presence or absence of BS at a significance level of 5%.

There is no consensus on adequate cutoff points for MBI-HSS results. The manual published by Maslach

et al.⁶ advises that each dimension be analyzed separately to obtain the diagnosis from high EE and DP indices and low rPA⁶. The five-point Likert scale was used according to the adaptation validated by Tamayo⁷, applied in some studies in Brazil^{8,9}. Individuals with mean response options equal to or higher than “sometimes” (a score of 3 on the Likert scale) for the EE and ED dimensions or scores of 3 or less for the rPA dimension were considered to have a high risk of BS.

RESULTS

A total of 126 physicians who were working during the pandemic were included, comprising 82 physicians who were on the front line (group 1) and 44 who were not (group 2). Females were prevalent in both the groups.

The mean age was 33.77 years in group 1 and 38.02 in group 2. The majority (54.9%) of the professionals in group 1 had COVID-19, compared with 4.5% in group 2. Descriptive statistics are presented in Table 1.

Through exploratory factor analysis (EFA), the fit of the data was observed, and 64.01% of the variance was explained. The adequacy of the original three-factor structure of the MBI-HSS was tested using CFA. The EE domain was composed of items 1, 2, 3, 6, 8, 13, 14, 16, and 20; the DP domain was composed of items 5, 10, 11, 15, and 22; and the rPA domain included items 4, 7, 9, 12, 17, 18, 19, and 21.

The CFA obtained the following results for the three-dimensional model: $\chi(206)=295.25$; $p<0.001$; comparative fit index (CFI)=0.965; Tucker-Lewis index (TLI)=0.961; and root mean square error of approximation (RMSEA)=0.059 with 95%CI 0.043–0.073, confirming the adequacy. The internal consistency estimated by Cronbach's alpha was substantial: 0.89 (EE), 0.66 (DP), and 0.82 (rPA).

The categorization of BS dimensions was performed using the cutoff points from the Maslach et al., manual⁶: for EE: ≥ 27 (high), 17–26 (moderate), and ≤ 16 (low); for DP: ≥ 13 (high), 7–12 (moderate), and ≤ 6 (low); for rPA: ≤ 31 (high), 38–32 (moderate), and ≥ 39 (low). Table 2 shows the distribution according to these levels.

The results of the chi-square test are shown in Table 3. The statistically significant variables at the 5% level were age between 24 and 33 years ($p=0.008$), not having children ($p=0.004$), working on the front line ($p<0.001$), working in the COVID ICU, being on-duty ($p=0.001$), and having contracted COVID-19 ($p=0.016$). Among the professionals whose results were compatible with BS, 85.5% worked on the front line and 14.5% worked off the front the line, and this difference was statistically significant ($p<0.001$).

Table 1. Distribution of individuals according to sociodemographic and labor characteristics and COVID-19 infection history.

| Variable | Front line | | Not front line | |
|--------------------------------|------------|------|----------------|------|
| | n | % | n | % |
| Gender | | | | |
| Female | 45 | 54.9 | 36 | 81.8 |
| Male | 37 | 45.1 | 8 | 18.2 |
| Marital status | | | | |
| Married | 52 | 63.4 | 36 | 81.8 |
| Other | 2 | 2.4 | 0 | 0 |
| Separated | 5 | 6.1 | 4 | 9.1 |
| Single ⁷⁵ | 23 | 28.0 | 4 | 9.1 |
| Color | | | | |
| Yellow | 1 | 1.2 | 2 | 4.5 |
| White | 55 | 67.1 | 30 | 68.2 |
| Brown | 26 | 31.7 | 12 | 27.3 |
| Comorbidities | | | | |
| Yes | 14 | 17.1 | 7 | 15.9 |
| No | 68 | 82.9 | 37 | 84.1 |
| Use of psychotropic drugs | | | | |
| Yes | 11 | 13.4 | 8 | 18.2 |
| No | 71 | 86.6 | 36 | 81.8 |
| Physical activity | | | | |
| Yes | 53 | 64.6 | 35 | 79.5 |
| No | 29 | 35.4 | 9 | 20.5 |
| Religious | | | | |
| Yes | 71 | 86.6 | 43 | 97.7 |
| No | 11 | 13.4 | 1 | 2.3 |
| Smoking | | | | |
| Yes | 3 | 3.7 | 1 | 2.3 |
| No | 79 | 96.3 | 43 | 97.7 |
| Alcoholic beverage consumption | | | | |
| Yes | 59 | 72.0 | 27 | 61.4 |
| No | 23 | 28.0 | 17 | 38.6 |
| Lives with | | | | |
| Friends | 1 | 1.2 | 0 | 0 |
| Family | 64 | 78.0 | 42 | 95.5 |
| Alone | 17 | 20.7 | 2 | 4.5 |
| Has children | | | | |
| Yes | 40 | 48.8 | 33 | 75.0 |
| No | 42 | 51.2 | 11 | 25.0 |

Continue...

Table 1. Continuation.

| Variable | Front line | | Not front line | |
|---|------------|-------|----------------|-------|
| | n | % | n | % |
| Type of service | | | | |
| COVID ward | 49 | 59.8 | 0 | 0 |
| COVID ICU | 33 | 40.2 | 0 | 0 |
| Other service (non-COVID) | 0 | 0 | 44 | 100 |
| Position | | | | |
| Day worker | 9 | 11.0 | 26 | 59.1 |
| On call | 73 | 89.0 | 18 | 40.9 |
| Weekly workload | | | | |
| Less than 40 h | 29 | 35.4 | 17 | 38.6 |
| Between 40 and 60 h | 25 | 30.5 | 25 | 56.8 |
| Over 60 h | 28 | 34.1 | 2 | 4.5 |
| Has more than one professional relationship | | | | |
| Yes | 74 | 90.2 | 35 | 79.5 |
| No | 8 | 9.8 | 9 | 20.5 |
| Considers their remuneration fair | | | | |
| Yes | 28 | 34.1 | 26 | 59.1 |
| No | 54 | 65.9 | 18 | 40.9 |
| Had COVID-19 | | | | |
| Yes | 45 | 54.9 | 2 | 4.5 |
| No | 37 | 45.1 | 42 | 95.5 |
| Total | 82 | 100.0 | 44 | 100.0 |

Source: Research data. The values highlighted in bold are intended to draw the reader's attention to statistically significant variables.

Table 2. Distribution of professionals on the front line (group 1) and off the front line (group 2) for each dimension.

| Level | Emotional exhaustion | | Depersonalization | | Reduced professional achievement | |
|----------|----------------------|--------------------|-------------------|--------------------|----------------------------------|--------------------|
| | Front line | Off the front line | Front line | Off the front line | Front line | Off the front line |
| High | 41 (50.0%) | 8 (18.2%) | 31 (37.8%) | 1 (2.3%) | 53 (64.6%) | 21 (47.7%) |
| Moderate | 32 (39.0%) | 30 (68.2%) | 45 (54.9%) | 35 (79.5%) | 27 (32.9%) | 21 (47.7%) |
| Low | 9 (11.0%) | 6 (13.6%) | 6 (7.3%) | 8 (18.2%) | 2 (2.4%) | 2 (4.5%) |

Source: Research data. The values highlighted in bold are intended to draw the reader's attention to statistically significant variables.

DISCUSSION

The present study explored the factors impacting the development of BS in physicians who worked at hospitals during the COVID-19 pandemic in Paraíba. The findings of this study showed that age between 24 and 33 years, not having children, working on the front line, working in the COVID ICU, being

on call, and having contracted COVID-19 were statistically significant variables in relation to the outcome (the presence or absence of BS).

This study also showed that serving on the front line during the COVID-19 pandemic was the main factor associated with professional burnout in the population studied.

Table 3. Results of the tests of association between the explanatory variables and the outcome (presence or absence of burnout syndrome).

| | Burnout | | No burnout | | p-value |
|---------------------------|---------|-------|------------|------|---------|
| | n | % | n | % | |
| Sociodemographic data | | | | | |
| Age, years | | | | | 0.008 |
| 24–34 | 32 | 58.2 | 22 | 31.0 | |
| 34–44 | 20 | 36.4 | 40 | 56.3 | |
| 44–55 | 3 | 5.5 | 9 | 12.7 | |
| Gender | | | | | |
| Female | 32 | 58.2 | 49 | 69.0 | 0.208 |
| Male | 23 | 41.8 | 22 | 31.0 | |
| Marital status | | | | | |
| Married | 36 | 65.5 | 52 | 73.2 | 0.523 |
| Single | 15 | 27.3 | 12 | 16.9 | |
| Divorced | 13 | 23.6 | 6 | 8.5 | |
| Other | 1 | 1.8 | 1 | 1.4 | |
| Color | | | | | |
| Yellow | 1 | 65.5 | 2 | 2.8 | 0.221 |
| White | 33 | 27.3 | 52 | 73.2 | |
| Brown | 21 | 23.6 | 17 | 23.9 | |
| Black | 0 | 0.0 | 0 | 0.0 | |
| Comorbidities | | | | | |
| Yes | 8 | 14.5 | 13 | 18.3 | 0.574 |
| No | 47 | 85.5 | 58 | 81.7 | |
| Use of psychotropic drugs | | | | | |
| Yes | 11 | 20.0 | 8 | 11.3 | 0.174 |
| No | 44 | 80.0 | 63 | 88.7 | |
| Physical activity | | | | | |
| Yes | 37 | 67.3 | 51 | 71.8 | 0.580 |
| No | 18 | 32.7 | 20 | 28.2 | |
| Religious | | | | | |
| Yes | 47 | 85.5 | 67 | 94.4 | 0.091 |
| No | 8 | 14.5 | 4 | 5.6 | |
| Smoking | | | | | |
| Yes | 0 | 0.0 | 4 | 5.6 | 0.074 |
| No | 55 | 100.0 | 67 | 94.4 | |
| Alcohol consumption | | | | | |
| Yes | 38 | 69.1 | 48 | 67.6 | 0.859 |
| No | 17 | 30.9 | 23 | 32.4 | |

Continue...

Table 3. Continuation.

| | Burnout | | No burnout | | p-value |
|---|---------|------|------------|-------------|--------------|
| | n | % | n | % | |
| Lives with | | | | | |
| Friends | 1 | 1.8 | 0 | 0.0 | 0.195 |
| Family | 43 | 78.2 | 63 | 88.7 | |
| Alone | 11 | 20.0 | 8 | 11.3 | |
| Has children | | | | | |
| Yes | 24 | 43.6 | 49 | 69.0 | 0.004 |
| No | 31 | 56.4 | 22 | 31.0 | |
| Hours of sleep | | | | | |
| Up to 6 | 37 | 67.3 | 37 | 52.1 | 0.086 |
| More than 6 | 18 | 32.7 | 34 | 47.9 | |
| Labor data | | | | | |
| Front line professional | | | | | |
| Yes | 47 | 85.5 | 35 | 49.3 | <0.001 |
| No | 8 | 14.5 | 36 | 50.7 | |
| Type of service | | | | | |
| COVID ICU | 22 | 40.0 | 11 | 15.5 | <0.001 |
| COVID ward | 25 | 45.5 | 24 | 33.8 | |
| Other | 8 | 14.5 | 36 | 50.7 | |
| Position | | | | | |
| On call | 48 | 87.3 | 43 | 60.6 | 0.001 |
| Day worker | 7 | 12.7 | 28 | 39.4 | |
| Workload | | | | | |
| Up to 40 h | 15 | 27.3 | 31 | 43.7 | 0.149 |
| 40–60 h | 24 | 43.6 | 26 | 36.6 | |
| More than 60 h | 16 | 29.1 | 14 | 19.7 | |
| More than one professional relationship | | | | | |
| Yes | 48 | 87.3 | 61 | 85.9 | 0.825 |
| No | 7 | 12.7 | 10 | 14.1 | |
| Satisfactory remuneration | | | | | |
| Yes | 20 | 36.4 | 34 | 47.9% | 0.195 |
| No | 35 | 63.6 | 37 | 52.1% | |
| Had COVID-19 | | | | | |
| Yes | 27 | 49.1 | 20 | 28.2 | 0.016 |
| No | 28 | 50.9 | 51 | 71.8 | |

Source: Research data. The values highlighted in bold are intended to draw the reader's attention to statistically significant variables.

Among the professionals with results compatible with BS, 85.5% worked on the front line. Similar findings were observed in the studies by Kannampallil et al.¹⁰, Giusti et al.¹¹, and Demartini et al.¹²; however, the findings differed from those reported by Wu et al.¹³, Dimitriu et al.¹⁴, and Dinibutum¹⁵, who found a higher prevalence of BS in professionals working off the front line than among those who dealt directly with the disease¹³⁻¹⁵.

The highly contagious nature of COVID-19 coupled with the increased workload due to the overload of health services exposes these professionals to the risk of contracting the disease and spreading it to their families, which causes increased levels of stress and anxiety and, consequently, professional exhaustion¹⁰⁻¹².

These findings should be considered because of their potential impact on clinical practice. The development of BS in health professionals, especially those in the medical field, can have serious consequences since it is associated with increased rates of medical error and decreased productivity, which compromises the quality of care for critically ill individuals¹⁶.

Studies conducted prior to the pandemic showed a prevalence of BS that was greater than 40% and was higher in professionals working in emergency departments and ICUs¹⁷. COVID-19 introduced additional stress factors, such as fear of contracting the infection, fear of spreading the infection to family members, and social isolation¹⁸; these additional factors caused symptoms of stress and depression that impacted the physical and mental health of health care professionals¹⁹.

The MBI is the most commonly used instrument for measuring occupational burnout and is considered the gold standard⁶. There is a lack of data in the literature applying this tool to professionals working directly with COVID-19. One of the first studies included 220 physicians and found a 25% increase in EE and DP and an approximately 50% increase in rPA¹³. In this case series, among physicians working on the front line, these rates were 50% (EE), 23% (DP), and 64% (rPA), with the latter two being similar to the findings of the cited study.

Comparatively, a study by Giusti et al.¹¹ that applied the MBI-HSS to 330 health professionals showed that 66.7% had moderate to high levels of EE and rPA and 25% had moderate to high levels of DP¹¹, similar to the indices found in the present study.

The results of the chi-square test showed that gender was not a significant factor, corroborating the findings of the literature^{20,21}; however, the results of the present study differ from those of Kannampallil et al.¹⁰ and a recent study conducted in Brazil that reported a higher prevalence of BS in females²².

Age was divided into three groups, and age between 24 and 34 years was found to be a significant factor, indicating a higher prevalence of BS in younger professionals ($p=0.008$). This finding that disagrees with that of Gunasingam et al.²³, in which there was no association between burnout and age. However, it was consistent with other studies in which younger participants had a higher prevalence of BS^{22,24}.

Working in the ICU was associated with a higher prevalence of burnout ($p=0.001$), similar to the findings of a case series that included 1001 European intensivists²⁵ in which BS was present in 52%. Finally, having contracted COVID-19 was associated with a higher prevalence of BS ($p=0.016$), with statistical significance for all constructs. Similar findings were observed in a study of 330 health professionals in northern Italy¹¹.

CONCLUSIONS

The occurrence of BS among health professionals (particularly those in the medical field) working on the front line of the COVID-19 pandemic is undeniable and is an important factor to consider not only because of its impact on the mental health of these professionals but also because of its potential to compromise patient care.

In this case series, a positive association was found between the development of BS and action on the front line of the pandemic among physicians in Paraíba. In addition, the following variables were identified as significant factors: age between 24 and 33 years, not having children, working on the front line, working in the COVID ICU, being on call, and having contracted COVID-19.

These results highlight the importance of the early diagnosis and management of BS in doctors working on the front line during the pandemic to establish concrete measures that can increase support for the physical and mental health of these professionals.

AUTHORS' CONTRIBUTIONS

ARQPF: Conceptualization, Data curation, Investigation, Writing – original draft, Writing – review & editing. **HFCC:** Formal analysis, Project administration, Supervision. **ABS:** Conceptualization, Writing – original draft. **LCLD:** Writing – review & editing. **RRC:** Writing – review & editing. **MTL:** Formal analysis, Methodology. **KDTA:** Writing – review & editing. **CMBLL:** Supervision, Project administration, Visualization.

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Prognostic factors in triple-negative breast cancer: a retrospective cohort

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SUMMARY

OBJECTIVE: Triple-negative breast cancer (TNBC) is characterized by lack of estrogen receptor, progesterone receptor, and human epidermal growth factor receptor 2 (HER2) expression and accounts for 15–20% of all breast cancers. This study aims to analyze prognostic factors related to a reduction in overall survival (OS), disease-free survival (DFS), and risk of mortality and recurrence in TNBC.

METHODS: This is a retrospective observational cohort study. Medical records of 532 patients with breast cancer diagnosed from 2007 to 2020 were analyzed. Of these patients, 93 (17%) were women with TNBC. Ten medical records were excluded, and the final sample was composed of 83 women with TNBC. OS and DFS were estimated by the Kaplan-Meier model. Univariate analysis (log-rank test) and multivariate analysis (Cox regression) were used to examine prognostic factors related to a statistically significant reduction ($p < 0.05$) in OS and DFS and increased risk of mortality and tumor recurrence.

RESULTS: Smoking, advanced clinical stage, larger tumor size, angiolymphatic invasion, positive sentinel lymph node, axillary node involvement, higher cancer burden, surgical treatment with mastectomy, and recurrence were related to a significant decrease in OS and/or DFS and increased risk of mortality and/or recurrence in TNBC. The 10-year OS and DFS was around 61 and 65%, respectively.

CONCLUSIONS: Advanced clinical stage, positive sentinel lymph node, axillary node involvement, surgical treatment with mastectomy, and higher residual cancer burden were related to a significant reduction in OS and DFS and increased risk of mortality and recurrence in TNBC.

KEYWORDS: Survival analysis. Prognosis. Medical records. Pathological conditions. Anatomical. Triple-negative breast neoplasms.

INTRODUCTION

Breast cancer is a heterogeneous disease involving multiple genetic alterations¹. It is classified into molecular subtypes, based on the lack of protein expression of estrogen receptor (ER) and progesterone receptor (PR) and the absence of overexpression of human epidermal growth factor 2 receptor (HER2). Triple-negative (TN) subtype is defined as a breast cancer with negative expression of

estrogen/progesterone (ER/PR) hormone receptors and human epidermal growth factor receptor-2 (HER2) (either by immunohistochemistry [IHC; 0–1] or by fluorescent in situ hybridization [FISH negative if 2+ on IHC])². TN cancer tends to be more aggressive than other types of breast cancer. It is also associated with a poor prognosis due to its clinical behavior and lack of molecular targets for cancer therapy. Therefore, chemotherapy remains

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the primary treatment of choice for patients diagnosed at early or late stages³.

In Brazil, the National Cancer Institute estimated that 66,280 new breast cancer cases occurred in women in 2020. Breast cancer was the leading cause of death from cancer among this population⁴. On the other hand, triple-negative breast cancer (TNBC) accounts for around 15–20% of all breast cancers⁵. This molecular subtype of cancer is most commonly observed in young black and Hispanic women. In addition, it is associated with a higher prevalence of BCRA gene mutations (particularly BRCA1)⁶.

In comparison to other subtypes of breast cancer, survival is shorter and mortality rate is 40% in patients with TNBC within the first 5 years of diagnosis, as shown by epidemiological data. TNBC is a highly invasive tumor, and approximately 46% of patients with TNBC develop distant metastasis. Median survival time after metastasis is only 13.3 months, and the recurrence rate after surgery achieves 25%. Brain and visceral metastases frequently occur. The mortality rate of patients with TNBC within 3 months of recurrence is up to 75%⁷.

In the literature, diverse prognostic factors have been associated with TNBC, including recurrence, lymphovascular invasion, tumor size, lymph node involvement, and Ki-67 expression, among others^{8,9}. The prognostic value of Ki-67 in TNBC remains controversial, partly due to the lack of agreement on the cutoff point, which is estimated at 10–61%⁹.

Recent studies have also evaluated other prognostic factors. Oshi et al. correlated a high CD8 T-cell score with increased survival rates in patients with TNBC. O’Conor et al. reported that CD44⁺/CD24⁻ and ALDH1⁺ stem cells are indicators of a poor prognosis, contributing to chemotherapy resistance and metastatic tumors. Furthermore, some ongoing trials currently investigate specific genes or microRNA¹⁰⁻¹².

The current study aimed to analyze prognostic factors related to a reduction in overall survival (OS), disease-free survival (DFS), and risk of mortality and recurrence in TNBC.

METHODS

This is a retrospective observational cohort study. Medical records of 532 patients diagnosed with breast cancer were analyzed. Patients were seen from 2007 to 2020 in a private oncology health care facility in the city of Teresina (PI), Brazil. Of these patients, 93 (17%) were women with TNBC. Ten medical records were excluded: four of patients who had not completed treatment by the end of the follow-up (December 2020) and six with incomplete

or missing data. The final sample was composed of 83 women with TNBC.

Data were tabulated using the Microsoft Excel 2010[®] program. Statistical analysis was conducted in the Stata 14[®] program. The absolute (n) and relative (%) frequencies of each variable of the study were calculated. OS and DFS were estimated by the Kaplan-Meier method. Univariate (log-rank test) and multivariate (Cox regression) analysis investigated which prognostic factors were related to a statistically significant reduction ($p < 0.05$) in OS and/or DFS and a higher risk of mortality and/or recurrence. To perform Cox regression, the hazard ratios along with their respective 95% confidence intervals (95% CI) were estimated.

In the OS and DFS curves presented, follow-up had occurred between the time of TNBC diagnosis and the time of patient death or tumor recurrence, respectively. The maximum follow-up period was 157 months.

The study complied with all Brazilian principles for ethical research (National Health Council Resolution no. 466/12) and was approved by the Research Ethics Committee of the State University of Piauí, Teresina (PI), Brazil (CAAE: 30154720.0.0000.5209).

RESULTS

Prognostic factors (variables) related to the risk of mortality and/or recurrence and impact on the decrease in OS and/or DFS analyzed by univariate and multivariate analysis in this study were age, number of pregnancies, smoking, alcohol dependence, comorbid conditions (hypertension and diabetes), family history (of breast cancer and other cancers), clinical stage, degree of differentiation, tumor size, angiolymphatic invasion, sentinel lymph node, axillary node involvement, Ki-67, residual cancer burden, surgical treatment, and tumor recurrence.

Smoking, advanced clinical stage, larger tumor size, angiolymphatic invasion, positive sentinel lymph node, axillary node involvement, higher residual cancer burden, surgical treatment with mastectomy, and recurrence were regarded as significant risks ($p < 0.05$) of mortality in TNBC and are associated with decreased OS (Table 1).

In contrast, advanced clinical stage, positive sentinel lymph node, axillary node involvement, higher residual tumor burden, and surgical treatment with mastectomy were also related to a significant risk ($p < 0.05$) of tumor recurrence in TNBC, presenting a reduction in DFS (Table 2).

Survival curves (Figure 1) showed 10-year OS and DFS of around 61% and 65%, respectively.

Table 1. Prognostic factors, deaths, and overall survival (157 months of follow-up).

| Variables | n (%) | Death(s) n (%) | Univariate analysis | | Multivariate analysis | |
|--------------------------------|-----------|-------------------|-------------------------------|-----------------------------|-----------------------|------------------------|
| | | | Overall survival n (95%CI) | Log-rank test p-value | RR (95%CI) | Wald's test p-value |
| Age at diagnosis | | | | | | |
| ≤59 years | 50 (60.2) | 7 (14.0) | 86.0 (73.2–94.2) | 0.930 | 1.0 | 0.931 |
| ≥60 years | 33 (39.8) | 5 (15.2) | 84.8 (68.1–94.9) | | 1.05 (0.33–3.33) | |
| Number of pregnancies | | | | | | |
| None | 17 (20.5) | 2 (11.8) | 88.2 (63.6–98.5) | 0.358 | 1.0 | 0.987 |
| 1 | 13 (15.7) | 2 (15.4) | 84.6 (54.6–98.1) | | 1.02 (0.14–7.28) | |
| 2 | 22 (26.5) | 5 (22.7) | 77.3 (54.6–92.2) | | 2.19 (0.42–11.41) | |
| 3 | 19 (22.9) | 1 (5.3) | 94.7 (74.0–99.9) | | 0.32 (0.03–3.53) | |
| 4 and more | 12 (14.5) | 2 (16.7) | 83.3 (51.6–97.9) | | 1.05 (0.14–7.71) | |
| Smoking | | | | | | |
| No | 79 (95.2) | 10 (12.7) | 87.3 (78.0–93.8) | 0.004 | 1.0 | 0.015 |
| Yes | 4 (4.8) | 2 (50.0) | 50.0 (6.8–93.2) | | 7.28 (1.48–35.80) | |
| Alcohol dependence | | | | | | |
| No | 78 (94.0) | 10 (12.8) | 87.2 (77.7–93.7) | 0.094 | 1.0 | 0.118 |
| Yes | 5 (6.0) | 2 (40.0) | 60.0 (14.7–94.7) | | 3.47 (0.73–16.46) | |
| Hypertension | | | | | | |
| No | 60 (72.3) | 7 (11.7) | 88.3 (77.4–95.2) | 0.517 | 1.0 | 0.520 |
| Yes | 23 (27.7) | 5 (21.7) | 78.3 (56.3–92.5) | | 1.46 (0.46–4.70) | |
| Diabetes | | | | | | |
| No | 73 (88.0) | 10 (13.7) | 86.3 (76.2–93.2) | 0.328 | 1.0 | 0.341 |
| Yes | 10 (12.0) | 2 (20.0) | 80.0 (44.4–97.5) | | 2.11 (0.45–9.81) | |
| Family history (breast cancer) | | | | | | |
| No | 57 (68.7) | 10 (17.5) | 82.5 (70.0–91.2) | 0.459 | 1.0 | 0.467 |
| Yes | 26 (31.3) | 2 (7.7) | 92.3 (74.9–99.0) | | 0.56 (0.12–2.62) | |
| Family history (cancers) | | | | | | |
| No | 42 (50.6) | 6 (14.3) | 85.7 (71.5–94.6) | 0.824 | 1.0 | 0.825 |
| Yes | 41 (49.4) | 6 (14.6) | 85.4 (70.8–94.4) | | 1.14 (0.36–3.54) | |
| Clinical stage | | | | | | |
| IB | 25 (30.1) | 1 (4.0) | 96.0 (79.6–99.9) | 0.019 | 1.0 | 0.651 |
| IIB | 24 (28.9) | 2 (8.3) | 91.7 (73.0–99.0) | | 1.74 (0.16–19.49) | |
| IIIB | 23 (27.7) | 5 (21.7) | 78.3 (56.3–92.5) | | 6.63 (0.77–57.31) | |
| IIIC and IV | 11 (13.3) | 4 (36.4) | 63.6 (30.8–89.1) | | 10.67 (1.19–95.66) | |

Continue...

Table 1. Continuation.

| Variables | n (%) | Death(s) n (%) | Univariate analysis | | Multivariate analysis | |
|------------------------|-----------|-------------------|-------------------------------|-----------------------------|-----------------------|------------------------|
| | | | Overall survival n (95%CI) | Log-rank test p-value | RR (95%CI) | Wald's test p-value |
| Grade | | | | | | |
| G2 | 45 (54.2) | 6 (13.3) | 86.7 (73.2–94.9) | 0.932 | 1.0 | 0.933 |
| G3 | 38 (45.8) | 6 (15.8) | 84.2 (68.7–94.0) | | 0.95 (0.30–2.98) | |
| Tumor size (cm) | | | | | | |
| 0–2.5 | 48 (57.8) | 4 (8.3) | 91.7 (68.7–94.0) | 0.025 | 1.0 | 0.036 |
| >2.5 | 35 (42.2) | 8 (22.9) | 77.1 (59.9–89.6) | | 3.73 (1.09–12.74) | |
| Lymphatic invasion | | | | | | |
| No | 63 (75.9) | 3 (4.8) | 95.2 (86.7–99.0) | <0.001 | 1.0 | <0.001 |
| Yes | 20 (24.1) | 9 (45.0) | 55.0 (31.5–76.9) | | 17.48 (3.72–82.17) | |
| Vascular invasion | | | | | | |
| No | 67 (80.7) | 5 (7.5) | 92.5 (83.4–97.5) | <0.001 | 1.0 | 0.001 |
| Yes | 16 (19.3) | 7 (47.8) | 56.2 (29.9–80.2) | | 7.59 (2.20–26.18) | |
| Sentinel lymph node | | | | | | |
| Negative | 63 (75.9) | 6 (9.5) | 90.5 (80.4–96.4) | 0.009 | 1.0 | 0.017 |
| Positive | 20 (24.1) | 6 (30.0) | 70.0 (45.7–88.1) | | 4.23 (1.29–13.88) | |
| Axillary involvement | | | | | | |
| No | 45 (54.2) | 3 (6.7) | 93.3 (81.7–98.6) | 0.025 | 1.0 | 0.039 |
| Yes | 38 (45.8) | 9 (23.7) | 76.3 (59.8–88.6) | | 3.98 (1.07–14.76) | |
| Ki-67 (%) | | | | | | |
| ≤60 | 34 (47.0) | 4 (10.3) | 89.7 (75.8–97.1) | 0.232 | 1.0 | 0.243 |
| >60 | 44 (53.0) | 8 (18.2) | 81.8 (67.3–91.8) | | 2.05 (0.61–6.87) | |
| Residual cancer burden | | | | | | |
| pCR | 42 (50.6) | 2 (4.8) | 95.2 (83.8–99.4) | <0.001 | 1.0 | 0.505 |
| RCB-I and RCB-II | 29 (34.9) | 2 (6.9) | 93.1 (77.2–99.1) | | 1.99 (0.26–15.08) | |
| RCB-III | 12 (14.5) | 8 (66.7) | 33.3 (9.9–65.1) | | 27.80 (4.74–162.9) | |
| Surgical treatment | | | | | | |
| Conservative | 61 (73.5) | 6 (9.8) | 90.2 (79.8–96.3) | 0.012 | 1.0 | 0.020 |
| Mastectomy | 22 (26.5) | 6 (27.3) | 72.7 (49.8–89.3) | | 3.93 (1.24–12.4) | |
| Recurrence | | | | | | |
| No | 65 (78.3) | 3 (4.6) | 95.4 (87.1–99.0) | <0.001 | 1.0 | 0.001 |
| Yes | 18 (21.7) | 9 (50.0) | 50.0 (26.0–74.0) | | 15.38 (3.26–72.53) | |

RR: relative risk; 95%CI: 95% confidence interval; pCR: pathological complete response; RCB-I: minimal burden (residual disease); RCB-II: moderate burden (residual disease); RCB-III: extensive burden (residual disease). The values highlighted in bold are intended to draw the reader's attention to statistically significant variables

Table 2. Prognostic factors, tumor recurrence, and disease-free survival (157 months of follow-up).

| Variables | n (%) | Recurrence(s) n (%) | Univariate analysis | | Multivariate analysis | |
|--------------------------------|-----------|------------------------|------------------------------------|-----------------------------|-----------------------|---------------------------|
| | | | Disease-free survival n (95%CI) | Log-rank test p-value | RR (95%CI) | Wald's test p-value |
| Age at diagnosis (year) | | | | | | |
| Up to 59 | 50 (60.2) | 12 (24.0) | 76.0 (61.8–86.9) | 0.529 | 1.0 | 0.533 |
| 60 or above | 33 (39.8) | 6 (18.2) | 81.8 (64.5–93.0) | | 0.73 (0.33–3.33) | |
| Number of pregnancies | | | | | | |
| None | 17 (20.5) | 2 (11.8) | 88.2 (63.6–98.5) | 0.001 | 1.0 | 0.140 |
| 1 | 13 (15.7) | 5 (38.5) | 61.5 (31.6–86.1) | | 3.44 (0.66–17.77) | |
| 2 | 22 (26.5) | 9 (40.9) | 59.1 (36.4–79.3) | | 4.88 (1.05–22.67) | |
| 3 or more | 31 (37.3) | 2 (6.4) | 93.6 (78.6–99.2) | | 0.47 (0.07–3.34) | |
| Smoking | | | | | | |
| No | 79 (95.2) | 12 (20.2) | 79.8 (69.2–88.0) | 0.041 | 1.0 | 0.062 |
| Yes | 4 (4.8) | 2 (50.0) | 50.0 (6.8–93.2) | | 4.20 (0.93–18.91) | |
| Alcohol dependence | | | | | | |
| No | 78 (94.0) | 16 (20.5) | 79.5 (68.8–87.8) | 0.350 | 1.0 | 0.362 |
| Yes | 5 (6.0) | 2 (40.0) | 60.0 (14.7–94.7) | | 1.99 (0.45–8.73) | |
| Hypertension | | | | | | |
| No | 60 (72.3) | 14 (23.3) | 76.7 (64.0–86.6) | 0.471 | 1.0 | 0.476 |
| Yes | 23 (27.7) | 4 (17.4) | 82.6 (61.2–95.0) | | 0.67 (0.22–2.03) | |
| Diabetes | | | | | | |
| No | 73 (88.0) | 16 (21.9) | 78.1 (66.9–86.9) | 0.791 | 1.0 | 0.793 |
| Yes | 10 (12.0) | 2 (20.0) | 80.0 (44.4–97.5) | | 1.22 (0.28–5.36) | |
| Family history (breast cancer) | | | | | | |
| No | 57 (68.7) | 13 (22.8) | 77.2 (64.2–87.3) | 0.897 | 1.0 | 0.898 |
| Yes | 26 (31.3) | 5 (19.2) | 80.8 (60.6–93.4) | | 0.93 (0.33–2.63) | |
| Family history (cancers) | | | | | | |
| No | 42 (50.6) | 9 (21.4) | 78.6 (63.2–89.7) | 0.930 | 1.0 | 0.930 |
| Yes | 41 (49.4) | 9 (22.0) | 78.0 (62.4–89.4) | | 1.04 (0.41–2.63) | |
| Clinical stage | | | | | | |
| IB | 25 (30.1) | 1 (4.0) | 96.0 (79.6–99.9) | 0.017 | 1.0 | 0.134 |
| IIB | 24 (28.9) | 6 (25.0) | 75.0 (53.3–90.2) | | 5.04 (0.61–41.9) | |
| IIIB | 23 (27.7) | 6 (26.1) | 73.9 (51.6–89.8) | | 7.33 (0.88–61.06) | |
| IIIC and IV | 11 (13.3) | 5 (45.4) | 54.6 (23.4–83.2) | | 15.25 (1.78–130.70) | |
| Grade | | | | | | |
| G2 | 45 (54.2) | 10 (22.2) | 77.8 (62.9–88.8) | 0.633 | 1.0 | 0.635 |
| G3 | 38 (45.8) | 8 (21.0) | 79.0 (62.7–90.4) | | 0.80 (0.31–2.03) | |
| Tumor size (cm) | | | | | | |
| 0–2.5 | 48 (57.8) | 8 (16.7) | 83.3 (69.8–92.5) | 0.144 | 1.0 | 0.154 |
| >2.5 | 35 (42.2) | 10 (28.6) | 71.4 (53.7–85.4) | | 1.97 (0.78–5.02) | |
| Lymphatic invasion | | | | | | |
| No | 63 (75.9) | 11 (17.5) | 82.5 (70.9–90.9) | 0.072 | 1.0 | 0.082 |
| Yes | 20 (24.1) | 7 (35.0) | 65.0 (15.4–59.2) | | 2.34 (0.90–6.10) | |

Continue...

Table 2. Continuation.

| Variables | n (%) | Recurrence(s) n (%) | Univariate analysis | | Multivariate analysis | |
|------------------------|-----------|------------------------|-------------------------------------|-----------------------------|-----------------------|---------------------------|
| | | | Disease-free survival n (95% CI) | Log-rank test p-value | RR (95%CI) | Wald's test p-value |
| Vascular invasion | | | | | | |
| No | 67 (80.7) | 13 (19.4) | 80.6 (69.1–89.2) | 0.336 | 1.0 | 0.343 |
| Yes | 16 (19.3) | 5 (31.2) | 68.8 (41.3–89.0) | | 1.65 (0.58–4.66) | |
| Sentinel lymph node | | | | | | |
| Negative | 63 (75.9) | 10 (15.9) | 84.1 (72.7–92.1) | 0.008 | 1.0 | 0.017 |
| Positive | 20 (24.1) | 8 (40.0) | 60.0 (36.0–80.9) | | 3.23 (1.27–8.22) | |
| Axillary involvement | | | | | | |
| No | 45 (54.2) | 5 (11.1) | 88.9 (75.9–96.3) | 0.009 | 1.0 | 0.016 |
| Yes | 38 (45.8) | 13 (34.2) | 65.8 (48.6–80.4) | | 3.57 (1.27–10.02) | |
| Ki-67 (%) | | | | | | |
| ≤60 | 34 (47.0) | 5 (12.8) | 87.2 (72.6–95.7) | 0.066 | 1.0 | 0.077 |
| >60 | 44 (53.0) | 13 (29.6) | 70.4 (54.8–83.2) | | 2.53 (0.90–7.11) | |
| Residual cancer burden | | | | | | |
| pCR | 42 (50.6) | 1 (2.4) | 97.6 (87.4–99.9) | <0.001 | 1.0 | 0.300 |
| RCB-I | 8 (9.6) | 1 (12.5) | 87.5 (47.3–99.7) | | 4.34 (0.27–69.60) | |
| RCB-II | 21 (25.3) | 5 (23.8) | 76.2 (52.8–91.8) | | 15.22 (1.77–130.82) | |
| RCB-III | 12 (14.5) | 11 (91.7) | 8.3 (0.2–38.5) | | 74.10 (9.39–584.45) | |
| Surgical treatment | | | | | | |
| Conservative | 61 (73.5) | 11 (18.0) | 82.0 (70.0–90.6) | 0.025 | 1.0 | 0.033 |
| Mastectomy | 22 (26.5) | 7 (31.8) | 68.2 (45.1–86.1) | | 2.83 (1.09–7.37) | |

RR: relative risk; 95%CI: 95% confidence interval; CR: pathological complete response; RCB-I: minimal burden (residual disease); RCB-II: moderate burden (residual disease); RCB-III: extensive burden (residual disease). The values highlighted in bold are intended to draw the reader's attention to statistically significant variables.

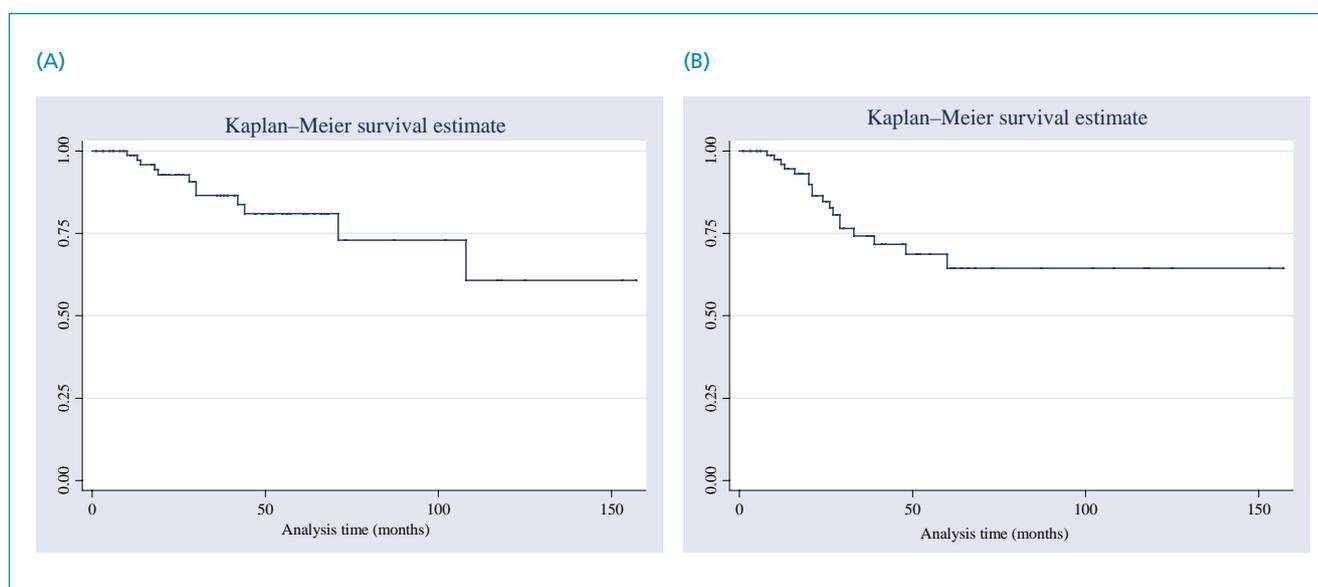


Figure 1. Overall survival (A) and disease-free survival (B) curves (157 months of follow-up).

DISCUSSION

Variables such as age, number of pregnancies, alcohol dependence, hypertension, diabetes, family history of breast cancer and other cancers, degree of differentiation, and Ki-67 did not show any significant reduction in OS and/or DFS in this study. Furthermore, these variables did not present an increased risk of mortality and/or recurrence.

In this study, 60.2% of the patients were diagnosed before the age of 59 years and 79.5% had a history of previous pregnancies. In a study investigating 841 patients with TNBC diagnosed from 1994 to 2015 in four large oncology centers, Urru et al.¹³ also described that TNBC predominated in young patients with previous pregnancies.

Alcohol dependence is a well-established risk factor for the development of breast cancer. However, the literature indicates that there is no relationship between alcohol dependence and increased risk of TNBC¹⁴. Alcohol dependence is also associated with a worse chemotherapy response (first-line treatment for TNBC), worsening survival in these cases¹⁵. Alcohol-dependent patients in this study did not show a worse OS and/or DFS and an increased risk of mortality and/or recurrence.

Studies have associated hypertension, diabetes, and tumor grade with increased mortality in TNBC^{16,17}. However, in this study, there was also no significant reduction in OS and/or DFS and increased risk in mortality and/or recurrence, in relation to these variables.

Ki-67 and family history of breast cancer and other cancers are considered useful in the prognosis of TNBC¹⁸. Nevertheless, the literature indicates that there is controversy surrounding the methods used for analysis of these prognostic factors^{9,18}. In this study, Ki-67 (with a cutoff point stipulated at 60%) and a family history of breast cancer and other cancers were not implicated in a significant decrease in OS and/or DFS and increased risk of mortality and/or recurrence.

Smoking, advanced clinical stage, larger tumor size, angiolymphatic invasion, positive sentinel lymph node, axillary node involvement, higher residual tumor burden, surgical treatment with mastectomy, and recurrence were prognostic factors significantly related to a decreased OS and/or DFS, representing an increased risk of mortality and/or recurrence in TNBC, respectively. These results are based on previous literature data¹⁹⁻²³.

In a study of 583 patients, Mousavi et al.²⁴ demonstrated that lymph node involvement was the only prognostic factor

related to decreased DFS in TNBC. However, other studies have demonstrated that a larger tumor size and residual tumor burden correlate with a higher recurrence risk and lower DFS in TNBC²⁵. Data in this study also demonstrated a higher recurrence risk and a lower DFS in relation to all these prognostic factors.

More recent analyses have indicated that breast-conserving surgery shows higher OS and DFS and lower risk of tumor recurrence, compared to mastectomy in TNBC, particularly at early stages²³. In this study, data also show a higher OS and DFS, along with a decreased risk of mortality and recurrence in patients with TNBC undergoing breast-conserving surgery.

Survival analysis in cancer is influenced by diverse variables inherent in each sample (tumor size, prevalence of tumor stage, and nature of prognostic factors, among others)²⁶. Fayaz et al.²⁷ conducted a study on the 10-year OS and DFS of 359 women diagnosed with TNBC from 1999 to 2009, indicating values of 66% for OS and 59% for DFS. These results were quite similar to findings in this study, showing that 10-year OS and DFS were 61 and 65%, respectively.

Limitations of this study were sample size, the retrospective nature of the study, and its performance in a single center.

CONCLUSION

Advanced clinical stage, positive sentinel lymph node, axillary node involvement, surgical treatment with mastectomy, and higher residual cancer burden were prognostic factors related to a statistically significant reduction in OS and DFS and an increased risk of mortality and recurrence in TNBC.

AUTHORS' CONTRIBUTIONS

REARC: Conceptualization, Data curation, Formal analysis, Methodology, Project administration, Writing – original draft, Writing – review & editing. **FTRO:** Conceptualization, Data curation, Formal analysis, Methodology, Project administration, Writing – original draft. **ALNA:** Conceptualization, Data curation, Formal analysis, Methodology, Project administration, Writing – review & editing. **SCV:** Conceptualization, Data curation, Formal analysis, Methodology, Project administration, Writing – review & editing. All authors have read and approved the final draft.

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The timing of micro-TESE: what is the ideal age for male and female partner to bring a child to home?

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SUMMARY

OBJECTIVE: The aim of this study was to analyze the results of microsurgical testicular sperm extraction (micro-TESE) and investigate the potential factors that may affect the successful sperm retrieval and timing of micro-TESE.

METHODS: A total of 56 patients with nonobstructive azoospermia (NOA) who underwent micro-TESE procedure between January 2017 and December 2019 were retrospectively analyzed. The patient age, marriage duration, infertility duration, smoking, chronic illness, varicocele status, previous scrotal surgeries, and the presence of genetic disease were noted by an urologist for all patients.

RESULTS: The mean age of patients was 33.28±4.4 (22–44) years. Our total sperm-retrieval rate was 55.4% (n:31). Sixteen (28.6%) pregnancies were achieved and 15 (26.8%) healthy live births could be managed. Only the marriage duration (p=0.016) and infertility duration (p=0.015) were detected to be the significant factors to manage successful sperm retrieval. Men with NOA younger than 35.2 years and having a female partner younger than 36.9 years seemed to have the best chance to have a living healthy baby.

CONCLUSIONS: The fertility decreased by both male and female age and for men with NOA. The early visit to doctor seemed to have positive effect.

KEYWORDS: Infertility. Live birth. Testicular sperm retrieval. Nonobstructive azoospermia. Pregnancy.

INTRODUCTION

Infertility is the inability of a sexually active couple to get pregnancy despite unprotected regular sexual intercourse for at least 1 year¹. Approximately 15% of the couples cannot get pregnancy in the first year and as a result they seek help from reproductive health care centers for infertility treatment^{2,3}. Male factor is responsible for approximately half of the infertility cases⁴. Azoospermia is the absence of spermatozoa in the ejaculate. It is found in approximately 10% of the males undergoing treatment for infertility^{3,5}. The majority of the cases are non-obstructive azoospermia (NOA), a condition that is essentially a spermatogenic impairment⁶. Impaired spermatogenesis may

be caused by idiopathic factors, cryptorchidism, orchid, radiation, gonadotoxic agents, systemic diseases, testicular trauma, and testicular torsion⁷.

Micro-TESE (microsurgical testicular sperm extraction) has been first described by Schlegel et al.⁸ and used as the most important method in retrieving sperm in the patients with NOA. Despite many studies on this field, unfortunately, sperm-retrieval rate (SRR) by micro-TESE reached approximately 50–60%^{5,9,10}. Even though sperm is retrieved with this method, clinical data related to pregnancy and live birth rates are limited since a follow-up process is necessary after sperm retrieval^{5,10}.

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There is no clinical parameter that definitely indicates whether spermatozoa are present in the testicles prior to micro-TESE in patients with NOA; studies on this subject are currently ongoing. The evaluated parameters included the result of the testicular biopsy, testicular size, serum hormone level, hormonal therapy (HT), genetic analysis result, and TESE method^{3,5,7,11}. In the light of these data, the chance of live birth for the couples increases with an increase in successful sperm retrieval by micro-TESE.

Advanced ages of both male and female spouses affect reproductive functions negatively. Sperm count and quality are reduced in males with advanced age¹². In the literature, there is no study on the relationship between the timing of micro-TESE procedure and the ideal age required for couples to bring a child to home. The present study aims to analyze the results of micro-TESE procedure as a minimally invasive, safe, and effective sperm-retrieval method and investigate the potential factors that may affect the successful sperm retrieval and timing of micro-TESE procedure.

METHODS

Participants and study design

A total of 56 patients with NOA who underwent micro-TESE procedure between January 2017 and December 2019 in our clinic were retrospectively analyzed. The diagnosis of azoospermia was confirmed by performing sperm analysis in accordance with the World Health Organization guideline from the ejaculates obtained by masturbations in two different times from all the patients¹². The patient selection criteria for micro-TESE were:

- a) infertility because of NOA;
- b) female partner with healthy reproductive systems;
- c) age at least 18 years;
- d) the absence of a mental illness or a psychiatric disorder; and
- e) the ability to read and write in Turkish language.

After obtaining medical history, the patients underwent a detailed physical assessment of urogenital system including secondary sexual characteristics, testicular consistency and size, the presence of vas deferens, and varicocele examination. The sociodemographic data such as patient and spouse age, duration of marriage and childbirth expectation, presence of child, cigarette smoking status, educational status, history of chronic disease, and surgery were enquired. The presence and type of previous treatment for azoospermia were questioned.

Hormonal assessment included serum follicle-stimulating hormone (FSH), luteinizing hormone (LH), and total testosterone (TT). The patients were divided into etiological groups as hypergonadotropic hypogonadism (hyper-hypo: high FSH

and LH, low TT), hypogonadotropic hypogonadism (hypo-hypo: low FSH, LH, and TT), and idiopathic (normal FSH, LH, and TT). All the hormone tests mentioned above were evaluated 1 month before micro-TESE.

Testicular size (mL), the presence of reflux flow in the venous system, and maximum venous diameter (mm) were assessed using scrotal color Doppler ultrasonography. The presence of varicocele was investigated radiologically.

The genetic analysis results of the patients including karyotype analysis and Y-chromosome microdeletion (AZFa, AZFb, and AZFc) were evaluated.

Data including the side of micro-TESE procedure, SRR, and the side of the testicle from which sperm was retrieved were recorded. At the end of the procedure, histopathological examination of the testicular tissue (tubular atrophy, Sertoli cell only, maturation arrest, hypospermatogenesis, normospermatogenesis, and granulomatous inflammation) was performed.

Micro-TESE procedure

A complete micro-TESE procedure was performed by two urologists experienced in microsurgery in the supine position under spinal anesthesia. Scrotal raphe was entered with midline longitudinal incision, and testicle was unilaterally exposed. Then, an incision was made in the tunica albuginea and testicular parenchyma was exposed in its equatorial plane. The dilated seminiferous tubules were detected under microscope (at 20x magnification) and adequate samples were obtained from the tissue that may contain spermatozoa. When no spermatozoa could be detected in one testicle, the other testicle was incised using same approach and spermatozoa were searched. These tubules were examined by the embryologist, and live spermatozoa were prepared to be used in intracytoplasmic sperm injection (ICSI) procedure or frozen if detected. In the same session, a biopsy was obtained from the testicular parenchyma and put into Bouin's solution and sent for histopathological examination. After obtaining the samples, the tunica albuginea was closed using 4/0 absorbable suture. Antibiotherapy, analgesic agent, and bed rest were recommended postoperatively for 5 days after the procedure.

Ovarian stimulation, fertilization, and embryo transfer

All recruited women had regular menstruation periods ranging from 24 to 35 days. Women who were treated with gonadotropin-releasing hormone (GnRH) antagonist-based protocols without pretreatment by hormonal suppression were also included. Controlled ovarian hyperstimulation was

performed with the administration of gonadotropin using recombinant FSH: either Gonal-F (Serono Laboratories, Germany) or human menopausal gonadotropin Menogon (Ferring Pharmaceuticals, Switzerland), individually or combined, starting on day 2 of the menstrual cycle. The GnRH antagonist Cetrotide (Serono) was given on day 6 of the stimulation at 0.25 mg/day subcutaneously and continued until human chorionic gonadotropin (hCG) was administered. Initial dosage of the gonadotropins was determined on the basis of patient's age, antral follicle count, day 3 FSH level, and body mass index. The stimulation was generally achieved with daily dosing of a total of 150–300 IU/day, with the gonadotropin dose being adjusted according to the ovarian response assessed by E2 levels and a transvaginal sonography. Oocyte maturation was triggered by 10,000 IU of hCG (Choriomon 5000 IU; IBSA) or recombinant hCG (Ovitrelle 250 mg; Serono) or 0.2 mg triptorelin, GnRH agonist (Gonapetyl 0.1 mg; Ferring), which was administered after at least two follicles had a mean diameter of 17 mm. Transvaginal oocyte retrieval was performed 36 h after hCG administration in the standard manner, with the patient under general anesthesia. All oocytes were inseminated with an ICSI. Luteal progesterone (P) supplementation was started 1 day after retrieval, using either 8% P vaginal gel (Crinone; Serono) daily or vaginal P suppositories (200 mg) three times a day or an additional bolus of 1.500 IU hCG on the day of oocyte retrieval in GnRH agonist trigger cycles. Embryo transfer was performed by a soft catheter (Gynetics, Belgium) with the guidance of transabdominal ultrasonography on day 3 or 5.

Serum β -hCG levels were determined 2 weeks after embryo transfer. A biochemical pregnancy was defined as a positive serum β -hCG test with no sonographically detectable gestational sac, whereas miscarriage was defined as pregnancy loss following ultrasound confirmation of an intrauterine gestation sac. The live birth was defined as delivery of a viable infant at ≥ 28 weeks of gestation after embryo transfer.

Ethical approval

This study was approved by the Ethics Committee of Gülhane Training and Research Hospital, Ankara, Turkey (approval number: 2020-44).

Statistical analysis

Statistical analysis was done using Statistical Package for Social Sciences 20.0 software for MAC (Chicago, USA) by an expert biomedical statistician. Kolmogorov-Smirnov test was used to assess normalization of the variables. Descriptive statistics were noted as mean \pm standard deviation (minimum-maximum) if the

variables are in normal distribution, and median (minimum-maximum) if the variables are in non-normal distribution, or as numbers or percentiles. Mann-Whitney *U* test was used for comparing groups. A $p < 0.05$ was accepted as statistically significant.

RESULTS

There were 56 male patients in our study. The mean age of patients and their spouses at the time of micro-TESE was 33.28 ± 4.40 (22–44) and 30.42 ± 4.62 (20–41), respectively. Only 3 (5.4%) patients had a child before. Sociodemographic characteristics and descriptive data of the patients are presented in Table 1.

Sixteen (28.6%) patients had a treatment for infertility before: 11 had TESE without any additional treatment, 2 had HT, and 3 had HT+TESE. Of the 11 (19.6%) patients who had TESE without any additional treatment before, 6 (54.7%) had successful sperm retrieval at the first micro-TESE and 2 (33.3 of 54.7 of 19.6%) had a child. Two (100 of 3.6%) patients who had HT before had successful sperm retrieval at masturbation and one (50 of 100 of 3.6%) had

Table 1. Sociodemographic characteristics, sonographic evaluation results, and micro-TESE results of patients with nonobstructive azoospermia.

| Factors | Mean \pm SD | Min–Max |
|---------------------------------|-----------------|---------|
| Marriage duration (years) | 5.14 \pm 2.53 | 2–11 |
| Infertility duration (years) | 3.42 \pm 2.15 | 1–10 |
| Factors | n | % |
| Smoking | 21 | 37.5 |
| Chronic illness | 8 | 14.3 |
| Education degree | | |
| Elementary and secondary school | 6 | 10.7 |
| High school | 31 | 55.4 |
| University | 19 | 33.9 |
| Previous inguinoscrotal surgery | 10 | 17.9 |
| Orchiopexy | 4 | 7.14 |
| Orchiectomy | 4 | 7.14 |
| Varicocelectomy | 1 | 1.78 |
| Herniorrhaphy | 1 | 1.78 |
| Etiological classification | | |
| Hyper-hypo | 27 | 48.2 |
| Idiopathic | 29 | 51.8 |

Continue...

Table 1. Continuation.

| Factors | n | % |
|----------------------------------|-----------|---------|
| Genetic diseases | | |
| Klinefelter syndrome | 3 | 5.4 |
| Microdeletion of Y chromosome | 2 | 3.6 |
| Physical examination | | |
| Right small testes | 17 | 30 |
| Left small testes | 21 | 37.5 |
| Palpable vas deferens | 56 | 100 |
| Varicocele | 18 | 32.1 |
| Right | 1 | 1.78 |
| Left | 17 | 30.3 |
| Factors | Mean±SD | Min–Max |
| Maximal vein diameter (mm) | | |
| Right | 0.11±0.5 | 0.2–2.3 |
| Left | 0.9±0.3 | 0.4–5.5 |
| Testicular volume (mL) | | |
| Right | 9.56±4.39 | 0–14.2 |
| Left | 9.57±4.42 | 0–14.8 |
| Factors | n | % |
| Side of micro-TESE | | |
| Right | 19 | 34 |
| Left | 10 | 18 |
| Bilateral | 27 | 48 |
| Sperm retrieval after micro-TESE | | |
| Sperm positive (presence) | 31 | 55.4 |
| Sperm negative (absence) | 25 | 44.6 |
| Sperm positive testicles | | |
| Right | 18 | 32.1 |
| Left | 10 | 17.9 |
| Bilateral | 3 | 5.40 |
| Pathologic examination | | |
| Tubular atrophy | 3 | 5.35 |
| Sertoli cell only | 15 | 26.78 |
| Maturation arrest | 8 | 14.28 |
| Hypospermatogenesis | 7 | 12.50 |
| Normospermatogenesis | 10 | 17.85 |
| Granulomatous inflammation | 1 | 1.78 |
| Missing | 12 | 21.42 |

a child. Three (100 of 5.4%) patients who had HT+TESE before had successful sperm retrieval at the first TESE, but none of them (0 of 100 of 5.4%) had a child.

The physical examination and sonographic evaluation results of the patients are presented in Table 2.

Our total SRR was 55.4% in 56 patients. Micro-TESE results of the patients are summarized in Table 1. Sixteen (28.6%) biochemical pregnancies were achieved, and 15 (93 of 28.6%) (26.8% of total) healthy live births could be managed. Miscarriage was noted in one case.

Only the marriage duration and infertility duration were detected to be the significant factors to manage successful sperm retrieval. The factors such as patient age, smoking status, having a chronic illness or not, education degree, previous scrotal surgeries, varicocele status, karyotype analyze, and Y-chromosome microdeletion were not found to affect SRR (Table 2). The marriage duration was 4.41 ± 3.91 and 6.04 ± 2.93 years in successful sperm-retrieval group and failure group, respectively ($p=0.016$). The infertility duration was 2.8 ± 1.7 and 4.2 ± 2.43 years in successful sperm-retrieval group and failure group, respectively ($p=0.015$).

For having a healthy live birth, concomitant use of patient and female partner age were found to be important factors. The receiver operating characteristic (ROC) curve of both these factors gives 0.611 as an area under curve value, implying the moderate strength for use. The SRR decreased significantly when age exceeded 35.2 years for men, and healthy live birth rate decreased significantly when the female partner age exceeded 36.9 years (Figure 1).

Table 2. Factors affecting the sperm retrieval in micro-TESE operations.

| Factors | p-value* | Odds ratio |
|---------------------------------|----------|------------|
| Patient age | 0.197 | 0.920 |
| Marriage duration | 0.016 | 0.894 |
| Infertility duration | 0.015 | 0.831 |
| Smoking | 0.790 | 0.835 |
| Chronic illness | 0.459 | 2.270 |
| Education degree | 0.072 | 2.726 |
| Previous inguinoscrotal surgery | 0.205 | 3.057 |
| Varicocele | 0.841 | 0.872 |
| Karyotype analyze | 0.828 | 1.572 |
| Y-chromosome microdeletion | 0.999 | 1.000 |

*Logistic regression.

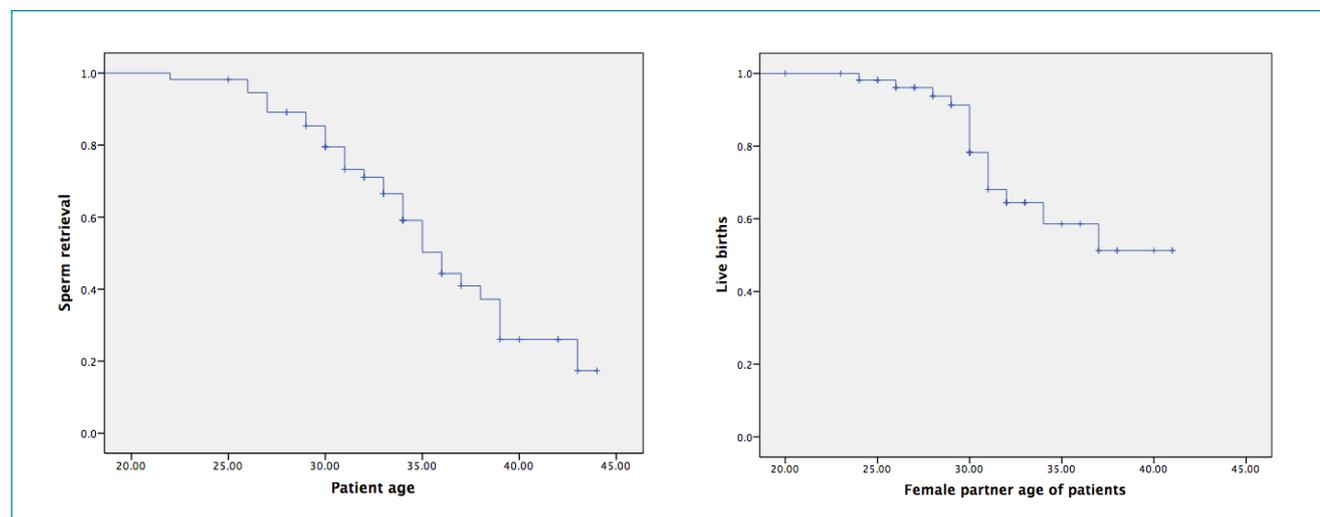


Figure 1. Sperm-retrieval rate according to patients' age and live birth rate according to the female partner age of patients who had micro-TESE.

DISCUSSION

NOA was historically accepted as an incurable condition which requires donor sperm for fertilization. Substantial improvements regarding fertilization have been achieved in patients with NOA after the introduction of micro-TESE procedure¹³. In the present time, the most beneficial and common treatment method for the males with NOA is combined micro-TESE and ICSI.

Mean age of the patients in our study (33.28 ± 4.4) was similar to the previous studies in the literature^{3,5,11,14,15}. In the literature, we found that even a 65-year-old patient had micro-TESE³. The oldest patient in our study was 44 years old. The relationship between patient age and sperm retrieval by micro-TESE has been investigated in many studies. Although assisted reproductive techniques have been accepted to be more effective in the young patients than in elderly ones, data on this subject vary¹⁶. In our study, we have found no statistically significant difference between SRR regarding patient age ($p=0.197$). Eken and Gulec⁵ conducted a study on sperm retrieval by micro-TESE procedure in patients with NOA and found no significant relationship between patient age and SRR ($p=0.14$). Spahovic et al.¹⁵ applied correlation test between the patients with positive and negative micro-TESE results and determined no statistically significant correlation in terms of age ($p>0.05$). Enatsu et al.¹¹ in a case series of Japanese males found interestingly a statistically significant correlation between advanced age and successful SRR ($p=0.01$). In contrast, Ramassamy et al.¹⁷ stated that patient age does not affect sperm retrieval negatively in the males who underwent micro-TESE and that elderly males predispose to acquired NOA.

Smoking is a well-documented risk factor that has many negative effects, particularly on sperm count and sperm morphology^{16,18,19}. We have detected in our patients that smoking is not predictive factor on successful sperm retrieval by micro-TESE ($p=0.79$). The patients were divided into two groups as smokers and nonsmokers in a study in which the results of TESE/ICSI procedures were performed on the azoospermic patients¹⁹. A higher sperm motility was detected in the non-smokers compared with smokers after TESE and before sperm freezing process (45.5 and 14.8%, respectively; $p<0.001$). No significant correlation was determined in another study that evaluated the relationship between successful sperm retrieval by micro-TESE and cigarette smoking ($p=0.535$)³. Pavan-Jukic et al.²⁰ have investigated the independent variables that may predict sperm retrieval prior to TESE. Cigarette smoking was found only to be a prominent statistically negative risk factor for sperm retrieval ($p=0.045$).

An analysis of patients with NOA may reveal surgery history such as orchiopexy, orchiectomy, varicocelectomy, and herniorrhaphy. It was determined that 10 (17.9%) of 56 patients had previous inguinoscrotal surgery. The most common previous surgeries were orchiopexy (n:4) and orchiectomy (n:4). In our study, these previous surgery histories were evaluated together and found to have no impact on sperm retrieval prior to micro-TESE ($p=0.205$). In contrast, another study has analyzed the inguinoscrotal surgeries separately and found only varicocelectomy to predict spermatozoa retrieval ($p=0.009$)³. Only 1 (10%) of 10 patients had previous varicocelectomy in the history of inguinoscrotal surgery (1.78% of 56 patients). A history of previous varicocelectomy may

be determined in a part of the patients with NOA since they have a long-term expectation of fertility. Although the rate of varicocele history (n:1; 1.78%) was low in our study, data reported in other studies were limited (19.5, 1.51, 10, and 17.7%, respectively)^{3,11,15,20}.

The presence of varicocele has a progressive harmful effect on the testicles in the normal population. Even though treatment of varicocele in patients with NOA is controversial, the number of the motile spermatozoa increase after varicocele; therefore, some studies recommended the treatment of varicocele before undergoing TESE/ICSI procedure^{6,21}. In contrast, the adverse studies suggest that many patients with NOA need ICSI procedure even in repaired varicocele⁶. Hence, the couples should be informed comprehensively about the necessity of varicocele in patients with NOA. We have detected varicoceles in 18 (32.1%) of 56 patients and most of them were left-sided varicoceles (n:17; 30.3%). Varicocele was found in varying frequencies (18.8, 9.42, and 29%, respectively) in this patient group^{3,11,20}. We have demonstrated that the presence of varicocele has no impact on successful sperm retrieval before micro-TESE (p=0.841). Other studies showed that the presence of varicocele did not make a statistically significant difference between the TESE-positive and TESE-negative groups (p=0.828 and p=0.263, respectively)^{3,20}.

Klinefelter syndrome (47,XXY) is the most commonly found chromosome anomaly associated with gender chromosomes in men and is responsible for 10% of the azoospermic patients^{2,6}. The patients with Klinefelter syndrome are usually azoospermic; however, spermatozoa have been encountered in 69% of patients by micro-TESE in the literature⁶. We have detected 3 (5.4%) patients with Klinefelter syndrome in our study. Of these three patients, spermatozoa were obtained by micro-TESE in two patients, and biochemical pregnancy in one patient with ICSI. However, this pregnancy did not result in live birth. AZF subregions (AZFa, AZFb, AZFc) related to sperm production are located in the q11 region on the long arm of Y chromosome. The microdeletions in this region may cause azoospermia^{2,6}. AZFc is the most commonly encountered microdeletion (75%) and is associated with higher chance of sperm retrieval. AZFc and AZFa+AZFc were determined in one patient each. However, biochemical pregnancy could be obtained in these two patients. SRR was not found to be significantly correlated with karyotype analysis and Y-chromosome microdeletion (p=0.828 and p=0.999, respectively).

As stated above, we have analyzed the various factors that may affect sperm retrieval before micro-TESE procedure. The marriage duration and infertility duration were found

to be statistically significantly effective on successful sperm retrieval (p=0.016 and p=0.015, respectively). Regarding marriage duration, the results of micro-TESE procedure were 4.41±3.91 and 6.04±2.93 years in the positive and negative groups, respectively. Boeri et al.²² have conducted an observational study with a large population to analyze the effect of infertility duration on the semen parameters and concluded that sperm concentration was negatively correlated with prolonged infertility duration. Additionally, higher rates of azoospermia were associated with longer infertility duration (p=0.03). In our study, infertility durations were 2.8±1.7 and 4.2±2.43 years in the positive and negative groups, respectively. From this point of view, prolonged duration of marriage and infertility can be considered as potential risk factors for fertilization.

In our study, SRR by micro-TESE was 55.4% (n:31). Taking into consideration that varicocele was found more commonly in the left side, we started micro-TESE procedure usually at the right side (except atrophic testicle). SRR in the right testicle (n:18; 32.1%) was found to be higher than the left testicle (n:10; 17.9%). Sperm could be retrieved from both testicles in 3 (5.4%) patients. Biochemical pregnancy (positive β -hCG) was monitored in 16 (28.6%) of 31 patients. Live birth was achieved in 15 (26.8) of these 16 patients. SRR by micro-TESE in patients with NOA is approximately 50–60%^{5,9,10,20}. Our testicular SRR was similar with the literature. Only a small number of studies have provided data on pregnancy and live birth following TESE procedure^{5,10,14}. Eken and Gulec⁵ have retrieved sperm in 95 (65.5%) of the 145 patients with NOA by micro-TESE. In their study, the numbers of clinical pregnancies and live births were 41 (28.2%) and 26 (17.9%), respectively. In a current meta-analysis, cumulative pregnancy and live birth rates per ICSI cycle were 29% and 24%, respectively¹⁰. SRR, pregnancy, and live birth rates in another study investigating the success of TESE/ICSI were 40.5, 18, and 13%, respectively¹⁴. In the light of the given data, our pregnancy rate was close to the literature data whereas our live birth rate was somewhat higher. Live birth did not occur in only 1 of the 16 patients in whom biochemical pregnancy was achieved. In other words, according to our data, live birth may occur with a great probability if biochemical pregnancy could be achieved by TESE/ICSI procedure in patients with NOA.

It is known that ages and reproductive reserves of the couples are substantial for a healthy live birth. The analysis of ROC curve with respect to the patient age and SRR in the males with NOA indicated that SRR significantly decreased if the patient age exceeds 35.2 years. Healthy live birth rate significantly decreased when age of the female partner exceeded 36.9 years. We have analyzed the relationship between the timing of

micro-TESE procedure and ages of the spouses, thereby providing additional information to the literature.

Two major limitations exist in our study. First is the retrospective design of the study and second is the lack of participants. Despite these limitations, our study has provided useful data on biochemical pregnancy rates, live birth rates, the effect of the patient age on SRR, and the effect of the female partner's age on the live birth rates. As a consequence, prospective randomized studies are needed in future to discover the effective parameters on sperm retrieval in patients with NOA.

CONCLUSIONS

The fertility decreased by both male and female age and for men with NOA. Men with NOA younger than 35.2 years and having a female partner younger than 36.9 years seemed to have the best chance to have a living healthy baby. The early visit to doctor seemed to have positive effect. The other factors were not statistically significant.

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ETHICS STATEMENT

The present study protocol was reviewed and approved by the institutional review board of Gülhane Training and Research Hospital, Ankara, Turkey (approval number: 2020-44).

AUTHORS' CONTRIBUTIONS

BT: Conceptualization, Data curation, Investigation, Methodology, Software, Writing – original draft. **TE:** Conceptualization, Writing – original draft. **SS:** Data curation, Validation. **EK:** Formal analysis, Validation, Writing – review & editing. **UF:** Resources, Writing – review & editing. **CK:** Resources. **STC:** Methodology, Writing – review & editing. **SB:** Software. **MG:** Supervision. **OFK:** Investigation, Visualization.

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Comparison of nonspecific inflammatory markers in endometrial cancer and hyperplasia

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SUMMARY

OBJECTIVE: This study aims to analyze inflammatory markers among patients with endometrial cancer, hyperplasia with atypia/endometrial intraepithelial neoplasia, hyperplasia without atypia, and normal controls, thus observing the stage at which inflammation becomes the most significant.

METHODS: A total of 444 patients who had endometrial sampling were included in the study (endometrial cancer, n=79; endometrial hyperplasia with atypia/endometrial intraepithelial neoplasia, n=27; endometrial hyperplasia without atypia, n=238; and normal controls, n=100). Neutrophil count, lymphocyte count, platelet count, platelet distribution width, neutrophil/lymphocyte ratio, platelet/lymphocyte ratio, CA-125, and endometrial thickness of the patients were recorded.

RESULTS: Comparing the groups for neutrophil count, the hyperplasia with atypia group had higher values compared with both the hyperplasia without atypia group and the control group (p=0.003). When compared for the lymphocyte count, the hyperplasia with atypia group had lower values compared with the control group (p=0.014). Neutrophil/lymphocyte ratio of the hyperplasia with atypia group was higher than all other groups, and neutrophil/lymphocyte ratio of the cancer group was higher than the control group (p=0.001). Platelet count, mean platelet volume, platelet distribution width, and platelet/lymphocyte ratio values were not significantly different among groups (p>0.05).

CONCLUSIONS: Considering the inflammatory markers, the most prominent result was that the hyperplasia with atypia group had neutrophilia, lymphopenia, and increased neutrophil/lymphocyte ratio compared with other groups.

KEYWORDS: Endometrial cancer. Endometrial hyperplasia. Neutrophil/lymphocyte ratio. Platelet/lymphocyte ratio. Endometrial intraepithelial neoplasia.

INTRODUCTION

Endometrial cancer (EC) is the most common gynecological malignancy in developed countries¹. The prevalence of EC is expected to increase with increasing elderly population and obesity². The major risk factor is excess estrogen without adequate opposition by progesterone. Majority of ECs are endometrioid-type adenocancers and have a background of endometrial hyperplasia (EH)³. Hyperplasia without atypia has a

low progression rate to cancer whereas hyperplasia with atypia/endometrial intraepithelial neoplasia (EIN) has a higher progression rate to cancer, one-third of these actually have concurrent EC⁴.

The link between inflammation and cancer was first suggested by Virchow in the 19th century after observing leukocyte influx to cancers developing in tissues with chronic inflammation⁵. Two pathways describing the link have emerged. The extrinsic

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pathway hypothesis suggests that inflammatory conditions promote cancer development⁶. The intrinsic pathway hypothesis suggests that the activation of different oncogenes leads to carcinogenesis which later increases inflammatory markers⁷.

Inflammatory mediators such as cytokines, prostaglandins, and leukocytes play role in inflammation that can be observed as thrombocytosis, neutrophilia, and lymphocytopenia³. Neutrophils produce angiogenic factors and proteases contributing to tissue remodeling⁸. Platelet count is increased with hypoxic tumor microenvironment, protecting tumor cells from lysis⁹. We aimed to compare the inflammatory markers among patients with EH, cancer, and controls, thereby observing the stage when inflammation becomes evident.

METHODS

This retrospective cross-sectional study was conducted with the data of patients having endometrial sampling between 2011–2017 in Haydarpaşa Numune Training and Research Hospital, Istanbul. Ethical approval was obtained (HNEAH-KAEK 2017/75). Pathology results of EC and hyperplasia were selected. Having an infection, rheumatological, inflammatory, collagen vascular, cardiovascular, hepatorenal or hematological disease, other malignancy, and using hormonal or corticosteroid therapy were the exclusion criteria. Out of 380 patients with EC and hyperplasia, 344 were suitable for the study. Another 100 women among the most recently biopsied patients who had physiological endometrium results were included as the control group (Group 4). Having a complete blood count tested no later than two weeks and having the pathological examination at the same hospital were required.

Full blood count data of the patients such as neutrophil, lymphocyte, platelet counts, and platelet distribution width (PDW) were recorded. The neutrophil/lymphocyte ratio (NLR) was defined as the neutrophil count divided by the lymphocyte count, and platelet/lymphocyte ratio (PLR) was defined as the platelet count divided by the lymphocyte count. CA-125 levels

were measured using radioimmunoassay. Transvaginal ultrasonography was performed prior to biopsy. The main outcome measure was the difference of neutrophil count, lymphocyte count, platelet count, NLR, PLR, and PDW among groups.

Statistical analysis was performed using MedCalc Statistical Software version 12.7.7. The Kruskal–Wallis test was used to compare the nonparametric variables. The Mann–Whitney U test with Bonferroni correction was used to assess differences among the groups. The chi-square test and the Fisher's exact test were used to analyze the relation of categorical variables. $p < 0.05$ was considered statistically significant.

RESULTS

A total of 344 patients with cancer/hyperplasia results were included, of whom 79 were presented with EC (Group 1), 27 with EH with atypia/EIN (Group 2), and 238 with EH without atypia (Group 3). Mean ages were 60 ± 11 (Group 1), 54 ± 8 (Group 2), 47 ± 7 (Group 3), and 52 ± 10 (Group 4). Patients with EC were older. There was no difference among groups for gravidity and parity. The percentage of premenopausal patients was higher in Group 3 than other groups (Table 1). CA-125 level and endometrial thickness were both significantly higher in Group 1 compared with other groups. Endometrial thickness was significantly lower in controls than Groups 1–3 (Table 2).

Neutrophil count was significantly different among groups. The *post hoc* analysis revealed that neutrophil count was higher in Group 2 compared with Groups 3 and 4 ($p = 0.003$). Lymphocyte count was also significantly different among groups. The *post hoc* analysis revealed that lymphocyte count was lower only in the hyperplasia with atypia/EIN group than the control group ($p = 0.014$). When the groups were compared for NLR, the values of Group 2 were significantly higher than all other groups. NLR of the cancer group was higher than the control group ($p = 0.001$). There was no significant difference among groups for PLR, platelet count, and PDW (Table 3).

Table 1. General characteristics of the patients.

| | Group 1 (Cancer) | Group 2 (Hyperplasia with atypia/EIN) | Group 3 (Hyperplasia without atypia) | Group 4 (Control) | p-value |
|-----------------------------------|------------------|---------------------------------------|--------------------------------------|-------------------|---------|
| Age ^a | 60.2±11.1 | 53.9±8.1 | 47.3±7.2 | 52.4±9.5 | 0.05 |
| Gravidity | 4.8±3.7 | 3.4±2.2 | 3.8±2.4 | 3.9±2.6 | 0.167 |
| Parity | 3.3±2.2 | 2.6±1.8 | 2.8±1.8 | 2.6±1.8 | 0.271 |
| Postmenopausal (n %) ^b | 57 (72) | 14 (52) | 48 (20) | 63 (63) | 0.001 |

^aGroup 1 was significantly older than other groups ($p < 0.05$). ^bThe percentage of premenopausal women was significantly higher in Group 3 when compared with other groups (Fisher's exact test; $p < 0.001$). EIN, endometrial intraepithelial neoplasia;

Table 2. CA 125 levels and endometrial thickness.

| | Group 1 | Group 2 | Group 3 | Group 4 | p-value |
|---|------------|-----------|------------|----------|---------|
| CA 125 level ^a (U/mL) | 79.6±23.9 | 16.08±5.8 | 18.02±10.8 | 13.8±6.6 | 0.001 |
| Endometrial thickness ^b (mm) | 21.2±13.05 | 15.9±6.1 | 14.5±6.2 | 8.9±3.5 | 0.001 |

^aCA 125 level was significantly higher in Group 1 ($p < 0.001$). ^bEndometrial thickness was significantly higher in Group 1 (Kruskal–Wallis test; $p < 0.001$).

Table 3. Comparison of hematological inflammatory markers.

| | Group 1 (Cancer) | Group 2 (Hyperplasia with atypia/EIN) | Group 3 (Hyperplasia without atypia) | Group 4 (Control) | p-value |
|--------------------------------------|------------------|---------------------------------------|--------------------------------------|-------------------|---------|
| Neutrophil (1/ μ L) ^a | 5,109.6±2,034.5 | 6,562.2±3,266 | 4,808.9±1,853 | 4,398.9±1,467.2 | 0.003 |
| Lymphocyte (1/ μ L) ^b | 2,354.8±777.4 | 1,988.6±1,003.7 | 2,384.0±759.6 | 2,516.7±909.9 | 0.014 |
| NLR ^c | 2.4±1.4 | 4.9±5.5 | 2.5±1.8 | 1.97±1.03 | 0.001 |
| PLR | 127.9±68.9 | 163.9±110.2 | 132.2±61.6 | 120.9±45.04 | 0.256 |
| Platelet (1/ μ L) | 273,228±76,503 | 255,222±58,016 | 288,431±80,237 | 276,960±74,573 | 0.093 |
| PDW | 17.2±2.1 | 17.2±2.6 | 16.9±2.3 | 17.5±1.3 | 0.293 |

^aNeutrophil count ($p = 0.003$), ^bLymphocyte count ($p = 0.0014$) and ^cNLR values were significantly different among groups. EIN: endometrial intraepithelial neoplasia; NLR: NLR: neutrophil/lymphocyte ratio; PLR: platelet/lymphocyte ratio; PDW: platelet distribution width.

DISCUSSION

The relation of inflammation and ECs is well established. The majority of publications focus on the relation of markers to prognosis. High NLR and PLR are the predictors of poor prognosis^{10,11}.

However, there is limited research on hematological inflammatory markers and EH. One of these is a study by Açmaz et al.¹² Subjects were grouped as EC, EH, and control, and atypia was not differentiated. NLR was higher in the EC group compared with the EH and control groups. PLR was higher in the EC and EH groups compared with controls¹². Another study grouping the subjects similarly reported higher neutrophil count, higher NLR, and lower PDW in the EC group compared with the control group. There was no difference between EC and EH groups. PLR was not different among the groups¹³. A similarly designed study reported that NLR was significantly higher in the cancer group than the hyperplasia and control groups. There was no significant difference between their PLR values¹⁴. The study by Kurtoglu et al.¹⁵ grouped their patients according to the hysterectomy results as benign and malignant. They did not observe a difference between NLR and PLR whereas MPV was higher and PDW was lower in the malignant group¹⁵. In our study, we did not observe a significant difference between groups in terms of platelet count, PLR, and PDW.

Prior studies comparing hyperplasia, cancer, and controls did not differentiate between the types of hyperplasia. Up to our knowledge, there is only one study in the literature grouping

the subjects as EH group with atypia, EH group without atypia, and normal controls. This study did not include EC. The hyperplasia with atypia group had significantly higher NLR and PLR than other groups¹⁶. This study is the first in the literature comparing all the four groups up to our knowledge. The intuitive expectation would be a gradual increase in NLR as the situation proceeds from normal to hyperplasia without atypia to with atypia to EC. In our study, NLR was significantly higher in the EC group compared with the control group, which was an expected finding compatible with the literature. NLR was significantly higher in the hyperplasia with atypia group compared with hyperplasia without atypia and control groups. NLR was also higher in the hyperplasia with atypia group compared with the EC group. PLR was highest in the hyperplasia with atypia group, but a statistically significant difference was not seen. The finding of higher inflammation in the hyperplasia with atypia compared with cancer was supported by a recent study aiming to investigate the inflammatory marker differences between complex atypical hyperplasia (CAH)/EIN and endometrioid-type grade 1 cancer using the pathological results of hysterectomy. Both NLR and PLR were higher in the CAH/EIN group than the cancer group¹⁷.

Information about the inflammation status of precancerous lesions can be valuable in the investigation of the etiopathogenesis of EC. Hormonal and genetic changes are the important risk factors in ECs. We know the role of genetic mutations such as PTEN and Kras, and these genetic

changes occur in the presence of increased cell proliferation caused by unopposed estrogen. There is a complex interaction between sex steroid hormones and cytokines/growth factors in the endometrium⁷. Proinflammatory milieu further increases estrogen *via* aromatase expression. Nasier et al. demonstrated the increasing expression of COX-2 from EH to invasive EC and suggested that COX-2 inhibition could potentially stop the progression of precursor lesions¹⁸. Sanderson et al. reported in their review that COX-2 needs to be further investigated as a potential biomarker of the progression of EH to EC². The inhibition of inflammation could be a therapeutic intervention for endometrial adenocarcinoma⁷.

The retrospective design is a limitation of our study since all confounding factors could not be excluded. Another limitation is not having compared the body mass index (BMI). Adipose tissue increases both estrogen and proinflammatory cytokines. The previously mentioned study compared the BMI

and nonspecific inflammatory markers of the groups, and no correlation was present¹⁶.

CONCLUSIONS

Considering the link between inflammation and EC, EH is worthy of investigation. Complete blood count being easily accessible and cheap would be a practical guide to reveal the systemic inflammatory condition of the patient. This study suggests that inflammation plays a role in the progression to EC, especially from the stage of hyperplasia with atypia/EIN. Future large-scale studies are needed to support this suggestion.

AUTHORS' CONTRIBUTIONS

ECDA: Conceptualization, Data Curation, Writing – Original Draft. **ADEC:** Conceptualization, Formal Analysis, Writing – Original Draft. **FV:** Supervision, Writing – Review & Editing.

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Early results of novel robotic surgery-assisted low anterior resection for rectal cancer and transvaginal specimen extraction by using Da Vinci Xi: initial clinical experience

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SUMMARY

OBJECTIVE: The aim of this study is to evaluate the early results of robotic surgery-assisted low anterior resection for rectal cancer and transvaginal specimen extraction, regarding the operative time, operative and early postoperative complications, hospital stay, and pathological reports in a series of 10 patients.

METHODS: From November 2016 to October 2019, case series study on patients diagnosed with RC was included in this study. All robotic-assisted low anterior resection of the rectum, vaginal removal of the specimen, colorectal anastomosis, and loop ileostomies were performed using the Da Vinci Xi system.

RESULTS: The mean age of patient was 64.8 (58–72) years. Low anterior resection was performed to seven patients, and very low anterior resection was performed to three patients. Total mesorectal excision of the rectum, transvaginal specimen extraction, transanal anastomoses, and protective ileostomy were performed in all 10 patients. The mean operative time was 275±30.50 min, and estimated blood loss was 50±10.50 mL. No patient required conversion to conventional surgery. Negative circumferential resection, proximal, and distal margins were accomplished negative. Mean number of lymph nodes harvested was 20±5.5. According to the pathological reports, all were adenocarcinoma. T1 stage was 80.0%, and T2 stage was 20.0%. Lymph node metastasis accounted for 80.0%.

CONCLUSIONS: To our literature search, this is the first study reporting the early outcomes of the novel robotic surgery-assisted low anterior resection for rectal cancer and transvaginal specimen extraction by using the Da Vinci Xi system. It can be performed safely and successfully in selected patients by providing an excellent cosmetic body image, which may be important for women.

KEYWORDS: Robotic surgical procedures. Rectum cancer. Procedures, minimally invasive surgical.

INTRODUCTION

Minimally invasive surgery has been evolved rapidly in the field of colorectal surgery since the first description of laparoscopic colectomy for colon cancer by Jacobs in 1991¹. Although colorectal resections can be performed with totally laparoscopic techniques, an additional incision is required for specimen extraction from the abdominal cavity. Every additional skin incision could increase the risk for postoperative complications such

as pain, infection, hematoma, and incisional hernia. Extraction of the specimen *via* natural orifices such as the vagina or rectum may decrease the risk related to a skin incision. In recent years, natural orifice transluminal endoscopic surgery^{2,3} has come on the scene. New techniques were applied to reduce the incision sizes⁴⁻⁷. However, the majority of the colorectal surgeons are not familiar with surgical access *via* the vaginal route and transvaginal specimen extraction (TVSE).

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The aim of this study is to present the initial experience on specimen extraction from the vagina after performing robotic surgery for rectal cancer (RC). We concluded that robotic-assisted low anterior resection (LAR) with lymphadenectomy for RC and TVSE was safe and feasible and gave good cosmesis but not justified for routine use due to its higher cost and lack of clinical benefits. In this study, we described our novel technique with an assessment of the short-term outcomes in a series of the first 10 patients who underwent this surgical approach at our institution.

METHODS

Study design

From November 2016 to October 2019, 10 patients with resectable RC without distant metastasis underwent LAR or very low anterior resection (VLAR) using the Da Vinci Xi system by two surgeons. All patient characteristics data were collected, retrospectively. We offered robotic resection and natural orifice specimen extraction (NOSE) *via* vagina to all patients. Exact details of the procedure were explained, and written informed consent was obtained from all patients.

Surgical technique

All the patients received mechanical bowel preparation and a single dose of prophylactic antibiotic (cefuroxime axetil 1 g) 1 h before the skin incision, and antithrombotic prophylaxis was administered with low-molecular-weight heparin 12 h before. A urinary catheter was inserted.

The procedure was performed using the Da Vinci Xi surgical system (Intuitive Surgical, Sunnyvale, CA, USA). We used Maryland fenestrated bipolar forceps, tip-up double fenestrated grasper, and monopolar scissors.

The operation was performed in two phases, namely, abdominal and pelvic phases. In the abdominal phase, after giving general anesthesia, the patient was placed in a modified dorsolithotomic position, with a 26 Trendelenburg position during the procedure. The Veress needle was inserted at the 10 cm lateral, the umbilical level, to insufflate the abdomen. After pneumoperitoneum was obtained, an 8 mm incision was made, the trocar was placed through the incision, and three other 8 mm lateral ports were placed under direct visualization. An additional 10 mm trocar for the assistant is placed in the right upper quadrant. Pneumoperitoneum was kept at 8–12 mm Hg. The robotic surgical system was docked using four arms. After induction of pneumoperitoneum and insertion of the 30° robotic camera and placing all the instruments, the routine whole abdominal cavity exploration was

performed. First, medial-to-lateral dissection, i.e., ligation of the inferior mesenteric artery, was performed at the root of the inferior mesenteric artery, and then, splenic flexure, sigmoid, and descending colons were mobilized medially. Then, rectal mobilization down to the pelvic floor was performed to achieve total mesorectal excision (TME). In this LAR case, division of the distal rectum was performed using two Laparoscopic Endo-Gia linear staplers (green cartridge, 60 mm, Ethicon Endo-Surgery, Inc., Cincinnati, OH, USA).

In the pelvic phase, after placing a vaginal speculum, an ovarian clamp was placed to the posterior fornix of the vagina. The posterior fornix of the vagina was opened intracorporeally with the electrocautery scissors over the clamp. Then, the distal side of the specimen was clamped and pulled throughout the vagina. Specimen was divided 15 cm proximal of the tumor with electrocautery, and the anvil of the circular stapler was put inside the colon and fixed with purse-string 2/0 PROLENE suture. After this procedure, the colon enters the abdomen. A sponge was pushed through the vagina to the posterior fornix. After the digital rectal examination, circular stapler (31 mm) was inserted inside the rectum. With the robotic assistance, both the anvil and the stapler entered together. After squeezing and firing the stapler, the colorectal anastomoses were performed. Finally, a diverting ileostomy was established at the right lower side of the abdomen to all patients. Following the placement of a vaginal tamponade and an abdominal drain to the pelvis, abdominal trocar site incisions were closed with 3/0 PROLENE sutures.

RESULTS

Table 1 shows the characteristics of the female patients (n=10). The mean age of patient was 64.8 ± 6.46 (58–72) years, and the mean body mass index (BMI) was 28.4 ± 2.32 kg/m².

The mean operation time was 275 ± 30.50 min (range, 180–360), and the mean estimated blood loss was 50 ± 10.50 mL (Table 1). The time to clear liquid intake in all patients was three days after operation. The mean length of hospital stay after surgery was 5 ± 0.50 days. No patient required conversion to open or conventional laparoscopic surgery. There were no perioperative complications, morbidity, or mortality.

According to the pathology report, the mean tumor size was 15 ± 2.40 (7–20) mm. The mean number of harvested lymph nodes and positive lymph nodes was 20 ± 5.50 and 6.0 ± 1.50 , respectively. Two patients were at stage II, and eight patients were at stage I according to the 7th edition of the *American Joint Committee on Cancer* system. No other complications or mortality occurred during surgery and early postoperative follow-up. Patients were followed up for six months or longer postoperatively.

Table 1. Characteristics of the patients.

| Number of cases (n) | 10 |
|--------------------------------------|-----------------------|
| Gender | Female |
| Age (years) | 64.8±6.46 (58–72) |
| Body mass index (kg/m ²) | 28.4±2.32 (25.2–30.0) |
| Tumor histology: Adenocarcinoma | 10 |
| Tumor | |
| T1 | 8 |
| T2 | 2 |
| Node | |
| N0 | 2 |
| N1 | 7 |
| N2 | 1 |
| Metastases | None |
| Stage | |
| I | 8 |
| II | 2 |
| Surgery | |
| Low anterior resection | 7 |
| Very low anterior resection | 3 |
| Mean operation time (min) | 275±30.50 (180–360) |
| Mean estimated blood loss (mL) | 50±10.50 (25–150) |
| Mean tumor size (mm) | 15±2.40 (7–20) |
| Mean lymph nodes removed | 20±5.50 (12–26) |
| Mean positive lymph nodes removed | 6±1.50 (0–8) |
| Mean hospital stay (days) | 5±0.50 (5–7) |
| Morbidity | None |
| Mortality | None |

DISCUSSION

Since the concept of TME has become a standard of care for low RC surgery⁸, there has been an increasing interest in new minimally invasive techniques, reducing the size of abdominal incisions to the minimum required for abdominal specimen extraction, although extraction specimen site infections and hernia are described in the literature^{9–11}. NOSE has aroused a great interest among colorectal surgeons as a way to reduce abdominal incision still further. Indications for NOSE procedures are strict and include T2–T3 tumors, with a maximum circumferential diameter (CD) of 3 cm and a BMI less than 30 kg/m² for transanal extraction and a CD of 3–5 cm and a BMI less than 35 kg/m² for transvaginal extraction^{12,13}. Moreover, we strictly adhered to these indications; all 10 patients were women who present the advantage of a wider pelvic outlet.

The minimally invasive operative approach for rectal surgery has progressed substantially in the past decades. Reducing the

trocac size and the number of ports is a logical solution for a less invasive and scarless surgery¹⁴. However, their applicability and overall value in clinical practice is questionable. Decreased wound size is associated with less wound-related complications, less pain, and enhanced cosmesis^{15,16}. Specimen extraction is the final step of every laparoscopic or robotic surgery. The incision can be performed by enlarging a trocar site incision or creating a new one. An additional incision augments pain, risk of wound infection, and hernia formation¹⁷. The transvaginal approach has been used for several years for specimen removal in minimally invasive gynecologic procedures^{18,19} and RC²⁰ to avoid abdominal wall incisions. Reduced trauma of the abdominal wall, shortened length of the skin incision, low or no wound-related complications, such as evisceration, infection, and incisional hernia, and less pain represent a faster recovery period and less intra-abdominal adhesion could be achieved with NOSE^{21–23}. No any wound infection, mortality, or any other complications were observed after surgery in our series. In addition to its use for specimen extraction, the vagina allows retraction, manipulating, clipping, stapling, and sutures during surgery by insertion of a trocar at the beginning of surgery⁶.

No patient required conversion to conventional laparoscopic or open surgery in this series; therefore, careful patient selection is needed. In addition, there were no intraoperative or postoperative complications or mortality occurred in the short term in this series. The complications of TVSE could be dyspareunia, infection, infertility, bleeding, rectovaginal fistula, trauma to pelvic structures, and the risk of pelvic adhesion¹⁴. In our study, we did not encounter such complications. The number of retrieved lymph nodes in the specimens was acceptable and comparable to other studies^{7,8}.

Although our study has a definite limitation due to retrospective nature and the small number of cases and short duration of follow-up, all patients were satisfied about their wounds and postoperative recovery. Obviously, comparative and prospective randomized trials with higher patient numbers are needed to figure out the role of using transvaginal way for specimen extraction in robotic-assisted rectal surgery.

CONCLUSIONS

Robotic-assisted LAR for RC and TVSE can be performed successfully with satisfying short-term outcomes in selected patients. Further comparative studies are required to verify the clinical advantages of our technique. Due to the unique advantages of the Da Vinci system, robotic-assisted LAR and TVSE for patients with RC can be performed safely and may be an effective approach in contrast to open or laparoscopic surgery. Besides, TVSE could provide an excellent cosmetic body image, which may be important

for women and could make patients feel less traumatized by presenting a scarless abdomen after the surgery. Besides presenting better cosmesis, this could reduce the complications associated with additional skin incisions and could upgrade the quality of life.

AUTHORS' CONTRIBUTIONS

TC: Conceptualization, Data curation, Formal Analysis, Writing – original draft. **AA:** Conceptualization, Writing – original draft, Writing – review & editing.

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Evaluation of progesterone receptor expression in low- and high-grade astrocytomas

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SUMMARY

OBJECTIVE: Gliomas are tumors originating from glial cells. Gliomas are the most common primary neoplasms of the central nervous system, with astrocytomas being the most prevalent glioma subtype. Progesterone regulates several reproductive processes, such as ovulation and sexual behavior, and influences neuronal excitability, learning, and the neoplastic proliferation of glial cells. Progesterone functions mainly by interacting with intracellular progesterone receptors to modify the expression of the genes involved in cell proliferation, angiogenesis, and epidermal growth factor production. As not many studies on the hormone receptors in glial tumors have been reported, the objective of this study was to evaluate the expression of these proteins in astrocytomas and to determine whether their expression levels vary according to the tumor grade.

METHODS: This was a retrospective study using glial tumor paraffin blocks obtained from the São Marcos Hospital Pathology Department archives. Forty cases were divided equally into two groups, based on histological types and the World Health Organization criteria (low- and high-grade tumors). Progesterone receptor expression was analyzed by immunohistochemistry. The data were statistically analyzed using the Mann-Whitney U test and Spearman's correlation coefficient; results with $p < 0.05$ were considered statistically significant.

RESULTS: There were no statistically significant differences between the mean nuclear progesterone receptor expression of low-grade (0.1495) and high-grade (0.0937) astrocytomas ($p = 0.2$).

CONCLUSION: Progesterone receptors are present in both low- and high-grade gliomas; however, there is no significant difference in the levels of progesterone receptor expression between the tumor grades.

KEYWORDS: Astrocytoma. Glioma. Glioblastoma. Progesterone receptor. Progesterone. Prognosis.

INTRODUCTION

Glioma is the most common primary tumor affecting the central nervous system, and astrocytoma is the most prevalent histological subtype of this tumor. According to the World Health Organization, there are four types of astrocytomas: grades I and II (low-grade or benign) and grades III and IV (high-grade or malignant). Astrocytomas are the most common primary malignant

central nervous system tumors in adults, with a reserved prognosis even when treated appropriately¹⁻⁴. To improve patient survival, there is a need to improve knowledge of the pathways that regulate the aberrant growth of these tumors, develop new diagnostic methods, and identify new prognostic biomarkers⁵⁻⁷.

Progesterone not only regulates ovulation, sexual behavior, and other reproductive processes but also influences learning,

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neuronal excitability, and the neoplastic proliferation of glial cells. Progesterone functions primarily by interacting with intracellular progesterone receptors (PRs)³.

There are two PR isoforms, A (PR-A) and B (PR-B), which modify the expression of the genes involved in cell proliferation, angiogenesis, and epidermal growth factor production⁸. The presence of these biomarkers in *in vitro* glial tumor models and their response to anti-progesterone drugs piqued our interest in studying the potential mechanisms of action of PRs in glial neoplasms⁹⁻¹¹. Due to the lack of published studies on hormone receptor expression in glial tumors, the objective of this study was to evaluate the expression of PRs in astrocytomas and determine whether their expression levels differ according to the tumor malignancy grade.

METHODS

Study design

This study used glioma paraffin blocks obtained from the São Marcos Hospital Pathology Department archives (Teresina, Piauí, Brazil). Only astrocytomas obtained from patients who had not undergone treatment before primary surgery and those stored for not more than five years were selected (histopathological samples were collected between June 2013 and June 2018). The Research Ethics Committee of the Federal University of Piauí, Brazil, approved this study (CAAE: 43447015.8.0000.5214). Our methodology also complies with the principles dictated by the Declaration of Helsinki. Forty cases were histologically divided into two groups (low- and high-grade astrocytomas). Each group contained 20 cases that were randomly chosen from the tumors that met the inclusion criteria.

Immunohistochemical method

Tumor tissue samples were fixed in formalin for 12–24 h and cut into 3- μ m thick slices. Tissue sections were then processed and stained with hematoxylin and eosin. The slides were dewaxed with xylol at 60°C for 15 min, dehydrated with decreasing concentrations of alcohol (100, 95, 80, and 70%) for 30 s each,

and washed with distilled water. To recover antigens, the sections were immersed in buffered citric acid and heated in a microwave for 15 min at maximum power. The samples were subsequently immersed in a buffered solution containing 3% of hydrogen peroxide (twice for 10 min each) and then washed with distilled water and phosphate-buffered saline.

The samples were incubated with a PR-specific monoclonal antibody (PgR 636, IgG1 κ isotype; Dako Corporation, California, United States) overnight at 4–8°C. As per the manufacturer's recommendations, the antibody was diluted to 1:40–1:80 in phosphate-buffered saline containing 1% of bovine serum albumin.

Quantitation method

An optical microscope (Nikon Eclipse E-400, Tokyo, Japan) connected to a color video camera (Samsung, CHC-370N, Seoul, Korea) was used to capture the images, which were transmitted to a computer equipped with the Imagelab software version 2.3 (Softium Informática Ltda., São Paulo, Brazil) for evaluation.

The number of PR-positive and PR-negative cells were counted (out of 600 cells) from the images taken at 400 \times magnification and beginning with the areas of higher expressions. The percentage of PR-positive cells on each slide was obtained from the ratio of cells with positively stained nuclei relative to the total number of cells multiplied by 100.

Statistical method

The data were stored in Microsoft Excel spreadsheets, and the statistical analysis was performed using the SPSS 20.0 software. The Kolmogorov–Smirnov normality test was used to analyze the data obtained. As the samples were independent and not normally distributed, the Mann-Whitney U test was used to compare the mean percentage of PR-positive nuclei in low- and high-grade gliomas. The significance level was set at $p < 0.05$.

RESULTS

There was a difference in the percentage of cells expressing nuclear PR in low-grade (0.1495) *versus* high-grade (0.0937) astrocytomas. However, this difference was not statistically significant ($p = 0.2$; Table 1; Figure 1).

Table 1. The mean percentage of progesterone receptor-positive nuclei in high- and low-grade gliomas.

| Groups | n | Mean | SE | SD | Minimum | Maximum | Median |
|----------------------------------|----|---------|--------|--------|---------|---------|--------|
| High-grade progesterone receptor | 20 | 0.0937 | 0.0237 | 0.1062 | 0 | 0.37 | 0.0459 |
| Low-grade progesterone receptor | 20 | 0.1495* | 0.0330 | 0.1479 | 0 | 0.55 | 0.0965 |

SE: standard error; SD: standard deviation. * $p = 0.2$.

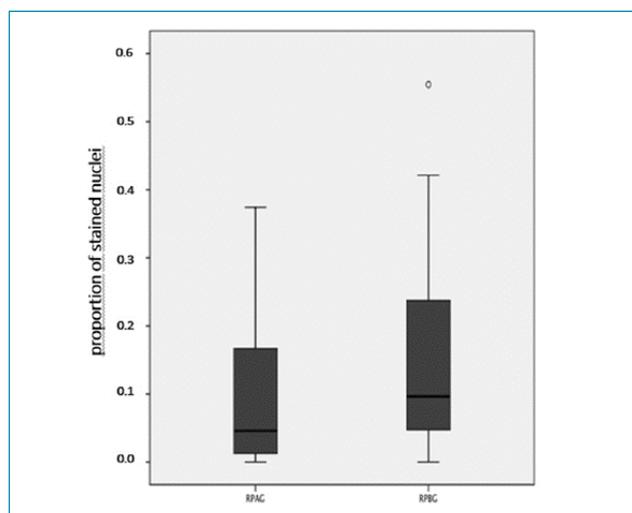


Figure 1. The mean percentage of progesterone receptor-positive nuclei in high- and low-grade gliomas. Progesterone receptor in high-grade astrocytomas; Progesterone receptor in low-grade astrocytomas.

DISCUSSION

Both *in vitro* and *in vivo* studies have shown that progesterone can stimulate astrocyte infiltration and migration into the cortex of the rat brain as well as the expression of the genes that are important for the growth and dissemination of these neoplasms^{11,12}. Progesterone is derived from cholesterol and acts *via* two main mechanisms, namely, classical and nonclassical signaling pathways. The first mechanism involves interaction with intracellular PRs, and the second mechanism involves the participation of membrane receptors and ion channels^{8,13}.

The PR is composed of a central DNA-binding domain and a carboxyl-terminal containing multiple regions, which is important for the activation or inhibition of this protein. In humans, the PR is encoded by a single gene located on chromosome 11q22. Different promoters in different organs and tissues (including the central nervous system) transcribe the two PR isoforms (i.e., PR-A and PR-B). These may have different functions as they are regulated by different promoters^{8,11,12,14-16}.

The receptors, such as meningiomas, chordomas, craniopharyngiomas, and gliomas, are also found in brain tumors. According to some studies, PR expression increases with malignancy, with the B isoform predominantly being found in malignant gliomas^{8,11,15,17-23}.

In an immunohistochemical study by Khalid et al.²³ there were significantly more PR-positive cells in glioblastoma

multiformes than in low-grade or anaplastic astrocytomas; they also reported that PR-positive glial tumors had a higher rate of proliferation than PR-negative tumors.

Assimakopoulou et al.¹⁸ demonstrated that PRs were expressed in 59% of glioblastomas, 45% of anaplastic astrocytomas, and 8% of low-grade gliomas and were absent in normal astrocytes. Carroll et al.²⁴ observed that PR expression was higher in high-grade tumors (62% of glioblastomas, 37% of anaplastic tumors, and 25% of low-grade astrocytomas).

Conversely, Khalid et al.²³ reported that all of their anaplastic astrocytoma samples were negative for PRs, while all of their glioblastoma samples expressed PRs.

This study found that low-grade tumors expressed more PRs than high-grade astrocytomas, but the difference was not statistically significant (Table 1; Figure 1). Our findings did not corroborate with the literature, possibly due to the small sample size used in this study. A larger number of tumors may generate results similar to those in the studies previously mentioned.

CONCLUSION

PRs are expressed by both low- and high-grade gliomas; although there was a difference in the level of expression between the two tumor grades, this difference was not statistically significant.

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AUTHORS' CONTRIBUTIONS

CBT: Conceptualization, Data curation, Formal Analysis, Writing – original draft. **FCSAGB:** Conceptualization, Data curation, Formal Analysis, Writing – original draft. **EBS:** Writing – original draft, Writing – review & editing. **HACSM:** Data curation, Formal Analysis, Writing – original draft, Writing – review & editing. **JNPOB:** Writing – original draft.

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The impact of hydroxychloroquine and azithromycin on the corrected qt interval in patients with the novel Coronavirus disease 2019

Bektas Murat^{1*} , Hakan Akgun² , Muhittin Akarsu² , Ahmet Ozmen³ , Selda Murat⁴ 

SUMMARY

OBJECTIVE: With the coronavirus disease 2019 (COVID-19) continuing to spread all over the world, although there is no specific treatment until now, hydroxychloroquine and azithromycin have been reported to be effective in recent studies. Although long-term use of hydroxychloroquine and azithromycin has been reported to cause QT prolongation and malign arrhythmia, there is not enough data about the effect of short-term use on arrhythmia. Therefore, this study aims to assess the effect of hydroxychloroquine alone and hydroxychloroquine + azithromycin on corrected QT (QTc).

METHODS: A baseline electrocardiogram and on-treatment baseline electrocardiogram were retrospectively collected in COVID-19 patients who received hydroxychloroquine and/or azithromycin. The QTc interval was calculated, and the baseline and peak QTc intervals were compared. In addition, the peak QTc intervals of monotherapy and combination therapy were compared.

RESULTS: Of the 155 patients included, 102 (65.8%) patients were using hydroxychloroquine, and 53 (34.2%) patients were using hydroxychloroquine + azithromycin combination. The use of both hydroxychloroquine alone and hydroxychloroquine + azithromycin combined therapy significantly prolonged the QTc, and the QTc interval was significantly longer in patients receiving combination therapy. QTc prolongation caused early termination in both groups, 5 (4.9%) patients in the monotherapy group and 6 (11.3%) patients in the combination therapy group.

CONCLUSION: In this study, patients who received hydroxychloroquine for the treatment of COVID-19 were at high risk of QTc prolongation, and concurrent treatment with azithromycin was associated with greater changes in QTc.

KEYWORDS: Hydroxychloroquine. Azithromycin. Coronavirus Disease-19. Cardiac arrhythmias.

INTRODUCTION

The new coronavirus disease 2019 (COVID-19) caused by the severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) pathogen soon spread all over the world¹. While the first case in Turkey was detected on March 11, 2020, the disease was declared as a pandemic by the World Health Organization (WHO) on March 12, 2020², and it continued to spread increasingly; there is no proven treatment for it so far.

In some published studies, it has been reported that the combined use of hydroxychloroquine (HCQ) and azithromycin (AZT) reduces the viral load and may have an effect on mortality and morbidity³⁻⁵. HCQ, a chloroquine analog thought to be safer than chloroquine (CQ), an antimalarial and immunomodulatory agent, has been shown to have an antiviral effect on SARS-CoV-2^{4,6}. AZT, a macrolide group antibiotic, has in vitro antiviral effects, such as viral replication, entry into the host cell,

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and potential immunomodulation⁷. An in vitro study has shown that the combined use of HCQ + AZT had synergistic effects on SARS-CoV-2⁸, and this combination therapy is widely used by clinicians in Turkey and in the world. Although, in some studies, both agents have been shown to prolong the QT interval, drug-induced torsades de pointes (TdP), and drug-induced sudden cardiac deaths, independently from each other, there is insufficient data on the effect of monotherapy or combination therapy on QT duration and malign arrhythmia development in COVID-19 patients^{9,10}. In this study, we aimed to investigate the effect of HCQ and AZT use alone or in combination on QT duration and arrhythmia in COVID-19 patients.

METHODS

This study was conducted retrospectively in Eskisehir City Hospital between 15 March and 15 August 2020. For inclusion in the study, 350 patients over the age of 18 years, who were proven positive by the polymerase chain reaction method or who were hospitalized (to ward and/or intensive care unit) with a high probability of COVID-19 as a result of thorax computerized tomography (CT), were screened. Of these patients, 155 patients met the inclusion criteria and were chosen for this study. These patients had baseline electrocardiogram (ECG) before starting HCQ or HCQ+AZT treatment and had ECG on a daily basis during the treatment. Patients who did not have a baseline ECG, ECG on a daily basis, difficulty obtaining an ECG, and ECGs that could not be evaluated clearly were not chosen for the study.

The treatment regimen of the patients hospitalized with the diagnosis of COVID-19 in our center was a 2× 400 mg oral loading dose for HCQ followed by 2× 200 mg for five days and a 500 mg loading dose for AZT followed by 250 mg per day for 5 days. The treatment continued for 10 days, for those who had symptoms, a persisted fever for five days, and whose polymerase chain reaction test was not negative. In all patients, the baseline ECG was obtained before starting the treatment, and daily ECGs were obtained during the treatment. All ECGs of the patients were evaluated, and the QRS, PR, and QTc intervals of the ECG obtained before the treatment were taken as basis for the baseline values. Although, for the peak values, the QTc interval was prolonged in daily ECG during treatment, time and day, when it is the longest, were taken into account. The last day of treatment was taken into account for patients whose QTc interval did not prolong. HCQ and/or AZT were not initiated as hospital treatment procedures for the patients with a QRS interval >500 ms on baseline ECG.

All ECGs were evaluated retrospectively by two independent cardiologists; when there was a conflict between them, ECGs were evaluated by a third cardiologist. The QT interval was measured

from the onset of the first deflection of QRS complex to the end of T wave. The end of the T wave was determined by the tangent method. QTc durations were calculated manually using the Bazett's formula. D2 lead was used to measure the QT interval. In cases where the T wave in D2 lead could not be clearly identified, V6 lead was used as an alternative. If there was a bundle branch block in the basal, the JT interval was measured and 120 ms was added to obtain the QT interval duration. Severe QTc prolongation was defined as an increase in QTc intervals of more than 60 ms ($\Delta\text{QTc}>60$) compared with baseline or as a QTc of 500 ms or greater¹¹. The treatment was discontinued for the patients with severe QTc prolongation during treatment. The demographic features, medical histories, medications, laboratory results, and ECG details of the patients were obtained from the hospital data recording system. This study has been approved by the Eskisehir Osmangazi University Ethics Committee and the Ministry of Health of the Republic of Turkey. Due to the retrospective nature of this study, the medical ethical committee waived the requirement for individual informed consent.

Statistical analysis

Data were analyzed using IBM SPSS Statistics version 23.0 (Armonk, New York, NY, USA). Continuous data are given as medians (Q1–Q3). Categorical data are given as percentage (%). Shapiro-Wilk's test was used to investigate the suitability of the data for normal distribution. In order to compare the groups that do not conform with the normal distribution, Mann-Whitney U test was used for the situations with two groups. In the analysis of the created cross-tables, Pearson's exact chi-square analysis was used. The Wilcoxon test was used to compare ECG changes during treatment with the patients' baseline ECGs. For statistical significance, $p<0.05$ value was accepted as a criterion.

RESULTS

The mean (SD) age of 155 patients (58.7 male, 41.3% female) included in the study with the diagnosis of COVID-19 was 52.4 ± 20.3 . The most common comorbid diseases were hypertension and diabetes mellitus in 63 (40.6%) and 37 (23.9%) patients, respectively. One hundred forty-four (92.9%) patients included in this study were hospitalized in the ward, while 11 (7.1%) patients were admitted to the intensive care unit. Of the 144 patients who were admitted to the ward, 15 (10.4%) patients were transferred to the intensive care unit after their medical condition worsened during their follow-up. Vasopressor treatment was given, and mechanical ventilation was applied to 16 (10.3%) patients. Nineteen (12.3%) patients died. One hundred and two (65.8%) patients were using HCQ, of which 53 (34.2%) patients were using a combination of HCQ+AZT. None of the patients

were using AZT alone. All patients were in sinus rhythm with baseline heart rate (SD) of 83 ± 17.8 beats/min. The median (IQR) baseline QRS, PR, and QTc durations of all patients were 91 (80–103), 145.5 (128.7–160.0), and 407 (385–426) ms, respectively. The demographic information, laboratory results, medical history, and medications of the patients are given in Table 1.

The QRS, PR, and QTc durations on-treatment were significantly longer in both the groups receiving HCQ alone and a combination of HCQ + AZT compared with the baseline ($p < 0.001$) (Table 2).

Comparing HCQ monotherapy and HCQ+AZT combination therapy, there was no significant difference between

median (IQR) baseline QRS (92.5 [80.75–105.50] ms *versus* 90.0 [80.0–102.5] ms; $p = 5$), baseline PR (147.0 [135.0–160.0] ms *versus* 144.0 [120.0–160.0] ms; $p = 0.53$), and baseline QTc (408.0 [389.2–427.5] ms *versus* 404.0 [384.0–420.0] ms; $p = 1$).

The median (IQR) maximum QTc duration on-treatment was significantly longer in patients who received combination therapy compared to those who received monotherapy (456.0 [422.0–467.5] ms *versus* 428.0 [412.75–449.25] ms; $p < 0.001$). At the same time, the median (IQR) change in QTc duration was 46.0 (40.5–54.5) ms in the group receiving HCQ+AZT and 18.0 (11.0–30.0) ms in the group receiving HCQ alone ($p = 0.001$) (Table 3). Of the 11 patients with significant

Table 1. Baseline characteristics of the patients.

| Characteristic (n=155) | Median (min–max) or number (%) |
|---|--------------------------------|
| Age (years) | 52.46±20.307 |
| Female sex | 64 (41.3) |
| Male sex | 91 (58.7) |
| Hypertension | 63 (40.6) |
| Hyperlipidemia | 12 (7.7) |
| Diabetes mellitus | 37 (23.9) |
| Obesity | 15 (59.7) |
| Smoking | 45 (29) |
| Coronary artery disease | 25 (16.1) |
| Chronic obstructive pulmonary disease/asthma | 32 (20.6) |
| Chronic kidney disease ≥ stage III | 12 (7.7) |
| Heart failure | 10 (6.5) |
| Prior Atrial fibrillation/flutter | 9 (5.8) |
| Prior permanent pacemaker/automated internal cardioverter defibrillator | 2 (1.2) |
| Malignancy | 10 (6.5) |
| Medications, n(%) | |
| Hydroxychloroquine | 101 (65.2) |
| Azithromycin | 0 |
| Hydroxychloroquine/azithromycin | 54 (34.8) |
| ACEI/ARB | 34 (21.9) |
| Beta blocker/nondihydropyridine calcium channel blocker | 21 (13.6) |
| Digoxin | 4 (2.6) |
| Antiplatelets | 13 (8.4) |
| Oral anticoagulants | 8 (5.2) |

Continue...

Table 1. Continuation.

| Characteristic (n=155) | Median (min–max) or number (%) |
|---|--------------------------------|
| LMWH | 106 (68.4) |
| Favipiravir | 29 (18.7) |
| Oseltamivir | 5 (3.2) |
| Laboratory results on admission, median (IQR) | |
| WBC ($10^3/\mu\text{L}$) | 6.90 (5.01–9.68) |
| Hemoglobin (g/dL) | 13.4 (12.10–15.30) |
| Platelet ($10^3/\mu\text{L}$) | 199.0 (166.0–254.0) |
| Lymphocyte ($10^3/\mu\text{L}$) | 1.59 (1.15–2.23) |
| Neutrophil ($10^3/\mu\text{L}$) | 3.75 (2.76–6.37) |
| Serum potassium (mmol/L) | 4.30 (4.00–4.30) |
| Serum sodium (mmol/L) | 138.0 (136.0–140.0) |
| Calcium (mg/dL) | 8.90 (8.40–9.40) |
| Creatinine (mg/dL) | 0.86 (0.76–1.13) |
| Ferritin | 100.0 (56.0–233.0) |
| D-dimer ($\mu\text{g/mL}$) | 0.60 (0.29–1.71) |
| CRP (mg/L) | 13.60 (2.30–61.90) |
| Troponin I (pg/mL) | 2.80 (0.960–15.10) |
| LDH (IU/L) | 195.0 (160.0–247.0) |
| Development of new arrhythmias, n(%) | |
| New AF | 3 (1.9) |
| VT | 1 (0.6) |
| Torsade de pointes | 1 (0.6) |
| VF | 1 (0.6) |

ACEI: angiotensin converting enzyme inhibitor; AF: atrial fibrillation; ARB: angiotensin receptor blocker; CRP: C-reactive protein; LDH: lactate dehydrogenase; LMWH: low molecular weight heparin; WBC: white blood count; VT: ventricular tachycardia; VF: ventricular fibrillation.

Table 2. Electrocardiographic changes of the study cohort.

| Durations, median (IQR) (ms) | Baseline | Peak | p-value |
|------------------------------|---------------------|---------------------|---------|
| QRS duration with HCQ | 92.5 (80.75–105.5) | 97.5 (88.0–109.2) | <0.001 |
| QRS duration with HCQ+AZT | 90.0 (80.0–102.5) | 95.0 (85.5–109.0) | <0.001 |
| PR duration with HCQ | 147 (135.0–160.0) | 159.0 (141.0–168.5) | <0.001 |
| PR duration with HCQ+AZT | 144.0 (120.0–160.0) | 156.0 (139.5–171.0) | <0.001 |
| QTc duration with HCQ | 408.0 (389.2–427.5) | 428.0 (412.7–449.2) | <0.001 |
| QTc duration with HCQ+AZT | 404.0 (384.0–420.0) | 456.0 (422.0–467.5) | <0.001 |

AZT: azithromycin; QTc: corrected QT; HCQ: hydroxychloroquine.

Table 3. Comparison of baseline characteristics and ECG findings of patients who received hydroxychloroquine and hydroxychloroquine+azithromycin.

| Characteristic | Total (n=155) | Hydroxychloroquine (n=102) | Hydroxychloroquine/azithromycin (n=53) | p-value |
|--|----------------------|----------------------------|--|---------|
| Length of stay at ward, mean±SD | 9.54±4.28 | 9.64±4.31 | 9.31±4.25 | 0.88 |
| Length of stay at intensive care unit, mean±SD | 7.92±3.76 | 7.18±3.18 | 8.46±4.15 | 0.29 |
| Radiographic findings of pneumonia | 118 (76.1) | 76 (74.5) | 42 (49.2) | 0.32 |
| Mechanically ventilation | 16 (10.3) | 7 (6.9) | 9 (17.0) | 0.049 |
| In hospital death | 19 (12.3) | 10 (9.8) | 9 (17.0) | 0.15 |
| Vasopressor support | 16 (10.3) | 7 (6.9) | 9 (17.0) | 0.049 |
| Comorbidities, n (%) | | | | |
| Hypertension | 63 (40.6) | 38 (37.3) | 25 (47.2) | 0.15 |
| Diabetes mellitus | 37 (23.9) | 26 (25.5) | 11 (20.8) | 0.32 |
| Heart failure | 10 (6.5) | 5 (4.9) | 5 (9.4) | 0.22 |
| Chronic kidney disease≥stage III | 12 (7.7) | 8 (7.8) | 4 (7.5) | 0.60 |
| Coronary artery disease | 25 (16.1) | 16 (15.7) | 9 (17.0) | 0.5 |
| Chronic obstructive pulmonary disease/asthma | 32 (20.6) | 21 (20.6) | 11 (20.8) | 0.56 |
| Malignancy | 10 (6.5) | 6 (5.9) | 4 (7.5) | 0.46 |
| Smoking | 45 (29) | 30 (29.4) | 15 (28.3) | 0.52 |
| ECG findings median (IQR) (ms) | | | | |
| Baseline QRS duration | 91.0 (80.0–103.0) | 92.5 (80.75–105.50) | 90.0 (80.0–102.5) | 0.5 |
| Post-treatment QRS peak | 97.0 (86.0–109.0) | 97.5 (88.0–109.25) | 95.0 (85.5–109) | 0.68 |
| ΔQRS | 4.0 (0.0–9.0) | 2.0 (0.0–8.25) | 5.0 (1.0–9.5) | 0.14 |
| Baseline QTc duration | 407.0 (385.0–426.0) | 408.0 (389.25–427.50) | 404.0 (384.0–420.0) | 0.1 |
| Post-treatment QTc peak | 437.0 (414.0–460.0) | 428.0 (412.75–449.25) | 456.0 (422.0–467.5) | <0.001 |
| ΔQTc | 27.0 (13.0–45.0) | 18.0 (11.0–30.0) | 46.0 (40.5–54.5) | <0.001 |
| Baseline PR duration | 145.50 (128.7–160.0) | 147.0 (135.0–160.0) | 144.0 (120.0–160.0) | 0.53 |
| Post-treatment PR peak | 159.0 (140.0–170.0) | 159.0 (141.0–168.50) | 156.0 (139.5–171.0) | 0.97 |
| ΔPR | 7.0 (1.0–13.0) | 5.0 (0.0–12.25) | 10.0 (5.0–15.0) | 0.022 |
| QTc peak day | 5.0 (4.0–5.0) | 5.0 (4.0–6.0) | 4.0 (3.0–5.0) | 0.022 |
| Drug withdrawal due to QRS prolongation | 11 (7.1) | 5 (4.9) | 6 (11.3) | 0.12 |

ΔPR, PR changes during treatment; ΔQRS, QRS changes during treatment; ΔQTc, QTc changes during treatment. The p-values indicated show that they are statistically significant. SD: standart derivation; ECG: electrocardiography; IQR: interquartile range; QTc: corrected QT.

prolongation in the QTc duration, 5 (4.9%) patients were in the monotherapy group, and 6 (11.3%) patients were in the group receiving combination therapy ($p=0.12$). The median (IQR) maximum QTc duration was significantly longer in patients who had stopped taking the drug in the combination group compared with the group receiving monotherapy treatment (478 [467.7–499.5] and 413.0 [410.0–444.5] ms; $p<0.001$). Moreover, it was observed that patients who received combination therapy reached the median (IQR) maximum QTc earlier than those who received monotherapy (4.0 [3.0–5] days *versus* 5.0 [4.0–6.0] days; $p=0.02$). Besides QTc prolongation, 3 (1.9%) patients developed new atrial fibrillation, and 1 (0.6%) patient developed severe arrhythmias, such as ventricular tachycardia (VT), ventricular fibrillation (VF), and TdP, during cardiopulmonary resuscitation and died. The maximum QTc duration of this patient was 444 ms. None of the patients had VT, VF, or TdP due to drug-induced QTc prolongation.

DISCUSSION

The most important findings of this study are as follows:

1. The use of both HCQ alone and HCQ+AZT combined therapy significantly prolonged the QTc.
2. HCQ alone prolonged the QTc interval by median (IQR) 18.0 (11.0–30.0) ms, while the combined use of HCQ + AZT prolonged it by median (IQR) 46.0 (40.5–54.5) ms.
3. VT, VF, or TdP due to QTc prolongation was not observed in both the groups. One patient developed a malign cardiac arrhythmia, whose maximum median (IQR) QTc duration was 444 ms.

Many treatments were tried for SARS-CoV-2 disease in Wuhan, China, in December 2019, and the disease was declared as a pandemic by the WHO on March 12, 2020. Among these therapies, chloroquine (CQ)/HCQ and/or HCQ+AZT have been shown to be effective by inhibiting virus cell fusion in some studies, so these drugs have become widely used^{12,13}. However, until now, there are a limited number of studies showing a positive effect of these two drugs on SARS-CoV-2. In a study of 30 patients, it was reported that CQ did not reduce the viral load or shorten the time taken for fever to decrease and did not stop the progression of the disease¹⁴. In another study, HCQ and/or HCQ+AZT were shown to be effective on morbidity and mortality¹⁵. The most feared side effects of these treatments are TdP and sudden cardiac death due to QTc prolongation. QT prolongation and development of TdP due to high-dose or chronic HCQ use are limited to a few case reports, and although QTc

prolongation is a predictive for TdP, it is not specific. The relationship between QT prolongation and TdP is not linear because drugs that prolong QT have not been consistently associated with cardiac arrhythmias. Among all QT-prolonging drugs, the TdP incidence of antiarrhythmic drugs was reported as 1–5%, while the TdP incidence of noncardiovascular drugs was reported as 0.001%¹⁶. Studies have reported that AZT, a macrolide group drug, prolongs the QT interval¹⁰. Although AZT was shown to cause sudden cardiac death in a study conducted in 2012, there is insufficient evidence regarding QTc prolongation and cardiac death due to TdP¹⁷. In a recent study, Bakhshaliyev et al. reported no arrhythmia and cardiac death in patients with COVID-19 who were treated with HCQ+AZT¹⁸. In addition, in many small-scale studies in which HCQ and/or AZT treatment was used in monotherapy or in combination increasingly upon the onset of the COVID-19 epidemic, it was shown that these two drugs did not cause TdP or sudden cardiac death due to QTc prolongation^{16,19–22}.

In our study, the QTc interval of the patients who received HCQ or HCQ+AZT was significantly longer compared with the baseline ($p<0.001$). When monotherapy and combination therapy were compared, QTc durations of the group receiving combination therapy were significantly prolonged compared with the group receiving monotherapy. In both groups, treatment of 11 (7.1%) patients was interrupted due to QTc prolongation, but no malign arrhythmia or TdP was observed even in this group. There was a patient who developed VT and VF, in which case such rhythms developed during cardiopulmonary resuscitation. At the same time, the time to reach the maximum QTc duration was shorter in the group receiving combination therapy in this study, compared with the monotherapy group.

The limitations of this study are the absence of a control cohort of patients with COVID-19 infections who were not treated with any of these medications. Although this would have provided a stronger analysis, nearly every hospitalized patient with COVID-19 received one or more of these medications during the course of their admission during this study period. The number of patients with underlying cardiac disease in the study is small, potentially limiting generalizability to that population.

CONCLUSION

In this study, it was shown that QTc interval was prolonged significantly after both monotherapy and combined therapy. QTc prolongation was significantly greater in the combination group. Despite this increase, very few patients had the medications discontinued prematurely due to QT prolongation.

The important point was that this study showed that QTc prolongation was not associated with malignant arrhythmia such as TdP and arrhythmic death in both groups.

AUTHOR CONTRIBUTIONS

BM: Conceptualization. **HA:** Data curation. **MA:** Writing – original draft. **SM:** Writing – review & editing.

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Physical activity and quality of life in adults and elderly individuals with lower limb amputation

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SUMMARY

OBJECTIVE: The aim of this study was to investigate the levels of physical activity (PA) and quality of life (QOL) in adults and elderly individuals with lower limb amputation (LLA).

METHODS: This was a cross-sectional observational study. Participants completed three surveys as follows: a demographic survey, the International Physical Activity Questionnaire, and the World Health Organization Quality of Life. Thirty-six individuals with lower limb amputation were separated into two different groups as follows: Adults-lower limb amputation (n=12), composed of individuals with lower limb amputation who aged from 18–59 years, and Elderly-lower limb amputation (n=24), composed of individuals with lower limb amputation who aged 60 years and above. Statistical differences were determined as $p < 0.05$.

RESULTS: Age and number of individuals with a low level of functional independency were higher in the Elderly-lower limb amputation group ($p < 0.05$). The International Physical Activity Questionnaire scores were reduced in the Elderly-lower limb amputation group ($p < 0.05$). The Pearson's correlation test between low metabolic equivalent task (MET), time since amputation, and family income presented positive significant results in the Elderly-lower limb amputation ($p < 0.05$). Adults-lower limb amputation just presents a positive significant correlation with the low family income ($p < 0.05$).

CONCLUSION: Elderly individuals with lower limb amputation are more susceptible to present negative health outcomes than adults with lower limb amputation.

KEYWORDS: Physical exercise. Amputee. Health. Aging.

INTRODUCTION

Amputation is considered a major life-changing event because it leads to permanent disability¹. The number of lower limb amputation (LLA) is supposed to be increased due to an increase in age expectation of living and to the increased incidence of diabetes and cardiovascular conditions². Walking with a prosthesis influences the heart rate and oxygen consumption³.

One of the most important aspects of rehabilitation procedures following LLA is supporting amputated individuals to engage in the regular practice of physical activity (PA) for physical, psychological, and social health benefits².

The PA can be defined as a routine of performing any type of body movement, such as swiping the floor or gardening, which burns calories at higher levels than in a rest state. The World Health Organization (WHO) recommendations say that lifting weights

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should be performed at a minimum weekly frequency of 2 days⁴. Aerobic exercises should be performed for at least 150 min at moderate intensity, or for 75 min at high intensity, at least 5 times per week⁵. According to the general sense, the regular practice of sports or PA is a fundamental part of developing and maintaining a healthy lifestyle⁶. Higher PA levels influence mental and general health positively⁷. The association of PA with health can be evaluated through the measurement of quality of life (QOL)⁸.

There are several factors that can influence the level of PA and the QOL in individuals with LLA, such as age and time of amputation⁹. Usually, disabled individuals present a lower level of PA and QOL than the nondisabled population¹⁰. It is known that sedentary behavior is associated with bad effects on general health⁹. However, there is a small body of evidence regarding PA and QOL among adults and elderly individuals with LLA and presenting conflicting results many times. For example, there are a small number of studies that reported individuals with LLA to be regularly physically active^{11,12}, while the majority of the published studies have reported lower levels of PA in these individuals^{10,13}. Thus, the aim of this study was to investigate the PA and QOL levels in adults and elderly individuals with LLA.

METHODS

Study design

This was a cross-sectional observational study. This study was carried out in four Family Health Units (FHUs). Participation in the study was voluntary and anonymous. Written informed consent was obtained from each participant. This study was performed in accordance with the Declaration of Helsinki and its later amendments.

Procedures and measures

Participants completed three surveys as follows: a demographic survey, the International PA Questionnaire (IPAQ) (short-term)¹⁴, and the World Health Organization QOL (WHOQOL) on its short version (WHOQOL-BREF)⁸. The surveys collected self-reported information. Individuals who aged above 18 years and had LLA were considered in this study. They were separated into two different groups as follows: Adults-LLA, composed of individuals with LLA who aged from 18–59 years, and Elderly-LLA, composed of individuals with LLA who aged 60 years and above. The exclusion criteria for the individuals were as follows: currently a hospital inpatient; unable to independently answer survey questions; or did not fulfill the IPAQ guidelines. The initial number of participants was 43, but 7 were excluded due to the responses to the IPAQ. As per the guidelines, responses were excluded from analysis if the IPAQ

- 1) was incomplete and
- 2) had unreasonably high scores (>16 hours of PA per day) (i.e., these issues could not be rectified as surveys were returned anonymously)¹⁴.

Finally, we had 36 individuals in the sample.

Demographic survey

The demographic survey evaluated the participant's age, gender, schooling, time since amputation, level of amputation, site of amputation, cause of amputation, functional level, and family income (i.e., number of salaries). Status of family income is subdivided into five levels, from A–E, where the level E comprehends individuals who receive up to two salaries; D from two up to four salaries; C from four up to 10 salaries; B from 10 up to 20 salaries; and A, over 20 salaries. We used as inclusion criteria for individuals who passed through LLA (i.e., unilateral or bilateral, at the thigh, leg, foot, or toe levels) in etiologies related to trauma, diabetes mellitus, infections, ischemia, or any others.

International Physical Activity Questionnaire

For the categorization of the individual's level of PA, the quantification standard of the IPAQ guidelines was adopted. The level of PA of each individual was, then, divided into three categories as follows:

- 1) high, to individuals who performed the high-intensity PA for at least three or more days a week reaching a minimum metabolic equivalent task (MET) of 1.500 or had seven days of any combination of PA (i.e., walking, moderate intensity, high intensity) reaching a minimum of 3.000 MET per week;
- 2) moderate, to individuals who performed the moderate-intensity PA for three or more days of intense activity for at least 20 min a day, or five or more days of moderate activity or walking for at least 30 min a day, or five or more days of any combination of PA (i.e., walking, moderate intensity, high intensity) reaching a minimum of 600 MET per week;
- 3) low, to individuals who did not meet any of the criteria that would allow them to be classified in the other two categories. The data from the IPAQ were processed and reported according to its guidelines.

World Health Organization Quality of life Brief Version

The QOL was verified through the WHOQOL-BREF questionnaire, which measures four domains, namely, physical, psychological, social relationship, and environment¹⁵.

Statistical analysis

For the comparison of qualitative variables, we used the chi-square test. For the quantitative variables, we used a two-way analysis of variance (ANOVA). To study the correlation between quantitative variables, we used the Pearson's correlation coefficient test. The qualitative variables were expressed in frequency (i.e., number/total number). The quantitative variables were expressed as mean and standard deviation (SD). Statistical differences were determined as $p < 0.05$. The statistical analysis was carried out using the GraphPad Prism 7.0 (version 7.00 for Mac OS X, GraphPad Software, San Diego, CA, USA).

RESULTS

A total of 36 individuals with LLA composed the sample. The sample characteristics were described in both groups, Adults-LLA and Elderly-LLA (Table 1). As expected, we found a statistical difference between the age of the groups ($p < 0.05$). Independent functional levels also presented statistical difference ($p < 0.05$) with the number of individuals with the low level being higher in the Elderly-LLA group. Schooling presented a tendency to have a statistical difference ($p = 0.0551$), with the number of individuals in primary school and not literate being higher in the Elderly-LLA group.

Table 1. Characteristics of adults and elderly individuals with lower limb amputation.

| General characteristics | Adults-LLA | Elderly-LLA | p-value |
|-------------------------|-------------|--------------|----------|
| Age (years) | 43.41±12.42 | 72.040±7.73 | <0.0001* |
| Gender | | | 0.8090 |
| Men | 5/12 | 9/24 | |
| Women | 7/12 | 15/24 | |
| Schooling | | | 0.0551 |
| University degree | 2/12 | N/A | |
| High-school | 2/12 | 3/24 | |
| Primary school | 6/12 | 13/24 | |
| Not literate | 2/12 | 8/24 | |
| Time since amputation | | | |
| Number of months | 77.41±67.66 | 70.58±101.65 | 0.1619 |
| Type of amputation | | | 0.4142 |
| Unilateral | 10/12 | 17/24 | |
| Bilateral | 2/12 | 7/24 | |
| Level of amputation | | | 0.3989 |
| Thigh | 6/12 | 10/24 | |
| Leg | 4/12 | 8/24 | |
| Foot | 1/12 | N/A | |
| Toe | 1/12 | 6/24 | |
| Cause of amputation | | | 0.1045 |
| Trauma | 5/12 | 3/24 | |
| Ischemia | 3/12 | 4/24 | |
| Diabetes mellitus | 2/12 | 13/24 | |
| Infections | 1/12 | 2/24 | |
| Other | 1/12 | 2/24 | |
| Rehabilitation | | | 0.4795 |
| Yes | 7/12 | 11/24 | |
| No | 5/12 | 13/24 | |

Continue...

Table 1. Continuation.

| General characteristics | Adults-LLA | Elderly-LLA | p-value |
|------------------------------|------------|-------------|---------|
| Prosthetic use | | | 0.6353 |
| Yes | 6/12 | 10/24 | |
| No | 6/12 | 14/24 | |
| Independent functional level | | | 0.0230* |
| Low | 4/12 | 18/24 | |
| Moderate | 5/12 | 4/24 | |
| High | 3/12 | 2/24 | |
| Family income | | | |
| Number of salaries | 2.33±1.77 | 2.21±1.81 | 0.3176 |

LLA: lower limb amputation; N/A: non-applicable. Age: time since amputation, and family income results are shown in mean±SD. *p<0.05. The other variables are presented as number/total number.

The IPAQ scores presented significant results ($p<0.05$), with the number of individuals presenting low scores in the Elderly-LLA group being 18–24. The categorization of the QOL of Adults-LLA and Elderly-LLA groups did not present any significant differences between the groups. However, there was a tendency to present lower scores in the physical domain ($p=0.0624$) and the social domain ($p=0.0925$) in the Elderly-LLA group (Table 2). These results suggest that physical function and social network may be more affected in the Elderly-LLA group.

The Pearson's correlation between MET below 600 kcal/kg/week, time since amputation, and family income presented positive significant results in the Elderly-LLA group ($p<0.05$). The Adults-LLA group just presents a positive significant correlation ($p<0.05$) between MET below 600 kcal/kg/week with the family income (Table 3).

DISCUSSION

It is widely known that the regular practice of PA induces lots of health-related benefits, such as improvement in cardiovascular¹⁶ and mental health¹⁷. The main findings in this study reveal that the lower levels of PA are applied in the Elderly-LLA group. The number of individuals with a low level of functional independency was also significantly higher in the Elderly-LLA group. Schooling seems to be influencing both groups ($p=0.551$). Both groups were revealed to receive salaries in the D level, which characterizes a low family income. We also identified a positive correlation between MET below 600 kcal/kg/week, time since amputation, and family income in the Elderly-LLA group. However, just family income presented a positive correlation with the Adults-LLA group.

It is necessary to study a broad spectrum of potential determinants over the lifetime that affects sedentary behavior⁹. In our study, the number of individuals who completed primary schooling and who were not literate seems to be influencing both groups. This indicates that the schooling level is an important social factor for avoiding amputation. The low family income was also associated with reduced PA levels in both Adults-LLA and Elderly-LLA groups. The causes of amputation are often reported to be influenced by the degree of industrialization of the country, the transportation system, and how easy is to have access to medical care¹⁸.

People with LLA are usually less physically active and participate less in sports activities¹³. However, comparisons between adults and elderly individuals with LLA regarding PA and functional levels are not usual in the scientific literature. Our results revealed lower functional independency and PA levels in the Elderly-LLA group. Interestingly, we did not find significant differences between the groups when evaluating the weekly metabolic expenditure. We hypothesized that this occurred because individuals with LLA, independently of the age, spend more energy for lack of training on how to use new motor coordination and balance strategies to successfully walk and do daily activities that may also influence the QOL.

The QOL is reported to be the individual's perception of his/her position in the culture and values in which he/she is inserted and with respect to his/her goals, expectations, principles, and concerns¹⁹. The QOL can be affected by many factors, such as hypertension and sleep disturbances²⁰. Many factors related to QOL in patients with LLA have been reported in the scientific literature, such as time since amputation and family income status²¹. Besides not presenting a statistical

Table 2. Categorization of physical activity and quality of life levels in adults and elderly individuals with lower limb amputation.

| IPAQ scores | Adults-LLA | Elderly-LLA | p-value |
|----------------------|------------|-------------|---------|
| Low | 3/12 | 18/24 | 0.0052* |
| Moderate | 5/12 | 4/24 | >0.9999 |
| High | 4/12 | 2/24 | 0.9998 |
| WHOQOL-BREF | Adults-LLA | Elderly-LLA | p-value |
| Physical domain | 14.38±3.79 | 12.12±3.07 | 0.0624 |
| Psychological domain | 15.39±2.86 | 13.72±2.88 | 0.1099 |
| Social domain | 16.44±2.15 | 14.61±3.32 | 0.0925 |
| Environmental domain | 13.17±2.00 | 12.77±2.67 | 0.6534 |
| Overall | 14.44±2.36 | 13.08±2.23 | 0.1005 |

PA: physical activity; IPAQ: International Physical Activity Questionnaire; LLA: lower limb amputation; WHOQOL: World Health Organization Quality of Life. The other variables are presented as number/total number. *p<0.05.

Table 3. Pearson's correlation between low level of weekly metabolic expenditure (below 600 MET), time since amputation, and family income in adults and elderly individuals with LLA.

| | p-value | |
|-------------------------------|------------|-------------|
| | Adults-LLA | Elderly-LLA |
| MET and age | 0.0550 | 0.4186 |
| MET and time since amputation | 0.7422 | 0.0009* |
| MET and family income | 0.0423* | 0.0017* |

LLA: lower limb amputation; MET: metabolic equivalent task (kcal/kg/week). Pearson's correlation was applied to individuals with less than 600 metabolic equivalent task, who were classified into the category "low level of physical activity" according to the International Physical Activity Questionnaire (Adults-lower limb amputation, n=5; Elderly-lower limb amputation, n=18), *p<0.05.

significance, our results point to a tendency that QOL can be diminished in the physical (p=0.0624) and social (p=0.0925) domains in the Elderly-LLA group.

To have a better understanding of the changes in PA and QOL in adults and elderly individuals with LLA over time and to better assess its determinant factors, it is necessary for the development of a multicentric approach containing larger samples. The community-based exercise programs supported by the government may provide an opportunity for clinicians to offer better healthcare and to improve the PA and QOL levels of individuals with LLA. Thus, disability education for future healthcare professionals is a must. Finally, the regular practice of physical exercise is necessary to avoid the development of negative outcomes over cardiovascular and mental health²².

CONCLUSIONS

Elderly individuals with LLA present lower levels of PA when compared to adults with LLA. Elderly individuals with LLA

are more susceptible to present negative health outcomes than adults with LLA.

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AUTHORS' CONTRIBUTIONS

VHM: Conceptualization, Methodology, Data curation, Formal Analysis, Investigation, Methodology, Validation, Visualization, Writing–review & editing. **RALS:** Conceptualization, Methodology, Data curation, Formal Analysis, Funding acquisition, Investigation, Methodology, Supervision, Validation, Visualization, Writing – original draft, Writing–review & editing. **ACIC:** Conceptualization, Methodology, Data curation, Formal Analysis, Writing – original draft, Writing–review & editing. **MAPN:** Conceptualization, Methodology, Data curation, Formal analysis, Investigation, Methodology, Supervision, Validation, Visualization.

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Trend analysis of clinical aspects of congenital syphilis in Brazil, 2009–2018

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SUMMARY

INTRODUCTION: Congenital syphilis is caused by the vertical transmission of bacteria, *Treponema pallidum*, from nontreated or inappropriately treated pregnant to the fetus.

OBJECTIVE: To evaluate the clinical aspects of Congenital syphilis in Brazil, between 2009–2018.

METHOD: It is an analytical cross-sectional study whose data were collected from the Department of Chronical Conditions and Sexually Transmitted Infections of Brazilian Health Ministry. Clinical variables were analyzed using the software Joinpoint Regression, which makes a segmented linear regression.

RESULTS: In the study period, 156,969 cases of Congenital syphilis and 1642 deaths by this disease were reported. The trend analysis indicates growing in diagnosis of maternal syphilis during prenatal care, appropriate treatment of pregnant, realization of prenatal care, maternal partner treatment, diagnosis of syphilis in children under seven days, and diagnosis of recent syphilis.

CONCLUSIONS: Although the trend analysis presents relative improvement in Congenital syphilis panorama in Brazil, the disease still related to high numbers of evitable perinatal morbidity and mortality. Therefore, the prenatal assistance with quality is fundamental to have a possible change in this field in the country.

KEYWORDS: Syphilis, congenital; Pregnancy complications, infectious; Maternal-child health services.

INTRODUCTION

Congenital syphilis (CS) is caused by the vertical transmission of the bacteria *Treponema pallidum*, from nontreated or improperly treated pregnant to the fetus, by transplacental or in the birth moment¹. This disease perdures as the most common congenital infection all over the world².

CS is classified as precocious, when diagnosed until one year, and late, when diagnosed after one year³. This illness can show clinical manifestations from asymptomatic form to congenital defects, spontaneous abortion, stillborn, or perinatal death⁴.

In Brazil, the ordinance n° 542 became the CS as a disease of compulsory notification in 1986; in pregnant, it is obligatory since 2005, through by ordinance n° 33. The congenital form of syphilis is a predictor of prenatal quality, because there is a

positive correlation between cases and child mortality, spontaneous abortion, and stillborn rates, demonstrating fragilities on primary assistance of health^{5,6}.

The pregnancy treatment, in Brazil, is considered proper when it is done with benzathine penicillin, initiated 30 days before birth, following the therapeutic scheme according to clinical status of syphilis and respecting the recommended gap between doses. Moreover, it is necessary to present regression on titration of non-treponemic test, in at least two dilutions in three months or four dilutions in six months, after the treatment conclusion^{3,6}.

However, despite the health organs recommendations, in reference of prevention, diagnosis, and treatment, CS shows an expressive number of cases in Brazil, being considered an

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important problem in public health in the country and in the world⁷. So, this article aims to evaluate the clinical aspects of CS in Brazil, between 2009–2018.

METHODS

It is a cross-sectional study that analyzes the CS trends in Brazil, between 2009–2018. The data were collected from the Department of Chronical Conditions and Sexually Transmitted Infections (Departamento de Condições Crônicas e Infecções Sexualmente Transmissíveis – DCCI) of the Health Surveillance Secretary (Secretaria de Vigilância em Saúde – SVS) of the Brazilian Health Ministry⁸.

The trend line was structured through variables related to clinical aspects of CS. The independent variable was the year, and the dependent variables were maternal diagnosis moment, maternal treatment scheme, maternal partner treatment, prenatal care, and child age at moment of diagnosis and final diagnosis.

After the analysis line drawing and the variables division, the data collected from DCCI/SVS were added and converted into percentage values, filling specific tables for each variable on Microsoft Office Excel. These tables were analyzed using software Joinpoint Regression version 4.1.1 (Statistical Methodology and Applications Branch, Surveillance Research Program, National Cancer Institute).

The Joinpoint Regression makes trend lines, estimating the annual percent change (APC) of segmented linear regression and the average annual percent change (AAPC) of all period. During the analysis, we can recognize inflection points (Joinpoints), showing trend changes –stationary, crescent, or decrescent. The 95% confidence interval was calculated for each trend and found significant level (p-value) 0.05 or 5%. The $p < 0.05$ were considered statistically significant.

This study uses public domain and open access data, without identification of patients. Therefore, the approval by Research Ethics Committee/National Research Ethics Commission was not necessary, according the resolutions n° 466, December 12, 2012; n° 510, April 07, 2016; and n° 580, March 22, 2018, from Health National Council that regulates research with human beings and inside of Brazilian public health system (Sistema Único de Saúde – SUS).

RESULTS

Between 2009 and 2018, according the data from Brazilian Health Ministry, 156,969 cases of CS – 156,456 (99.8%) were diagnosed before one year – and 1642 deaths caused by the disease were recorded.

First, characterization of the clinical aspects of CS (Figure 1) showed that most women (78.3%) who had children with the disease had passed during the prenatal care, and more than half of the cases (51.2%) were diagnosed during this period of assistance. Second, the maternal treatment scheme is considered proper in one-third (35.8%) of congenital cases and the sexual partners treatment is quite neglected – done only in 14.9% of partners. Finally, the precocious diagnosis was done in 96.3% of cases – less than seven days of life – and the final diagnosis was recent CS in 92.6% of children of time cut studied.

The analysis of indicators shows that the maternal diagnosis moment was crescent during the prenatal care (AAPC 5.0; $p=0.0$) and decrescent at the moment of birth/curettage and after birth. This last variable shows an inflection point in 2014, accentuating the decrescent trend (Figure 2A). The segments “unrealized” and “ignored” in this indicator were stationary in period.

With regard to maternal treatment scheme, the proper treatment presents growing trend during all time of study (AAPC 4.4; $p=0.0$), becoming more significant in 2013 (APC 10.9; $p=0.0$), when had an inflection point (Figure 2B). Although the inadequate treatment has also crescent trend (AAPC 2.1; $p=0.0$). The segment “unrealized” has a decrescent line (AAPC -4.3; $p=0.0$). Then, the partner treatment had crescent line in all time cut (AAPC 8.7; $p=0.0$), increasing from 2016 (APC 20.8; $p=0.0$). Moreover, the prenatal care “done” showed crescent trends to “yes” and decrescent to “no” and “ignored.”

Further, the child age at the moment of diagnosis exhibits crescent trend lines to “under seven days” and decrescent to ages between seven and 27 days, 28 and 364 days, and five and 12 years. The trend is stationary in ages from one–four years. Yet, the final diagnosis of recent CS presents light growing trend, while late CS and abortion by syphilis have decreasing lines; stillborn by syphilis presents an inflection point in 2013 – stationary trend that became decrescent (APC -7.5; $p=0.0$) (Figure 2C). Finally, both trends of cases and death (Figure 2D) related to CS are crescent during the study period and deaccelerate in 2013 and 2012, respectively.

DISCUSSION

The CS and its deaths in Brazil presented crescent trends in the study period. Although there is a reduction in CS cases since 2013, the nation did not get to aim the target of 0.5 cases per 1000 born alive established by Pan American Health Organization⁹. The trends of increasing of this disease can be related to ampliation of a statal program called Family’s Health Strategy, with improvement of investigation, notification, detection, and treatment during the prenatal care⁵. Also, it can be

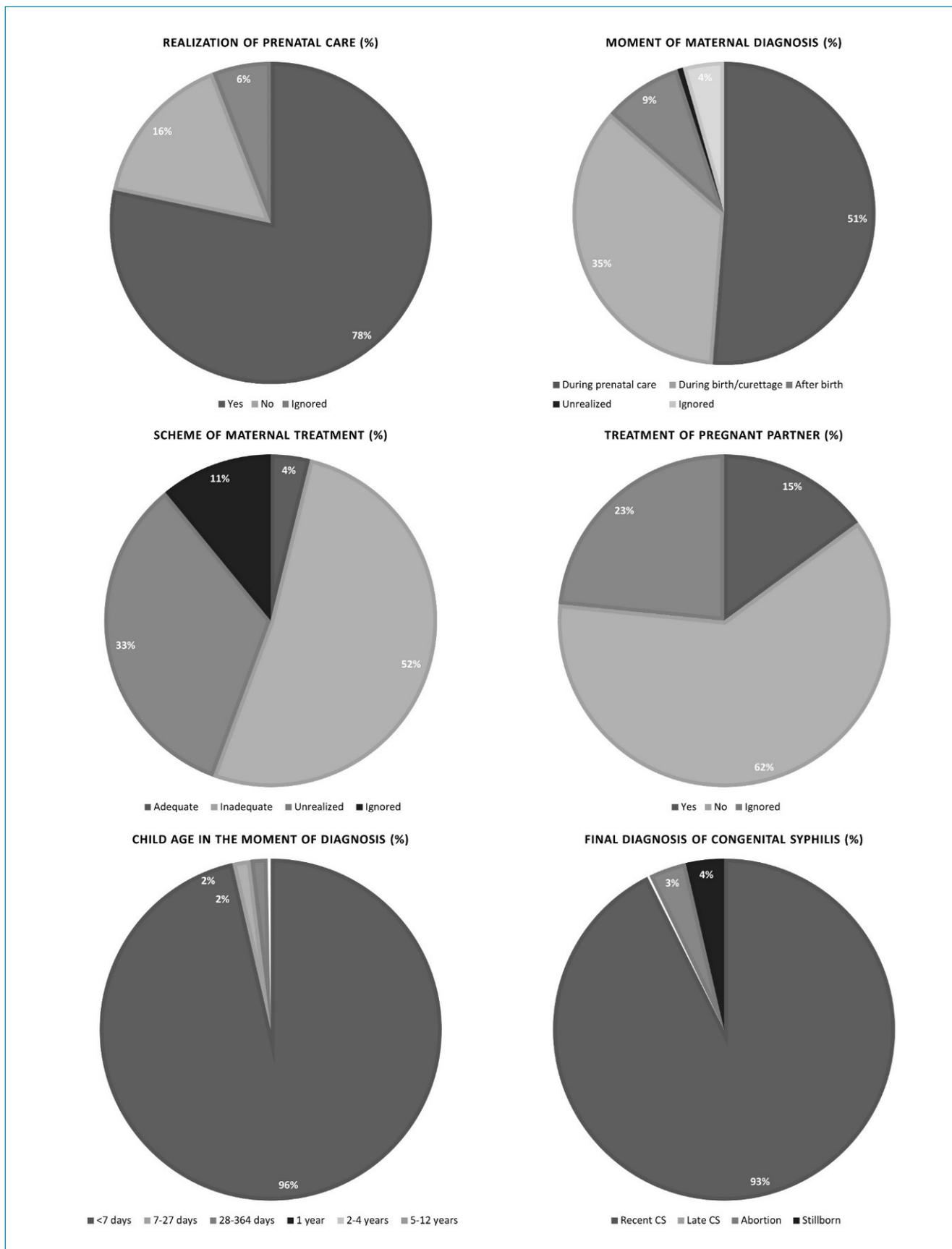


Figure 1. Characterization of indicators correlated with the clinical aspects of congenital syphilis in Brazil, 2009–2018.

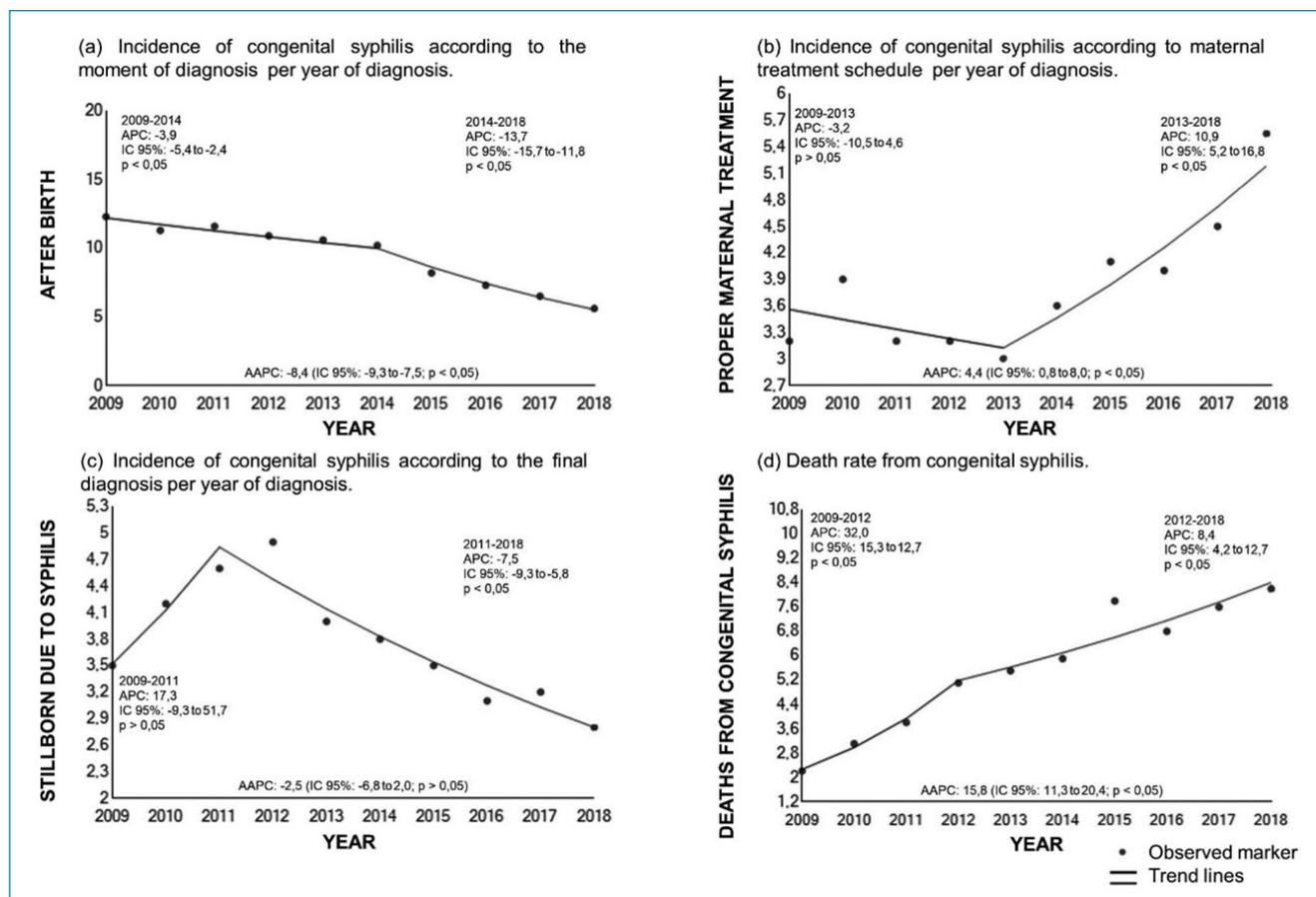


Figure 2. Trends in the clinical aspects of congenital syphilis in Brazil, between 2009–2018.

attributed to reduction in preservative use and shortage of penicillin³. Beyond Brazil, other countries face the CS, such as the United States, where the disease is rising¹⁰.

The prenatal care presented crescent trend. This article evidenced that most of pregnant did it and that the diagnosis was done in this moment. However, the inappropriate treatment and nonrealized are against the eradication of CS. A study in municipality of Porto Velho, state of Rondônia, found possible obstacles to precocious diagnosis and proper treatment, failure in precocious detection of syphilis and inappropriate treatment with over doses, or lack of partners' treatment. And, despite the prenatal care, the diagnosis does not occur at same proportion¹¹. A French paper also detected problems in prenatal assistance related to cases of CS¹². In this aspect, all CS cases must be seen as a failure in health public system in providing quality in prenatal care⁷.

The late diagnosis of syphilis in pregnant women, during prenatal, also shows a serious problem itself. Another study, in municipality of Caxias, state of Maranhão, identified high frequency of diagnosis in the third trimester, indicating late beginning of prenatal, as low as effectivity of offered service¹³.

The low prenatal efficiency, in reference of diagnosis and treatment of syphilis, is discussed in a paper that uses data from *Estudo Nascer* (free translation: To Born Study), by Domingues and Leal¹⁴, which identified that more than 90% of pregnant were under prenatal care. Though, the CS incidence, vertical transmission, and occurrence of negative outcomes have high rates. This, therefore, indicates the lack of control of gestational syphilis in Brazil. Therefore, investigation and precocious treatment are necessary to reduce/eliminate the CS in the long term, through interprofessional strategies that promote a preventive and collaborative approach¹⁰.

According to Clinical Protocol and Therapeutic Guidelines to Integral Attention to People with Sexually Transmitted Infection of Brazilian Health Ministry, the treatment is considered appropriate for pregnant women when it is done with benzathine penicillin, initiated 30 days before birth, following the therapeutic scheme based on clinical status, respecting the gap between doses, and presenting regression on titration of non-treponemic test, in at least two dilutions in three months or four dilutions in six months, after the treatment conclusion. Proper treatment is important to effective immune response. However, even though

it is easy to diagnose and treat, with available and cheap medicine, potential barriers, as role of health professionals, block the disease control⁶. One study, between 2007–2013, in municipality of Montes Claros, state of Minas Gerais, identified that 64.8% of cases had inappropriate treatment of pregnant¹¹. In municipality of Ipojuca, state of Pernambuco, an article shows that most of 49% of pregnant had inappropriate treatment too¹⁵. In Cape Town, South Africa, between 2011–2013, it was stated that 56% of pregnant in research did not pass during prenatal care and 98% were inappropriately treated¹⁶. Thus, low-quality prenatal care is a risk factor of CS¹⁷.

Beyond the inappropriate maternal treatment, the lack of partners treatment is a severe problem – only 14.9% of pregnant partners is treated in Brazil. The Brazilian conjecture is a reflex of its municipalities. This is corroborated with a study of Apucarana, state of Pará, in which 52.4% of partners did not receive treatment and in notification it is ignored¹⁵. Similarly, in state of Tocantins capital, Palmas, 83% of pregnant did not have their partners treated¹⁸.

In reference to death by CS, Brazil presents a crescent trend, in temporal cut, with a total of 1642 deaths. The occurrence of abortion by syphilis (3.6%) and stillborn (3.6%) is an important and severe problem in the country yet. Most of stillborn (98%) happens in low- and middle-income countries and 7.7% of these deaths are related to syphilis¹⁹.

Nascimento and collaborators²⁰ identified that 11% of pregnancies had deaths as outcome. This study highlighted the presence of high titrations on VDRL, in the end of gestation and in preterm newborn, demonstrating the lack of proper treatment during prenatal care. Another relevant problem consists in under-reporting of neonatal and infant deaths related to CS in Brazil²¹.

Thus, in view of panorama of CS in Brazil and related factors, it is evident the importance of primary attention in

offering adequate assistance to pregnant and fighting against the maternal-fetal transmission of syphilis. Its prevention, beyond avoiding adverse consequences to mother and her child, can reduce costs related to health²². So, the primary attention could collaborate effectively to change the epidemiology of disease.

CONCLUSIONS

CS is one of the main indicators of prenatal assistance quality; therefore, reduction in this cause is the aim of several health spheres. According to analyzed studies, the ampliation of access to primary health care and of testing is not enough to solve the Brazilian panorama.

CS is a multicausal disease. Adequate treatment of mother and her partner, surveillance, and health education actions are fundamental to interrupt the transmission chain – remember that the vertical transmission causes sequels that can prejudice a child's life. Although all drawn strategies and actions, some trends did not present satisfactory outcomes, for example, higher deaths by CS.

Finally, it must have adequation between professionals of primary care and the others who follow the pregnant, the puerperal woman, and her child to fight against gestational syphilis and CS. In this way, it can create spaces to social participation, which can help improve aspects related to prenatal and vertical transmission of syphilis²³.

AUTHORS' CONTRIBUTION

BQSM: Data curation, Formal Analysis, Writing – Original Draft. **AOF:** Data curation, Formal Analysis. **RAW:** Conceptualization, Writing – review & editing. **MFm:** Conceptualization, Writing – review & editing.

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The impact of healthcare-associated infections on COVID-19 mortality: a cohort study from a Brazilian public hospital

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SUMMARY

OBJECTIVE: This study aims to analyze the risk factors for in-hospital mortality in a cohort of patients admitted to a newly adapted intensive care unit in a public hospital in Rio de Janeiro.

METHODS: This was an observational, retrospective, and descriptive study. Data were obtained from electronic medical records. Coronavirus disease 2019 (COVID-19) was diagnosed by detecting viral ribonucleic acid using reverse transcription polymerase chain reaction. Factors associated with the risk/protection from death were determined using the odds ratio and adjusted odds ratio.

RESULTS: Fifty-one patients were admitted to the hospital. The median age of the patients was 63 years, 60% were male patients, and 54% were white patients. Sixty-seven percent of the patients were diagnosed with COVID-19. Sepsis at admission increased the chance of in-hospital death by 21 times (adjusted odds ratio=21.06 [0.79–555.2]; $p=0.06$). The strongest risk factor for death was the development of septic shock during hospitalization (adjusted odds ratio=98.56 [2.75–352.5]; $p=0.01$), and one in four patients had multidrug-resistant bacteria. Mechanical ventilation, vasopressors, neuromuscular blockers, and sedatives were also the risk factors for in-hospital mortality. The in-hospital mortality rate was 41%, and the mortality rate of patients on mechanical ventilation was 60%. The diagnosis of COVID-19 was not statistically related to the adverse outcomes.

CONCLUSIONS: In this cohort, the strongest risk factor for in-hospital death was the development of nosocomial septic shock. Healthcare-associated infections have a significant impact on mortality rates. Therefore, to have a better outcome, it is important to consider not only the availability of beds but also the way healthcare is delivered.

KEYWORDS: SARS-CoV-2. COVID-19. Healthcare associated infection. Mortality. Patient safety.

INTRODUCTION

In December 2019, the first cases of a new type of pneumonia were identified in Wuhan, Hubei, China. Initially, it was thought to be related with seafood products and the local market. However, in less than 30 days, the viral etiology was

established as a new type of coronavirus, the severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2)¹. From the increasing number of cases, mainly between healthcare professionals, human transmissibility was observed, and the effective reproductive number (R_t) was high^{2,3}. Within two months,

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the World Health Organization (WHO) declared coronavirus disease 2019 (COVID-19) a pandemic⁴. In all countries, local healthcare systems were engaged after noting a sudden increase in the number of patients requiring hospitalization⁵.

In Rio de Janeiro, which has a population of approximately 6.72 million people⁶, the number of cases estimated was at least an order of tens of thousands. In May 2020, the Institute for Health Metrics and Evaluation (IMHE) projected that the daily cases would be approximately 30,000⁷. Therefore, besides social isolation, one of the adopted strategies to provide more beds to critically ill patients was the conversion of a ward unit in an intensive care facility. In this context, the pneumology ward, from a public tertiary hospital in Rio de Janeiro, Brazil, has become an intensive care unit (ICU) for COVID-19 suspects and confirmed cases. The main goal of this study was to analyze this cohort of patients from the pneumology ward adapted to the ICU to identify the main risk factors for in-hospital mortality in this strategy and the contributing factors that most affected in-hospital mortality.

METHODS

Study design and population

This was an observational, retrospective, and descriptive study of a cohort of patients admitted to the newly converted ICU in the Pedro Ernesto University Hospital, Rio de Janeiro, Brazil, from April 25 to June 31, 2020. All patients who met the inclusion criteria were included, and the exclusion criteria included a hospital stay of <24 h. This study was approved by the National Committee of Ethics and Research (registration number CAAE-30135320.0.0000.5259).

The diagnosis of COVID-19 was made by detecting viral ribonucleic acid (RNA) using reverse transcription polymerase chain reaction (RT-PCR) by collecting samples of nasopharyngeal secretions using swabs. At least two tests were performed in cases of negative or inconclusive results. In the presence of a positive result, the case was considered confirmed.

Sepsis was defined according to the Sepsis 3.0 criteria as when the patient was admitted without sepsis criteria or developed sepsis criteria during hospitalization (after 48 h)⁸.

Data were obtained from electronic medical records. Sociodemographic characteristics such as sex, age, comorbidities, and previous pharmacological, clinical, laboratory, imaging, and therapeutic data gathered during the hospitalization process and clinical evolution until discharge from the unit and hospital were collected.

The description of the cohort of patients was based on their sociodemographic and clinical characteristics. For continuous variables, we used medians, interquartile intervals, and nonparametric

Mann-Whitney U tests. For nominal variables, we used absolute and relative frequency values, and Fisher's exact tests to test the correlation between these variables and the variable death due to the disease at the time of the study. To determine factors associated with risk/protection from death, fixed-effects generalized linear parametric models with a logistic link function (binomial family) were used. The effect's size, the measure of association, was presented as a function of odds ratios adjusted by covariables of confounding (aOR) or not (OR). P-values and confidence intervals of these effects were corrected by the number of comparisons with the reference level using the Holm-Sidak method. All analyses were conducted using the R version 3.6.3.

RESULTS

A total of 51 patients were admitted to the hospital. The median patient age was 63 years. Considerably, most of the patients were Caucasian men. More than 70% of patients had hypertension, and approximately 50% of these were the users of an angiotensin-converting enzyme inhibitor (ACEI) or angiotensin-receptor blocker (ARB). Previous use of ACEI or ARB was suggested as an in-hospital protection factor for death (aOR=0.091 [0.007–1.221]; p=0.07). The most prevalent comorbidities in this case series were hypertension (72.5%), dyslipidemia (64.7%), and type 2 diabetes mellitus (37.3%) (Table 1). Since only four patients did not have comorbidities upon admission, it was not possible to establish an association between these comorbidities and in-hospital death after adjustments for confounding variables. On the contrary, the presence of depression was also considered a risk factor for in-hospital death (aOR=1211 [1.7–2.733]; p=0.02) (Table 2).

In total, 35 patients were diagnosed with COVID-19, accounting for 67% of the hospitalized patients. We found no association between SARS-CoV-2 positivity and in-hospital death (aOR=0.83 [0.114–6.082]; p=0.85). In the subgroup of patients with in-hospital confirmation of COVID-19, approximately 47 had >50% radiologic pulmonary involvement. In the subgroup with the SARS-CoV-2–negative swab, four patients presented tomographic features suggestive of viral pneumonia, with involvement between 25 and 50% of the lung parenchyma.

The presence of sepsis at admission increased the chance of in-hospital death by an average of 21 times (aOR=21.06 [0.79–555.2]; p=0.06). In this context, the development of septic shock during hospitalization increased the chance of death by 98 times on an average when compared with those without in-hospital septic shock (aOR=98.56 [2.75–3525]; p=0.01). This was the highest risk factor for in-hospital mortality.

The presence of multidrug-resistant organisms (MDR) occurred in one of four hospitalized patients, which was considered a risk

Table 1. Sociodemographic characteristics and their distribution in this population.

| | Overall (n=51) | Survivor without COVID-19 (n=8) | Survivor with COVID-19 (n=22) | Death without COVID-19 (n=8) | Death with COVID-19 (n=13) |
|---------------------------------|----------------|---------------------------------|-------------------------------|------------------------------|----------------------------|
| Age | 63 (IQR=16) | 56 (IQR=22) | 64.5 (IQR=26.25) | 67 (IQR=14.75) | 65 (IQR=20) |
| Ethnicity (%) | | | | | |
| Caucasian | 28 (54.9) | 4 (7.8) | 13 (25.5) | 4 (7.8) | 7 (13.7) |
| Brown | 14 (27.5) | 3 (5.9) | 4 (7.8) | 3 (5.9) | 4 (7.8) |
| Afro-Brazilian | 6 (11.8) | 1 (2) | 2 (3.9) | 1 (2) | 2 (3.9) |
| Yellow | 3 (5.9) | 0 (0) | 3 (5.9) | 0 (0) | 0 (0) |
| Sex (%) | | | | | |
| Male | 31 (60.8) | 7 (13.7) | 12 (23.5) | 5 (9.8) | 7 (13.7) |
| Female | 20 (39.2) | 1 (2) | 10 (19.6) | 3 (5.9) | 6 (11.8) |
| BMI | 35 (IQR=4.25) | 35 (IQR=0) | 33 (IQR=5) | NA (IQR=NA) | 35 (IQR=0) |
| Hypothyroidism (%) | 2 (3.9) | 0 (0) | 0 (0) | 0 (0) | 2 (3.9) |
| Hypertension (%) | 37 (72.5) | 4 (7.8) | 17 (33.3) | 5 (9.8) | 11 (21.6) |
| ACEI/ARB (%) | 26 (51) | 4 (7.8) | 12 (23.5) | 3 (5.9) | 7 (13.7) |
| T2D (%) | 19 (37.3) | 3 (5.9) | 8 (15.7) | 2 (3.9) | 6 (11.8) |
| Coronary disease (%) | 14 (27.5) | 1 (2) | 6 (11.8) | 2 (3.9) | 5 (9.8) |
| Cardiac failure (%) | 12 (23.5) | 1 (2) | 5 (9.8) | 2 (3.9) | 4 (7.8) |
| Peripheral arterial disease (%) | 5 (9.8) | 1 (2) | 0 (0) | 2 (3.9) | 2 (3.9) |
| Dyslipidemia (%) | 18 (35.3) | 1 (2) | 10 (19.6) | 2 (3.9) | 5 (9.8) |
| CKF without dialysis (%) | 8 (15.7) | 1 (2) | 2 (3.9) | 2 (3.9) | 3 (5.9) |
| CKF with dialysis (%) | 7 (13.7) | 1 (2) | 2 (3.9) | 3 (5.9) | 1 (2) |
| Ischemic cerebral disease (%) | 4 (7.8) | 0 (0) | 1 (2) | 1 (2) | 2 (3.9) |
| Dementia (%) | 6 (11.8) | 0 (0) | 1 (2) | 2 (3.9) | 3 (5.9) |
| Immunosuppressants (%) | 6 (11.8) | 0 (0) | 1 (2) | 3 (5.9) | 2 (3.9) |
| Depression (%) | 3 (5.9) | 0 (0) | 1 (2) | 0 (0) | 2 (3.9) |
| Autoimmune disease (%) | 3 (5.9) | 0 (0) | 1 (2) | 1 (2) | 1 (2) |
| COPD (%) | 4 (7.8) | 2 (3.9) | 2 (3.9) | 0 (0) | 0 (0) |
| Asthma (%) | 1 (2) | 0 (0) | 1 (2) | 0 (0) | 0 (0) |
| Tuberculosis (%) | 2 (3.9) | 1 (2) | 0 (0) | 0 (0) | 1 (2) |
| Tabagism (%) | 16 (31.4) | 5 (9.8) | 4 (7.8) | 1 (2) | 6 (11.8) |
| Cancer (%) | 6 (11.8) | 0 (0) | 1 (2) | 1 (2) | 4 (7.8) |

Data are expressed as medians and interquartile ranges (IQRs) for continuous data and as absolute (relative) frequencies for categorical data. Percentages may not sum to 100 because of rounding. BMI, body mass index; ACEI: angiotensin-converting-enzyme inhibitor; ARB: angiotensin II receptor blocker; T2D: type 2 diabetes mellitus; CKF: chronic kidney failure; COPD: chronic obstructive pulmonary disease; NA: not available; NC: not computed.

factor for in-hospital death (aOR=14.42 [1.02–204.18]; p=0.04). Approximately 40% of the deaths had microbiological evidence of MDR microbes. All hospitalized patients received antibiotic therapy. More than 80% of the patients received azithromycin, and 47% of the patients were moved to the carbapenem regimen. Furthermore, the use of vasopressors, sedation, neuromuscular blockers, and corticosteroids was also considered a risk factor for

in-hospital mortality. From the laboratory point of view, the last records of leukocytosis and lymphopenia were risk factors for death (aOR=25.53 [2.08–313.48]; p=0.06, and aOR=8.76 [1.42–54]; p=0.09, respectively). Other markers, such as D-dimer, ferritin, lactate dehydrogenase, and total bilirubin, were not associated with mortality. The SOFA score was used, and values above 8 were associated with in-hospital death (aOR=206 [4.4–9557]; p=0.006).

Table 2. Logistic analysis for death during hospitalization.

| | Overall (%) | aOR (95%CI) ^a | p-value |
|---------------------------|----------------|--------------------------|---------|
| SARS-CoV-2 positive | 35 (68.6) | 0.83 (0.11–6.08) | 0.85 |
| SOFA admission | 4 (IQR=4) | 1.36 (0.11–16) | 0.80 |
| In-hospital SOFA | 8 (IQR=7.5) | 206 (4.48–9557) | 0.006 |
| Septic shock in admission | 8 (15.7) | 21 (0.79–555) | 0.06 |
| Septic shock in hospital | 17 (33.3) | 98 (2.75–3525) | 0.01 |
| Vasopressors | 27 (52.9) | 69.66 (1.76–2733) | 0.02 |
| Inotropic | 4 (7.8) | 0.148 (0.001–24.17) | 0.46 |
| Sedation | 30 (58.8) | 69 (1.77–2733) | 0.03 |
| Benzodiazepine | 28 (54.9) | 70 (1.8–2763) | 0.02 |
| Neuromuscular blocker | 17 (33.3) | 126 (3.73–4277) | 0.007 |
| Corticoid | 27 (52.9) | 50 (2.2–1136) | 0.01 |
| Chloroquine | 15 (29.4) | 0.4 (0.017–9.71) | 0.57 |
| Oseltamivir | 22 (43.1) | 3.4 (0.37–32) | 0.27 |
| Carbapenems | 24 (47.1) | 3.8 (0.46–32) | 0.21 |
| Betalactamic | 25 (49) | 3.3 (0.4–26) | 0.26 |
| Cephalosporin | 24 (47.1) | 0.53 (0.05–4.91) | 0.58 |
| Glycylcycline | 3 (5.9) | 2.6 (0.05–134) | 0.63 |
| Macrolide | 41 (80.4) | 3.65 (0.36–37) | 0.27 |
| Glycopeptide | 20 (39.2) | 8.75 (0.66–109) | 0.09 |
| Polymyxins | 10 (19.6) | 25.42 (0.79–814) | 0.06 |
| Quinolone | 10 (19.6) | 10.6 (0.51–220) | 0.12 |
| Antifungals | 7 (13.7) | 9.63 (0.36–255) | 0.17 |
| Prophylactic enoxaparin | 20 (39.2) | 1.119 (0.11–10) | 0.92 |
| Anticoagulation | 39 (76.5) | 0.343 (0.04–2.92) | 0.32 |
| Dialysis | 16 (31.4) | 4.39 (0.481–40.13) | 0.18 |
| MDR bacteria | 16 (31.4) | 14 (1.02–204) | 0.04 |
| Nasal catheter | 29 (56.9) | 0.11 (0.01–0.92) | 0.04 |
| NIMV | 1 (2) | NC | NC |
| IMV | 28 (54.9) | 70 (1.8–2763) | 0.02 |
| Days in IMV | 2 (IQR=9) | 89 (1.4–5614) | 0.03 |
| Auto prone | 12 (23.5) | 1.67 (0.11–24) | 0.7 |
| ARDS | 12 (23.5) | 25 (0.814–654) | 0.06 |
| In-hospital stay | 17 (IQR=17.75) | 0.31 (0.053–1.82) | 0.55 |
| In ICU stay | 9 (IQR=10) | 1.82 (0.28–11.65) | 0.52 |

^aOdds ratios were adjusted for confounding variables ("Septic Shock Admission," "Peripheral Arterial Disease," "Dementia," "Immunosuppressants," "Cancer," "Urea Admission value," "DHL Admission value," "SOFA Admission value," and "BMI"), which were considered at least suggestive by bivariate analyzes and were present before the study. SARS-CoV-2: severe acute respiratory syndrome coronavirus 2; SOFA: sequential organ failure assessment; MDR: multidrug resistant; NIMV: non-invasive mechanical ventilation; IMV: invasive mechanical ventilation; ARDS: acute respiratory distress syndrome; ICU: intensive care unit.

The use of invasive mechanical ventilation (IMV) was also a risk factor for in-hospital death (aOR=70.5 [1.8–2763.9]; $p=0.02$). About 60% of the patients who underwent IMV resulted in death. Being on IMV for >2 days was enough to find an association with in-hospital death (aOR=89 [1.4–5614.2];

$p=0.03$). Since only one patient received non-invasive mechanical ventilation (NIMV) support, it was not possible to establish a statistical relationship with in-hospital outcomes. In parallel, the use of a nasal oxygen catheter was a protective factor against in-hospital death (OR=0.1 [0.01–0.92]; $p=0.04$). In addition,

approximately 33% of patients developed renal dysfunction and required hemodialysis. However, no association was found between dialysis support and in-hospital death (aOR=4.39 [0.48–40.13]; $p=0.18$). In total, the in-hospital mortality rate was 41%, and the mortality rate of patients with IMV was 60%.

DISCUSSION

This study is the first to analyze the strategy of converting ward units into an ICU, as a solution to the deficit in intensive care beds in the face of the pandemic. Through data collection and careful statistical analysis, it was possible to identify the factors that contributed to in-hospital mortality. Furthermore, this allowed us to understand the function and approach of this strategy.

The COVID-19 pandemic caused a significant increase in the number of patients requiring hospitalization and intensive care. Based on this demand, a contingency plan was needed to receive these patients⁹. For example, the strategy of adapting a hospital unit exists for another purpose in an ICU¹⁰. The quality of intensive care in developing countries was recognized as a challenge¹¹, which did not arise with the pandemic but as evidenced by it¹². Undoubtedly, it was necessary to increase the supply of intensive care beds. In Rio de Janeiro, the deficit of beds was already known in the public Brazilian healthcare system, which is responsible for serving most of the population. The ratio of ICU beds per 10 thousand inhabitants in Rio de Janeiro is 0.97; the WHO recommended one to three beds per 10 thousand inhabitants (in a context outside the pandemic)¹³. Furthermore, in addition to the availability of beds, the manner of healthcare delivery for critical care patients was also important¹⁴.

In this cohort, the most evident risk factor for in-hospital mortality was the development of in-hospital septic shock. Hence, for patients who did not meet the sepsis criteria but developed during hospitalization, an infection and septic shock of probable nosocomial origin increased the probability of mortality by 98 times as compared to those who did not manifest similar conditions.

The use of ventilatory support was recurrent, with more than 50% of patients progressing to IMV. In other retrospective analyses, this percentage varied from 13–31%^{15,16}. Furthermore, the mortality of these patients ranged from 24.5–76.5%¹⁷. In this study, the mortality rate for the subgroup of patients with COVID-19 who required IMV was 60%.

Only 67% of patients had a positive nasal swab for SARS-CoV-2. In total, 25% of patients who had negative results had images suggestive of viral pneumonia. In this case series, the quantitative method of detecting genetic material by RT-PCR was used, as recommended by the WHO¹⁷. The sensitivity of this method varied between 53.6–73.3%, according to the previous meta-analyses performed¹⁸. To optimize the sensitivity of

the diagnosis, serial tests were performed, and tests with different methodologies were used to detect patients with suggestive tomographic changes, despite the negative admission test¹⁹. Interestingly, the diagnosis of COVID-19 was not a risk factor for in-hospital mortality, corroborating the impact of nosocomial infections on the outcome of these patients.

This study had limitations owing to its design and the number of participants. Hence, it was not possible to establish the cause and consequences. The beneficial or harmful effects of treatment cannot be listed for this number of patients. However, results revealed relevant issues regarding the organizational strategy, as represented by the impact that in-hospital infections had on the mortality of patients hospitalized because of confirmed or suspected COVID-19. These infections were probably associated with healthcare measures and were potentially preventable. Moreover, this study highlighted that this was a window of opportunity to work on strategies, such as educational programs, to apply proven protocols and checklists that could improve the quality of care¹⁹.

CONCLUSIONS

The pandemic has challenged healthcare systems worldwide to adapt to a sudden increase in the number of patients. The transformation of a ward into an ICU was one of the strategies employed, thereby allowing a quick and necessary response. Nevertheless, the creation of an ICU is complex, and several challenges need to be overcome. Much is discussed about drug therapies and invasive devices of high cost and technology. However, more organizational measures of safety and quality would allow better in-hospital outcomes, making it a cost-effective strategy to optimize the care of critically ill patients.

The method of responding to the increase in cases in the Brazilian health system was much more in order to increase the number of beds than to reduce the number of cases. The effect of this policy ended in the creation of units with improvised structures and had an important impact on the mortality of admitted patients.

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AUTHORS' CONTRIBUTIONS

BCP: Conceptualization, Data curation, Formal Analysis, Investigation, Methodology, Writing – original draft. **TB:** Conceptualization, Data curation, Formal

Analysis, Methodology, Writing – review & editing. **AJL:** Conceptualization. **CHC:** Conceptualization, Investigation. **RR:** Conceptualization, Formal Analysis, Methodology, Project administration, Supervision, Writing – original draft,

Writing – review & editing. **APGS:** Investigation. **TTM:** Investigation. **MCSC:** Investigation. **JGP:** Investigation. **LPB:** Investigation. **MRA:** Formal Analysis, Methodology, Writing – original draft.

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Effects of mobilization treatment on sacroiliac joint dysfunction syndrome

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SUMMARY

OBJECTIVE: This study aims to reveal the short-term effects of exercise therapy and manual therapy plus exercise therapy on pain, quality of life, and physical examination results in the treatment of sacroiliac joint dysfunction syndrome (SIJDS).

METHODS: In this study, 64 patients who were participated were divided into two groups. The first group (exercise group) was assigned with the sacroiliac joint (SIJ) home exercise program and the second group (mobilization group) with the combined SIJ manual therapy and home exercise program. Physical examination tests, visual analog scale, and SF-36 evaluation were performed at the beginning of the study, at 24 h, at 1 week, and 1 month after the treatment.

RESULTS: Both groups showed that the rate of pain in the posttreatment, after the first week, and the first month; the presence of pain in the sacroiliac region; and VAS values of the patients with SIJDS compared to pretreatment values were clearly decreased ($p < 0.05$). All tests performed in the SIJ physical examination showed significant improvement within both groups ($p < 0.05$). However, there was no statistical difference between the two groups in 1-month period ($p > 0.05$).

CONCLUSIONS: We found that the home exercise program and the manual therapy plus exercise program significantly improved pain intensity, quality of life, and the findings of specific tests in patients with SIJDS. In addition, superiority between the two groups in terms of pain intensity, quality of life, and specific tests was not determined.

KEYWORDS: Sacroiliac. Exercise. Mobilization.

INTRODUCTION

The sacroiliac joint dysfunction syndrome (SIJDS) is an ongoing controversial issue and an important source of low back pain (LBP)¹. It has been emphasized in many studies that the pathologies of sacroiliac joint (SIJ) are a source of pain in the lumbar spine and hip region^{2,3}. The prevalence of SIJDS in patients with chronic mechanical LBP is between 15 and 30%⁴.

Confirmation of diagnosis with medical history and physical examination as well as different movement palpation tests and pain provocation tests are recommended^{5,6}. The pain associated with SIJDS is tingling and blunt and can permeate to

the gluteal region, lower and upper lumbar region, groin, abdomen, and the entire lower extremity^{4,7}.

Standard physical therapy interventions can be used to cure the underlying pathology and relieve symptoms of SIJDS^{8,9}. The effectiveness of manipulation therapy has been presented in various studies and is recommended in the treatment of SIJDS¹⁰. A review of the literature reveals that there are very few studies analyzing the efficiency of manual therapy and SIJ dysfunction in patients with SIJDS. In this study, the effectiveness of manual therapy and SIJD exercises was analyzed in patients with a follow-up on SIJDS diagnosis and who are not responding to their current therapy.

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This study aims to evaluate the effects of SIJ manual therapy and home exercises on pain and quality of life in patients with SIJDS.

METHODS

In this study, we used data from 64 patients diagnosed with SIJDS based on their detailed anamnesis and SIJ-specific tests. Sample size was calculated using G*Power software. Analysis was done with *F* test for parameters such as effect size, 0.3, significance 0.05; power level 85%; the number of groups is 2; the number of measurements is 4, and dropout rate is 10%. We confirmed that this study would include a minimum of 64 subjects, with each group consisting of 32 subjects.

Subjects were randomized into two groups using the 1:1 ratio method. The first group (exercise group) was assigned with SIJ home exercise program (n=32), and the second group (mobilization group) with SIJ manual therapy and home exercise program (n=32). One patient in the exercise group dropped out of the study due to unbearable pain during the study period without completing the exercise program.

Inclusion criteria of the study were patients who had sacroiliac pain in the past month scored at least 3 points on visual analog scale (VAS), aged between 18 and 60 years, and diagnosed with SIJDS according to the diagnostic criteria recommended by the International Association for the Study of Pain. The patients should also be tested positive in at least three of six validated and reliable SIJD provocation and motion palpation tests. The validity and reliability of SIJD provocation tests have been conducted and resulted with at least three of six tests being positive and one having motion palpations test. These six provocation tests include distraction, compression, Gaenslen, posterior friction test, sacral thrust, and FABER tests¹¹.

Exclusion criteria were those with neurological deficits in the lower extremity, findings of sacroiliitis at X-ray, spondylolisthesis, a prediagnosed disease of central nervous system or

peripheral nervous system, the presence of rheumatological disease, those who had major surgery of lower extremity and spine, and pregnant women.

Physical examination tests, VAS, and SF-36 evaluation were performed at the beginning of the study, at 24 h, at 1 week, and 1 month after the treatment, by a physiatrist experienced in manipulation.

Home exercise program consists of SIJ stretching and strengthening exercises. All patients were assigned stretching exercises such as hamstring stretches, hip adductor stretch, piriformis stretch, quadriceps stretch, one knee to chest stretch, both knees to chest stretch, lower trunk rotation, and pelvic rotation stretch. Strengthening exercises were assigned after stretching exercises. Isometric hip abduction/adduction strengthening and prone position lumbar/hip strengthening exercises were given as strengthening exercises (Figure 1). Each exercise should be repeated five times, two sessions a day. Home exercises were given to both groups for 3 weeks.

In our study, SIJ mobilization, mobilization techniques with anterior innominate, posterior innominate, maigne technique, selling technique, and stoddart cross technique were applied for three sessions (one session per week for 3 weeks) in the mobilization group (Figure 2). Each technique was applied to each patient, separately.

The study was approved by the Ethics Committee, Istanbul Medical Faculty, Istanbul University (approval number: 2013/795). All procedures performed in this study involving human participants were in accordance with the ethical standards of the institutional ethics committee and with the 1964 Helsinki Declaration and its later amendments or comparable ethical standards. Written informed consent was obtained from all individual participants who participated in the study.

Statistical analysis was performed using IBM SPSS Statistics for Windows, version 24.0. Descriptive data were expressed as mean±standard deviation or number and frequency.

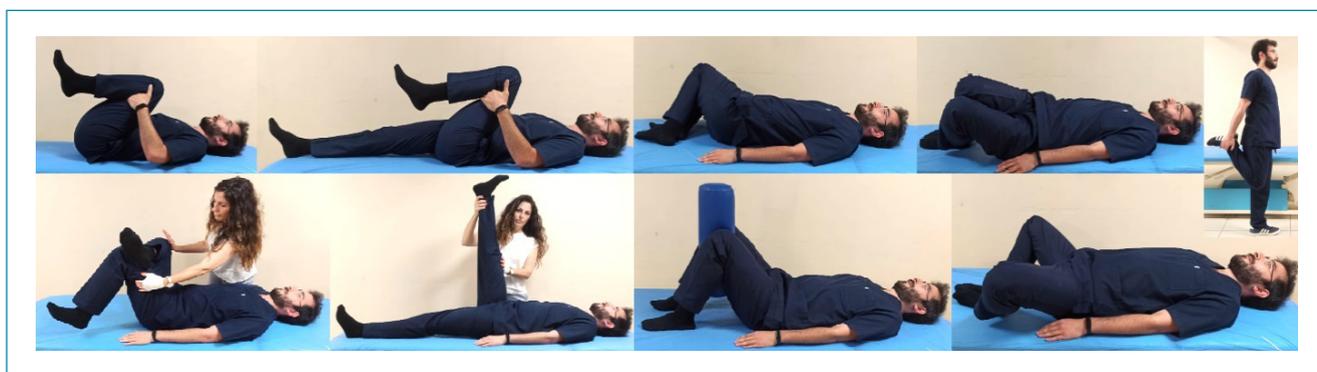


Figure 1. Stretching and strengthening exercises.

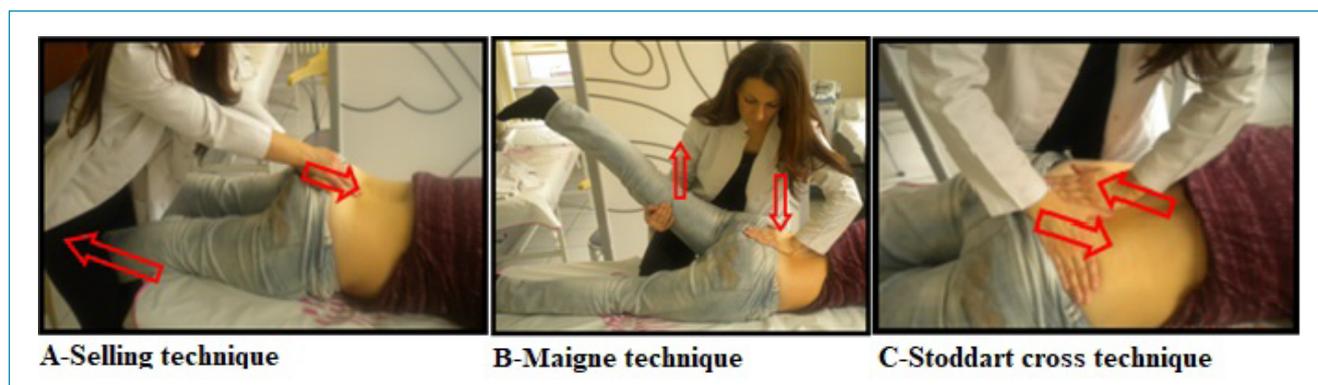


Figure 2. Mobilization techniques.

The distribution of the variables was controlled by Shapiro-Wilk test. The within-group comparisons were made using the Friedman test. A post hoc analysis with Wilcoxon signed-rank tests was conducted with a Bonferroni correction. Repeated-measure analysis of variance was used where appropriate, followed by Bonferroni post hoc test. The within-group categorical variables comparisons were made by Cochran's q test, followed by post hoc Dunn test. Between-group comparisons were performed by Kruskal-Wallis test to find the difference between pre- and posttreatment of the first month. A $p < 0.05$ was accepted as statistically significant.

RESULTS

In this study, 63 patients who were participated were divided into two groups. The first group (exercise group) was assigned with the SIJ home exercise program ($n=31$) and the second group (mobilization group) with the combined SIJ manual therapy and SIJ home exercise program ($n=32$). The exercise group diagnosed with SIJDS consisted of 19 (61.3%) females and 12 (38.7%) males, and mobilization group had 24 (75%) females and 8 (25%) males ($p=0.243$). The mean age of the patients was 35.1 ± 13.9 in the exercise group and 39.0 ± 11.3 in the mobilization group ($p=0.237$). The body mass index values were 24.3 ± 3.0 in the exercise group and 24.0 ± 3.5 in the mobilization group ($p=0.758$). There was no significant difference in the initial values of the patients between the two groups ($p < 0.05$).

Within-group comparison, both exercise and mobilization groups, showed that the rate of pain in the posttreatment, after the first week, and the first month; the presence of pain in the sacroiliac region; and VAS values of the patients with SIJDS compared to pretreatment values were clearly decreased ($p < 0.05$). However, there was no statistical difference between the two groups in 1 month, pretreatment, and posttreatment period ($p > 0.05$) (Table 1).

The quality of life of patients was evaluated by SF-36, and improvement was observed in five subparameters (physical function, physical role, body pain, vitality, and general health) in both exercise and mobilization groups ($p < 0.05$). In the subparameters social function and emotional role, improvement was found only in the mobilization group, in posttreatment compared to pretreatment, at the end of the first month ($p < 0.05$). In the mental health assessment, improvement was detected only in the exercise group in posttreatment at the first week ($p < 0.05$). There was no statistically significant difference between the groups in the pre- and posttreatment at the end of the first month ($p > 0.05$) (Table 1).

When examining the tests performed on our patients, the motion palpations tests were found to be 100% positive; and of the six provocation tests mentioned earlier, distraction and compression test results were 85.7%, Gaenslen 88.9%, posterior friction 93.7%, sacral thrust 100%, and FABER was 52.4% positive. All tests performed in the SIJ physical examination showed significant improvement within both groups ($p < 0.05$), and no statistically significant difference was found between the two groups ($p > 0.05$) (Table 2).

DISCUSSION

SIJD has been a controversial issue for years in terms of both diagnosis and treatment methods. Although the number of studies on the subject has increased in recent years, the role and importance of manipulation therapies are still not clear in the literature. In our study, we aimed to reveal the short-term effects of exercise therapy and manual therapy plus exercise therapy on pain, quality of life, and physical examination results in the treatment of SIJD.

The literature review and studies comparing manipulation and exercise treatments have shown that no difference was found between the two groups; in some, manual therapy

Table 1. Posttreatment comparisons of visual analog scale and SF-36 scores

| | | PreT. (0) Mean±SD | PostT. Mean±SD | PostT. 1 week (2) Mean±SD | PostT. 1 month (3) Mean±SD | p | Post hoc | Between- group differences at visit 0-3 Mean±SD | p |
|---|-----------------|----------------------|--------------------|---------------------------------|----------------------------------|--------|---|---|-------|
| VAS rest Mean±SD (min/ med/max) | Exerc | 3.50±2.74 1/3/7 | 2.23±1.99 0/2/7 | 1.86±1.80 0/2/6 | 1.73±1.83 0/2/5 | <0.001 | <0.001 ⁽⁰⁻³⁾⁽⁰⁻²⁾ | 1.76±2.54 | 0.236 |
| | Mob.+ Exerc. | 4.00±2.58 1/4/8 | 2.96±2.73 0/3/7 | 1.70±2.36 0/2/6 | 1.36±2.22 0/1/5 | <0.001 | <0.001 ⁽⁰⁻³⁾⁽⁰⁻²⁾ 0.016 ⁽¹⁻³⁾ | 2.63±2.55 | |
| Vas activity Mean±SD (min/ med/max) | Exerc | 6.93±1.98 3/6/10 | 5.00±2.37 0/5/9 | 4.06±1.95 0/4/8 | 3.63±2.01 0/3/7 | <0.001 | <0.001 ⁽⁰⁻³⁾⁽⁰⁻²⁾⁽¹⁻³⁾ 0.003 ⁽⁰⁻¹⁾ | 3.30±2.39 | 0.408 |
| | Mob.+ Exerc. | 7.60±1.95 3/7/10 | 6.16±2.53 0/6/9 | 4.66±2.17 0/5/7 | 4.03±2.15 0/4/7 | <0.001 | <0.001 ⁽⁰⁻³⁾⁽⁰⁻²⁾ 0.002 ⁽¹⁻³⁾ | 3.56±2.63 | |
| SF-36 Physical function Mean±SD | Exerc | 69.51±16.79 | 78.54±19.28 | 78.54±19.41 | 81.12±20.84 | <0.001 | <0.001 ⁽⁰⁻³⁾ , 0.012 ⁽⁰⁻²⁾ 0.007 ⁽⁰⁻¹⁾ | 11.61±23.81 | 0.217 |
| | Mob.+ Exerc. | 70.66±18.17 | 73.66±16.60 | 74.33±16.22 | 78.83±15.95 | <0.001 | <0.001 ⁽⁰⁻³⁾ 0.048 ⁽¹⁻³⁾ | 8.16±11.70 | |
| SF-36 Physical role Mean±SD | Exerc | 51.14±14.76 | 58.66±8.18 | 57.24±8.44 | 56.06±13.06 | 0.004 | 0.035 ⁽⁰⁻²⁾ 0.003 ⁽⁰⁻³⁾ | 4.37±17.45 | 0.580 |
| | Mob.+ Exerc. | 52.08±16.24 | 54.33±17.34 | 56.58±15.42 | 58.41±16.30 | <0.001 | <0.001 ⁽⁰⁻³⁾⁽⁰⁻²⁾⁽¹⁻³⁾ 0.016 ⁽¹⁻²⁾ | 6.33±15.01 | |
| SF-36 Body pain Mean±SD | Exerc | 59.27±18.3 | 69.51±19.67 | 68.30±16.42 | 69.03±16.49 | <0.001 | 0.004 ⁽⁰⁻¹⁾ <0.001 ⁽⁰⁻³⁾ | 9.75±23.99 | 0.616 |
| | Mob.+ Exerc. | 60.58±16.59 | 72.16±20.11 | 70.75±20.35 | 68.41±20.51 | 0.003 | 0.004 ⁽⁰⁻¹⁾ 0.032 ⁽⁰⁻²⁾ | 7.83±21.56 | |
| SF-36 Vitality Mean±SD | Exerc | 53.87±16.91 | 62.41±16.37 | 61.61±15.45 | 61.45±18.17 | <0.001 | 0.002 ⁽⁰⁻³⁾ , 0.022 ⁽⁰⁻²⁾ 0.016 ⁽⁰⁻¹⁾ | 7.58±15.04 | 0.988 |
| | Mob.+ Exerc. | 55.66±17.02 | 65.33±17.41 | 64.33±17.79 | 64.16±17.66 | 0.023 | 0.009 ⁽⁰⁻¹⁾ 0.028 ⁽⁰⁻²⁾ | 8.50±19.43 | |
| SF-36 Emotional role Mean±SD | Exerc | 45.47±12.79 | 48.16±8.81 | 48.69±8.57 | 50.25±8.59 | 0.534 | – | 4.78±14.29 | 0.323 |
| | Mob.+ Exerc. | 41.88±14.06 | 44.66±10.49 | 45.77±9.47 | 49.66±8.07 | 0.010 | 0.046 ⁽⁰⁻³⁾ | 7.7±14.33 | |
| SF-36 General health Mean±SD | Exerc | 52.25±15.59 | 58.70±18.43 | 59.03±18.72 | 59.83±19.16 | <0.001 | 0.001 ⁽⁰⁻³⁾ , 0.005 ⁽⁰⁻²⁾ 0.010 ⁽⁰⁻¹⁾ | 7.58±12.17 | 0.850 |
| | Mob.+ Exerc. | 50.83±15.37 | 57.83±13.93 | 57.16±13.24 | 57.66±14.66 | 0.019 | 0.016 ⁽⁰⁻¹⁾⁽⁰⁻²⁾ 0.028 ⁽⁰⁻³⁾ | 6.83±15.22 | |
| SF-36 Social function Mean±SD | Exerc | 74.19±15.45 | 79.83±16.67 | 79.83±16.02 | 79.83±17.49 | 0.059 | – | 4.83±17.28 | 0.301 |
| | Mob.+ Exerc. | 70.83±15.85 | 75.00±17.05 | 76.66±16.32 | 79.58±17.82 | 0.014 | 0.014 ⁽⁰⁻³⁾ | 8.75±13.19 | |
| SF-36 Mental health Mean±SD | Exerc | 62.19±13.65 | 69.29±11.75 | 69.03±11.69 | 66.19±14.07 | 0.003 | 0.030 ⁽⁰⁻²⁾ 0.016 ⁽⁰⁻¹⁾ | 4.00±15.17 | 0.856 |
| | Mob.+ Exerc. | 61.73±14.54 | 66.26±13.72 | 66.63±12.88 | 67.46±14.16 | 0.276 | – | 5.73±14.08 | |

PreT: Pretreatment; PostT: Posttreatment; VAS: Visual analog scale; Exerc.: exercise group; Mob.+Exerc.: mobilization group.

Table 2. Posttreatment comparisons of sacroiliac joint dysfunction syndrome motion palpation and provocation tests.

| | Group | PreT. (0) | PostT. (1) | PostT. 1 week (2) | PostT. 1 month (3) | Cochran's q p | Post hoc | PreT-Post T1. month difference (%) | p |
|---------------|------------------|-----------|------------|-------------------|--------------------|---------------|---|------------------------------------|-------|
| Gillet | Exerc. (n) | 31 (100) | 22 (71) | 17 (54.8) | 11 (35.5) | <0.001 | <0.001 ⁽⁰⁻²⁾⁽⁰⁻³⁾ =0.037 ⁽⁰⁻¹⁾ =0.005 ⁽¹⁻³⁾ | 64.5 | 0.868 |
| | Mob.+ Exerc. (n) | 32 (100) | 15 (46.9) | 13 (40.6) | 10 (31.3) | <0.001 | <0.001 ⁽⁰⁻¹⁾⁽⁰⁻²⁾⁽⁰⁻³⁾ | 62.5 | |
| FF | Exerc. (n) | 31 (100) | 22 (71) | 19 (61.3) | 11 (35.5) | <0.001 | <0.001 ⁽⁰⁻²⁾⁽⁰⁻³⁾ =0.033 ⁽⁰⁻¹⁾ =0.004 ⁽¹⁻³⁾ | 64.5 | 0.926 |
| | Mob.+ Exerc. (n) | 32 (100) | 16 (50) | 13 (40.6) | 11 (34.4) | <0.001 | <0.001 ⁽⁰⁻¹⁾⁽⁰⁻²⁾⁽⁰⁻³⁾ | 65.6 | |
| Standing FF | Exerc. (n) | 31 (100) | 22 (71.0) | 18 (58.1) | 13 (59.4) | <0.001 | <0.001 ⁽⁰⁻²⁾⁽⁰⁻³⁾ =0.023 ⁽⁰⁻¹⁾ (1-3) | 58.1 | 0.916 |
| | Mob.+ Exerc. (n) | 32 (100) | 17 (53.1) | 16 (50.0) | 13 (40.6) | <0.001 | <0.001 ⁽⁰⁻¹⁾⁽⁰⁻²⁾⁽⁰⁻³⁾ | 59.4 | |
| Distrac. | Exerc. (n) | 22 (71.0) | 17 (58.4) | 20 (64.5) | 18 (58.1) | =0.015 | =0.018 ⁽⁰⁻¹⁾ | 18.1 | 0.136 |
| | Mob.+ Exerc. (n) | 32 (100) | 15 (46.9) | 19 (59.4) | 23 (71.9) | <0.001 | <0.001 ⁽⁰⁻¹⁾⁽⁰⁻²⁾ =0.018 ⁽⁰⁻³⁾ =0.049 ⁽¹⁻³⁾ | 28.1 | |
| Comp. | Exerc. (n) | 22 (71.0) | 16 (51.6) | 20 (64.5) | 19 (61.3) | =0.008 | =0.004 ⁽⁰⁻¹⁾ | 13.6 | 0.478 |
| | Mob.+ Exerc. (n) | 32 (100) | 20 (62.5) | 24 (75.0) | 27 (84.4) | <0.001 | <0.001 ⁽⁰⁻¹⁾ =0.010 ⁽⁰⁻²⁾ =0.036 ⁽¹⁻³⁾ | 15.6 | |
| Ganslen | Exerc. (n) | 27 (87.1) | 15 (48.4) | 19 (61.3) | 17 (54.8) | <0.001 | <0.001 ⁽⁰⁻¹⁾⁽⁰⁻³⁾ =0.009 ⁽⁰⁻²⁾ | 32.3 | 0.055 |
| | Mob.+ Exerc. (n) | 29 (90.6) | 10 (31.3) | 10 (31.3) | 11 (34.4) | <0.001 | <0.001 ⁽⁰⁻¹⁾⁽⁰⁻²⁾⁽⁰⁻³⁾ | 62.0 | |
| Thigh thrust | Exerc. n (%) | 31 (100) | 19 (61.3) | 23 (74.2) | 21 (67.7) | <0.001 | <0.001 ⁽⁰⁻¹⁾⁽⁰⁻³⁾ =0.009 ⁽⁰⁻²⁾ | 32.2 | 0.153 |
| | Mob.+ Exerc. (n) | 28 (87.5) | 9 (28.1) | 10 (31.3) | 12 (37.5) | <0.001 | <0.001 ⁽⁰⁻¹⁾⁽⁰⁻²⁾⁽⁰⁻³⁾ | 57.1 | |
| Faber | Exerc. (n) | 18 (58.1) | 10 (32.3) | 12 (38.7) | 16 (54.16) | 0.001 | =0.001 ⁽⁰⁻¹⁾ =0.033 ⁽⁰⁻²⁾⁽¹⁻³⁾ | 32.2 | 0.414 |
| | Mob.+ Exerc. (n) | 15 (46.9) | 9 (28.1) | 9 (28.1) | 11 (34.4) | 0.002 | =0.006 ⁽⁰⁻¹⁾⁽⁰⁻²⁾ | 27.1 | |
| Sacral thrust | Exerc. (n) | 31 (100) | 24 (77.4) | 20 (64.5) | 18 (58.1) | <0.001 | <0.001 ⁽⁰⁻²⁾⁽⁰⁻³⁾ | 41.9 | 0.378 |
| | Mob.+ Exerc. (n) | 32 (100) | 21 (65.5) | 21 (65.6) | 22 (68.8) | <0.001 | <0.001 ⁽⁰⁻¹⁾⁽⁰⁻²⁾⁽⁰⁻³⁾ | 31.3 | |

PreT: Pretreatment; PostT: Posttreatment; FF: Forward flexion; Distrac.: Distraction; Comp.: Compression; Exerc.: exercise group; Mob.+Exerc.: mobilization group.

was superior, while the exercise group improved significantly in others^{12,13}. A systematic review by Assendelft et al. investigating the effect of manipulation in the treatment of chronic LBP suggests that manipulation therapy is not particularly beneficial than other traditional methods such as exercise therapy, needling, and analgesics¹⁴. In another systematic review, Standaert et al.¹⁵ on LBP and Al-Subahi et al.⁹ on SIJDS found

the effectiveness of manual therapy and exercise, but not the superiority to each other.

Nejati et al. compared exercise therapy, manual therapy, and combination therapy in patients with SIJD and stated that exercise and manual therapy alone reduced pain and disability of the patients, but the combined therapy did not show a significant advantage¹⁶. In our study, similar to the one by Nejati

et al.¹⁶, significant improvement in pain scores and quality of life was detected in both groups, but the significance of combination therapy was not shown to be superior to the exercise group. Few studies conducted on this subject have shown that the difference in patient selection, duration, and density of the application methods results in different outcomes.

Since there are no direct methods for the diagnosis of SIJDS, some tests that are specific to this joint have been defined¹⁷. According to the second criterion of the International Pain Study Association, SIJDS is diagnosed with pain felt in the SIJ region, which can be provoked by special provocation tests such as Gillet, Derbrolowsky, standing flexion, compression, distraction, FABER, Gaenslen, thigh push, sitting flexion, prone extension, supine to sit, Yeoman, tests, sacral sulcus tenderness, sacral compression, palpation of iliac crest spina iliaca posterior superior, and spina iliaca anterior superior while sitting and standing¹⁷⁻²⁰. The reliability of these tests was found to be low, and these tests were positive in 20% of asymptomatic individuals and that the sensitivity and specificity of standing flexion and Gillet tests were poor compared with the SIJ block as the gold standard²¹.

In studies conducted by Lasslett et al.¹⁸, evaluating the same subject, three or more positive provocative tests showed 94% and 91% sensitivity and 78% specificity in both studies. They reported that three or more positive stress tests have a

distinct ability for the diagnosis of SIJ pain^{18,20}. In our study, we included patients receiving three positive provocative tests and one positive motion palpation test and found the lowest positivity in Faber test (52.4%) and other tests with (85.7–100%) good positivity.

The lack of a control group, due to ethical issues, is the limitation of this study.

CONCLUSIONS

As a result, we found that the exercise program and the manual therapy plus exercise program significantly improved pain intensity, quality of life, and the findings of specific tests in patients with SIJDS. In addition, superiority between the two groups in terms of pain intensity, quality of life, and specific tests was not determined.

AUTHORS' CONTRIBUTIONS

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

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Suboptimal health status of nurses in Wuhan, China during the COVID-19 outbreak

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SUMMARY

OBJECTIVE: This study analyzes the suboptimal health status (SHS) and influencing factors of nurses in Wuhan Hospital, China during the coronavirus disease 2019 (COVID-19) outbreak.

METHODS: This study was conducted through an online survey, from March 1–7, 2020, in Wuhan, China. The data collection tools, such as Suboptimal Health Status Questionnaires, Generalized Anxiety Disorder, and Chinese version of the Perceived Stress Scale, were used.

RESULTS: The average value of suboptimal health status was 28.44 (standard deviation=15.15). The overall prevalence of SHS was 35.1%. Suboptimal health status of the nurses was significantly different based on their gender, age, whether they directly care for COVID-19 patients, anxiety level, and stress perception expect education. Multivariate analysis found that average sleep times per day, female, age, directly participate in the rescue of COVID-19, self-infection, and anxiety were the influencing factors of suboptimal health status.

CONCLUSIONS: First-line nurses have poor suboptimal health status in Wuhan.

KEYWORDS: Health. Nurses. Anxiety. China. COVID-19.

INTRODUCTION

At the end of December 2019, the first patient with clustering pneumonia of unknown was discovered in Wuhan, Hubei province, China¹. The World Health Organization (WHO) has confirmed that unknown pneumonia is caused by a new coronavirus (2019-nCoV). Due to the interpersonal transmission of coronavirus disease 2019 (COVID-19)², it quickly spread throughout the world, and the number of suspected and confirmed cases worldwide increased exponentially. The WHO declared COVID-19 as a public health emergency of international concern on January 30, 2020³. In the process of combating infectious diseases, frontline medical staff are facing enormous psychological and physical pressure. The first-line

nurses not only have to take care of the diagnosed and suspected patients but also face the risk of COVID-19 and bear the double pressure of body and mind⁴. Anxiety, depression, insomnia, and other serious threats to the physical and mental health of the first-line nurses⁵ may lead to a decline in the immune system and often cause nurses to have suboptimal health status (SHS)⁶. Yan et al demonstrated the relationship between chronic psychological stress and SHS⁷. SHS is a moderate state of health between health and disease, which is described as weakness, chronic fatigue, decreased physical function, and ability to adapt⁸. Previous studies have shown that the increased burden of cardiovascular disease and other chronic diseases is also caused by SHS⁶. Therefore, SHS may have a huge impact

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on the physical and mental health of nurses, the quality of hospital care, and patient safety. However, most of the earlier studies have focused on investigating the prevalence of depression and anxiety among nurses^{5,9}. Few studies have focused on the SHS of first-line nurses during the COVID-19 outbreak. The advantage of our research is that this is the first study to investigate the SHS and analyze its related factors of frontline nurses during COVID-19 in Wuhan, China.

METHODS

Participants

This study was conducted through an online survey with the questionnaire star, from March 1–7, 2020, in Wuhan, China. Participants are nurses working in the n°8 Hospital in Wuhan.

Measurement of demographic characteristics

This mainly includes the basic information of the participants, such as gender, age, occupation, marital status, education level, whether infected with COVID-19, and whether responsible for nursing COVID-19 patients.

Suboptimal health status questionnaires

A self-reported questionnaire Suboptimal Health Status Questionnaires (SHSQ-25) was used to assess SHS⁷. The questionnaire included 25 items and encompassed 5 subscales as follows: fatigue, cardiovascular system, digestive tract, immune system, and mental status. Each subject was asked to rate a specific statement on a 5-point Likert-type scale based on how often they suffered various specific complaints in the preceding three months. A high score represents a high level of SHS (poor health). A total score of more than 35 points indicates the state of suboptimal status. The Cronbach's α was 0.95 in the current sample.

Generalized anxiety disorder

The anxiety of the participants over the past two weeks was assessed by the Generalized Anxiety Disorder (GAD-7). Each item of the GAD-7 is scored from 0 (not at all) to 3 (nearly every day), and the total score is from 0–21. Respondents who scored five or higher were indicated anxiety symptoms¹⁰. The Cronbach's α was 0.95 in the current sample.

Chinese version of the perceived stress scale

The Chinese version of the Perceived Stress Scale (CPSS) was used to measure the stress status. This scale comprised 14 items that addressed perceptions of stress during the month prior

to the survey. The items were rated on a 5-point Likert-type scale and ranged from 0 (never) to 4 (very often). Following previous practice, we defined the severe stress when the CPSS score ≥ 25 ¹¹. The Cronbach's α was 0.82 in the current sample.

Statistical analyses

The data were analyzed using SPSS software version 21 for the statistics of the data. The χ^2 test analysis and the binomial logistic regression analysis were used to test the influencing factors of SHS. $p < 0.05$ was considered statistically significant.

RESULTS

Risk factors for suboptimal health status

The χ^2 test analysis of variance was used to test the differences in SHS among categorical variables and is shown in Table 1. Female, older, directly nursing COVID-19 patients, infected with COVID-19, anxiety, and severe stress were more likely to suffer SHS. In addition, those who reported longer average sleep times per day and self-rated good physical health were less likely to suffer SHS. There were no significant differences on educational level.

Multiple logistic regression analysis

A binomial logistic regression analysis was performed (Table 2). Self-rated good physical health and longer average sleep times per day were protective factors. Female, age, direct contact with COVID-19 patients, infected with COVID-19, anxiety, and severe stress were six risk factors for SHS.

DISCUSSION

This study investigated the SHS and related factors of nurses during the COVID-19 in Wuhan, China. The results found that the incidence of SHS was 35.1% lower than the results of Liang et al.⁶. Liang et al. found that the incidence of SHS was 49% during a cross-sectional survey of medical personnel over the age of 40. This difference may be due to the fact that the majority of the participants in our study were relatively young (21–40 years old accounted for 82.3%), and the mental and physical conditions of the young nurses were generally better. In addition, at the time of our investigation, it was nearly three months before the first COVID-19 patient was diagnosed in Wuhan. New coronary pneumonia has been controlled in China. As of March 9, 2020, the number of newly diagnosed cases of COVID-19 dropped sharply from 3,000 cases to less than 20 cases¹². Hundreds of medical teams with more than 30,000 people across the country arrived in Wuhan to fight against the COVID-19¹³, and the work pressure of nurses in Wuhan hospitals has been significantly

Table 1. The differences of suboptimal health status among categorical variables.

| | Number of cases | SHS | | χ^2 | p-value |
|---------------------------------------|-----------------|------------|-----------|----------|---------|
| | | No | Yes | | |
| | n(%) | n(%) | n(%) | | |
| Gender | | | | 7.485 | 0.006 |
| Male | 99(3.6) | 77(77.8) | 22(22.2) | | |
| Female | 2661(96.4) | 1714(64.4) | 947(35.6) | | |
| Age group (years) | | | | 32.294 | <0.001 |
| 20–25 | 683(24.7) | 498(72.9) | 185(27.1) | | |
| 26–30 | 829(30.0) | 535(64.5) | 294(35.5) | | |
| 31–35 | 587(21.3) | 371(63.2) | 216(36.8) | | |
| 36–40 | 308(11.2) | 183(59.4) | 125(40.6) | | |
| 41–45 | 149(5.4) | 86(57.7) | 63(42.3) | | |
| 46–50 | 142(5.1) | 84(59.2) | 58(40.8) | | |
| ≥51 | 62(2.2) | 34(54.8) | 28(45.2) | | |
| Education | | | | 3.447 | 0.328 |
| Professional school | 22(0.8) | 15(68.2) | 7(31.8) | | |
| Junior college | 588(21.3) | 400(68.0) | 188(32.0) | | |
| Undergraduate | 2112(76.5) | 1351(64.0) | 761(36.0) | | |
| Graduate or above | 38(1.4) | 25(65.8) | 13(34.2) | | |
| Average sleep times per day (h) | | | | 138.843 | <0.001 |
| 5 | 165(6.0) | 64(38.8) | 101(61.2) | | |
| 6 | 806(29.2) | 443(55.0) | 363(45.0) | | |
| 7 | 1102(39.9) | 756(68.6) | 346(31.4) | | |
| 8 | 611(22.1) | 461(75.5) | 150(24.5) | | |
| ≥9 | 76(2.8) | 67(88.2) | 9(11.8) | | |
| Self-rated physical health | | | | 350.388 | <0.001 |
| Very poor | 51(1.8) | 20(39.2) | 31(60.8) | | |
| Poor | 180(6.5) | 55(30.6) | 125(69.4) | | |
| Fair | 1398(50.7) | 772(55.2) | 626(44.8) | | |
| Good | 917(33.2) | 742(80.9) | 175(19.1) | | |
| Very good | 214(7.8) | 202(94.4) | 12(5.6) | | |
| Direct contact with COVID-19 patients | | | | 79.278 | <0.001 |
| No | 1963(71.1) | 1375(70.0) | 588(30.0) | | |
| Yes | 797(28.9) | 416(52.2) | 381(47.8) | | |
| Infected with COVID-19 | | | | 13.055 | <0.001 |
| No | 2667(96.6) | 1747(65.5) | 920(34.5) | | |
| Yes | 93(3.4) | 44(47.3) | 49(52.7) | | |
| Anxiety | | | | 740.964 | <0.001 |
| No | 1651(59.8) | 1406(85.2) | 245(14.8) | | |
| Yes | 1109(40.2) | 385(34.7) | 724(65.3) | | |
| Severe stress | | | | 418.889 | <0.001 |
| No | 1403(50.8) | 1167(83.2) | 236(16.8) | | |
| Yes | 1357(49.2) | 624(46.0) | 733(54.0) | | |

SHS: suboptimal health status.

reduced. Most general hospitals in Wuhan have established a shift system to take turns to care for COVID-19 patients¹³, which allows the nurses to get adequate rest.

Compared with men, female nurses are more likely to have higher levels of SHS, which may be related to the physiological and psychological differences between genders¹⁴. Studies have also found that female nurses have more severe depression and anxiety symptoms⁵. It is worth noting that female nurses also need to face the discomfort of special physiological conditions during the COVID-19, especially wearing protective clothing and protective

glasses for a long time, which will consume more physical and mental energies of female nurses. Our research also found that the shorter the average daily sleep time for nurses, the higher the risk of SHS. In a recent report, Singhal (2020) found that the SHS of Chinese adults is closely related to less than 6 h of sleep per day¹⁵. Our research shows that about one-third of nurses sleep less than 6 h per day. Adequate sleep has an important impact on physical health, and people who lack sleep will express more negative emotions¹⁵. Our research shows that age is related to SHS. Compared with nurses aged 21–25, nurses of other ages have a significantly higher chance of developing SHS. This may be related to the law of human development. With the increase of age, individual functions and physical conditions begin to gradually decline. Therefore, older nurses increase the risk of SHS, such as insomnia, fatigue, and weakened immune systems.

This study found that nurses who were directly involved in nursing COVID-19 patients were 1.81 times more likely to suffer from sub-health than nurses who were not directly involved in nursing COVID-19 patients, although both of these nurses work in the same high-risk area (Wuhan) and high-risk occupation (nursing). However, nurses who are directly involved in the care of COVID-19 patients must wear heavy, sealed, and high-temperature full-body protective equipment, including protective masks and protective clothing. Closer contact with patients with COVID-19 has a higher potential risk of infection, resulting in more physical and mental stress, which increases the risk of SHS. A total of 93 nurses infected with COVID-19 were included in this study. Once infected with COVID-19, nurses will have depression and anxiety, and most of them will also have physical symptoms such as cough and fever, which will obviously cause them to have more SHS.

Nurses often cannot live normally during the COVID-19, as they belong to a high-risk group and cannot return home after completing their work. They need to be isolated in the hotel, which will have a lot of negative effects on nurses. The longer the nurse is quarantined, the more likely anxiety, anger, and avoidance behaviors will occur⁹. Both overloaded stress and psychological distress can cause them to develop SHS. Our results confirm this conclusion. The prevalence of SHS among nurses in an anxious state is 1.77 times that of nurses in a non-anxious state. Therefore, giving first-line nurses relief of work pressure and providing necessary psychological counseling services may be the important tasks for the government and hospital administrators during the new coronary pneumonia.

CONCLUSIONS

First-line nurses have poor SHS in Wuhan. Average sleep times per day, female, age, directly participate in the rescue of

Table 2. Binomial logistic regression analysis of suboptimal health status.

| | B | SE | Odds Ratio | p-value |
|--|--------|-------|------------|---------|
| Demographic data | | | | |
| Gender (reference male) | 0.665 | 0.296 | 1.944 | 0.025 |
| Age (years) (reference 20–25) | | | | |
| 26–30 | 0.453 | 0.141 | 1.573 | 0.001 |
| 31–35 | 0.508 | 0.153 | 1.662 | 0.001 |
| 36–40 | 0.761 | 0.182 | 2.140 | <0.001 |
| 41–45 | 0.704 | 0.238 | 2.021 | 0.003 |
| 46–50 | 0.889 | 0.249 | 2.434 | <0.001 |
| ≥51 | 1.253 | 0.351 | 3.501 | <0.001 |
| Average sleep times per day (h) (reference 5 h) | | | | |
| 6 | -0.233 | 0.221 | 0.792 | 0.293 |
| 7 | -0.505 | 0.220 | 0.603 | 0.022 |
| 8 | -0.604 | 0.235 | 0.547 | 0.010 |
| ≥9 | -1.308 | 0.465 | 0.270 | 0.005 |
| Self-rated health (reference very poor) | | | | |
| Poor | 0.202 | 0.402 | 1.224 | 0.615 |
| Fair | -0.297 | 0.360 | 0.743 | 0.408 |
| Good | -1.166 | 0.368 | 0.312 | 0.002 |
| Very good | -2.249 | 0.480 | 0.105 | <0.001 |
| Direct contact with COVID-19 patients (reference n°) | 0.591 | 0.117 | 1.805 | <0.001 |
| Infected with COVID-19 (reference n°) | 0.508 | 0.256 | 1.661 | 0.048 |
| Anxiety (reference n°) | 1.774 | 0.107 | 5.893 | <0.001 |
| Severe stress (reference n°) | 0.957 | 0.111 | 2.603 | <0.001 |

B: regression coefficient; SE: standard error.

COVID-19, self-infection and anxiety were the influence factors of SHS. The results of this study can provide a reference for alleviating the SHS of nurses responding to COVID-19. Government and hospital managers should provide first-line nurses with medical security and psychological counseling services, reduce nurses' workload and night shifts, and increase support for nurses, thereby reducing nurses' stress levels and improving nurses' health.

AUTHORS' CONTRIBUTION

LH: Formal analysis, Writing - review & editing. **HL:** Conceptualization, Methodology, Data curation, Writing – original draft. **GW:** Formal analysis, Writing - review & editing. **XT:** Conceptualization, Methodology, Data curation, Writing – original draft. **YZ:** Conceptualization, Methodology, Data curation, Writing – original draft. **JF:** Writing – review & editing

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Survival outcome of pulmonary metastasectomy among the patients with colorectal cancers

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SUMMARY

OBJECTIVE: Pulmonary metastasectomy for the treatment of metastatic colorectal cancer is essential, but high ranked evidence of survival benefit is lacking. Here, we aimed to examine the prognostic factors after pulmonary metastasectomy in patients with colorectal cancer.

METHODS: This is a single-center, retrospective hospital-based observational case series study. We reviewed data for 607 patients with metastatic colorectal cancer (mCRC) who were treated and observed from 2012 to 2019. Of the 607 patients with mCRC, 87 were with solitary lung metastases. Of the 87 patients, 39 were not appropriate for metastasectomy, while 15 patients recognized as suitable candidates by the multidisciplinary thoracic tumor board rejected metastasectomy. Consequently, only 33 patients were included in the final analysis.

RESULTS: Rectum was detected as the primary site in 16 (48.5%) patients. Over 80% of patients had metachronous lung metastases, with a median of 29.0 months from initial diagnosis. Video-assisted thoracic surgery with wedge resection was performed in 20 (60.6%) patients. Over 90% of patients had solitary metastasis resected, with 97% of R0 resection. Median tumor size was 23.0 mm (min: 10; max: 90). Adjuvant treatment was given to 31 (93.9%) patients, while neoadjuvant treatment was given only to 8 (25%) patients. Of the 33 patients, there were 25 (75.7%) relapses. The most frequent site of relapse was lung in 15 (45.5%) patients. Interestingly, there were only 4 (12.2%) patients who had a relapse in the liver after lung metastasectomy. We found that median disease-free survival (DFS) and overall survival (OS) were 43.0 (13.0–73.0) and 55.0 (31.6–78.4) months, respectively.

CONCLUSIONS: Pulmonary metastasectomy was associated with significantly long-time survival rates in mCRC (43 months of DFS and 55 months of OS). The second relapse occurred in 25 (75.7%) patients, with isolated lung metastases in nearly half of the patients (45.5%). Therefore, lung metastases in mCRC were unique and a multidisciplinary team including a thoracic surgeon should manage these patients.

KEYWORDS: Colorectal cancer. Pulmonary metastasectomy. Second relapse. Surgical resection. Oligometastases.

INTRODUCTION

Colorectal cancer (CRC) is the fourth most common and third deadly cancer diagnosed with 1.8 million new cases and almost 861,000 deaths in 2018 according to the World Health Organization GLOBOCAN database¹. Twenty-five percent of newly diagnosed colorectal cancer cases had distant metastases. The recurrence rate of the curatively resected colorectal cancer was reported as 30%². Therefore, over 50% of CRC eventually

become metastatic, and similar to other solid tumors, metastases are the principal cause of death in these patients with CRC. Distant metastases, notably the liver, lung, and peritoneum, are virtually the most significant prognostic factors for CRC.

The lung is the second common metastatic site in CRC, and approximately 10–20% of patients with CRC develop pulmonary metastases³. However, the resection rate in lung metastases was far lower than that in liver metastases. Yedibela

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et al. reported that four percent of all mCRC patients had isolated lung metastases but only half of them (2% of mCRC) were candidate for curative resection⁴. Nonetheless, respectable studies have shown that 40–60% of 5-year survival rate can be reached in curatively resected lung metastases from mCRC⁵. However, there is a paucity of evidence from clinical trials that prove a survival benefit of lung metastasectomy in mCRC. The PulMicc trial, which is the only single randomized trial, showed nonsignificant benefit in 5-year survival rate (38 versus 29%) for metastasectomy over non-metastasectomy but had extremely low accrual rate (only 10% of the planned subjects were recruited)⁶. Despite lack of high-quality evidence, there is a strong rationale. So, European Society for Medical Oncology (ESMO) and National Comprehensive Cancer Network (NCCN) guidelines recommend for the evaluation of lung similar to liver metastases by the multidisciplinary team for possible resection.

In the current study, we conducted a retrospective hospital-based observational study of lung metastasectomy for patients with mCRC. The primary aim of this study was to explore the outcomes of the patients with lung metastasectomy in mCRC. Secondary aims were to examine the rate of lung metastasectomy in patients with mCRC and define clinicopathological characteristics of these patients, which may stratify outcomes after metastasectomy.

METHODS

Patients

The current retrospective hospital-based observational case series study was conducted with 607 patients with mCRC treated and observed at Baskent University Faculty of Medicine, Adana Dr Turgut Noyan Research and Treatment Centre, between 2012 and 2019. Of the 607 patients with mCRC, 87 were with lung metastases. Of the 87 patients, 39 were found to be ineligible for metastasectomy, while 15 of them rejected pulmonary metastasectomy although they were evaluated as suitable candidates by multidisciplinary thoracic tumor board. Therefore, 33 patients were included in the final analysis (Figure 1).

Main demographic and clinicopathological characteristics including age, sex, primary site, European Cooperative Oncology Group (ECOG) performance, primary tumor stage, time to relapse, type of surgery, the number of metastases, size of metastases, surgical outcome, and whether treated with adjuvant versus neoadjuvant chemotherapy are summarized in Table 1.

Statistical analysis

We present all the results as the rate for categorical values or mean/median for continuous variables. Overall survival (OS) was defined as the time from lung metastasectomy to death or

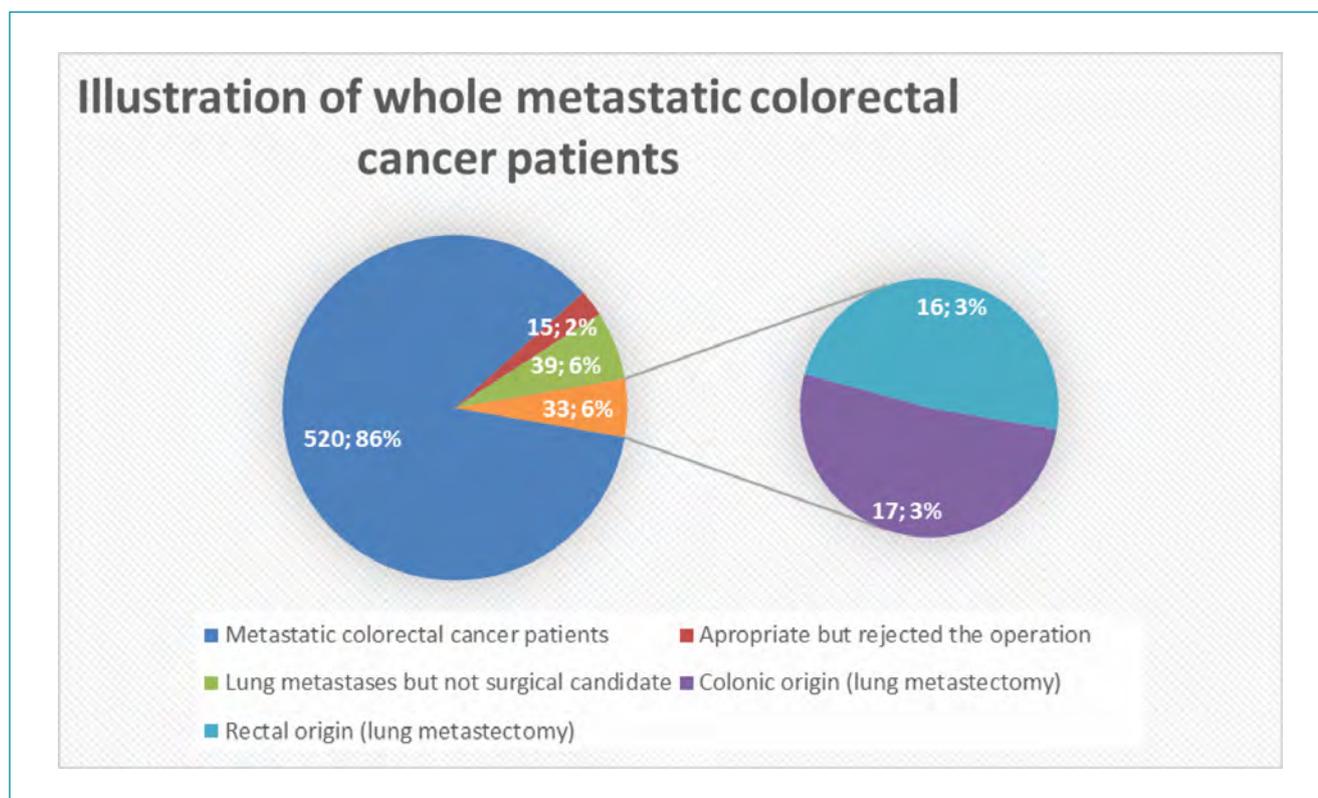


Figure 1. Illustration of whole metastatic colorectal cancer patients.

Table 1. Demographic and clinical characteristics of the study cohort.

| Number of patients (n) | Whole group |
|--|-------------------------|
| | 33 |
| Sex: female, n (%) | 13 (39.4) |
| Age (mean) | 60.4 (SD:12.13) |
| ECOG 0, n (%) | 33 (100) |
| Rectal origin, n (%) | 16 (48.5) |
| Stage at diagnosis, n=20 (missing in 13 patients), n (%) | |
| II | 5 (25) |
| III | 11 (55) |
| IV | 4 (20) |
| Time to relapse, months, n=33, median (range) | 29.0 (0–67) |
| Type of surgery, n (%) | |
| VATS wedge | 20 (60.6) |
| Open lobectomy | 9 (27.3) |
| VATS lobectomy | 2 (6.1) |
| Segmentectomy | 1 (3.0) |
| Thoracotomy wedge | 1 (3.0) |
| Metastatic site(s), right lung, n (%) | 18 (54.5) |
| Number of metastases, n (%) | |
| Solitary | 30 (90.9) |
| <3 | 3 (9.1) |
| Size of tumor, mm, (median) | 23.0 (min: 10; max: 90) |
| The surgical outcome with R0, n (%) | 32 (97.0) |
| Neoadjuvant treatment, n=31, n (%) | 8 (25.0) |
| Adjuvant treatment after surgery, n=33, n (%) | 31 (93.9) |
| Presence of relapse after lung surgery, n (%) | 25 (75.7) |
| Sites of relapse, n=25, n (%) | |
| Lung | 15 (45.5) |
| Liver | 2 (6.1) |
| Lung plus liver | 2 (6.1) |
| Other organs | 6 (18.1) |
| Median follow-up period, months, median (range) | 30.0 (2.0–79.0) |
| DFS, months, median (range), 95% CI | 43.0 (13.0–73.0) |
| OS, months, median (range), 95% CI | 55.0 (31.6–78.4) |

ECOG: Eastern Cooperative Oncology Group; VATS: video-assisted thoracic surgery; DFS: disease-free survival; OS: overall survival.

last control date and was reported in terms of months. Disease-free survival (DFS) was defined as the time to relapse or time between the resection of the primary tumor and the first diagnosis of pulmonary lesions and was reported in months. Survival was estimated using Kaplan-Meier curve, and log-rank tests were used for univariate statistical comparisons. Adjusted hazard ratio (HR) and 95% confidence interval (95%CI) were used for estimation. All statistical data were analyzed using the SPSS version 25.0, and a $p < 0.05$ was considered statistically significant. Recurrence-free survival (RFS) was defined as the time between pulmonary metastasectomy and metastatic recurrence and was reported in terms of months.

RESULTS

Patients characteristics

Thirty-three patients with mCRC who had undergone pulmonary metastasectomy were included in the final analysis. Most of the patients were male (20, 60.6%), and the mean age of the participants was 60.4 years (SD 12.1). All patients had an ECOG performance score of 0 at the time of surgery. In all, 16 patients had rectum and 17 had colon as the primary site, with 11 at stage III, 5 at stage II, and 4 at stage IV at the time of diagnosis. Data about the initial stage of the tumor were missing for 13 patients.

Thirty patients had solitary metastasis, while three had multiple metastases (1–3) to the lung. Lung metastases were commonly located in the right lung, 18 (54.5%). Resection was performed on all patients for lung metastasis, and the type of surgery was based on the size and location of the tumor. The median size of the tumor was 23.0 mm (min: 10; max: 90).

Treatments and outcomes

Video-assisted thoracic surgery (VATS) wedge resection with R0 surgical outcome was the principal surgical method performed in our patients. Wedge resection was performed in 20 patients, open lobectomy in 9, VATs lobectomy in 2, segmentectomy in 1, and wedge thoracotomy in 1. There was no surgery-related mortality.

Thirty-one patients received neoadjuvant treatment, and all patients received (33) adjuvant treatment after surgery. Chemotherapy was given to patients depending on the perceived benefits based on the characteristics and their ECOG status to withstand the treatment.

Survival analysis was done using Kaplan-Meier curves; the median DFS was 43.0 months (95%CI 13.0–73.0) and OS was 55.0 months (95%CI 31.6–78.4). Recurrence occurred in 25 (75.7%) patients after pulmonary metastasectomy, with

the lung being the major site of relapse. In all, 15 (45.5%) patients had a recurrence in the lung, 2 (6.1%) in the liver, and 2 (6.1%) in the lung and liver, while 6 (18.1%) patients had relapsed at other organs.

Univariate statistical analysis failed to demonstrate significant effect of the number of metastases, size and site of the tumor, stage at diagnosis, and types of surgery on DFS or OS ($p>0.05$) (Table 2). Multivariate analysis was not done because all univariate analysis had p value below 0.2.

DISCUSSION

Although most of the CRC is diagnosed at the local stage, 30% and 70% of patients at stages II and III CRC become metastatic in 24–36 months of initial diagnosis⁷. At the metastatic stage, if patient's metastatic sites could be resected with R0, 30% of these patients can be potentially cured⁸. Most frequent sites of metastases of the CRCs were the liver and lung in 70% and 15% of the patients, respectively. Unfortunately, in patients with CRC, metastatic sites could be resected in only 15% of metastatic patients⁹.

In our study, only 5% (33/607) of patients with mCRC underwent curative lung metastasectomy. Rectum was detected as the primary site in 16 (48.5%) patients. Over 80% of patients became metastatic after initial primary treatment with curative resection and adjuvant treatments, with median of 29.0 months (0–67). VATS with wedge resection was performed in 20 (60.6%) patients. Over 90% of patients had solitary metastasis resected with 97% R0 resection. Median tumor size was 23.0 mm (min: 10; max: 90). Adjuvant treatment was given to 31 (93.9%) patients, while neoadjuvant treatment was given only to 8 (25%) patients. Of the 33 patients, there were 25 (75.7%) relapses. The most frequent site of relapse was the lung in 15 (45.5%) patients. Interestingly, there were only 4 (12.2%) patients who had relapsed in the liver after lung metastasectomy. The median DFS and OS were found to be 43.0 (13.0–73.0) and 55.0 (31.6–78.4) months, respectively.

In the literature, Zhang et al. evaluated over 80,000 patients with cCRC and reported that isolated lung metastases and resection rate were 8.2% and 3.6%, respectively. In our results, over 600 patients with mCRC, 14% ($n=87$) of the patients had isolated lung metastases, 8% ($n=42$) of them were suitable for the lung metastasectomy, and 6% ($n=33$) were resected⁸. These numbers showed a smaller group of patients compared to liver metastasectomy and, therefore, could easily be overlooked in daily practice and patients can lose the chance of curative metastasectomy. We found that 80% of patients developed metachronous lung metastasis, and

Table 2. Univariate analysis of disease-free survival and overall survival

| Variable | Univariate analysis, median time, months (95% CI) | p |
|------------------------------|---|------|
| Number of metastases, n=33 | | |
| Solitary, n=30 | 43.0 (15.0–71.0) | 0.73 |
| 1–3, n=3 | Not reached | |
| Size of the tumor, n=33 | | |
| ≤2.5 cm, n=20 | 43.0 (19.9–35.6) | 0.89 |
| >2.5, n=13 | Not reached | |
| Site of the tumor, n=33 | | |
| Right, n=18 | 43.0 (12.9–73.3) | 0.94 |
| Left, n=15 | 28.0 (26.1–54.3) | |
| The stage at diagnosis, n=20 | | |
| Stages II and III, n=16 | 22.0 (14.4–29.6) | 0.66 |
| Stage IV: n=4 | 21.1 (17.5–24.7) | |
| Origin of the tumor, n=33 | | |
| Colon, n=17 | 43.0 (15.0–71.0) | 0.43 |
| Rectum, n=16 | Not reached | |
| Type of surgery | | |
| VATS, n=22 | 28.0 (NA) | 0.27 |
| Open, n=11 | 43.0 (NA) | |
| Number of metastases, n=33 | | |
| Solitary, n=30 | 55.0 (26.8–83.2) | 0.56 |
| 1–3, n=3 | 48.0 (NA) | |
| Size of the tumor, n=33 | | |
| ≤2.5 cm, n=20 | 65.0 (31.7–98.2) | 0.55 |
| >2.5, n=13 | 48.0 (27.2–68.7) | |
| Site of the tumor, n=33 | | |
| Right, n=18 | 41.0 (16.7–65.3) | 0.21 |
| Left, n=15 | 65.0 (45.7–84.3) | |
| Stage at diagnosis, n=20 | | |
| Stages II and III, n=16 | 65.0 (17.7–112.3) | 0.49 |
| Stage IV: n=4 | 28.0 (NA–66.9) | |
| Origin of the tumor, n=33 | | |
| Colon, n=17 | 48.0 (24.6–71.4) | 0.33 |
| Rectum, n=16 | Not reached | |
| Type of surgery | | |
| VATS, n=22 | 55.0 (25.0–85.0) | 0.95 |
| Open, n=11 | 48.0 (13.9–78.4) | |

VATS: video-assisted thoracic surgery. Any of the variables had no p -value below 0.2; therefore, no multivariate analysis was made.

rectum was the primary site in 16 (80%) patients. Also, our data showed that median RFS was 29 months. Our results were compatible with the literature by Sadahiro et al. reporting that the development of the distant metastasis from rectal cancer required significantly longer times (26 months versus 17 months) compared to colon cancer. In addition, they showed that the development of the lung metastasis appeared significantly later in comparison with colon cancer ($p=0.04$)⁷. With these results, the inclusion of the appropriate imaging of the thorax in surveillance of the patients with CRC beyond 24 months could be appropriate.

In our center, a limited number of lung metastases were resected along with the decision of the tumor board. Therefore, of the 33 patients, 30 (90%) were solitary, and accordingly, 67% of our operation were performed by the VATS technique. Though we know the prognostic effect of the mediastinal lymph node positivity of the lung metastases, routine lymph node dissection with lung metastasectomy was not done in our center. Ihn et al.¹⁰ reported that involvement of mediastinal lymph nodes showed poor prognosis, but making routine lymph node dissection did not improve RFS in CRC. In the literature, new studies also reported a high rate of solitary metastases and wedge resection with VATS and no benefit of the segmentectomy or lobectomy was shown with respect to wedge resection¹¹⁻¹³. There are no phase III randomized data that show the significant benefit of adjuvant treatment after curatively resected mCRC. However, NCCN and ESMO guidelines suggested that 6 months of adjuvant chemotherapy may be given perioperatively. If neoadjuvant treatment included biological agents like bevacizumab and anti-EFGR, we can also include these agents in the regimen after the curative surgical resection^{7,8}. In the current study, 31 (93.9%) patients were treated with the neoadjuvant treatment and 33 (100%) patients with adjuvant 6 months of systemic chemotherapy. We did not use a biological agent in the adjuvant setting, but if we started a biological agent at neoadjuvant setting, we must complete the 6-month systemic chemotherapy with the same regimen.

Although lung metastasectomy was made by curative intent, 75.7% ($n=25$) of the whole group relapsed, with a median RFS of 43 months. Median RFS in this study was better than those reported in previous multi-center trials¹³. We found out that over 90% of patients in our study had solitary metastasis with a median size of 23 mm and R0 resection rate of 97% ($n=32$). Most of the studies showed that solitary metastases with R0 resection and relatively small size were good prognostic factors in these patients^{7-13,15}. Interestingly, after initial lung metastasectomy, the second relapse site of these patients was isolated lung metastases in 45.5% of the

cases. Whereas isolated liver relapse and synchronous lung and liver relapse were detected in 6.1% and 6.1% of the entire group, consecutively. In the literature, most of the studies reported a higher rate of lung recurrence after lung metastasectomy^{7,9,11,13}. Therefore, we have to make a vigilant follow-up for the second lung relapse to seize an opportunity for the second metastasectomy, which was shown to increase survival in retrospective analysis¹³.

Our results provide relevant data about mCRC with lung metastasectomy with curative intent. However, some limitations are worth noting. The retrospective nature of the present study and the small size of the main cohort represent limitations that prevented us from drawing general conclusions. In addition, our study had limited data for the type of adjuvant chemotherapy and biological agent used and details about some important prognostic genomic characteristics like KRAS, NRAS, and B-RAF mutation status. Finally, our study also lacks chemotherapy toxicity and postoperative complication data. However, the information was retrospectively retrieved from hospital records and filtered from 607 patients with mCRC, of which 87 of them had isolated lung metastases but only 33 of them underwent curative lung metastasectomy, which is somehow cumbersome.

CONCLUSIONS

Our findings showed that isolated lung metastases occurred in significantly fewer patients and at a later time compared to liver metastases. Surgical resection of the lung metastases from mCRC is associated with unexpectedly high long-time survival rates (43 months of DFS and 55 months of OS). The second relapse occurred in 25 (75.7%) patients and isolated lung metastases in near half of the patients with CRC (45.5%). Therefore, lung metastases in mCRC were unique and these patients have to be managed by a multidisciplinary team including a thoracic surgeon along with a medical and surgical oncologist.

AUTHORS' CONTRIBUTIONS

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

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Gamma-glutamyl transpeptidase–platelet ratio, systemic immune inflammation index, and system inflammation response index in invasive *Aspergillosis*

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SUMMARY

OBJECTIVE: Gamma-glutamyl transpeptidase-platelet ratio, system inflammation response index, and systemic immune inflammation index are three systemic immune and inflammation indexes that were investigated for their diagnostic and prognostic proficiencies in cardiovascular diseases and cancers. However, their predictive values for invasive aspergillosis have not yet been studied. The aim of this study was to evaluate Gamma-glutamyl transpeptidase-platelet ratio, system inflammation response index, and systemic immune inflammation index levels and their diagnostic values in invasive aspergillosis.

METHODS: A total of 23 patients with invasive aspergillosis and 23 sex- and age-matched healthy participants were included in this study. Complete blood count parameters and liver function tests were studied. Gamma-glutamyl transpeptidase-platelet ratio, system inflammation response index, and systemic immune inflammation index were calculated.

RESULTS: Leukocyte, neutrophil, lymphocyte, and monocyte levels were statistically significantly higher in IA group ($p=0.031$, $p=0.027$, $p=0.033$, and $p=0.001$, respectively). In invasive aspergillosis group, platelets were numerically lower; Aspartate transaminase, alanine aminotransferase, and lactic dehydrogenase levels were numerically higher than those in control group but differences between levels were not statistically significant ($p>0.05$). The γ -glutamyl transpeptidase levels of patients were statistically significantly higher ($p=0.007$), and in addition, statistically significant differences were found between groups in terms of gamma-glutamyl transpeptidase-platelet ratio, system inflammation response index, and systemic immune inflammation index ($p<0.001$, $p=0.037$, $p=0.001$, respectively). Receiver operating characteristic analysis was performed, and areas under the curves were evaluated. gamma-glutamyl transpeptidase-platelet ratio had the higher area under the curve than systemic immune inflammation index and system inflammation response index (AUC 0.849, 0.798, 0.693, respectively). The results from receiver operating characteristic analysis of the data suggested that the use of a cutoff value of 0.15 for gamma-glutamyl transpeptidase-platelet ratio would be optimum for clinical use to confirm independent predictors of patients with invasive aspergillosis.

CONCLUSIONS: Gamma-glutamyl transpeptidase-platelet ratio is an independent, a useful predictor, and is superior to other evaluated markers in the diagnosis of inflammation in invasive aspergillosis. Gamma-glutamyl transpeptidase-platelet ratio may also be a helpful biomarker for clinicians to follow-up the inflammatory process of these patients.

KEYWORDS: Aspergillosis. Gamma-glutamyl transpeptidase. Platelet. Inflammation.

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INTRODUCTION

Aspergillus species are widely found in soil and rotting plants as saprophytic fungus. In parallel with the increase in susceptible patient groups, there is an increase in *Aspergillus* infections globally. The clinical picture of these infections varies according to the underlying diseases and facilitating factors. For example, invasive aspergillosis (IA) has a high mortality rate in neutropenic patients, whereas fungus balls (aspergilloma) are seen in the presence of cavitory sequelae after diseases such as pulmonary tuberculosis or sarcoidosis. Especially, *Aspergillus fumigatus* is a major cause of IA, severe disseminated fungal infection, and causes high morbidity and mortality in patients with immunodeficiency¹. IA can be seen not only in patients with long-term neutropenia, allogeneic hematopoietic cell, or solid organ transplantation but also in patients using high doses of corticosteroids or immunosuppressive drugs and in patients with severe genetic immunodeficiency².

Platelet-mediated inflammation has been demonstrated in various acute and chronic infections, and it has been stated that platelets contribute to antimicrobial defense mechanisms. In *in vitro* studies, it is stated that platelets may have a role in the immune response against *Aspergillus*³. In a recent study by Deshmukh et al., it is suggested that fungal galactosaminogalactans initiate the interaction between complement and platelets, and this situation contributes to excessive inflammation, thrombocytopenia, and thrombosis⁴.

Aspartate transaminase (AST), alanine aminotransferase (ALT), and γ -glutamyl transpeptidase (GGT) are transferase enzymes with high clinical relevance, and they are primary biomarkers of liver functions⁵. GGT-platelet (PLT) ratio (GPR) is an inflammatory marker used in the early determination of the prognosis of liver diseases⁶. Recently, two new inflammatory markers comprising platelet and leukocyte subgroups, the systemic immune inflammation index (SII) and the system inflammation response index (SIRI), have been associated with poor prognosis in various diseases and cancers^{7,8}. However, there is no study in the literature regarding the diagnostic and prognostic value of these three markers in IA patients. This study aims to determine the diagnostic values of GPR, SII, and SIRI in IA patients for the first time in the literature.

METHODS

Study groups

The study group consisted of 23 patients who were treated for IA infections between June 2011 and May 2012 at the University Hospital. All patients had underlying medical histories including tuberculosis, sarcoidosis, acute lymphoblastic leukemia, lung

cancer, colon cancer, breast cancer, and chronic renal failure with renal transplantation. The control group consisted of 23 age- and gender-matched participants who applied to our hospital outpatient clinics and whose laboratory test results were not in favor of infection and/or inflammation.

Laboratory analysis

Clinical samples of 23 patients diagnosed with IA or possible IA in the University hospitals in line with the criteria of the European Cancer Research and Treatment Organization Mycosis Study Group (EORTC-MSG)⁹ were included. Complete blood count parameters such as leukocyte (WBC), platelet (PLT), neutrophil (N), lymphocyte (L), and monocyte (M) in both groups were analyzed using the Siemens ADVIA 2120i autoanalyzer, biochemical test parameters such as lactic dehydrogenase (LDH), aspartate transaminase (AST), alanine aminotransferase (ALT), and γ -glutamyl transpeptidase (GGT) were analyzed using the Abbot Architect C8000 autoanalyzer, and all these results were evaluated retrospectively. GPR, SII (using the $PLT \times N/L$ formula), and SIRI (using the $N \times M/L$ formula) were calculated.

In studies for the identification of *Aspergillus* species, microscopic and macroscopic features of clinical samples were defined first^{10,11}. Colonies growing on Sabouraud dextrose agar were inoculated into potato dextrose agar to increase their conidia and to produce pigments and then inoculated to Czapek–Dox agar for the identification of the species. Colony color, morphology, and growth characteristics at 25, 35, and 44°C were recorded for each growing species. Lactophenol cotton blue was prepared for microscopic examination, and conidia formation and its color, number of sterigmata, shape of vesicles, structure of conidiophores, and shapes of Hulle cells were examined. More detailed studies using the molecular methodology of DNA sequencing analysis confirmed this preliminary identification^{12,13}. Sequencing of the Internal Transcribed Spacer (ITS)-1 (5'-TCCGTAGGTGAACCTGCGG-3') and ITS-4 (5'-TCCTCCGCTTATTGATATGC-3') regions flanking 5.8S ribosomal DNA were used as a reference method for all isolates studied in the determination of species. Subsequently, thermal environments for 3 min at 94°C, followed by 35 cycles of 1 min at 94°C, 1 min at 55°C, and 1 min 30 s at 72°C, followed by the final thermal environment for 10 min at 72°C were used. Purification of amplicons was done by using the MinElute PCR kit (QIAGEN, Germany). Sequencing of both chains with primer ITS-1 or ITS-4 and BigDye Terminator Cycle Sequencing Kit (Applied Biosystems, USA) were performed using the ABI Prism 3100 genetic analyzer (Applied Biosystems)¹⁴. The elongation of PCR products was sequenced, and the species were identified using the Basic Local Alignment Search Tool (BLAST; <http://www.ncbi.nlm.nih.gov/BLAST/>)

database. The obtained isolates were matched with the species showing 99% sequence identity in the searched database.

This study was approved by the University Medical Sciences Research Ethics Committee (Resolution number: TSA-11-3244).

Statistical analysis

Data were analyzed using the Windows SPSS version 23.0 (SPSS Inc., USA) program. The Mann–Whitney U test was used to evaluate the differences between groups, and the results were shown as median and interquartile range (25–75%). The receiver operating characteristic (ROC) curves were drawn to show the diagnostic performance of inflammation markers in IA, and the best cutoff point was determined. Values of $p < 0.05$ were considered statistically significant.

RESULTS

The demographic data and laboratory results of 9 female and 14 male patients included in the IA group and 9 female and 14 male participants included in the control group are presented in Table 1.

A. fumigatus in 12 samples, *Aspergillus flavus* in seven samples, *Aspergillus niger* in three samples, and *Aspergillus terreus* in 1 sample were isolated as a result of DNA sequence analysis of 23 samples including lung tissue, eye tissue, and bronchoalveolar lavage fluid. The mean ages of the patients and control group participants were 43 ± 20 years and 42.71 ± 17.98 years, respectively. There was no statistically significant difference in terms of age between both groups ($p > 0.05$).

Table 1. Demographical data and laboratory findings of patients with invasive aspergillosis and control participants.

| | IA group (n=22) | Control group (n=22) | p-value |
|------------------------------|--------------------------|--------------------------|----------------------|
| Age | 43±20 ^b | 42.71±17.98 ^b | p>0.05 |
| Sex (female/male) | 9/13 | 9/13 | – |
| Underlying diseases | | | |
| Tuberculosis | 1 | – | – |
| Sarcoidosis | 1 | – | – |
| Acute lymphoblastic leukemia | 4 | – | – |
| Lung cancer | 10 | – | – |
| Colon cancer | 2 | – | – |
| Breast cancer | 1 | – | – |
| Renal transplantation | 3 | – | – |
| Fungal infection sites | | | |
| Lung | 20 | – | – |
| Eye | 2 | – | – |
| WBC | 11.74 (8.14–16.20) | 6.70 (5.44–9.31) | p=0.031 ^a |
| Neutrophil (%) | 64.70 (55.80–83.70) | 58.30 (52.40–60.70) | p=0.027 ^a |
| Lymphocyte (%) | 19.50 (10.30–32.30) | 31.70 (29.50–36.90) | p=0.033 ^a |
| Monocyte (%) | 5.80 (4.70–6.70) | 7.90 (6.50–8.40) | p=0.001 ^a |
| Platelet | 256 (180–410) | 270 (215–291) | p=0.303 |
| SII | 1104.91 (521.39–2315.15) | 477.76 (321.54–581.92) | p=0.001 ^a |
| SIRI | 19.14 (10.72–67.50) | 13.29 (10.32–16.53) | p=0.037 ^a |
| LDH | 357.23 (246.0–414.62) | 278.0 (204.50–333.50) | p=0.097 |
| AST | 25 (17–36) | 19 (13.75–31.25) | p=0.191 |
| ALT | 22 (16.25–44.82) | 17.50 (13.50–40.0) | p=0.364 |
| GGT | 79.0 (32.0–91.64) | 32.50 (19.0–46.75) | p=0.007 ^a |
| GPR | 0.25 (0.12–0.63) | 0.08 (0.06–0.14) | p<0.001 ^a |

WBC: leukocyte; LDH: lactic dehydrogenase; AST: aspartate transaminase; ALT: alanine aminotransferase; GGT: γ -glutamyl transpeptidase; SII: systemic immune inflammation index; SIRI: system inflammatory response index; GPR: γ -glutamyl transpeptidase-platelet ratio. The Mann–Whitney U test was used; data were summarized as median and interquartile range (25–75%). ^aStatistically significant, $p < 0.05$. ^bData were summarized as mean±SD.

Complete blood count parameters, such as WBC, neutrophil, lymphocyte, and monocyte levels, were evaluated in patients with IA and found to be statistically significantly higher than the values of the controls ($p=0.031$, $p=0.027$, $p=0.033$, and $p=0.001$, respectively). There was no statistically significant difference between the patients and the controls in terms of platelet values ($p>0.05$).

Among the biochemical parameters, AST, ALT, and LDH values were found to be numerically higher in the patient group, whereas no statistically significant differences were found between these three enzyme levels in both groups ($p>0.05$). However, GGT values were statistically significantly higher in the patient group compared with the control ($p=0.007$). SII, SIRI, and GPR indices, which were the inflammation markers calculated by their formulae, were also shown to be statistically significantly higher in the patient group compared with the controls ($p=0.001$, $p=0.037$, and $p<0.001$, respectively; (Table 1). The ROC analysis was performed, and the curves were drawn to determine the diagnostic performances of inflammatory markers in IA. Areas under the curves were compared (Table 2). It was stated that GPR values were statistically significantly higher than SII and SIRI values in determining IA patients. Then, the optimal cutoff point for GPR was determined using the maximum value of Youden's index (sensitivity+specificity-1). It was predicted that the values above 0.15 for GPR can be used in the diagnosis of IA with 70% of sensitivity and 85% of specificity (Table 2, Figure 1).

DISCUSSION

IA is an infectious disease that causes deterioration in liver functions. Liver dysfunction and liver fibrosis are common pathological processes in various liver diseases. Early detection of liver failure or fibrosis in these patients is an important factor in planning treatment and predicting prognosis. Also,

Table 2. Receiver operating characteristic analysis of γ -glutamyl transpeptidase-platelet ratio, systemic immune inflammation index, and system inflammatory response index in patients with *Aspergillus* infection.

| | Area under the curve | standard deviation error | p-value | Asymptotic 95% confidence interval | |
|------|----------------------|--------------------------|---------|------------------------------------|-------------|
| | | | | Lower bound | Upper bound |
| GPR | 0.849 | 0.059 | <0.001 | 0.732 | 0.965 |
| SII | 0.798 | 0.080 | 0.001 | 0.641 | 0.954 |
| SIRI | 0.693 | 0.089 | 0.037 | 0.518 | 0.867 |

GPR: γ -glutamyl transpeptidase-platelet ratio; SII: systemic immune inflammation index; SIRI: system inflammatory response index.

the presence of significant liver fibrosis is a strong indication to start antiviral therapy¹⁵. The gold standard in liver fibrosis is liver biopsy, but it cannot be performed in every hospital because of its invasive procedure, sample errors, or complications. Therefore, the use of combinations of biochemical markers in the determination of liver fibrosis or liver function damage has become an important research subject in recent years¹⁶. In vitro studies state that platelets may play a role in the immune response against *Aspergillus*³. Therefore, by investigating the combination of two important parameters, such as GGT and PLT, in this study, it was thought that these two pathological conditions could be evaluated together and the diagnostic values could be compared in IA patients with inflammation and liver dysfunction. Wang et al. reported that the diagnostic performance of GPR is higher than ALT, AST, and GGT in patients with chronic hepatitis B and especially in the presence of HBeAg positivity. They also suggested that GPR could be a new and easy-to-use index for determining significant liver inflammation in chronic hepatitis B¹⁷. In this study, although the AST, ALT, and LDH levels of IA patients were statistically higher than the control group values, the differences were statistically insignificant, but GGT values of the IA patients were statistically significantly higher than the controls ($p=0.007$). In recent studies, it has been stated that the predictive values of SII and SIRI in cancers are higher than the N-L ratio (NLR) and P-L ratio (PLR)^{18,19}. However, the relationship of these parameters with fungal infections such as IA has not yet been evaluated. Therefore, for the first time in the literature, GPR, SII, and SIRI levels in IA patients were evaluated in this study, and the diagnostic performances of these parameters in IA were compared. In addition, the diagnostic

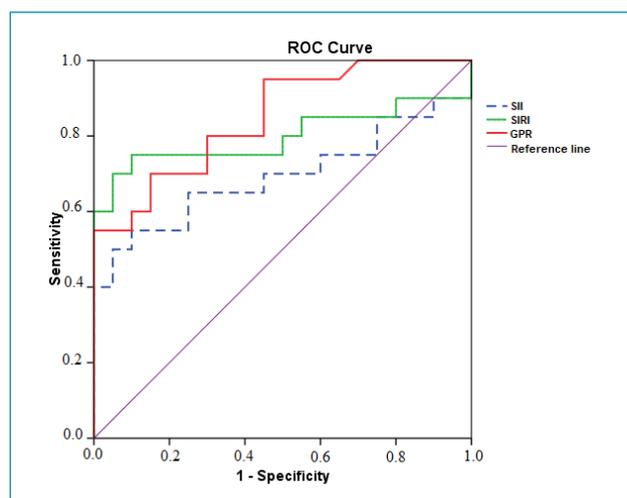


Figure 1. Receiver operating characteristic curves of GPR, SII, and SIRI in patients with *Aspergillus* infection.

performance of GPR in IA patients has been shown to be more significant and higher than ALT, AST, and GGT, in addition to SII and SIRI values (Table 2).

CONCLUSION

It is anticipated in this study that SII, SIRI, and especially GPR values, which are easy to achieve and easy to use in assessing the inflammation and liver dysfunction, may also be useful in evaluating inflammation and liver function in IA. Since this

was a single-centered retrospective study with relatively small study groups, these results should be supported with further prospective studies with a larger number of participants.

AUTHORS' CONTRIBUTIONS

NC: Data Curation, Investigation, Methodology, Resources, Supervision, Validation, Writing – Review & Editing. **ANK:** Data Curation, Investigation, Methodology, Resources, Supervision, Validation, Writing – Review & Editing.

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An evaluation of the relationship between vitamin D level and CTRP-9, tumor necrosis factor-alpha, thiol-disulfide hemostasis in women

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SUMMARY

OBJECTIVE: Many chronic diseases such as malignancy, cardiovascular diseases, endothelial dysfunction, and autoimmune diseases, which have been shown to be related to vitamin D in various studies; have similar relations with CTRP-9, TNF α , and thiol-disulfide hemostasis. We aimed to contribute to the literature by evaluating the relationship between CTRP-9, TNF α , and thiol-disulfide hemostasis and vitamin D levels, which we thought may have some effects on the pathogenesis of vitamin D deficiency.

METHODS: In our study, 78 female volunteers older than 18 years were included. Volunteers were divided into three groups according to the reference values of vitamin D levels. Biochemical parameters, CTRP-9, TNF α , and thiol/disulfide hemostasis tests taken from all volunteers were studied.

RESULTS: In this study, there was a significant difference in CTRP-9, TNF α , total thiol (TT), native thiol (NT), DIS (disulfide), TT/DIS, and NT/DIS levels in vitamin D groups ($p < 0.05$). There was a significant negative correlation between vitamin D and TNF α and DIS, while a significant positive correlation was found with CTRP-9, TT, NT, TT/DIS, and NT/DIS ($p < 0.05$).

CONCLUSIONS: It was determined that vitamin D deficiency causes a significant decrease in CTRP-9 level and a significant increase in TNF α level, as well as an increase in thiol/disulfide hemostasis in favor of disulfide, which may be a risk factor for increased oxidative stress. We considered that these changes may play mediator roles for many chronic diseases and metabolic disorders that are increasing in frequency due to vitamin D deficiency.

KEYWORDS: Vitamin D. CTRP-9. TNF α . Total Thiol. Native Thiol. Disulfides.

INTRODUCTION

It was originally thought that vitamin D had effects mainly on calcium and bone metabolism. In preclinical studies, it has been determined that vitamin D exerts its effects through vitamin D receptors. It has been shown that these receptors are found not only in bone structure but also in many tissues and organs¹⁻³. In recent years, vitamin D deficiency and insufficiency has been found to be associated with many chronic diseases, including

a number of cancers, cardiovascular diseases, endothelial dysfunction, metabolic syndrome, infectious and autoimmune diseases^{4,5}. Vitamin D deficiency is likely to be a risk factor for many acute and chronic diseases⁶. It is significantly higher in women than in men⁷. Risk factors for vitamin D deficiency include advanced age, genetic factors, living in a traditionally closed society, being in a closed environment, use of protective sunscreen, physical inactivity, smoking, air pollution, kidney

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disease, liver disease, anticonvulsants, and glucocorticoids, affecting vitamin D metabolism. including the use of drugs⁸.

CTRP-9 (the C1q TNF-related protein) is a newly described adipokine secreted from adipose tissue, which shares the highest amino acid sequence (54%) as well as being the closest paralogue of adiponectin. The metabolic roles of CTRP-9 functionally overlap with those of adiponectin. CTRP-9 is produced at higher levels in women than in men⁹. Its anti-inflammatory and anti-atherosclerosis properties led it to play a cardioprotective role in the coronary artery disease process. CTRP-9 inhibits the expression of adhesion molecules in endothelial cells and reduces the secretion of proinflammatory cytokines such as tumor necrosis factor alpha (TNF α). It increases the production of nitric oxide in the atherosclerotic plaque, leading to vasodilation, decreasing endothelial dysfunction, also inhibiting the inflammatory responses of macrophages and consequently increasing the stability of the atherosclerotic plaque^{10,11}. Due to the reduced neointimal formation of CTRP-9 following vascular injury with treatments that can increase CTRP-9 production, it is thought that the frequency of vascular restenosis can be reduced after angioplasty¹².

Tumor necrosis factor alpha has important properties in the initiation and maintenance of inflammation in autoimmune diseases. It has also multiple effects on inflammation, infection, immunity, cytotoxicity, endothelial dysfunction, oxidative stress, cardiovascular events, and tissue remodeling. Due to these versatile effects, anti-TNF drugs have been developed which are used in the treatment of many diseases¹³.

Oxidative stress is defined as the impairment of molecular and cellular functions as a result of the loss of the balance between the production of free radical or reactive oxygen species and the antioxidant system. Reactive oxygen radicals are primary molecules that cause oxidative damage when they exceed physiological levels. Dynamic thiol/disulfide balance state has critical roles in antioxidant defense, detoxification apoptosis, regulation of enzyme activities, transcription and cellular signal transduction mechanisms. Abnormal thiol/disulfide balance levels is involved in the pathogenesis of various diseases such as diabetes mellitus, cardiovascular diseases, endothelial dysfunction, malignancy formation, rheumatoid arthritis, chronic renal failure, Parkinson's and Alzheimer's diseases¹⁴⁻¹⁶.

In the literature review, there are a limited number of studies evaluating vitamin D level, thiol-disulfide hemostasis, and TNF α separately in some diseases. However, there was no study examining the relationship between CTRP-9 and vitamin D. Also, no study was found in which all these parameters were evaluated together. We aimed to contribute to the literature by evaluating the relationship between CTRP-9, TNF α , and thiol-disulfide hemostasis and vitamin D levels, which we thought may have some effects on the pathogenesis of vitamin D deficiency.

METHODS

After the approval of the ethics committee of Bezmialem Vakif University, dated 18/12/2019 and decision number 24/17, 78 female volunteers over the age of 18 years, who applied to the internal medicine outpatient clinic of our hospital between May 2020 and November 2020, were included in our study. Patients with a known chronic disease, pregnancy, or surgery in the last 6 months were not included in our study. Also, patients who used antioxidant drugs, vitamin supplements, lipid-lowering drugs, smoking, alcohol use, and those who used vitamin D in the last 1 month were excluded from the study. Patients with normal C-reactive protein (CRP) levels were included in our study. If vitamin D level is <20 ng/mL, it indicates deficiency, if it is 20–30 ng/mL, it indicates insufficiency, and if it is above 30 ng/mL, it indicates sufficient level¹⁷. Volunteers were divided into three groups according to the reference values of vitamin D levels. For biochemical parameters (glucose, creatinine, aspartate aminotransferase [AST], alanine aminotransferase [ALT], calcium, magnesium, phosphorus, free tetraiodothyronine [fT4], thyroid-stimulating hormone [TSH], parathyroid hormone [PTH], total cholesterol, triglyceride, low-density lipoprotein-cholesterol [LDL-K], high-density lipoprotein-cholesterol [HDL-K]), CTRP-9, TNF α , and thiol/disulfide hemostasis tests from all volunteers, venous blood samples, were taken into a gel tube between 8:00 a.m. and 9:00 a.m. after 12 h of fasting and centrifuged at 3,600 rpm for 10 min and the serums were separated. After the serums of all volunteers were transferred to Eppendorf tubes, they were stored at -80°C until the day of the study.

Measurement of dynamic thiol/disulfide homeostasis

Serum thiol/disulfide homeostasis was determined with a recently developed measurement method by using the Thermo Scientific Varioskan Flash multimode reader. DIS was mathematically determined according to the formula $(TT-NT)/2$ ¹⁴.

Measurement of CTRP-9 and TNF α

Concentrations of CTRP-9 and TNF α in the serum were measured by a specific commercial ELISA kit according to the manufacturer's instructions (CTRP-9: E3848Hu and TNF α : E0082Hu, Bioassay Technology Laboratory, China). Concentrations were determined with a spectrophotometric microtiter plate reader (Varioskan Flash Multimode Reader, Thermo, Waltham, USA) at 450 nm optical density¹⁸.

Statistical analyses

IBM SPSS statistics 22.0 program was used for statistical analysis in the study. While evaluating study data, descriptive

RESULTS

statistical methods (mean, standard deviation, and frequency) were used. Skewness and kurtosis values were used together with the Shapiro-Wilk test to evaluate the normal distribution of the data. While the one-way ANOVA test was used to compare more than two normally distributed variables, the Kruskal-Wallis test was used to evaluate more than two non-normally distributed variables. In order to evaluate the correlation between data, Pearson's correlation analysis was used for normally distributed data, and Spearman correlation analysis was used for non-normal distribution data. Results were evaluated at 95% confidence interval and significance level of $p < 0.05$.

The mean age of 78 women who joined the study was 34.06 ± 10.89 (20–61) years, while their average body mass index (BMI) was 24.57 ± 4.60 (16.8–35.0) kg/m^2 . When we divided volunteers according to their vitamin D levels into three groups (Group 1: vitamin D < 20 ng/mL ; Group 2: vitamin D between 20 and 30 ng/mL ; Group 3: vitamin D > 30 ng/mL): Group 1: age and BMI average were 32.26 ± 10.06 years, 24.76 ± 4.86 kg/m^2 ; Group 2: 35.86 ± 12.95 years, 24.03 ± 4.74 kg/m^2 ; and Group 3: 35.15 ± 9.92 years, 24.85 ± 4.13 kg/m^2 . There was no statistically significant difference between the groups in terms of age and BMI ($p > 0.05$) (Table 1).

Table 1. Evaluation of age, body mass index, the C1q TNF-related protein, tumor necrosis factor-alpha, total thiol, native thiol, disulfide, total thiol/disulfide, native thiol/disulfide, and biochemical parameters levels in vitamin D groups.

| | Group 1 Vitamin D < 20 ng/mL n:36 | Group 2 Vitamin D 20–30 ng/mL n:22 | Group 3 Vitamin D > 30 ng/mL n:20 | p |
|---|---|--|---|-------|
| Age (years) | 32.36 ± 10.06 | 35.86 ± 12.95 | 35.15 ± 9.92 | 0.438 |
| BMI (kg/m^2) | 24.76 ± 4.86 | 24.03 ± 4.74 | 24.85 ± 4.13 | 0.809 |
| CTRP-9 (ng/L) | 90.45 ± 25.57 | 145.20 ± 13.98 | 145.42 ± 22.76 | 0.001 |
| TNF α (ng/L) | 249.29 ± 29.59 | 182.23 ± 22.97 | 142.35 ± 19.13 | 0.001 |
| TT (μM) | 449.66 ± 53.58 | 524.48 ± 56.40 | 530.11 ± 52.47 | 0.001 |
| NT (μM) | 205.95 ± 37.96 | 316.03 ± 57.10 | 342.20 ± 43.64 | 0.001 |
| DIS (μM) | 121.85 ± 15.39 | 104.22 ± 2.58 | 93.95 ± 38.30 | 0.001 |
| TT/DIS | 3.70 ± 0.35 | 5.03 ± 0.57 | 6.89 ± 3.77 | 0.001 |
| NT/DIS | 1.70 ± 0.35 | 3.03 ± 0.57 | 4.89 ± 3.77 | 0.001 |
| Glucose (mg/dL) | 92.11 ± 7.43 | 91.04 ± 8.81 | 90.40 ± 5.64 | 0.693 |
| Creatinine (mg/dL) | 0.69 ± 0.05 | 0.69 ± 0.04 | 0.71 ± 0.08 | 0.354 |
| AST (U/L) | 17.05 ± 4.88 | 16.86 ± 3.79 | 17.05 ± 3.61 | 0.153 |
| ALT (U/L) | 17.72 ± 8.84 | 14.81 ± 5.01 | 14.40 ± 4.61 | 0.225 |
| Calcium (mg/dL) | 9.34 ± 0.30 | 9.42 ± 0.44 | 9.36 ± 0.39 | 0.726 |
| Magnesium (mg/dL) | 1.94 ± 0.14 | 1.95 ± 0.15 | 1.90 ± 0.11 | 0.415 |
| Phosphorus (mg/dL) | 3.55 ± 0.43 | 3.38 ± 0.35 | 3.63 ± 0.51 | 0.177 |
| PTH (ng/L) | 63.22 ± 21.31 | 60.79 ± 15.31 | 47.61 ± 17.02 | 0.012 |
| fT4 (pg/mL) | 12.29 ± 1.39 | 12.89 ± 1.59 | 12.65 ± 1.21 | 0.280 |
| TSH (mU/L) | 1.65 ± 0.71 | 1.50 ± 0.61 | 1.46 ± 0.55 | 0.518 |
| Total cholesterol (mg/dL) | 181.50 ± 34.17 | 171.13 ± 21.89 | 189.85 ± 38.50 | 0.179 |
| Triglyceride (mg/dL) | 79.86 ± 44.33 | 74.63 ± 29.80 | 77.06 ± 35.01 | 0.878 |
| LDL-K (mg/dL) | 105.41 ± 31.68 | 90.57 ± 29.57 | 115.69 ± 31.95 | 0.036 |
| HDL (mg/dL) | 60.46 ± 14.85 | 60.36 ± 13.62 | 57.52 ± 15.14 | 0.745 |

BMI: body mass index; CTRP-9: the C1q TNF-related protein; TNF α : tumor necrosis factor-alpha; TT: total thiol; NT: native thiol; DIS: disulfide; AST: aspartate aminotransferase; ALT: alanine aminotransferase; PTH: parathormone; fT4: free tetraiodothyronine; TSH: thyroid-stimulating hormone; LDL-K: low-density lipoprotein-cholesterol; HDL-K: high-density lipoprotein-cholesterol.

Between vitamin D groups, while there was no significant difference found ($p > 0.05$) in terms of glucose, creatinine, AST, ALT, calcium, magnesium, phosphorus, fT4, TSH, total cholesterol, triglyceride, HDL-K, there was a significant difference ($p < 0.05$) found in terms of CTRP-9, TNF α , total thiol (TT), native thiol (NT), disulfide (DIS), TT/DIS, NT/DIS, PTH, and LDL-K (Table 1). The change of vitamin D, CTRP-9, TNF α , TT, NT, DIS,

TT/DIS, and NT/DIS levels were shown in vitamin D groups (Figure 1).

In the evaluation of the correlation between vitamin D and age, BMI, CTRP-9, TNF α , TT, NT, DIS, TT/DIS, NT/DIS, and other biochemical parameters, a significant negative correlation was found with TNF α , DIS, PTH, while a significant positive correlation was found with CTRP-9, TT, NT, TT/DIS, and NT/DIS ($p < 0.05$; Table 2).

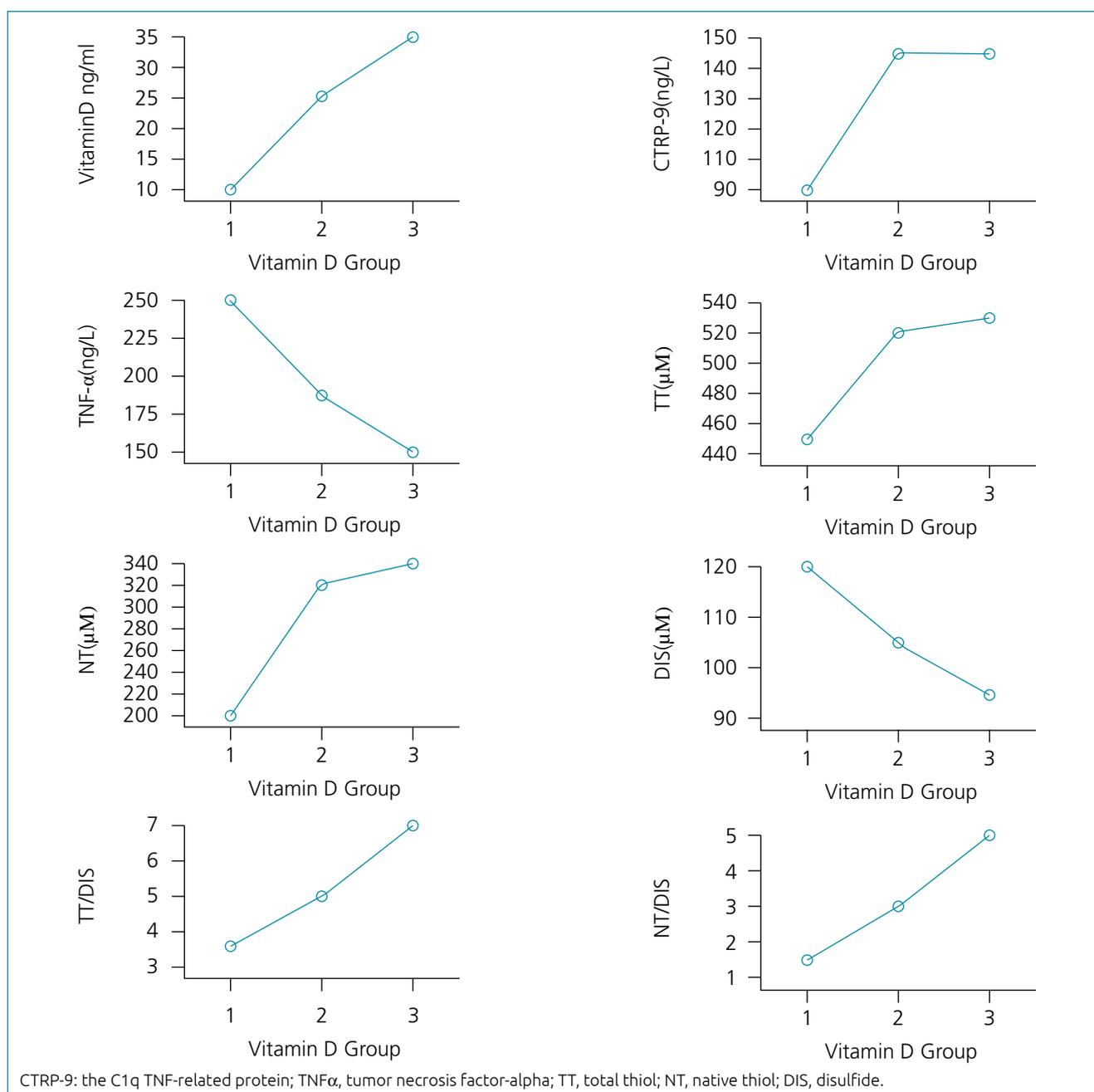


Figure 1. Evaluation of vitamin D, the C1q TNF-related protein, tumor necrosis factor-alpha, total thiol, native thiol, disulfide, total thiol/disulfide, and native thiol/disulfide levels in vitamin D groups.

Table 2. Evaluation of the correlation between vitamin D level and levels of age, body mass index, the C1q TNF-related protein, tumor necrosis factor-alpha, total thiol, native thiol, disulfide, total thiol/disulfide, native thiol/disulfide and biochemical parameters.

| | r | p |
|---------------------------|--------|-------|
| Age (years) | 0.144 | 0.209 |
| BMI (kg/m ²) | -0.002 | 0.983 |
| CTRP-9 (ng/L) | 0.781 | 0.001 |
| TNF α (ng/L) | -0.815 | 0.001 |
| TT (μ M) | 0.805 | 0.001 |
| NT (μ M) | 0.852 | 0.001 |
| DIS (μ M) | -0.245 | 0.031 |
| TT/DIS | 0.459 | 0.001 |
| NT/DIS | 0.459 | 0.001 |
| Glucose (mg/dL) | -0.072 | 0.695 |
| Creatinine (mg/dL) | 0.119 | 0.298 |
| AST (U/L) | 0.039 | 0.736 |
| ALT (U/L) | -0.184 | 0.107 |
| Calcium (mg/dL) | 0.053 | 0.644 |
| Magnesium (mg/dL) | -0.116 | 0.351 |
| Phosphorus (mg/dL) | 0.012 | 0.918 |
| PTH (ng/L) | -0.372 | 0.002 |
| fT4 (pg/mL) | 0.163 | 0.154 |
| TSH (mU/L) | -0.115 | 0.318 |
| Total cholesterol (mg/dL) | 0.026 | 0.822 |
| Triglyceride (mg/dL) | 0.014 | 0.906 |
| LDL-K (mg/dL) | 0.072 | 0.531 |
| HDL (mg/dL) | -0.170 | 0.137 |

r: correlation coefficient; BMI: body mass index; CTRP-9: the C1q TNF-related protein; TNF α : tumor necrosis factor-alpha; TT: total thiol; NT: native thiol; DIS: disulfide; AST: aspartate aminotransferase; ALT: alanine aminotransferase; PTH: parathormone; fT4: free tetraiodothyronine; TSH: thyroid-stimulating hormone; LDL-K: low-density lipoprotein-cholesterol; HDL-K: high-density lipoprotein-cholesterol.

DISCUSSION

In addition to the fact that vitamin D deficiency is a very important hormone for bone and calcium metabolism, various studies have shown that it is associated with many important diseases including some cancers, cardiovascular diseases, endothelial dysfunction, metabolic syndrome, infectious and autoimmune diseases. This has led to an increase in the relevant awareness of vitamin D and therefore the use of vitamin D preparations^{4,5,17,19}. Despite this, as a result of the decrease

in the exposure to sunlight due to reasons such as living in a closed environment, the use of high factor creams that protect against the harmful effects of the sun, clothing style, seasonal characteristics, decrease in food quality, insufficient and short-term use of vitamin D preparations for treatment. Vitamin D deficiency is still a common occurrence today²⁰.

In our study, there was a significant difference between vitamin D groups in terms of CTRP-9 level, and a significant positive correlation was found between vitamin D level and CTRP-9 level ($p < 0.05$). CTRP-9 is the closest paralog of adiponectin and shows a high level of amino acid sequence similarity. Both molecules have antiatherogenic, anti-inflammatory, and antiproliferative effects. Additionally, both molecules prevent insulin resistance and endothelial dysfunction²¹. In the literature scan that has been carried out, we did not come across a study that examined the relationship of CTRP-9 and vitamin D. However, there are a limited number of studies examining the relationship between vitamin D and adiponectin, Rambhojan et al., in their study on 117 adolescents, found that adiponectin levels were significantly lower in patients with vitamin D deficiency compared with those without vitamin D deficiency²². However, in the study Mohammedi et al. conducted to the first-degree relatives of 64 type 2 diabetic patients, a significant decrease in adiponectin levels was found after the vitamin D replacement treatment done on the patients²³. In our study, CTRP-9, whose relationship with vitamin D was examined, has high similarities with adiponectin both structurally and functionally, as well as being a different molecule; again in the study of Mohammedi et al.²³, since the effects of vitamin D replacement treatment are evaluated, it may be thought that the results are different. The lower levels of CTRP-9 in vitamin D deficient patients in our study suggest that it may play some mediator roles for increased atherogenesis, endothelial dysfunction, cardiovascular, and inflammatory events as a result of vitamin D deficiency. However, these possible mechanisms should be supported by some comprehensive studies.

In our study, there was a significant difference between vitamin D groups in terms of TNF α level as well as a significant negative correlation between vitamin D level and TNF α level ($p < 0.05$). TNF α has multiple effects on the initiation and maintenance of inflammation, endothelial dysfunction, cytotoxicity, oxidative stress, and cardiovascular events¹³. El Hajj et al. have carried out the study on 88 type 2 diabetics patients after the vitamin D replacement treatment. TNF α levels were found to be significantly lower than before replacement²⁴. In the study conducted by Azizieh et al. on 112 healthy women, participants were divided into two groups according to their vitamin D levels (above and below of 25 nmol/l [10 ng/ml]). Although TNF α level was found to be lower in the group with

vitamin D level below 25 nmol/l, no significant difference was detected between the groups²⁵. In terms of TNF α level, the results of our study are similar to the results of the study conducted by El Hajj et al. However, we considered that the difference between the results of the study by Azizieh et al.²⁵ and this study may be due to the fact that different patient groups have been studied in terms of vitamin D levels. In our study, a significant negative correlation was found between CTRP-9 and TNF α ($p < 0.05$). This suggests that molecules such as CTRP-9 and adiponectin may exert their anti-inflammatory effects by decreasing the level of TNF α .

In our study, while there was a significant difference between vitamin D groups in terms of TT, NT, DIS, TT/DIS, and NT/DIS levels, and a significant positive correlation was found between vitamin D level and TT, NT, TT/DIS, and NT/DIS level, a significant negative correlation was found with DIS level ($p < 0.05$). Dynamic thiol/disulfide balance state has critical roles such as antioxidant defense, detoxification, and apoptosis. It has been determined that oxidative stress, which occurs as a result of the deterioration of this balance in favor of disulfide, plays a role in the pathogenesis of various diseases such as diabetes mellitus, cardiovascular diseases, endothelial dysfunction, and malignancy¹⁴⁻¹⁶. In the literature scan, we came across very few studies examining vitamin D and thiol/disulfide hemostasis in different patient groups. In the results of the study that Mertoglu et al. carried out on 203 healthy children to examine the relationship between vitamin D level and thiol/disulfide, it was found that thiol/disulfide hemostasis was impaired in patients with severe vitamin D deficiency, but this disorder did not improve with vitamin D replacement. As a result of their studies, they stated that it may be more beneficial to increase the endogenous production of vitamin D²⁶. In the study conducted by Alvarez et al. on 693 adults, it was found that vitamin D deficiency was associated with oxidative stress by causing disruption in

glutathione and cysteine thiol/disulfide balance²⁷. The results of our study are also similar to both studies. We considered that the triggering role of vitamin D deficiency in the increase of oxidative stress may be effective in its risk factor for many chronic diseases and metabolic disorders. In addition to the benefits of vitamin D replacement therapy, it is thought that increasing endogenous vitamin D production may provide additional benefits in reducing oxidative stress. However, more accurate results can be obtained with more comprehensive studies on this subject.

Relatively less number of patients and the fact that it was performed only in women were the limitations of this study, whereas the evaluation of several interrelated parameters together was the strength.

CONCLUSIONS

As a result of this study, it was determined that vitamin D deficiency causes a significant decrease in CTRP-9 level and a significant increase in TNF α level, as well as an increase in thiol/disulfide hemostasis in favor of disulfide, and could be a risk factor for increased oxidative stress. These changes might play an intermediary role in many chronic diseases and metabolic disorders that occur in vitamin D deficiency, as well as contributing to the formation of the multifactorial effects of vitamin D. However, these possible roles need to be supported by some comprehensive studies.

AUTHORS' CONTRIBUTIONS

MK: Conceptualization, Investigation, Project administration, Writing – original draft. **AS:** Data curation, Writing – review & editing. **EMG:** Formal analysis, Methodology. **MT:** Resources, Validation. **MC:** Validation, Visualization. **CK:** Data curation, Software. **MZ:** Supervision, Writing – review & editing

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Effect of learning curve on the perioperative course of robotic-assisted laparoscopic donor nephrectomy compared with laparoscopic donor nephrectomy

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SUMMARY

OBJECTIVE: This study was designed to compare the standard and robotic-assisted laparoscopic donor nephrectomy in terms of perioperative course, short-term postoperative outcome, and to evaluate the effect of surgeon's learning curve on these parameters.

METHODS: This was a prospective randomized study including 60 patients (mean age, 47 years; age, 21–72 years; 26 males, 34 females) who had been planned laparoscopic donor nephrectomies in our clinic. For comparison of standard and robot-assisted techniques and to evaluate the impact of learning curve, patients were randomized into three groups by a computer, each group containing 20 patients. Group 1: standard laparoscopic donor nephrectomies; Group 2: the first 20 patients who underwent robot-assisted laparoscopic donor nephrectomy; and Group 3: the next 20 patients who underwent robot-assisted laparoscopic donor nephrectomy.

RESULTS: Operative time was significantly higher in Group 2 (221.0±45.1 min) than both Group 1 (183.5±16.9 min, $p=0.001$) and Group 3 (186.5±20.6 min, $p=0.002$). Similarly, time for laparoscopic system setup was significantly higher in Group 2 (39.5±8.6 min), which contained the first cases of robot-assisted laparoscopic donor nephrectomy where surgeon had least experience than Group 1 (19.3±3.7 min, $p<0.001$) and Group 3 (24.0±9.4 min, $p<0.001$). On the other hand, duration of operation and time for laparoscopic system setup was similar between Groups 1 and 3.

CONCLUSIONS: Learning curve extends the operative time and laparoscopic system setup time in robotic-assisted laparoscopic donor nephrectomy, however, after the learning process was completed, these parameters were similar between robotic-assisted and standard laparoscopic nephrectomy.

KEYWORDS: Laparoscopy. Nephrectomy. Robotics. Renal transplantation. Donor.

INTRODUCTION

Renal transplantation is the most effective treatment for patients with end-stage renal failure. However, the increasing number of patients on the kidney waiting list along with the lack of kidney available for transplantation is a common problem in this area. For this reason, living donor kidney

transplantation has become an increasingly preferred practice¹. The living donor nephrectomy can be done either with conventional open technique or laparoscopic technique, which gained widespread acceptance in the last decades. Although there is no difference between these two techniques in terms of organ function, laparoscopic donor nephrectomy

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is associated with less postoperative pain, faster recovery, and better cosmetic results^{2,3}. For this reason, laparoscopy, which has been first implemented in 1995⁴, has been widely used since then in donor nephrectomy, and increased the number of live kidney donations⁵.

Laparoscopic donor nephrectomy has been performed with the aid of a two-dimensional image obtained with a single camera. However, the da Vinci Robotic Surgical System (Intuitive Surgical Inc., Sunnyvale, CA, USA), developed in recent years, enabled robotic-assisted laparoscopic procedures⁶. In this system, a three-dimensional image with a sense of depth is provided, and the operation area can be enlarged 10–12 times^{7,8}. These advantages offer remarkable comfort to the surgeon who performs the surgery. Previous reports proved that in comparison with standard laparoscopic donor nephrectomy, robotic-assisted donor nephrectomy provides better renal function, lower morbidity, and shorter hospital stay even in the presence of vascular anomalies^{9–12}. However, system and procedural training and practice, commonly referred as learning curve, is needed for surgeons to master the da Vinci Robotic Surgical System^{13–15}.

In this study, we aimed to present our experience with robotic-assisted laparoscopic donor nephrectomy in our clinic, to compare the standard and robotic-assisted laparoscopic donor nephrectomy in terms of perioperative course and short-term postoperative outcome, and to evaluate the effect of learning curve of surgeon on these parameters.

METHODS

This was a prospective randomized study including 60 consecutive patients (mean age, 47 years; age range, 21–72 years; 26 males and 34 females) who had been planned laparoscopic donor nephrectomies in our clinic. Laparoscopic donor nephrectomies were performed by one surgeon who had experience on laparoscopic surgery.

For comparison of standard and robot-assisted techniques and to evaluate the impact of learning curve, patients were randomized into three groups by a computer. Group 1 was formed by standard laparoscopic donor nephrectomies, Group 2 was formed by the first 20 patients who underwent robot-assisted laparoscopic donor nephrectomy, and Group 3 was formed by the latter 20 patients who underwent robot-assisted laparoscopic donor nephrectomy.

The study was conducted in accordance to the latest version of Helsinki Declaration and approved by the Institutional Ethics Committee of Ankara Yıldırım Beyazıt University Faculty of Medicine (no 26,379,996/216). All donors were informed about the study and gave their written consent.

Surgical procedures

Standard laparoscopic donor nephrectomy

While the patient was in the lumbar position and under general anesthesia, a 10 mm port was placed into the abdomen through a 1 cm incision made on the midclavicular line approximately 5 cm from the left side of the umbilicus. Standard gas insufflation was performed to obtain an intra-abdominal pressure of 13 mmHg. Subsequently, under direct vision, two ports were inserted at 10 mm from the left arcus costarum midclavicular line junction and 5 mm from the left lumbar region, respectively. The ureter was dissected until the iliac vascular structure. Suprarenal and gonadal veins were clipped and cut. All the dissections were performed by using LigaSure™ Maryland Jaw Laparoscopic Sealer/Divider (Medtronic, USA). Subsequently, peritoneum was reached by cutting the percutaneous and subcutaneous fat tissue and muscles with a transverse incision of about 5 cm in the lower quadrant. When renal transplant patient is ready, ureter was cut after placing Hem-o-lok® clip (Teleflex Incorporated, Wayne, PA, USA). Afterwards, renal artery and renal vein were cut by using vascular endoscopic stapler (Endo-GIA, Covidien PLC, USA). The kidney was taken out from the incision in the left lower quadrant.

Robotic-assisted laparoscopic donor nephrectomy

While the patient was in the lumbar position and under general anesthesia, the peritoneum was reached by cutting the percutaneous and subcutaneous fat tissue and muscles through a transverse 5 cm incision in the lower left quadrant. A 15 mm port was placed, and standard gas insufflation was performed to obtain an intra-abdominal pressure of 13 mmHg. An 8 mm port was placed into the abdomen through a 1 cm incision made on the midclavicular line approximately 5 cm from the left side of the umbilicus. Subsequently, under direct vision, two ports were inserted at 8 mm from the left arcus costarum midclavicular line junction and 8 mm from the left lower quadrant, respectively. Ports were matched with Da Vinci robot. The ureter was dissected until the iliac vascular structure. Left suprarenal and gonadal veins were clipped and cut. When renal transplant patient is ready, ureter was cut after placing Hem-o-lok® clip (Teleflex Incorporated). Afterwards, renal artery and renal vein were cut by using vascular endoscopic stapler (Endo-GIA, Covidien PLC). The kidney was taken out from the incision in the left lower quadrant.

Outcome measures

Patients were followed up postoperatively until discharge from hospital. The following pre-, peri-, and postoperative parameters were recorded: age, gender, body mass index (BMI), previous abdominal operations, preoperative donor kidney size

by ultrasonography, the American Society of Anesthesiologists (ASA) physical status classification, laparoscopic system setup time, number of renal arteries, complications, conversion to open nephrectomy, operative time, primary warm ischemia time, and drain volume on the first postoperative day.

Statistical analysis

Study data were summarized by using descriptive statistics, which were mean and standard deviation for continuous variables, and frequency and percentage for categorical variables. Shapiro-Wilk's test was used for testing normal distribution. Since study data were normally distributed, the significance of the difference between the independent groups was examined with the Student's *t* test for two groups and by the analysis of variance test for more than two groups. Post hoc Tukey test was used to make pair-wise comparisons between groups. The analysis of categorical data in cross tables was performed by the chi-square or the Fisher's exact test. Analysis of the data was performed by the IBM SPSS Statistics 20.0 software (IBM Corporation, Armonk, NY, USA). The results were considered statistically significant when $p < 0.05$.

RESULTS

Study groups were comparable with respect to gender, age, and BMI ($p > 0.05$). APA physical status score was 2 or lower for all donors, indicating that patients were either healthy or had a mild systemic disease (Table 1). A total of 10 patients had a history for

a previous abdominal operation (cesarean section in 5 patients, total abdominal hysterectomy+bilateral salpingo-oophorectomy in 2 patients, inguinal hernia repair in 2 patients, and laparoscopic cholecystectomy in 1 patient). Study group did not show significant difference in terms of APA score and previous abdominal operation (Table 1). Double renal arteries were present in 7 (11.7%) patients (3 in Group 1, 26 in Group 2, and 2 in Group 3; $p = 0.944$). Conversion to open nephrectomy was required for two patients, both in Group 2, for bleeding in one patient and difficulty in anatomic dissection in other one (Table 1).

Only one patient, who was among the first cases of robot-assisted laparoscopic donor nephrectomy, had a postoperative complication, chylous fistula. None of the other donors had any postoperative complication (Table 1).

There was also no difference between study groups in terms of donor or remnant kidney size, primary warm ischemia time, and drain volume on first postoperative day (Table 2). However, duration of operation was significantly higher in Group 2 (221.0 ± 45.1 min) than both Group 1 (183.5 ± 16.9 min, $p = 0.001$) and Group 3 (186.5 ± 20.6 min, $p = 0.002$). Similarly, time for laparoscopic system setup was significantly higher in Group 2 (39.5 ± 8.6 min), which contained the first cases of robot-assisted laparoscopic donor nephrectomy where surgeon had least experience than both Group 1 (19.3 ± 3.7 min, $p < 0.001$) and Group 3 (24.0 ± 9.4 min, $p < 0.001$; Table 2). In contrast, duration of operation and time for laparoscopic system setup was similar between Groups 1 and 3 (Table 2).

Table 1. Demographic and clinical characteristics of study groups (categorical variables).

| | | Group 1 Standard LDN (n=20) | Group 2 First cases of robot-assisted LDN (n=20) | Group 3 Later cases of robot-assisted LDN (n=20) | p |
|--------------------------------|---|-----------------------------------|--|--|-------|
| Sex (male/female) | | 9/11 | 9/11 | 8/12 | 0.865 |
| ASA physical status | 1 | 0 (0%) | 2 (10.0%) | 1 (5.0%) | 0.844 |
| | 2 | 20 (100.0%) | 17 (85.0%) | 19 (95.0%) | |
| | 3 | 0 (0%) | 1 (5.0%) | 0 (0%) | |
| Previous abdominal operation* | | 3 (15.0%) | 4 (20.0%) | 3 (15.0%) | 0.937 |
| Conversion to open nephrectomy | | 0 (0%) | 2 [†] (10.0%) | 0 (0%) | 0.985 |
| Rate of complications | | 0 (0%) | 1 [‡] (5.0%) | 0 (0%) | 0.985 |
| Number of renal arteries | 1 | 17 (85.0%) | 18 (90.0%) | 18 (90.0%) | 0.944 |
| | 2 | 3 (15.0%) | 2 (10.0%) | 2 (10.0%) | |

LDN: laparoscopic donor nephrectomy; ASA: The American Society of Anesthesiologists. According to ASA physical status classification, ASA 1 indicates a normal healthy patient and ASA 2 indicates a patient with mild systemic disease, and ASA 3 indicates a patient with severe systemic disease that is a constant threat to life.

*2 cesarean sections, 1 inguinal hernia repair in Group 1; 2 cesarean sections, 2 total abdominal hysterectomy+bilateral salpingo-oophorectomy in Group 2; and 1 cesarean sections, 1 inguinal hernia repair, 1 laparoscopic cholecystectomy in Group 3; [†]Conversion to open nephrectomy was performed for bleeding in one patient, and difficulty in anatomic dissection in another patient; [‡]Chylous fistula.

Table 2. Clinical, operative, and postoperative findings of study groups (continuous variables).

| | Group 1 Standard LDN (n=20) | Group 2 First cases of robot-assisted LDN (n=20) | Group 3 Later cases of robot-assisted LDN (n=20) | p value for pair-wise comparison | | | |
|--|--------------------------------------|---|---|-------------------------------------|----------------------|----------------------|-------|
| | | | | Groups 1 versus 2 | Groups 1 versus 3 | Groups 2 versus 3 | |
| Age (years) | 44 (21–69) | 40 (24–72) | 39 (26–68) | - | - | - | |
| Body mass index (kg/m ²) | 25.8±4.0 | 28.1±4.2 | 27.6±4.6 | 0.218 | 0.317 | 0.936 | |
| Donor kidney size on preoperative US (mm) | Length | 105.4±8.2 | 106.7±8.9 | 104.9±8.3 | 0.886 | 0.981 | 0.789 |
| | Width | 47.4±6.0 | 45.7±5.8 | 45.6±7.1 | 0.659 | 0.653 | 0.985 |
| Primary warm ischemia time (s) | 115.0±14.4 | 96.6±19.7 | 106.7±21.0 | 0.635 | 0.342 | 0.205 | |
| Laparoscopic system setup time (min) | 19.3±3.7 | 39.5±8.6 | 24.0±9.4 | <0.001 | 0.131 | <0.001 | |
| Operative time (min) | 183.5±16.9 | 221.0±45.1 | 186.5±20.6 | 0.001 | 0.947 | 0.002 | |
| Drain volume on 1st postop day (mL) | 53.5±25.4 | 67.0±36.9 | 66.5±37.3 | 0.418 | 0.415 | 0.999 | |

LDN: laparoscopic donor nephrectomy; US: ultrasonography. Data are given as mean (range) or mean±standard deviation.

DISCUSSION

In this study, we primarily showed that learning curve extends the operative time and laparoscopic setup time in robotic-assisted laparoscopic donor nephrectomy.

Laparoscopic donor nephrectomy has become the procedure of choice in living kidney donor transplantation¹⁶. Since the publication of first series of robotic-assisted laparoscopic donor nephrectomy, robotic-assisted surgery has become the most preferred technique with various advantages to surgeon and patient^{7,17}. It improves patient safety with minimal rate of complications and conversion to open surgery and provides short hospital stays allowing donor patient to return normal life earlier and decreasing total cost of procedure^{11,18}. Recent studies even improved the cosmetic outcomes of robotic-assisted donor nephrectomy by using single-site platform, however, there is still need for further study to evaluate benefit of this technique considering its increased cost and complexity^{19,20}. Although recent advances in robotic-assisted surgery also allowed shortening of learning curve of surgeons, it is necessary to be performed by a well-trained and experienced surgical team in order to obtain best surgical and clinical outcome¹⁸.

Horgan et al.¹⁸ evaluated 214 robotically assisted donor nephrectomies and found that only 4 patients converted to open surgery, the mean warm ischemia time was 98 s and the operative time was 201 min for the first cases and 103 min for the last cases ($p<0.001$), and complications decreased significantly after the first cases. Similarly, in our study, conversion to open nephrectomy was required for two patients, both being the first cases of robot-assisted laparoscopic donor nephrectomy, for bleeding in one patient and difficulty in anatomic dissection in other one. In this group, only 1 patient had a postoperative complication, which was chylous fistula. None of the patients in standard laparoscopy group or later cases of robot-assisted laparoscopic donor nephrectomy group

experienced any postoperative complications. The warm ischemia time was 96.6 s for first cases robot-assisted laparoscopic donor nephrectomy, which was not significantly different than standard laparoscopy. Laplace et al.¹⁰ reported that in 100 cases of robotic-assisted laparoscopic living donor nephrectomy, mean operative time and warm ischemia time were 174 min and 4.8 min, respectively. In the present study, although the operative time was longer in first robot-assisted cases (221.0±45.1 min) than standard laparoscopy cases (183.5±16.9 min, $p=0.001$), it was significantly shortened in late robot-assisted cases (186.5±20.6 min) and became similar to standard laparoscopy group. Similarly, time for laparoscopic system setup was significantly higher in first robot-assisted cases (39.5±8.6 min) than standard laparoscopy group (19.3±3.7 min), but in late robot-assisted cases this duration was not significantly different from standard laparoscopy group (24.0±9.4 min). These findings suggest that as the experience of surgeon increases, time required for operation and laparoscopic system setup does not show significant difference between standard and robot-assisted laparoscopic donor nephrectomy. Our findings was also similar to the finding of a recent study by Yang et al.²¹.

The main limitation of our study was the lack of assessment of critical clinical outcomes for donor nephrectomy surgery such as renal function, morbidity, and hospital stay, which limits effective comparison of robotic-assisted donor nephrectomy and standard laparoscopic donor nephrectomy.

CONCLUSIONS

As the experience of surgeon increases in the robotic surgery, the time needed for laparoscopic system setup and operation gets shorter approaching standard laparoscopic donor nephrectomy. Our findings did not show a clear advantage of

robot-assisted laparoscopic donor nephrectomy over standard laparoscopic nephrectomy during perioperative and short-term postoperative course. Further cost-benefit studies are needed to conclude on the advantages of robot-assisted laparoscopic donor nephrectomy.

AUTHORS CONTRIBUTIONS

EGD: Conceptualization, Writing – original draft, Writing – review & editing. **IK:** Data curation. **OP:** Formal analysis. **MO:** Project administration. **BD:** Software. **SK:** Methodology. **MK:** Supervision, Investigation.

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Neutrophilic inflammation in stroke

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INTRODUCTION

Stroke is one of the main diseases affecting society, i.e., in Brazil, it is the second leading cause of death and the first in the case of disabilities. From a neuroanatomical perspective, it can manifest itself in two ways, namely, hemorrhagic and ischemic¹. In both cases, neuronal tissue can be damaged, which results in the lysis of tissue cells¹. As a result of this lysis, some substances are released in the injured territory, thereby initiating a local inflammatory process²⁻⁴.

Inflammation is the process by which the immune system tries to eliminate an offending agent by means of different mechanisms, in an attempt to restore the body's homeostasis⁵.

The neuroinflammation in stroke occurs due to bleeding or ischemia. Neurons and glial cells suffer from the effects of ischemia and exhibit lysis, thus releasing pathogen-associated molecular patterns (PAMPs) and damage-associated molecular patterns (DAMPs), which in turn activate microglia²⁻⁴. Microglia release cytokines and chemokines, attracting inflammatory cells to the central nervous system (CNS)². Different cells infiltrate into the CNS within a few hours, increasing brain damage and thus worsening the prognosis^{2,3}.

OBJECTIVE

This study aims to review the neutrophilic inflammatory in stroke.

METHODS

A narrative review of the literature over the last 20 years (2000–2020) was carried out. The review was based on the following descriptors: stroke, inflammation, CNS, neutrophils, microglia, and cytokines. Inclusion criterion is as follows: only articles published in Portuguese or English were considered. The following

bibliographic databases/search engines were used: LILACS, SciELO, and PubMed.

RESULTS

Neutrophils in Stroke

It became evident that the presence of a large number of neutrophils is related to more severe strokes, with worse clinical progression².

Neutrophils are the first cells of the immune system to reach the CNS following a stroke². Their peak concentration is reached, between the first and third days after the stroke, modifying the injured environment⁴. This significant increase is due to the release of cytokines by local cells, such as the microglia that have become activated shortly after injury was sustained. Neutrophils reach the CNS in two ways as follows: passively, after the loss of vessel integrity in the ischemic core or through the leptomeninges; or actively, by means of the transendothelial migration of post-capillary venules reaching to the perivascular spaces following ischemia⁴.

After neutrophil migration, these cells become activated. They start to release proteases, elastases, reactive oxygen species (ROSs), and neutrophil extracellular traps (NETs)². Such mechanisms, as well as the release of more cytokines by the cells at the site, accelerate the inflammatory process, aggravating the ischemic process and causing additional damage².

NETs, in addition to their role in the attempt to eliminate pathogens, can activate the coagulation cascade, which in turn generates thrombi and worsens ischemia. In contrast, platelets also lead to the release of NETs when they come into contact with neutrophils, through the action of platelet P-selectin, thus generating a self-activation cycle⁶.

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Among neutrophil-released proteases, metalloproteinases (MMP) stand out since they can degrade extracellular components such as laminae, fibronectin, and type IV collagen. Metalloproteinase-9 (MMP-9), in addition to degrading these components, can lead to injuries to the blood–brain barrier, rendering brain microvilli fragile and predisposing them to rupture and hemorrhage.

The elastase released by neutrophils acts in a similar way to that of MMPs. Neutrophil elastase is released during inflammation and has some paracrine effects as follows: it acts on the platelet activating factor; increases the release of CXCL-8 by local endothelial cells; degrades structural matrix proteins, such as elastin, collagens, and fibronectin, resulting in increased vascular permeability and hemorrhage in non-brain tissues; degrades additional substrates of the extracellular matrix, interrupting the homeostasis of neurons and glial cells; activates clotting during systemic infections; mediates the expression of the intracellular adhesion molecule-1 (ICAM-1) in CD11+/CD18+ endothelial cells and neutrophils; and regulates the transendothelial migration of leukocytes into peripheral venules in response to proinflammatory stimuli. Inhibition and genetic exclusion of neutrophilic elastase result in less edema, interruption of damage to the blood–brain barrier, and reduced leukocyte adhesion to cortical venule endothelial cells, resulting in reduced infarction volume⁷.

Neutrophil Phenotypes in Stroke

In murine models of sepsis⁸ and cancer⁹, the existence of neutrophils with proinflammatory and anti-inflammatory characteristics, called N1 and N2, respectively, was demonstrated. N1 neutrophils have been described as CD11b^{low} cells, which produce IL-12 and exhibit cytotoxic activity against tumor cells, whereas N2 neutrophils, CD11b^{high}, produce IL-10, ROS and have the ability to inhibit TCD8⁺ lymphocyte activation. More recent studies have shown that N1 and N2 neutrophils can be found in individuals with cancer¹⁰, severe inflammation¹¹ or vascular diseases¹².

N2 neutrophils can also be characterized by the expression of arginase I (ArgI), CCL2, CCL5, Ym1, and mannose receptor (CD206)¹³. ArgI leads to L-Arg depletion, thereby suppressing the functions of T lymphocytes, since T cells fail to express the CD3 subunit, necessary for their transduction and proliferation, thus causing immunosuppression¹⁴. Ym1, in turn, is associated with matrix reorganization, wound healing, negative regulation of inflammation; the expression thereof in brain has been associated with neuroprotection. The expression and secretion of Ym1 by neutrophils is important in neuroprotection after cerebral ischemia. Finally, CD206 serves as a marker antigen for the neuroprotective phenotype¹³.

N2 neutrophils have some peculiarities, such as the presence of the Peroxisome Proliferator-Activated Receptor-gamma (PPAR- γ) receptor, which is associated with neuroprotection and inflammation resolution after stroke, since it induces neutrophil polarization toward the N2 phenotype. The PPAR- γ receptor also decreases microglia/macrophage activation markers and neutrophil infiltration in the brain, two or three days after stroke onset³. In addition, activation of this receptor leads to an earlier infiltration of neutrophils, as well as dispersion of this cell type after about two days. The N2 phenotype promotes its own clearance by means of phagocytosis, since the activation of its receptor increases neutrophil clearance. N2 phagocytosis results in the release of anti-inflammatory mediators, contributing to create a favorable scenario for the brain's recovery process following stroke. However, the attempt so far to treat patients with the PPAR- γ agonist has failed to induce neuroprotection by neutrophil depletion¹³.

Other important receptors involved in the recognition of neutrophil phenotypes are TLRs¹⁵. Such receptors, in conjunction with others, are responsible for discriminating among various pathogen recognition patterns. They are present in different cells of the immune system, such as neutrophils, macrophages, and monocytes¹⁶. In neutrophils, TLR4 is important since it also plays a role in neutrophils' polarization and function. The absence of TLR4 increases the infiltration of neutrophils and induces a polarization of these cells toward the N2 phenotype. In general, TLR4 inhibition or blockade reduces inflammation and ischemic damage, preventing hemorrhagic transformation induced by tissue plasminogen activator (t-PA), a possible treatment for stroke², stimulating neutrophils toward cytoprotective phenotypes¹⁵.

Microglia and Neutrophilic Inflammation in Stroke

Microglia, activated by DAMPs and PAMPs, release cytokines and chemokines that attract immune cells to the affected site². In addition to this attractive effect, microglia have the function of controlling the concentration of neutrophilic infiltrate in the area injured by the stroke. This control is maintained by phagocytosis, which is in turn performed by neutrophils that are in excess. Thus, microglia remove neutrophils from the parenchyma, perivascular, and subpial spaces following brain ischemia⁴.

At the periphery of the infarction, microglia continue to proliferate and increase in number. In this way, these cells phagocytose neutrophils present at the periphery of the injury, preventing the accumulation thereof in that region. Neutrophils in the core of the lesion do not undergo clearance, which results in their accumulation in the core of the stroke injury. For these

reasons, microglial dysfunction and lysis are associated with the accumulation of neutrophils in injured brain tissue⁴, worsening the prognosis of stroke patients. The microglia recognize both endothelial damage and neutrophilic invasion, and in a cooperative fashion, microglia and the blood–brain barrier form cytoplasmic processes that physically protect activated endothelia and capture infiltrated neutrophils¹⁷.

Mast cells and Neutrophilic Inflammation in Stroke

Mast cells represent the first line of defense against toxic agents and brain damage. They contain granules with potent preformed substances as follows: vasoactive (histamine and bradykinin), anticoagulant (heparin), proteolytic (tryptase and chymase), and chemotactic factors, which are released upon their activation. This activation has two phases as follows: secretion of preformed granules and *de novo* synthesis of new granules having vasoactive mediators, chemotactic factors (prostaglandins, platelet activation factor, and leukotrienes), and cytokines (tumor necrosis factor [TNF])¹⁸.

Mast cells release chemotactic factors, platelet-activating factor, TNF, IL-4, IL-5, and CXCL-8¹⁸. These substances attract neutrophils, macrophages, and eosinophils.

Mast cells also participate in the regulation of early post-ischemic deficiency, brain swelling, and inflammation, in addition to MMP-2 and MMP-9, which degrade type IV collagen. The constituents of mast cell granules, especially histamine, heparin, and bradykinin, produce microcirculatory effects, and the modulation of their release during ischemia influences the extent of ischemic injury¹⁹.

Interleukins 1, 6, and 10 in Stroke

As in other inflammatory processes, several cytokines are involved in stroke and, in particular, IL-1. This cytokine is an important mediator of acute brain injury and regulates inflammation during the host's defense response. IL-1 also induces the expression of a series of mediators, several of which form part of the systemic inflammatory response after stroke, especially acute phase proteins¹⁵. Thus, IL-1 increases ischemic damage to an extent that is similar to that of lipopolysaccharide, in addition to exacerbating cerebral edema and worsening stroke¹⁸.

IL-1 acts synergistically with IL-6 and chemokines, especially CXCL-8, resulting in neutrophil mobilization and greater cortical infiltration, even before the changes that are brought about by ischemic damage. Therefore, acute systemic inflammatory stimuli by IL-1 and IL-6 are harmful after a stroke, with IL-1 being a critical mediator in this condition¹⁹.

Conversely, IL-10, an immunoregulatory cytokine synthesized by CNS cells, inhibits IL-1 production by decreasing

the expression of IL-1 receptors and has been related to an improvement in the ischemic condition during the acute phase of stroke, as our group has previously described²⁰.

Stroke Recurrence

Patients who had a stroke are more likely to suffer from another stroke when compared with individuals without this history³. Neutrophils are associated with this recurrence, as they interact with clotting factors and platelets, activating the coagulation cascade shortly after ischemia^{2,3}. In addition, the intravascular accumulation of neutrophils prevents the local blood flow, thereby generating a new ischemia²¹.

A factor that increases the chance of recurrence is systemic infections, either acute or chronic ones, as they are triggers for the occurrence of stroke and are associated with a less favorable clinical outcome. Infections modulate the incidence of stroke and the functional recovery of the affected area. Systemic inflammatory stimuli act in conjunction with the ischemic condition, amplifying innate systemic immune responses and leading to exacerbated brain damage. Hence, the systemic inflammatory pathways provide a point of convergence and synergism when the stroke coincides with an associated inflammatory stimulus¹⁹.

Inflammatory Markers Associated with the Prognosis of Stroke Patients

Cerebral edema is indicative of a poor stroke prognosis and affects two thirds of stroke patients¹². The greater number of neutrophils is related to greater severity, size of ischemic infarction, greater area of cerebral infarction, a tendency to hemorrhage in stroke. In addition, they can bring about a second ischemic wave, further worsening tissue damage caused by the first wave, which is predictive of a worse prognosis. A high neutrophil count at hospital admission is associated with an increased risk of a new stroke in a high-risk population. Death, about three months after stroke, may be associated with the interaction among endothelium, platelets, and NETs hyperactivity.

Another relevant marker is the neutrophil–lymphocyte ratio, a marker for an easy detection of systemic inflammation. A high neutrophil–lymphocyte ratio is associated with a worse prognosis and predicts mortality within a short period of time. The neutrophil–lymphocyte ratio is correlated with the infarction volume in the anterior circulation stroke but not with that in the posterior circulation stroke²².

Some cytokines can assist in the prognosis of stroke patients' progression. The large increase in cytokines indicates a poor prognosis, since they are associated with the maintenance of inflammation and attraction of cells, such as neutrophils, to the ischemic region¹⁸. IL-6, as well as C-reactive protein, is probably ominous inflammation markers as far as stroke

Chart 1. Inflammatory components in stroke.

| Components | Characteristics |
|-------------|---|
| Neutrophils | Large number is related to more severe strokes and worse clinical progression. |
| Microglia | Dysfunction and lysis are associated with accumulation of neutrophils in central nervous system. |
| Mast cells | Participate in the regulation of post-ischemic deficiency, brain swelling and inflammation. |
| Cytokines | Interleukin-1 and interleukin-6: increase the inflammatory process; interleukin-10: decreases the inflammatory process. |

progression is concerned²¹. Conversely, high levels of IL-10 were correlated with a better prognosis in the acute phase of stroke²⁰. The components involved in stroke and discussed in this article are shown in Chart 1.

CONCLUSION

Having the knowledge about the neutrophilic inflammatory process that occurs in stroke has attracted increasing interest,

especially as it is a means of decreasing and improving prognosis. In the near future, it is even anticipated to allow for stroke prevention.

AUTHORS' CONTRIBUTIONS

SCG, TM, RJG, WCNF: Conceptualization, Data curation, Formal Analysis, Writing – original draft, Writing – review & editing. All authors contributed equally to this study.

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Systematic review of finasteride effect in women with hirsutism

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INTRODUCTION

Hirsutism is the most frequent complaint of women during their reproductive lifetime. It negatively impacts their perception of femininity, wellness, and quality of life. Therefore, antiandrogen therapy is important to mitigate the consequences of such a condition¹⁻³.

Chronic use of antiandrogens, for example, cyproterone, spironolactone, and flutamide, may cause, however, several side effects like hepatotoxicity, depression, anxiety, gastrointestinal dysfunction, and menstrual disorders. These affections may require the discontinuance of long-term treatments⁴. There are, nevertheless, some authors who have suggested that one of the antiandrogen drugs, i.e., finasteride, exerts a milder effect, making it a promising medication for long-term use².

Finasteride inhibits 5 α -reductase type 2, the action of which competitively inhibits testosterone conversion into dihydrotestosterone (DHT), a potent stimulator of loss of hair from scalp skin follicles but of growth of body hair. Thus, the action of the drug may reduce hirsutism⁵. Nevertheless, it is necessary to compare the literature data to assess the true effectiveness and safety of finasteride use in the treatment of women with idiopathic hirsutism and polycystic ovary syndrome (PCOS).

METHODS

A systematic review of computer-collected research data was carried out using the Medline and PubMed databases. The keywords used in the search were hirsutism and finasteride.

The review included only randomized clinical trials in which finasteride was used in the treatment of women with hirsutism, idiopathic hirsutism, or related to PCOS scored with the

modified Ferriman–Gallwey (F–G) scale^{6,7}. In addition, finasteride action had to be set against that of other antiandrogen medications and/or placebo treatment.

All studies were excluded which were not randomized clinical trials (e.g., nonrandomized clinical trials, case series, case controls, literature review, etc.), which involved women whose hirsutism was brought on by other causes (e.g., steroid-producing tumors, hyperprolactinemia, enzyme deficiency of the adrenal glands, Cushing's syndrome, and thyroid dysfunction), which compared finasteride with treatments other than oral antiandrogen medications (e.g., cosmetic treatments and GnRH analogs), and which were not in Portuguese, English, or Spanish. This initial screening was followed by reassessment of the remaining studies leading to the exclusion of those with an F–G score lower than 8 and those with unstated causes of hirsutism. Adverse effects resulting from finasteride use were deemed secondary outcomes.

Research was limited to women and covered the years from 1990–2015.

The studies that were selected fell into three categories:

1. comparison of finasteride and placebo and of different finasteride regimens,
2. comparison of finasteride and other medications [i.e., spironolactone, flutamide, and cyproterone acetate (CPA) with ethynyl estradiol (EE)], and
3. comparison of finasteride associations and finasteride was associated with in isolation (i.e., spironolactone and CPA with EE).

A total of 75 papers were retrieved from the Medline and PubMed databases. No studies were found before 1990 using the aforementioned descriptors. Figure 1 shows the study flowchart.

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The initial screening left out 55 studies for two main reasons: they were observational studies or literature reviews. A second screening excluded three articles: one for not meeting the hirsutism criteria adopted in this review and the other two for not stating the causes of hirsutism. Our analysis followed the PRISMA Statement for systematic reviews.

RESULTS

The results were classified into three categories:

1. comparison of finasteride and placebo and different finasteride regimens (n=4),
2. comparison of finasteride and other medications (i.e., spironolactone, flutamide, and CPA with EE; n=9), and
3. comparison of finasteride associations and finasteride was associated with in isolation (i.e., spironolactone and CPA with EE; n=4).

The two studies in which finasteride was compared with placebo showed that hirsutism improved with finasteride^{8,9},

especially after six months of treatment. No improvement was observed in the placebo groups, and no changes in libido were observed in either group. Ciotta et al.⁶ reported side effects in both the study group and the placebo group. In the study by Lakryc et al.⁹, there were no reports of severe side effects, but four patients dropped out owing to diarrhea and nausea (n=3) and allergic symptoms (n=1). After the third month of treatment, 17% of the total patients from both groups complained about dizziness, and most of them were from the finasteride group.

The comparison of different finasteride dosages is included in Table 1. Bayram et al. found no differences in the final F-G score up to six months of treatment. Thereafter, the larger dose of 5 mg/day produced better results than the smaller dose of 2.5 mg/day. The quantity and intensity of side effects were greater with the dose of 5 mg; the main sequelae were dry skin, reduction in libido, headache, and gastrointestinal dysfunction¹⁰. It appears that, in a 10-month period, intermittent use of 2.5 mg of finasteride has the same effect as continuous administration of the same dose of the drug on the F-G score but with smaller adverse effects¹¹.

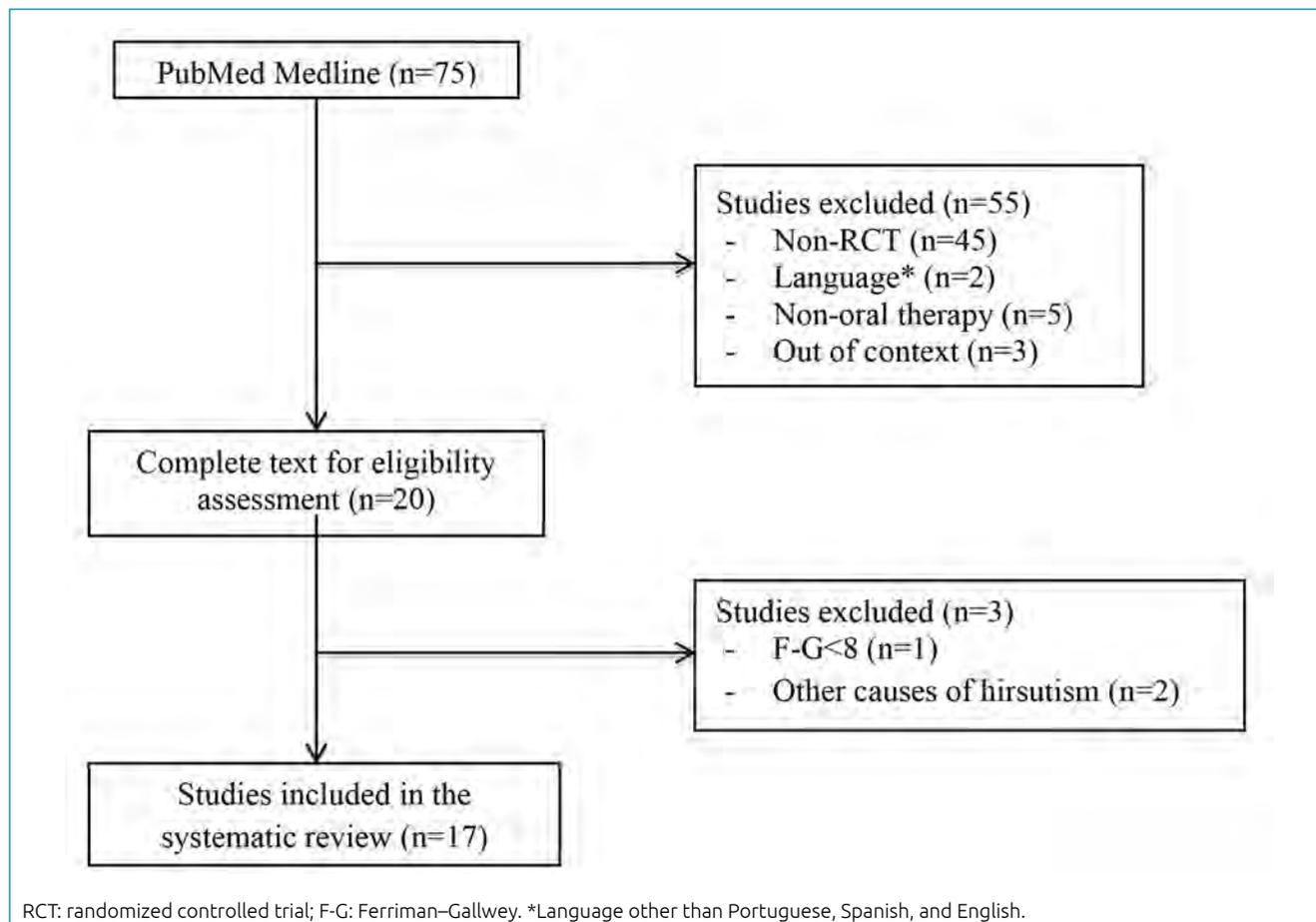


Figure 1. Flowchart of study selection.

Table 1. Effects of finasteride on hirsutism: comparing finasteride with other drugs.

| Author | Type of clinical trial | Duration (months) | Treatment | Age (years) | Results | Adverse effects* |
|-------------------------------|---|-------------------|--|-------------|----------------------------|--|
| Wong et al. ¹² | Randomized and without placebo | 6 | Finasteride ^a (n=9) versus spironolactone ^b (n=5) | 15–40 | Finasteride spironolactone | No side effects |
| Ciotta et al. ²¹ | Randomized single-blind | 9 | Finasteride ^a (n=9) versus placebo (n=9) | 20.6±0.43 | Finasteride>placebo | Headache (n=4) and depression (n=2) |
| Lakryc et al. ^{9,α} | Randomized double-blind; placebo-controlled | 6 | Finasteride ^b (n=12) versus placebo (n=12) | 19–40 | Finasteride>placebo | No severe adverse effects |
| Bayram et al. ¹⁰ | Randomized and without placebo | 12 | Finasteride 2.5 mg/day (n=29) versus finasteride 5 mg/day (n=27) | 18–41 | 5 mg/day>2.5 mg/day | 2.5 mg: dry skin (n=1), reduction in libido (n=1), headache (n=2), and gastrointestinal disorders (n=1). 5 mg: dry skin (n=3), reduction in libido (n=4), headache (n=1), and gastrointestinal disorders (n=4) |
| Tartagni et al. ²³ | Randomized and without placebo | 10 | Finasteride 2.5 mg/day (n=19) versus 2.5 mg every three days (n=19) | 18–34 | Continuous intermittent | Continuous: small reduction in libido (n=1, 5 months; n=2, 10 months) and mild and transient gastrointestinal discomfort (n=1). Intermittent: no adverse effects |
| Erenus et al. ¹⁴ | Randomized and single blind | 9 | Finasteride ^a (n=7) versus spironolactone ^b (n=9) ^α | 21.3±4.6 | Finasteride<spironolactone | No side effects |
| Falsetti et al. ¹⁸ | Randomized and without placebo | 6 | Finasteride ^a (n=22) versus flutamide ^c (n=22) | 22.9±4.9 | Finasteride flutamide | Dry skin (n=6), reduction in libido (n=3), and headache (n=2) |
| Sahin et al. ²⁴ | Randomized and without placebo | 9 | Finasteride ^a (n=21) versus CPA+EE ^d (n=21) | 21.8±0.97 | Finasteride<CPA+EE | No effects |
| Falsetti et al. ²⁰ | Randomized and without placebo | 12 | Finasteride ^a (n=55) versus flutamide ^e (n=52) ^γ | 18–29 | Finasteride<flutamide | Dry skin (n=13), headache (n=7), and reduction in libido (n=6) |

Continue...

Table 1. Continuation.

| Author | Type of clinical trial | Duration (months) | Treatment | Age (years) | Results | Adverse effects* |
|-------------------------------|--|-------------------|--|-------------|--|---|
| Falsetti et al. ²⁰ | Randomized and without placebo | 12 | Finasteride ^a (n=23) versus flutamide ^e (n=21) ^δ | 18–29 | Finasteride<flutamide | Dry skin (n=5), headache (n=3), and reduction in libido (n=2) |
| Fruzetti et al. ¹⁵ | Randomized and without placebo | 12 | Finasteride ^a (n=14) versus CPA+EE ^e (n=13) versus flutamide ^e (n=15) | 16–29 | Finasteride CPA+EE flutamide | No side effects |
| Moggetti et al. ¹³ | Randomized, double-blind, and placebo-controlled | 6 | Finasteride ^a (n=10) versus spironolactone ^b (n=10) versus flutamide ^g (n=10) versus placebo (n=10) | 20.4±0.5 | Finasteride spironolactone flutamide>placebo | Finasteride: transient sensation of bloating (n=1) |
| Beigi et al. ¹⁶ | Randomized and without placebo | 9 | Finasteride ^a (n=20) versus CPA+EE ^h (n=20) | 16–29 | Finasteride CPA+EE | No side effects |

*Adverse effects of finasteride. ^aLoss of four cases due to allergy (n=1) plus nausea and diarrhea (n=3). Finasteride dosages: ^a7.5 mg/day; ^b5 mg/day. *Adverse effects of finasteride. ^cThirteen patients in the finasteride group and six in the spironolactone group dropped out of the study at six months because of poor efficacy of treatment (n=13 in the finasteride group, n=3 in the spironolactone group) or inadequate response according to the patient's opinion and the Ferriman–Gallwey score (n=3 in the spironolactone group). ^dTwo patients dropped out in the flutamide group, one due to nausea and vomiting, and one because of high transaminase levels. ^eThree patients dropped out in the flutamide group, two because of high transaminase levels after six months, and one at seven months due to nausea and vomiting. ^fTwo women (8.7%) in the flutamide group dropped out of the study at seven months: one (4.3%) because of nausea and vomiting and another (4.3%) because of high transaminase levels. CPA: cyproterone acetate; EE: ethinyl estradiol. Dosages: ^a5 mg/day of finasteride. ^b100 mg/day of spironolactone. ^c150 mg/day of flutamide two times. ^d2 mg/day of CPA plus 35 µg/day of EE on days 5–25. ^e250 mg/day of flutamide two times. ^f25 mg/day of CPA on days 1–10 of the menstrual cycle plus 20 µg of EE every day for 21 days. ^g250 mg/day of flutamide. ^h25 mg/day of CPA on days 5–14 plus 20 µg/day of EE on days 5–25.

Three studies compared finasteride with spironolactone (Table 1). In all these studies, hirsutism decreased with both drugs from baseline measurements. Wong et al.¹² and Moggetti et al.¹³ reported that finasteride was not superior to spironolactone. However, Erenus et al.¹⁴ observed that the change in the percentage in the hirsutism score with spironolactone treatment was significantly higher than that with the finasteride treatment (at six and nine months). Despite the significant results, after the sixth month, 19 out of the 40 women in the study comprised initially dropped out because of inadequate responses. Additionally, five patients from the spironolactone group could not be included in the final analysis at nine months owing to irregular uterine bleeding and the need for hormonal contraceptive use.

Neither Wong et al.¹² nor Erenus et al.¹⁴ reported adverse effects of finasteride use. Moggetti et al.¹³ reported one patient with a transient sensation of overall bloating. Adverse effects, particularly nausea and abnormal uterine bleeding, were reported with the use of spironolactone^{12–14}, but Wong et al.¹² did not report any side effects with its use.

Two of the studies comparing finasteride with CPA associated with EE; Table 1) found no significant differences between

the groups^{15,16}. Sahin et al.¹⁷ showed the CPA+EE association was more effective than finasteride after six months of treatment. No adverse effects were reported during the studies^{15–17}.

Five studies were reviewed comparing finasteride with flutamide (Table 1). All of them showed a significant reduction in the F–G score with both medications^{13,15,18–20}. In three of them, Falsetti et al.¹⁸, Fruzzetti et al.¹⁵, and Moggetti et al.¹³ did not find any differences between the two treatments. Falsetti et al.^{19,20} suggested the superiority of flutamide after 12 months of treatment.

There were more reports of side effects with flutamide, and these were more severe, namely, nausea, vomiting, dry skin, and reduction in libido in three studies^{18–20}, hyporexia in one¹³, and acute hepatitis in another as evidenced by a pronounced increase in transaminases¹⁹. Two studies reported dropouts because of such effects^{19,20}. There was no loss of patients with finasteride, but there were complaints about the reduction in libido (8.7–13.6%), headache (9.1–13%), dry skin (21.7–27.3%)^{18,20}, and bloating (10%)¹³.

Table 2 shows a summary of the studies in which finasteride associated with spironolactone or with CPA and EE is

Table 2. Effects of finasteride associated with other drugs on hirsutism.

| Author | Type of clinical trial | Duration | Treatment | Age (years) | Results | Adverse effects* |
|----------------------------------|--------------------------------|----------|--|-------------|---|---------------------------------|
| Tartagni et al. ²³ | Randomized and single-blind | 6 | Finasteride+CPA+EE ^a (n=23) versus CPA+EE ^b (n=23) | 18–35 | Finasteride+cyproterone +EE>cyproterone+EE | Lower libido (n=2) |
| Sahin et al. ²⁴ | Randomized and double-blind | 12 | Finasteride+CPA+EE ^c (n=18) versus CPA+EE ^d (n=16) | 27.1±5.8 | Finasteride+ CPA+EE>CPA+EE | No side effects in either group |
| Unlühizarci et al. ²² | Randomized and without placebo | 6 | Finasteride+spironolactone ^e (n=16) versus spironolactone ^f (n=18) | 20.4±0.5 | Finasteride+ spironolactone> spironolactone | Polymenorrhea (n=2) |
| Keleştimur et al. ²¹ | Randomized and single-blind | 12 | Finasteride+spironolactone ^e (n=33) versus spironolactone ^f (n=32) | 20.9±0.3 | Finasteride+ spironolactone> spironolactone | Polymenorrhea (n=9) |

*Adverse effects of finasteride. CPA: cyproterone acetate; EE: ethynyl estradiol. Dosages: ^a5 mg of finasteride on days 1–14 plus 2 mg/day of CPA plus 35 mcg/day of EE on days 1–21. ^b2 mg/day of CPA plus 35 mcg/day of EE on days 1–21. ^c5 mg/day of finasteride continuously plus 2 mg of CPA plus 35 mcg/day of EE on days 5–25. ^d2 mg of CPA plus 35 mcg/day of EE on days 5–25. ^e5 mg/day of finasteride plus 100 mg/day of spironolactone. ^f100 mg/day of spironolactone.

compared with these drugs in isolation. In general, the finasteride association achieved a better score on the F–G scale^{21,22}. Tartagni et al.²³ showed that the combination of the three drugs (i.e., finasteride+CPA+EE) produced an earlier and more effective result. However, Sahin et al.²⁴ found that the superior efficacy of the triple association did not manifest so early, not before 12 months. In the study by Tartagni et al., the side effects of the finasteride association (20%) were greater than those of the association without it (10%), and the main complaint was a reduction in libido²³. The other study did not report any significant effects²⁴.

Table 2 also shows two more studies of finasteride administered together with spironolactone set against spironolactone alone. Keleştimur et al.²¹ compared the F–G scores at baseline and at 12 months, whereas Unlühizarci et al.²² contrasted the basal scores to those at six months. In both studies, the association was found to achieve a significantly larger reduction than spironolactone alone. The main side effect was abnormal uterine bleeding, which occurred more frequently with spironolactone used in isolation (50–60.7%) than in association with finasteride (20–47.3%)^{21,22}.

DISCUSSION

Hirsutism impacts significantly the quality of life of a woman lowering the perception she has of her femininity. It is a long-term treatment and the drugs required for it have important

side effects that may interfere with her sexuality because they reduce her libido¹⁻³. One such drug is finasteride; it is effective and safe, its side effects are not as marked as those of two other drugs, namely, spironolactone and flutamide, and its interference in sexuality is less^{12-14,18-20}.

In the studies contrasting finasteride to placebo only, many of the adverse effects (i.e., anxiety, depression, and migraine) that were reported might have been due to the psychic influence of the placebo^{8,9} or due to the lack of results with respect to cutaneous hyperandrogenism, which decreases women's femininity and self-esteem²⁵.

In one study, finasteride was inferior to spironolactone, but the study was short-term (9 months) and had few participants¹⁴. In some cases, long-term treatments (over two years) are necessary to produce important cosmetic results in women with hirsutism. Nevertheless, the side effects of finasteride were less frequent than those of spironolactone. This drug may act directly on ovarian function, determining menstrual irregularities, which some women find unbearable. Hence, finasteride would have the advantage of not unduly influencing women's menstrual cycle^{9-12,14,18-20}.

Although the administration of intermittent or smaller doses of finasteride results in fewer side effects, it cannot be concluded that such doses are just as effective as the customary dosage, given the scarce number of participants and the duration of the study, which is not long-term (over two years)^{10,11}. Thus, these facts hinder the assessment of the best dosage.

Therefore, our review shows the potential benefit of finasteride in the treatment of hirsutism, but further randomized double-blind studies should be conducted not only to overcome the aforementioned limitations but also to assess the influence of finasteride in steroidogenesis.

AUTHORS' CONTRIBUTIONS

DZG: Project Administration, Data Curation, Formal Analysis, Writing—Original Draft, Writing—Review & Editing. **JMSJ:** Project

Administration, Data Curation, Formal Analysis, Writing—Original Draft, Writing—Review & Editing. **RSS:** Project Administration, Data Curation, Formal Analysis, Writing—Original Draft, Writing—Review & Editing. **ECAV:** Project Administration, Data Curation, Formal Analysis, Writing—Original Draft, Writing—Review & Editing. **CLR:** Writing—Original Draft, Writing—Review & Editing. **ICES:** Writing—Original Draft, Writing—Review & Editing. **MCPB:** Writing—Original Draft, Writing—Review & Editing. **ECB:** Formal Analysis, Project Administration, Writing—Original Draft, Writing—Review & Editing.

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Review of cost-effectiveness of antithrombotic alternatives in patients with atrial fibrillation

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INTRODUCTION

A cerebrovascular accident is a pathological entity with the vascular impairment of sudden onset, which leads to the lowering of the level of consciousness, differentiating it into ischemic or hemorrhagic, with emphasis on cases related to atrial fibrillation (AF)^{1,2}.

Stroke is one of the main reasons for the use of public health resources, both in the inpatient and outpatient phases of the disease. Its expenses may be associated with the loss of early economic productivity, the development of psychological damage, the decrease in social interaction, and the loss of quality of life for the individual and their family^{3,4}.

It is estimated that Brazil has more than 2 million people over 18 years of age who have a stroke, with a higher prevalence in older adults⁵. Stroke is the second leading cause of death worldwide and the main cause of disability after a traumatic event. It is among the main problems in hospital urgencies and emergencies, representing 5.7 of a total of 58 million global deaths⁶.

It is estimated that the mean hospitalization cost per type of stroke in Brazilian services is US\$3,827 per year and increases to US\$9,505 in those patients with AF, while in countries such as the United States, it exceeds US\$40,743 if intravenous thrombolysis is associated^{7,8}.

The prevention of stroke and its complications by the administration of anticoagulants is one of the main objectives of the treatment for this public⁹. Most of the costs for stroke treatment are incurred in the first year after the injury, incurred by the highly complex procedures performed in this period⁷.

Currently, the therapeutic strategies available on a larger scale are vitamin K antagonists, such as warfarin, which reduce the risk of stroke complications by up to 64%⁹.

This study analyzes the evidence on the cost-effectiveness of antithrombotic alternatives in patients with AF as stroke prevention.

METHODS

This study comprises an integrative literature review. The research took place from August to September 2019 with the following steps:

1. The identification of the topic and selection of the research question using the Population (inpatients), Intervention (cost and cost analysis), Comparison (not applicable to the study), and Outcome (stroke, critical care, and AF) strategy. The research question was as follows: what is the scientific evidence on the cost-effectiveness of antithrombotic alternatives in patients with AF as stroke prevention?
2. The establishment of the inclusion and exclusion criteria: articles available electronically; originals; patients older than 18 years of age; studies published in Portuguese, English, or Spanish; and met the cost-effectiveness analysis method. There was no time limit. Those that did not address the investigated theme were excluded.
3. The establishment of a search strategy: Nursing Database (Base de dados em Enfermagem), Latin American and Caribbean Literature on Health Sciences database, Medical Literature Analysis and Retrieval System Online database, SCOPUS Preview, and Cumulative Index to Nursing and Allied Health Literature. In each database, the subject descriptors in the Medical Subject Heading of PubMed were delimited and crossed, and the following were used: Inpatients, Stroke, Critical Care,

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and Costs and cost analysis and their Descritores em Ciências da Saúde, with the Boolean operators AND and OR, in a paired manner by two different researchers. Titles were assessed, followed by abstracts and finally the full texts according to the exclusion and inclusion criteria established.

4. The presentation of the search and selection of data from the Preferred Reporting Items for Systematic Review and Meta-Analyses review protocol (Figure 1).
5. The evaluation and synthesis of studies: studies were evaluated according to the seven levels of evidence¹⁰. The data are presented in tables and narratives.

RESULTS

This review included 18 articles (Table 1)¹¹⁻²⁸ assessed according to authors, year of publication, study design, country of publication, therapeutic alternatives versus cost, and principal conclusions. In the cost analysis, the main currencies of circulation were the euro^{11-13,19-23} and the dollar^{14-18,20-22,24,25}.

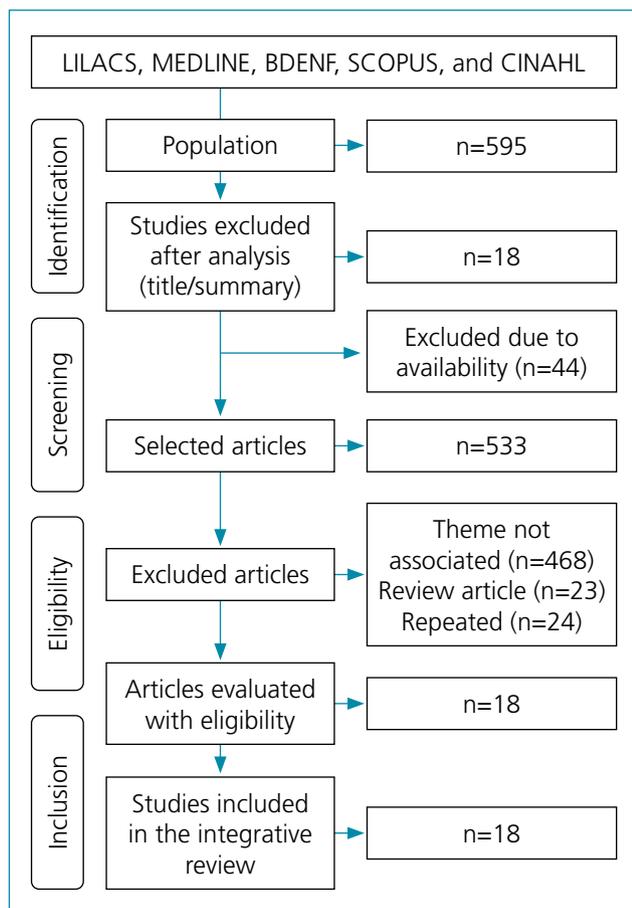


Figure 1. Flowchart of the article search and selection process, Brazil, in 2020.

The best quality-adjusted life years (QALYs) were conferred by the following: dabigatran, apixaban, warfarin, rivaroxaban, and edoxaban.

Apixaban effectively reduces the number of cardiovascular events in relation to the vitamin K analogs apixaban and warfarin. It may be the first-line treatment for stroke prevention in patients with AF¹¹ and is cost-effective¹⁷. Dabigatran was more cost-effective than rivaroxaban and warfarin for patients with AF, besides reducing the risk of stroke, pulmonary embolism, and intracranial hemorrhage with low bleeding^{12,14-20}.

DISCUSSION

It is known that AF is a cardiac abnormality characterized by the total disorganization of atrial electrical activity²⁹ and that stroke is one of the main complications³⁰. Therapy with oral anticoagulants plays a key role in the treatment of AF, avoiding the risk of thromboembolic stroke, although this therapy may bring some risk of intracerebral hemorrhage³¹.

The highest costs of stroke in healthcare systems are incurred by patients with AF, causing a burden of more than US\$1.5 million³² due to the multi-professional care required by these patients.

The economic impact caused by stroke is great, especially when associated with patients with AF³³, and therapeutic choices should be precise to minimize the associated costs. Thus, anticoagulant therapy is the most effective alternative for the prevention and treatment of thromboembolic diseases^{9,34}. Therefore, it is relevant to discuss the costs related to the effectiveness of the therapeutic options found in the market.

It was observed that the Markov model had more acceptances in the analyzed studies. This model is used for economic evaluations in healthcare systems, considering the evaluation of costs and clinical outcomes, especially in evaluating chronic diseases³⁵, which justifies its use in most of the studies included here.

Hospital services are overloaded with the demand from stroke centers, with an average of 10 patients/day⁹. This leads to the construction of research directed at pharmacological therapy with the best evidence of cost-effectiveness. A study on patients with ischemic and hemorrhagic stroke sequelae showed that the severity of symptoms was greater in those with AF, which is the group with significant expenses⁸.

Dabigatran is associated with significantly fewer hospitalizations in patients with AF than warfarin, and there was no significant difference in the mean cost of expenses between the two drugs³⁶. This corroborates the data obtained here regarding the decrease in total expenses by the addition of dabigatran therapy.

Dabigatran is also indicated with a decrease of US\$2,119,252,605 in 3 years in patients with nonvalvular

Table 1. Characterization of the articles included in the review regarding the research components, Brazil, in 2020.

| Author/year/drawing/country/level of evidence | Alternative/monetary cost for better QALYs* | Main conclusions |
|---|--|--|
| Athanasakis et al. ¹¹ , 2017 Cost-effectiveness analysis with adapted Markov model/Cohort with 1,000 patients/Greece/IV | Apixaban/warfarin (€3,210.11) and VKA analogs (€2,019.29) | Apixaban is predictive in reducing the number of cardiovascular events compared with the vitamin K analogs apixaban and warfarin. Apixaban may be the first-line choice in stroke prevention treatment in patients with AF. It reduces mortality and morbidity and provides health system resolutions for populations with multiple comorbidities. |
| Shah et al. ¹² , 2016 Cost-effectiveness analysis with Markov model/Cohort with 10,000 patients/United States/IV | Dabigatran, rivaroxaban, apixaban, and edoxaban in the comparison between apixaban and warfarin (€25,816) and between ACO and warfarin (€100,000) | Oral anticoagulants (ACO) are the most effective alternative when the dose of warfarin is adjusted. Apixaban has high QALYs in AF patients. Dabigatran has higher QALYs for stroke risk. The QALYs of ACO have cost-effectiveness sensitive to the main drugs. |
| Esquivias et al. ¹³ , 2014 Cost-effectiveness analysis with the model adapted from Dorian/Cohort with 1,000 patients/Spain/IV | Apixaban (€30,000) | Apixaban is cost-effective in preventing stroke in patients with nonvalvular AF compared with acenocoumarol by 87%. |
| Peng et al. ¹⁴ , 2017 Markov model health cost-effectiveness panel/Cohort with 10,000 patients/United States/IV | Dabigatran/dabigatran (US\$3,343) rivaroxaban (US\$3,339) | Dabigatran is more cost-effective than rivaroxaban for patients with AF. Dabigatran further reduces the risk for stroke and pulmonary embolism with low bleeding and interdrug costs. |
| Lee et al. ¹⁵ , 2016 Cost-effectiveness analysis with Markov model/Cohort/China/IV | Apixaban (US\$53,315), rivaroxaban (US\$51,064), dabigatran 150 mg (US\$43,946), dabigatran 110 mg (US\$42,712), LAAO (US\$37,789), warfarin (US\$28,090), clopidogrel plus AAS (US\$26,287), AAS (US\$12,777) | LAAO is cost-effective compared with apixaban, rivaroxaban, dabigatran 150 mg, dabigatran 110 mg, warfarin, clopidogrel plus, and AAS in the prevention of stroke with nonvalvular AF. |
| Lee et al. ¹⁶ , 2012 Incremental cost-effectiveness with the Markov model/Randomized controlled trial/United States/II | Apixaban/apixaban (US\$44,232) and aspirin (US\$50,066). | Apixaban is more effective than aspirin; over time, it has become cost-effective and economically dominant. |
| Harrington et al. ¹⁷ , 2013 Cost-effectiveness analysis with Markov model/Cohort/United States/IV | Apixaban, dabigatran, rivaroxaban/compared warfarin with apixaban, apixaban (US\$7,513) was more cost effective. | Apixaban is cost-effective in treatment with thresholds >US\$40,000 per QALY. Warfarin is the most cost-effective AC in the treatment of patients with AF as prophylactic prevention of stroke. |
| Chang et al. ¹⁸ , 2013 Cost-effectiveness analysis/Cohort with 244 patients/China/IV | Dabigatran/dabigatran (US\$1,061) and warfarin (US\$1,306) | Dabigatran was cost-effective compared with warfarin, and the drug can be used for stroke prevention in patients with AF. |
| Wouters et al. ¹⁹ , 2013 Cost-effectiveness analysis with Markov model/Cohort with 10,000 patients/Belgium/IV | Dabigatran/dabigatran (€2,807) and warfarin (€20,000) | Dabigatran is the most cost-effective treatment for stroke prevention in patients with AF, representing good monetary value for healthcare settings. |

Continue...

Table 1. Continuation.

| Author/year/drawing/country/level of evidence | Alternative/monetary cost for better QALYs* | Main conclusions |
|---|---|--|
| Kansal et al. ²⁰ , 2012 Cost-effectiveness analysis with Markov model/Cohort with 100 patients/England/IV | Dabigatran and warfarin/ dabigatran (€10,424) and warfarin (€9,919) | Dabigatran treatment reduces the risk of stroke and intracranial hemorrhage compared with warfarin. Dabigatran is the cost-effective first-line alternative for patients with AF and decreases the risk of stroke. |
| Coyle et al. ²¹ , 2013 Cost-effectiveness analysis with the Markov model/Cohort/Canada/IV | Apixaban (€11,742), dabigatran (€50,000), warfarin and rivaroxaban | Rivaroxaban and dabigatran 110 mg are cost-effective, with dabigatran having less impact on bleeding. |
| Morais et al. ²² , 2014 Cost-effectiveness analysis with the Markov model/Nonrandomized study/Portugal/III | Rivaroxaban (€3,895), warfarin (€3,494) | Rivaroxaban showed greater cost-effectiveness than vitamin K analogs and is the indicated therapy for stroke prophylaxis in patients with AF. |
| Stevanovic et al. ²³ , 2014 Using efficacy by ARISTOTLE and AVERROES Markov Model/Cohort with 1,000 patients/Netherlands/IV | Apixaban (€14,113) and VKA (€14,904) | Apixaban is the most cost-effective alternative and has high treatment importance. However, due to the effects, it will be the second choice of treatment. |
| Reddy et al. ²⁴ , 2015 Cost-effectiveness analysis with the Markov model/Nonrandomized study/United States/III | Right atrial appendage closure (US\$20,892) and ACO (US\$20,924) | Appendix closure and OAC are cost-effective alternatives to stroke prevention in patients with AF |
| Ali et al. ²⁵ , 2012 Prospective observational study with 402 patients/United States/V | The cost of warfarin (US\$2,073) and dabigatran (US\$17,535) | Warfarin becomes more cost-effective for patients with AF in stroke prevention because dabigatran has the highest price. |
| Miguel et al. ²⁶ , 2013 Cost-effectiveness analysis with the Markov model/Nonrandomized study with 117 patients/Portugal/III | Dabigatran/dabigatran (€8,409) | Dabigatran reduces the risk of ischemic and hemorrhagic stroke and intracranial hemorrhage. It is shown to be cost-effective by waiving the international standardization rate. |
| Miguel and Ferreira ²⁷ , 2016 Cost-effectiveness analysis with the Markov model/Comparative study RE-LY and ROCKET AF with 71.693/Portugal/IV | Dabigatran and rivaroxaban/dabigatran (€11,858) and rivaroxaban (€12,223) | Dabigatran, in patients with AF, provides better clinical results than rivaroxaban in the same indication. |
| Magnuson et al. ²⁸ , 2015 Cost-effectiveness analysis with Markov model and ENGAGE AF-TIMI 48 with 21.105/Cohort study/United States/IV | Edoxaban and warfarin/ edoxaban (€43,370) and warfarin (€26,986) | Edoxaban becomes the most cost-effective alternative due to its wide sensitivity with impacts on post-stroke quality of life and bleeding. |

QALY: quality-adjusted life-year; VKA: vitamin K antagonist; AF: atrial fibrillation; ACO: oral anticoagulant; LAAO: right atrial appendage transcatheter; AAS: acetylsalicylic acid; Monetary values were taxed according to the currency of each country at the time of the research.

AF in Colombia, being a viable alternative compared with apixaban, rivaroxaban, and warfarin in the medium term³⁷. In this study, the increase was more than US\$42,000, reinforcing that in years of gains, this therapeutic alternative exceeds the expectations of the payer, such as the public system, and improves the quality of life of the population that uses the drug.

Dabigatran and rivaroxaban have low medical costs for preventing stroke in people with AF³⁸. Other drugs are also noted for their cost-effectiveness. In this study, the new oral

anticoagulants (dabigatran, 110 mg; apixaban and rivaroxaban, 150 mg each) were found to be cost-effective compared with conventional strategies⁹.

CONCLUSIONS

Antithrombotic alternatives have been the target of international studies with the purpose of reducing public service costs and increasing patients' quality of life, considering alternatives

that are more effective in patients with different pathologies and those with direct impacts on public spending.

Apixaban and dabigatran were shown to be cost-effective regarding the quality years of life gained; both can be used in patients with AF, including the critically ill, to prevent hematological disorders and cardiovascular events such as stroke.

Studies in this area enable the first-line treatment in disease prevention and significantly reduce public spending, taking into account the years of life gained, reducing mortality and in-hospital morbidity. Research on this topic

is also suggested in the Brazilian scenario to provide evidence for cost-effective alternatives with lower public service expenses.

AUTHORS' CONTRIBUTIONS

JCN: Conceptualization, Investigation, Writing – original draf. **LOB:** Data curation, Writing – original draf. **SSF:** Visualization, Writing – review & editing. **MGCS:** Supervision, Writing – review & editing.

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Leukocyte filters: a review of the mechanisms and applications in hemotherapy

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INTRODUCTION

The leukodepletion through specific filters to remove leukocytes from hemocomponents has been applied as a preventive measure of transfusion complications (Figure 1). The whole blood contains about 2×10^9 – 3×10^9 leukocytes; Brazilian legislation determines that leukodepleted components should contain less than 5×10^6 , meaning the reduction of 99% of leukocytes after filtration^{1,2}.

Blood banks and industries have sought to reduce transfusion risks. In Brazil, tests for Chagas disease, hepatitis B and C, human T-cell lymphotropic virus (HTLV), human immunodeficiency virus (HIV), syphilis, *plasmodium falciparum* research in endemic areas of malaria, and cytomegalovirus in specific situations are performed^{2,3}. The institution of nucleic acid test for the HIV and hepatitis B and C was introduced to reduce the immune window². Besides infectious risks, immediate reactions to the transfusion may be highlighted, which are currently less controlled^{2,4-6}.

Blood components undergoing depletion, irradiation, phenotyping and washing procedures are called special and used in various situations, for example: immunosuppressed patients benefit from irradiated components, polytransfused phenotyped erythrocytes and immunoglobulin A (IGA) deficiency of washed erythrocytes.

This study aims to understand the mechanisms and leukocyte filter applications in hemotherapy and focuses on the use of leukodepleted hemocomponents in Brazil.

METHODS

This work adopted, as initial criteria, the query to the Index Medicus Medline concerning the use of the keywords “leukocyte filters,” “hemotherapy,” “filter mechanisms,” “hemocomponent filtering,” “leukodepletion,” and “adverse effects.” This selection sought articles in English and Portuguese published during the past 30 years. A careful analysis of 35 articles and related national legislations were performed, and filtered cells’ studies and other types of filtration were not considered.

DISCUSSION

During an allogeneic blood transfusion, the patient receives the donor’s leukocytes, and these cells are recognized as strange by the immune system that can result in adverse reactions^{5,6}. The main complications related to the presence of leukocytes in the blood are non-hemolytic febrile transfusion reactions (NHFR), alloimmunization to human leukocyte antigens (HLA), platelet refractoriness, graft-versus-host disease (GVHD), and immunomodulatory effects. The transmission of infectious agents such as cytomegalovirus (CMV), HTLV-I/II, and Epstein–Barr virus (EBV) as well as other viruses and parasites may also be associated⁶.

Another undesirable effect of leukocytes is the increased incidence of postoperative infections documented in cardiac surgery; however, factors such as age, previous cardiac surgery, type of surgery, and platelet counts during the preoperative

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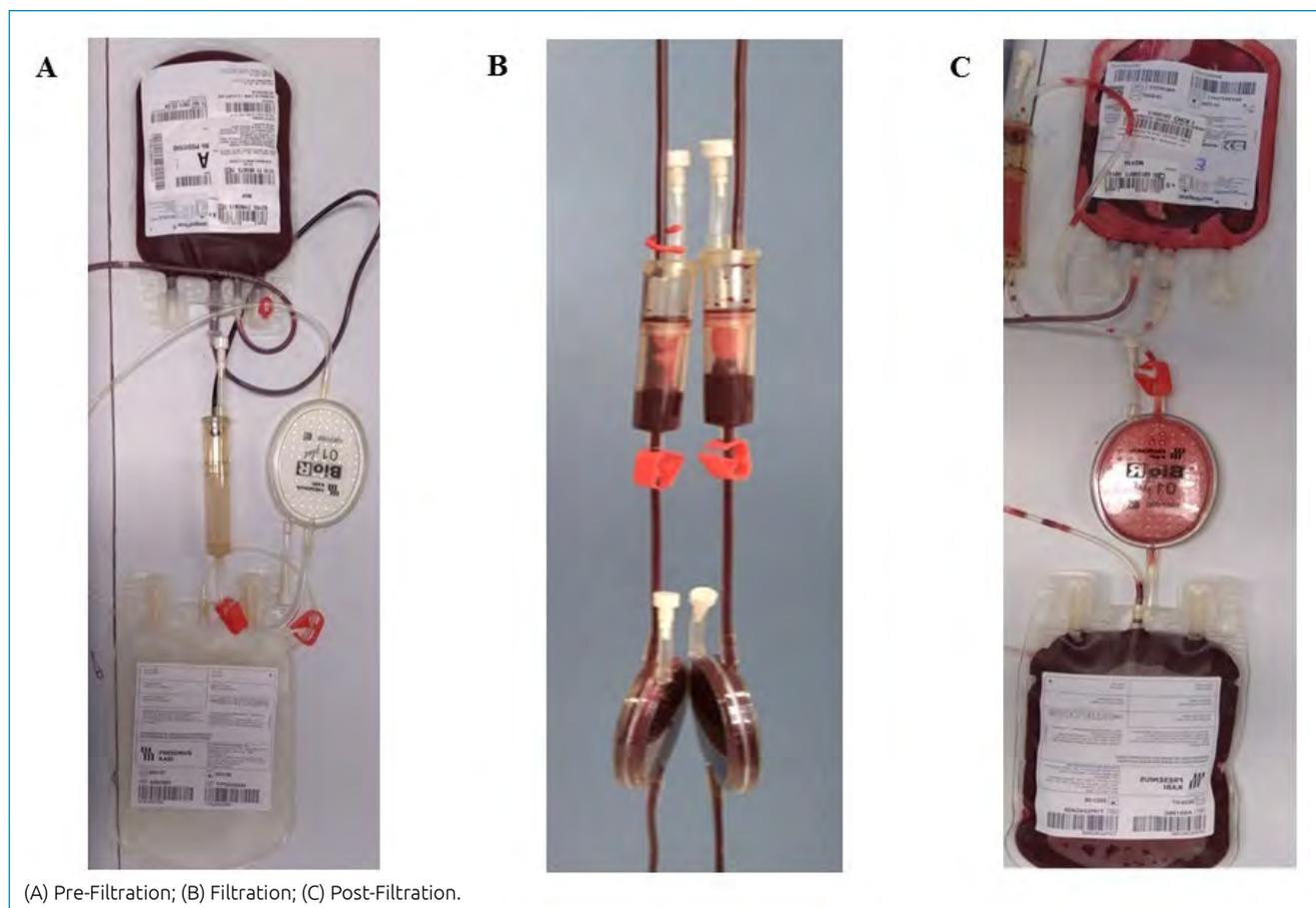


Figure 1. Filtration process of the concentrated red blood cell component.

phase related to higher mortality may interfere with the actual analysis of the effect of leukocytes in these patients^{6,7}.

In contrast, therapeutic granulocyte transfusion may be beneficial in patients with neutropenia (<500 neutrophils/mm³) and infection, which is not responsive to therapy.

Leukocyte filters

The fact that allogeneic leukocytes may promote adverse reactions justifies the reduction of white blood cells^{5,6,8}. The reduction of 100–1,000 times (2–3 log) provided by the available leukocyte filters has shown a decrease in the frequency of many adverse reactions⁵.

In order to prevent NHFR, studies demonstrated that the level of necessary reduction is less than 90%, the transmission of some infectious agents 99.9%, platelet alloimmunization 99.9%, and to avoid immunomodulation, this percentage is not known⁵.

The filtration after the development of microaggregate filters removes more than 95% of the leukocytes, and the loss of red blood cells is less than 10%. The filtration of leukocytes is the most used method to prepare blood poor in leukocytes.

The process is simple, fast, effective, and does not require expensive equipment. Furthermore, it preserves the product's life^{6,9}.

Universal leukodepletion (100% of the blood components produced) has been a transfusion safety policy considered in some countries. Several authors who discuss the costs consider that this analysis is complex due to the difficulty in dimensional long-term morbidity attributed to transfusion. However, they claim that filter indications should be reserved for specific situations because of the competition for resources to other serious public health problems⁶.

The first filters (first generation) developed with the aim to reduce leukocytes present in the blood to be transfused had the capacity to hold approximately 1 log of white blood cells. With the development of a technique “centrifuge, cool, filter,” the second generation filters arose promoting retention of about 3 log with verified efficacy to prevent NHFR (10). Currently, third or fourth-generation filters remove more than 99.9–99.99% (>3 log) of leukocytes originally present in the donated blood. These filters have pores ranging from 5–50 micrometers and are able to meet current hemocomponents' quality standards^{1,10-12}.

Filtering mechanisms

Filters have small pores that allow the retention of individual cells and increase adsorption capacity. Two main mechanisms are involved as follows: the mechanical entrapment (sieving), dependent on the size of the pores and of deformability of cells, and physical–chemical entrapment or adhesion^{1,6,9,13}.

Different factors may be responsible for adherence of white cells to surfaces, such as chemical characteristics, charge, and surface morphology (porosity and roughness). Filters have several layers with different diameter pores, which permit depth filtration. The filter pore size then determines the sieving of particles bigger than 30 µm being the adhesion and depth filtration responsible for retaining particles smaller than 1 µm. Particles of size between 1 and 30 µm are retained by the simultaneous action of both processes^{1,9,14}.

The filter surface charge can be adjusted by the coating with methacrylate polymers to create a strong positive charge and hence to increase the adhesion surface^{9,15}. Some properties of the diverse cells such as diameter, density, deformability, and adhesiveness are essential for the filtration process success¹.

Moment of filtration

The blood filtration may be done at the time of processing, post-processing, or at the transfusion moment. However, the prestorage leukodepletion presents the following advantages^{1,4,6,16}:

- Minor accumulation of leukocyte cytokines during storage, which ensures greater efficiency in preventing non-hemolytic transfusion reactions;
- It minimizes HLA alloimmunization risk in multiple transfusion patients, since it removes leukocytes intact during filtration. The filtration during transfusion (bedside) allows the passage of leukocytes fragments and may alloimmunize the receptors;
- It minimizes the risk of lymphotropic virus transmission, which with the degradation of leukocytes and the release of intracellular organisms after 72 hours of storage are no longer retained.
- Besides, it allows the performance of laboratory analysis of quality control.

In Brazil, leukodepletion with bench filters for CH has often been held up to 48 hours after collection, while for platelets, it is often performed at the bedside. The hemocomponents produced by apheresis already gone through the reduction of leukocytes during processing.

Recommendations on the use of leukocyte filters in Brazil

The use of leukocyte filters has been recommended for hemoglobinopathies, hereditary hemolytic anemia, history of two or more febrile not hemolytic reactions, congenital immunodeficiency syndrome, candidates for bone marrow transplantation, aplastic anemia, acute myeloid leukemia, severe onco-hematological disease till the correct diagnosis and platelet disease patients with the need of a frequent transfusion. For the prevention of CMV, filtration has been indicated in the following conditions: HIV-positive patients with negative serology for CMV; candidate for organ and bone marrow transplantation if the donor and recipient are negative for CMV; intrauterine transfusion, pregnant with nonreactive serology or unknown to CMV, premature newborn, and of low birth weight (1,200g); newborns (NB) whose mothers present negative CMV or unknown serology. The effectiveness of leukocyte filters is equivalent to the realization of serology for the prevention of CMV².

Other leukocyte filter applications

Virus Transmission Prevention.

It has been recognized that allogeneic leukocytes from the donor blood are responsible for the virus transmission, such as CMV, human T-lymphotropic virus (HTLV), or EBV^{14,15,17,18}. Cytomegalovirus, HTLV-I, and HTLV-II are only transmitted by cellular products' transfusion. If the universal leukoreduction was adopted, these viruses would be removed by filtration, and the blood test to these potential contaminants is not necessary⁶.

Serologic testing for cytomegalovirus in blood banks is recommended for individuals who underwent stem cell and organ transplantation with no positive serology for CMV, newborn children of mothers with CMV negative or unknown serology and who weigh lower than 1,200 g, and intrauterine transfusion, but deleukotized hemocomponents can replace this serology². The serological screening for HTLV has been routinely made for all donors, which makes the use of leukocyte filters deprecated for this purpose².

Bacteria transmission prevention.

Current studies indicate that a significant percentage of healthy blood donors carry *Chlamydia pneumoniae* in their blood. The clinical significance of these results is unknown; however, the eradication of these bacteria was verified in leukoreduced units through real-time PCR and immunostaining tests that identified bacteria trapped in the filter mesh¹⁹.

Prion transmission prevention

Prions are infectious proteins related to a variety of progressive and fatal neurodegenerative diseases collectively referred to as transmissible spongiform encephalopathies^{6,20,21}. Contamination of leukocytes in the blood raises the risk of abnormal protein prion transmission, probable causative agent of the new variant Creutzfeldt–Jakob disease (CJD)^{20,21}.

Leukoreduction reduces up to 42% of infectivity associated with the infectious prion. Modifications of the specific affinity to prion surface have been developed to increase the filtering efficiency for this end^{10,20}. Some countries in Europe and the UK had the universal leukodepletion implemented under this risk¹¹. In Brazil, clinical screening eliminates people who were diagnosed with CJD, family history of CJD, significant stay in the UK or Republic of Ireland after 1980, who have received growth hormone or other pituitary origin not recombinant drugs, use of bovine insulin, corneal transplantation and dura mater, and those who have received transfusions of hemocomponents in the UK after 1980¹¹.

Parasite transmission prevention

The risk of infection by a parasite associated with transfusion is mainly determined by the following factors: the prevalence of infection, the capacity of survivability of parasites stored in the blood, and the immune competence of the recipient²². There was an inexplicable decrease in the incidence of malaria transmitted by transfusion in recent years. This fact parallels the increased use of leukocyte filters and the fact that Brazil has clearly defined clinical criteria to prevent transmission, and besides, in endemic areas, tests for plasmodium or plasmodium antigens are mandatory^{2,22}.

There are studies that provide evidence that leukocyte reduction filters are effective to reduce the number of parasites in the infected blood such as *Trypanosoma cruzi*, and this effectiveness depends in part on the concentration of parasites in the artificially infected blood²³. Fabron Junior evaluated *Trypanosoma cruzi* retention mechanisms by leukocyte filters. Concentrated samples of red blood cells and platelets were infected with the parasite and then filtered to measure the removal capacity, showing the reduction of approximately 3 log. An analysis of the filter fibers demonstrated that *T. cruzi* parasites were removed by direct adherence to the filter fibers, suggesting a biological

mechanism probably mediated by the surface proteins of the parasite²³. The serology for Chagas' disease research is part of blood banks routine, which is the reason why the use of filters is not necessary for this purpose².

The prevalence of positive serology for visceral leishmaniasis in asymptomatic individuals has been observed in endemic areas²⁵. There are few cases in the literature pointing out to transfusion as a likely cause of transmission of this disease²⁵. Cardo (2006) demonstrated, in intentionally contaminated blood, the substantial reduction of this parasite after filtration²⁵.

TRALI prevention

Acute lung injury related to transfusion (TRALI) has been associated with transfusions of anti-leukocyte antibodies from the donor which react with alloantigen on the receptors' leukocytes. This potentially fatal complication occurs more frequently in the blood donation of multiparous women. The use of leukocyte filters has been described as a way to mitigate this risk⁵.

CONCLUSION

It is concluded that in view of the diverse applications of leukocyte filters in hemotherapy, the implantation of universal leukodepletion deserves further studies that determine the cost and benefit of this measure.

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AUTHORS' CONTRIBUTIONS

EVRU: Conceptualization, Methodology, Writing – original draft. **LFT:** Formal analysis, Writing – review & editing. **JFL:** Formal analysis, Writing – review & editing. **FNG:** Formal analysis, Writing – review & editing. **AGV:** Formal analysis, Writing – review & editing. **TCMS:** Formal analysis, Writing – review & editing. **CUR:** Data curation. **IAP:** Data Curation. **SFGC:** Formal analysis, Writing – review & editing

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Hydronephrosis associated with pelvic organ prolapse: a review study

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INTRODUCTION

Pelvic organ prolapse (POP) is a common condition affecting more than 3 million women worldwide¹. It may lead to bothersome pelvic pressure, bulge symptoms, and voiding dysfunction from bladder outlet obstruction, which may manifest as reduced flow rates and elevated postvoid residual volumes. Therefore, POP can also be associated with recurrent urinary tract infections, ureteral obstruction, and hydronephrosis (HD)^{1,2}.

The prevalence of HD in women with advanced POP has been reported to range from 3.6–30.6%, with more severe prolapse associated with more HD. This condition is concerning because it can be completely asymptomatic. In addition, HD can result in silent kidney damage, which may lead to chronic or even end-stage renal failure^{1,2}.

Despite the possible unfavorable outcome of advanced prolapse in renal function, there are currently no recommendations or guidelines regarding the evaluation of the upper tracts in patients with POP¹. The majority of patients studied with POP experienced resolution of HD with treatment¹.

The treatment of POP can be conservative or surgical. Pessary therapy is a conservative and practical option for patients with POP who were refusing surgery or being unsuitable candidates for surgery². In cases with HD and renal failure, a simple pessary and transurethral catheter should be placed immediately to allow for complete bladder emptying².

Faced with this background, the objectives of this review were to report the prevalence of POP associated with HD, to propose a practical diagnostic management, and to suggest immediate treatment options for POP on the resolution of HD.

METHODS

This study was conducted by a search of studies on Medline and PubMed using the terms “pelvic organ prolapse”, “hydronephrosis”, “pessary”, and “pessary management”. The Medline and PubMed searches identified 85 citations. First, all types of abstracts were selected (Books and Documents, Clinical Trials, Meta-Analysis, Randomized Controlled Trial, Review, and Systematic Review). Second, the abstracts were screened for the availability of the full text in English and 10 years publication date, resulting in the initial exclusion of 55 studies from the analysis.

Other 19 studies were excluded because they were case reports or they did not address the objectives of this review. A classic study (published in 1941) was included due to its relevance to describe the possible pathophysiological mechanisms associated with HD and POP. Therefore, 12 relevant studies were selected for this review. As this study was a review without access to patient documents, approval from the Institutional Review Board or Ethics Committee and informed consent were not needed.

RESULTS

Table 1 shows the relevant reviews and outcomes in the management of women with POP and HD according to evidence-based medicine.

Based on the most relevant and commonly management for HD associated with POP, the following didactic original algorithm with 10 steps is proposed immediately to diagnose and solve that association:

1. History and physical examination;
2. Diagnosis of POP: The Pelvic Organ Prolapse Quantification system (POP-Q) is clinically standardized and recommended;

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Table 1. Review of managing and treating HD in POP according to relevant evidence-based medicine.

| Author | Population or setting | Study design | Aims | Results (%) |
|----------------------------|--|---|--|--|
| Dongol et al. ⁷ | Population of 140 cases with POP who underwent surgical management. | Prospective study | To establish the association of renal impairment with the degree and duration of POP. | Total 5 (3.57) patients had HD. Total 49 (34.1) patients had moderate-to-severe renal failure. |
| Dancz et al. ¹⁰ | Population of 180 participants with advanced POP. | Prospective study on the prevalence of HD in women with advanced POP. | To determine the proportion of women who demonstrate improvement in HD after pessary placement for advanced POP. | Successful pessary use improved HD in over 75% of women with advanced POP. |
| Hui et al. ¹² | Population of 233 patients with POP were followed by sonographic measurement of bilateral renal pelvis to identify the presence of HD. | Prospective observational study. | To study the prevalence of HD and its associated factors in women with POP | HD resolved in 95% of patients after they received treatment for POP. |

HD: hydronephrosis; POP: pelvic organ prolapse.

3. Urinalysis and culture to investigate urinary tract infection;
4. Blood test: urea and creatinine to search renal insufficiency and blood count and culture to investigate possible sepsis;
5. Abdominal ultrasound (US) or abdominal computed tomography (CT) to identify the presence or absence of HD;
6. Treatment of POP: conservative option—Pessary. Pessaries are considered, according to this review, a wise choice to correct immediately the POP and minimize the deleterious effects of postrenal obstruction;
7. Drain bladder: spontaneously or with bladder catheterization;
8. If urosepsis: antibiotics;
9. Evaluate HD drainage (multidisciplinary team to provide, if necessary, nephrostomy);
10. Treatment of POP: surgical options can replace pessary treatment.

DISCUSSION

HD was more common in patients with advanced prolapse and among studies that used the POP-Q system (10.3–30.6%) than Baden–Walker system (3.6–20.6%)¹. However, the prevalence can also vary by underdiagnosis, since this possibility of finding this association cannot be ruled out even in initial cases of prolapse^{1–3}.

The mechanism by which POP causes HD is unclear; however, several theories have emerged. The pathophysiology is hypothesized to be somewhat different in patients with uterovaginal prolapse compared with those with vaginal vault prolapse. Multiple authors suggest that when the uterus is *in situ*, the genital hiatus entraps the ureters against the fundus of the uterus leading to ureteral compression^{1–3}.

Others proposed that with procidentia, the uterine arteries cause ureteral compression by exerting downward traction on the ureters. Similarly, in patients with vaginal vault prolapse, the weakened cardinal ligaments could compress the ureters as the vaginal apex descends. Another possible mechanism could be obstruction at the level of the urethra causing backup of urine; however, this would not support the finding of a difference between uterovaginal and vaginal vault prolapse. Although the exact mechanism is unclear, additional discussion and possible upper tract imaging may be warranted in patients with severe uterovaginal prolapse^{1–3}.

Clinical factors associated with HD include the degree of anterior or apical POP and diabetes mellitus^{4,5}. In addition, the possible complications of the association of POP and HD, which can be a postrenal obstruction or renal impairment, are serious conditions, especially in elderly women, and require resolution of POP.

Recommendations for routine renal imaging for diagnostic purposes in patients with POP are widely disparate. HD can be assessed with renal US or CT imaging. Renal impairment can be assessed based on evaluations of serum urea and

creatinine levels. If the increase in serum creatinine value is detected, possibly ureteral obstruction and renal insufficiency should be considered. If renal insufficiency is suspected, the US can be sufficient, particularly when the finding of bilateral HD is documented⁶.

Renal involvement linked to POP ranges from acute to chronic renal failure and may also lead to end-stage renal failure. Prolonged duration and the severity of POP are responsible for renal impairment. Dongol et al. reported among 140 cases of pelvic prolapse, a total of 3.57% of patients with HD. All 49 (34.1%) patients had moderate-to-severe renal failure. And, 46 (32%) patients in stage three showed moderate reduction in creatinine clearance, two (1.4%) patients with severe reduction, and one (0.7%) patient in end-stage renal failure⁷. Literature data show that untreated HD may progress to severe renal damage, suggesting that the resolution of HD results in either recovery or improvement of renal function¹⁷.

Both surgery and pessaries have shown a comparably positive effect on the symptoms of POP², which suggests that there may be utility in performing a workup to investigate HD and correct POP. Therefore, if the HD is promptly diagnosed in patients with POP, the correction of POP, whether by pessary or surgery, can resolve HD^{2,8,9}.

The use of a pessary to treat POP is a valid noninvasive option or conservative treatment and can solve in a conservative way the HD associated with POP. Some authors generally recommend a pessary trial for all new patients with POP. Many patients are surprised with the significant improvements they experience with a pessary trial⁸.

Furthermore, the use of a pessary can be a practical alternative to re-establish renal function in patients with HD awaiting surgery schedule for POP correction. An interventional trial, which aimed to evaluate the effect of the use of pessary on HD in women with advanced POP, determined an improvement in HD after pessary placement. According to the results, 75% of women demonstrated an improvement in HD after pessary placement^{9,10}.

Despite the benefits of pessary use, there are some complications that are usually associated with neglected, oversized, or misplaced pessaries. Major complications may include fistulas, bowel or bladder erosion, and even HD⁶. In cases of pessary presence with a concomitant increase in serum creatinine value, a possible ureteral obstruction is suspected. In order to assess the presence of HD and its underlying causes, a CT scan should be performed to assess the mechanism of urinary tract obstruction. In case of renal insufficiency, abdominal US could be sufficient. If HD is detected in a patient with no signs of urosepsis, it is recommended a conservative management by the removal of the pessary and catheter placement. When urosepsis

is suspected, it is mandatory to administer antibiotic therapy and evaluate the HD drainage by nephrostomy⁶.

Another option to approach HD and POP is surgical treatment^{9,11}. In a retrospective case study on 250 patients presenting with severe uterovaginal prolapse, the authors evaluate the effect of the whole surgical correction of pelvic floor on HD due to severe prolapse⁸. As a result, HD was found in 32 (13.7%) of 234 cases. According to that review, vaginal hysterectomy, axial vaginal apex suspension, and anterior and posterior repair result in either complete resolution or improvement of HD¹¹.

In a prospective observational study, 233 patients with POP were staged by the POP-Q system, followed by abdominal US measurement of bilateral renal pelvis to identify the presence of HD. The follow-up scan for HD was performed after the patients were treated for the POP¹². The prevalence of HD was 10.3% (95% confidence interval [CI], 6–14%). Although patient's age, higher parity, and the presence of diabetes mellitus and hypertension were more common in the group with HD, the logistic regression analysis indicated that only the severity of POP was an independent risk factor for HD. The odds ratio in stages 3–4 POP for HD was 3.4 (95%CI 1.3–9.2), and HD resolved in 95% of patients after receiving treatment for POP¹².

A suggested follow-up, similar to that in conservative or surgical treatment, could be performed through an abdominal US during the diagnostic phase, before surgery, three days after surgery, and four weeks and six months after surgery. The HD cure criterion can be defined as no residual HD four weeks and six months after surgery^{11,12}.

Strengths and limitations

There are currently few recommendations or guidelines regarding the evaluation of the upper tracts in patients with POP. This is a positive impact of the present review with a practical and objective approach to identify HD in women with POP. In addition, reviews such as this can stimulate the development of prospective studies with responses with a greater level of evidence on the importance of diagnosing renal complications in women with POP.

Another relevant aspect of this review is to value the association between POP and HD. Offering knowledge that POP correction can provide not only quality of life but also the recovery of a urinary system at risk of failure can make a difference in patient care.

The limitations of this study include the retrospective characteristics of the data collection, scarcity of data on this topic with no high-quality prospective or even randomized trials, and the lack of a long-term follow-up of the HD treatment in women with POP. These factors do not detract from the study because they should be the focus of a prospective trial.

CONCLUSIONS

HD is not rare and is frequently found in patients with advanced POP. It is important for the medical team to be attentive and diagnose this possible renal complication in patients with POP. Most obstructive uropathy resolves with pessary use or surgical correction. For the future, prospective studies for this patient cohort should be planned.

AUTHORS' CONTRIBUTIONS

GVM: Data curation, Writing – review & editing. **SBM:** Data curation, Writing – review & editing. **LMO:** Data curation, Writing – review & editing. **MMD:** Data curation, Writing – review & editing. **CCT:** Data curation, Writing – review & editing. **MGFS:** Conceptualization, Data curation, Writing – review & editing.

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Evaluation of taste and smell disorders in pediatric COVID-19 cases

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Coronavirus disease 2019 (COVID-19), the infection associated with severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2), was declared as pandemic by the WHO in March 2020 and caused more than 146,000,000 infections and more than 3,000,000 deaths in April 2021¹. Children appear to be less commonly affected than adults, and most of the cases have mild disease. Although a minority of cases required hospitalization, symptomatic infection appears to be relatively uncommon in children²⁻⁴.

The most common symptoms are fever, cough, and shortness of breath; however, these symptoms may be unrecognized before the diagnosis in children^{5,6}. Loss of smell or taste is reported in approximately 10% of children less than 20 years of age⁶. However, altered smell or taste is one of the symptoms most strongly associated with a positive SARS-CoV-2 swab test result⁷. Loss of smell is significantly

associated with a decreased rate of hospitalization, intensive care unit admission, intubation, and acute respiratory distress syndrome, and it has been reported as an independent positive prognostic factor of a less severe COVID-19 infection in adults⁸.

Although it is well known in adults, there are scanty reports about smell and taste disorders in children with COVID-19 in the literature⁹. In this issue of the article, Elmas et al.¹⁰ reported that 7 children below the age of 18 had a positive SARS-CoV-2 PCR test result and were admitted with taste and/or smell disorder. These authors are involved in presenting the clinical manifestations and laboratory results of the patients at the time of admission and follow-up. In addition, cranial MRI and thoracic computed tomography (CT) scans of all cases during admission are also evaluated and discussed in the light of literature.

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

Guotao Wang¹ , Qiang Zhong¹ , Daojian Xu^{1*} 

Dear Editor,

We have carefully read the research literature of Wang Dalong and others on “dexamethasone can reduce the inflammatory response and thus reduce the myocardial injury in Stanford type A aortic dissection patients”¹. This study compared the heart rate, mean arterial pressure at different time points, serum creatine kinase MB, cardiac troponin I, C-reactive protein, and tumor necrosis factor- α between the dexamethasone group and the control group, and proposed that “dexamethasone treatment can reduce perioperative myocardial injury in patients with Stanford type A aortic dissection and its mechanism may be related to resistance to inflammatory response and oxidative stress.” As a clinician in the emergency department, this study has a high reference value for our clinical work. However, we still have several problems to discuss with the channel.

First of all, we know that Stanford’s classification of aortic dissection is a rough classification. In recent years, many scholars have proposed a variety of subtype schemes for Stanford type

A aortic dissection based on their clinical experience, anatomical location, prognosis, and other factors^{2,3}. We hope that this study will further show the general demographic characteristics of the selected cases, as well as the specific anatomical location of Stanford type A aortic dissection and other individual case characteristics, so as to further judge the clinical application scope and value of this study.

Second, the prognostic indicators of Stanford type A aortic dissection patients, such as survival time follow-up, incidence of complications, and postoperative physical recovery, are the key results that directly reflect the effect of dexamethasone in the perioperative period. We hope that the follow-up research of this study can fully show.

AUTHORS’ CONTRIBUTIONS

DX: Writing – original draft, Writing – review & editing.

GW: Writing – original draft, Writing – review & editing. **QZ:** Writing – original draft, Writing – review & editing.

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Comment on “Predictors of left atrial thrombus in acute ischemic stroke patients without atrial fibrillation: a single-center cross-sectional study”

Wenyng Zhao¹ , Lianping He^{1*} 

We are happy to read the article¹ published by Cinar research team. Their findings suggest that patients with acute ischemic stroke with low ventricular ejection fraction and elevated platelet volume should undergo further transespiratory echocardiogram to verify the possibility of myocardial origin. In addition, this study may provide new information on the applicability of mean platelet volume to predict left atrial appendages in patients without atrial fibrillation. This study is of great significance for the treatment and prognosis of patients with stroke. However, there are some problems need to be further explored.

First of all, the author did not describe the selection process of patients and controls in detail. According to the results in Table 1, the age difference between the patients and the

control group was statistically significant. We think that the two groups can be further compared as there is no significant difference in gender and age. It is necessary to introduce the inclusion criteria and exclusion criteria in detail.

Second, because of the age difference between the two groups, the results in Table 2 need to be further explored. If the author carries out logit regression analysis, the age variable should be changed to classification variable, and the author's grouping method of age should be described in detail.

AUTHORS' CONTRIBUTION

WZ: Writing – original draft, Writing – review & editing.

LH: Writing – original draft, Writing – review & editing.

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Publications, by different surgical specialties, on patient-reported outcomes of oncoplastic surgery

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SUMMARY

OBJECTIVE: This study aimed to compare the publications authored by plastic surgeons with those from other specialties' surgeons on patient-reported outcomes of oncoplastic surgery.

METHODS: A review was carried out on the Medline database, encompassing five years (2015-2020). Studies about partial breast reconstruction after conservative treatment, immediate or delayed, by any technique, which presented patient-reported outcomes, were included.

RESULTS: We found 292 articles, from which 142 met the eligibility criteria. Publications were stratified into groups 1 (plastic surgeons) and 2 (other surgical specialties), and also into groups A (only plastic surgeons), B (only other specialties) and C (both), and compared statistically. Most publications (60.6%) were attributed to specialties other than plastic surgery. Nineteen percent had only plastic surgeons as authors, 50% only other specialties' surgeons, and 31% had both. There was no difference between groups regarding the impact factor of the journals in any of the stratifications, and the majority was published in journals with impact factor ≤ 2 . **CONCLUSION:** In the last years, surgeons from specialties other than plastic surgery published more about the results of the oncoplastic surgery reported by the patients. There was no statistical difference between the groups regarding the impact factor of the journals.

KEYWORDS: Breast neoplasms. Mastectomy, segmental. Surgery, plastic. Specialties, surgical. Journal impact factor.

INTRODUCTION

The treatment of breast cancer has undergone a dramatic change in the past decades, moving away from radical procedures toward breast conservation techniques in order to provide patients with greater aesthetic satisfaction¹. The concept of partial mastectomy followed by postoperative radiation therapy, known as conservative breast treatment (CBT), is currently the standard treatment for early stage breast cancer¹⁻³.

However, CBT does not always achieve a good aesthetic outcome. About 30–40% of patients evolve with a visible aesthetic deformity and sequelae, which results in negative body

image, self-esteem, and quality of life³⁻⁷. Oncoplastic surgery, which combines plastic surgery techniques with cancer resection, aims to achieve better aesthetic results, in addition to allowing the indication of CBT for larger tumors^{5,7-12}.

Oncoplastic surgery allows important goals to be achieved as follows: cancer safety combined with psychological well-being and good quality of life. Therefore, it is widely accepted and adopted currently in clinical practice^{6-8,13,14}.

The assessment of the oncological results of breast cancer treatment remains essential. However, the quality of health services provided has also been increasingly valued. Currently, there

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is a growing demand to assess how patients perceive treatment results^{12,15}. The term “patient-reported outcomes” (PRO) was established to emphasize the value of assessing and quantifying results from a patient’s perspective. PRO measures include satisfaction with results, functioning in daily life and quality of life, and have become highly valued and widely applied in supporting medical decisions^{13,16}.

There is a consensus that the use of oncoplastic techniques brings various advantages to patients^{3,6-8,13,14,17-24}. Nevertheless, there are many controversies about specialties’ (e.g., plastic surgery, mastology, cancer surgery, general surgery, and gynecology) ideal training and education to perform this type of procedure^{2,18}. Therefore, this study was designed to compare the publications authored by plastic surgeons or surgeons of other specialties on PRO in oncoplastic surgery.

METHODS

This is an analytical study, with non-probabilistic sampling. A research was performed in the MEDLINE database through PubMed. The electronic search strategy included the terms (“oncoplastic” OR “partial breast reconstruction”) AND (“aesthetic” OR “patient satisfaction” OR “quality of life”). It was limited to a period of five years.

Studies published between January 2015 and March 2020, related to oncoplastic surgery by any technique, either immediate or late, and assessed PRO as a main outcome (e.g., aesthetic results, quality of life, and satisfaction with results) were included. Articles published in languages other than English, Portuguese, or Spanish, studies on breast reconstruction after mastectomy and those whose primary outcome was the evaluation of cancer results (e.g., survival and relapses), and others were excluded.

Two authors independently read the abstracts of the retrieved references. Whenever there was a doubt, it was discussed with the senior author in a consensus meeting. All retrieved articles that met the eligibility criteria were included. Authors’ data were checked, their affiliations were recorded, and the studies were stratified, according to specialty, into two groups: Group 1 (plastic surgery) and Group 2 (other surgical specialties).

When there were authors from different areas in the same study, including nonsurgical specialties, we considered the following criteria to identify the surgical specialty to attribute that paper:

1. affiliation of the corresponding author;
2. affiliation of the first author; and
3. affiliation of the last author.

To verify the integration of specialties in scientific production, we again stratified the studies into three groups: Group

A (only plastic surgeons), Group B (other surgical specialties without any plastic surgeon), and Group C (plastic surgeons and surgeons of other specialties).

We also recorded and analyzed country and type of service (public/philanthropic or private assistance, university, or research center) where the study was conducted and the journal’s impact factor.

The Bioestat[®] version 5.3 software (Instituto Mamirauá, Amazonas and Pará, Brazil) was used for statistical analysis. The significance level of 0.05 was established for all tests.

The Mann-Whitney U test and χ^2 test were applied to compare Groups 1 and 2 regarding numerical and categorical variables, respectively. Kruskal-Wallis test was applied to compare Groups A, B, and C regarding journals’ impact factors. Whenever there was a statistical difference between these groups, the multiple comparison test was used to verify which group significantly differed from the others.

RESULTS

The electronic search retrieved 292 references. After reading the abstracts and agreeing on their relevance, 150 studies were excluded (Figure 1).

Thus, 142 publications were included. Most of them (60.6%) were performed by specialties other than plastic surgery. Most studies (57%), in both groups, were published in journals with impact factor ≤ 2 . The overall median impact factor was 1.85 (Table 1). The majority (83%) of the publications were collected from university services (Figure 2), and the European surgeons authored 40.9% of the publications (Figure 3).

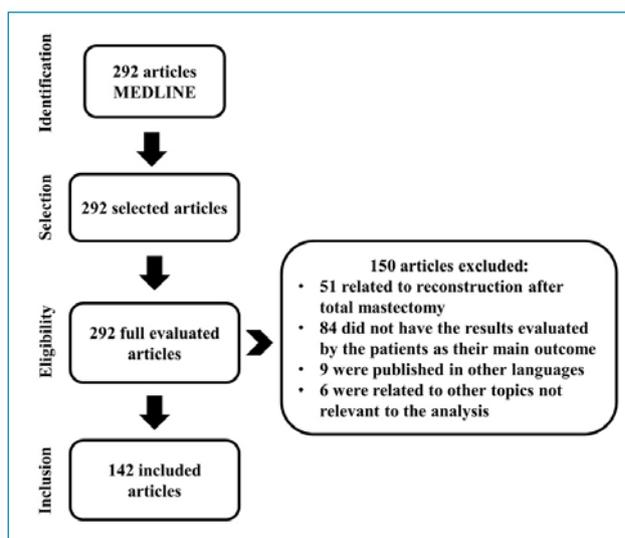
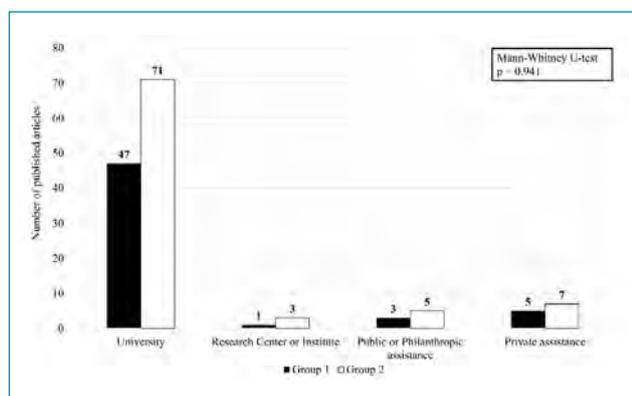
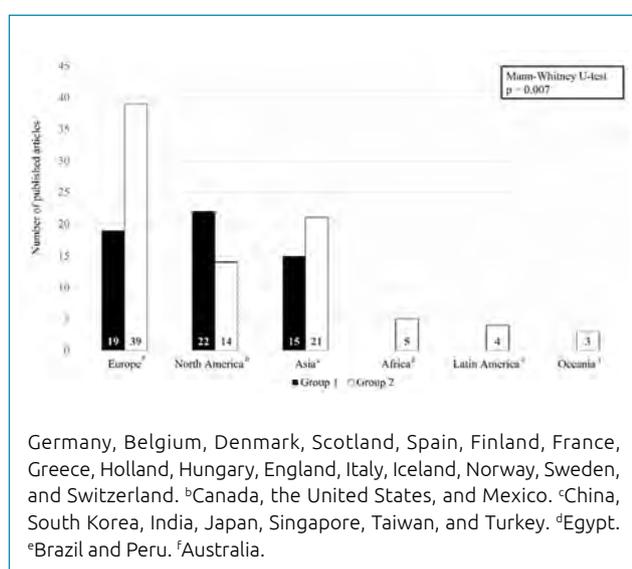


Figure 1. Flow diagram of articles.

Table 1. Comparison between Groups 1 (plastic surgeons) and 2 (other surgical specialties) regarding the impact factor of the journals.

| | Group 1 (n=56) | Group 2 (n=86) | Group 1 × Group 2 |
|------------------|-------------------|-------------------|---------------------|
| Impact factor | | | Mann-Whitney U test |
| Range | 0.000–5.586 | 0.000–35.386 | p=0.756 |
| Median±IQR | 1.721±1.43 | 1.866±2.39 | |
| Mean±SD | 1.912±1.25 | 2.327±3.79 | |
| | n (%) | | χ ² test |
| Impact factor ≤2 | 36 (64.3) | 45 (52.3) | p=0.159 |
| Impact factor >2 | 20 (35.7) | 41 (47.7) | |

IQR: interquartile range; SD: standard deviation.

**Figure 2.** Comparison between Groups 1 (plastic surgeons) and 2 (other surgical specialties) regarding the type of service where the studies were conducted.**Figure 3.** Comparison between Groups 1 (plastic surgeons) and 2 (other surgical specialties) regarding the continent/country of origin of the study.

Stratification into Groups A, B, and C is shown in Table 2. Considering the publications that had the participation of at least one plastic surgeon (Group A+Group C), it was observed that they corresponded to 50% of the total (n=71). When compared with publications made by other specialties (without any plastic surgeon author), there was also no statistical difference regarding the impact factors (Mann-Whitney U test; p=0.670).

DISCUSSION

The overall survival of breast cancer patients increases annually. Consequently, there is a growing emphasis on cancer survival, with professional and accreditation organizations outlining guidelines for high-quality survival care; in other words, care that guarantees quality of life¹⁷.

Plastic surgeons are pioneers and have leadership in the field of breast reconstruction, mastering volume replacement techniques through the use of autologous flaps or implants^{14,24}. However, current surgical treatment for breast cancer requires that breast surgeons and plastic surgeons work together, using oncoplastic techniques to provide superior oncological and aesthetic results^{19,25}.

In the European model, various techniques of oncoplastic surgery, including both volume displacement and volume replacement techniques, are commonly practiced by general surgeons and breast surgeons^{21,23,25}. The mainstream consideration is that, although the oncoplastic approach is more complicated and time-consuming than the conventional CBT approach, it provides better results and satisfaction rates for cancer. Therefore, breast surgeons must also be trained in plastic surgery or, at least, collaborate with plastic surgeons while performing oncoplastic surgery⁶.

Our review of the publications on PRO in oncoplastic surgery confirmed the European leadership in the use of oncoplastic

Table 2. Comparison among Groups A (only plastic surgeons), B (only surgeons of other specialties), and C (both) regarding the impact factor of journals.

| | Group A (n=27) | Group B (n=71) | Group C (n=44) | Groups A × B × C |
|------------------|-------------------|-------------------|-------------------|---------------------|
| Impact factor | | | | Kruskal–Wallis test |
| Range | 0.000–3.946 | 0.000–35.386 | 0.000–3.946 | p=0.661 |
| Median±IQR | 1.837±2.37 | 1.922±2.48 | 1.792±1.35 | |
| Mean±SD | 2.057±1.30 | 2.463±4.16 | 1.759±1.01 | |
| | n (%) | | | χ^2 test |
| Impact factor ≤2 | 16 (59.3) | 37 (52.1) | 28 (63.6) | p=0.463 |
| Impact factor >2 | 11 (40.7) | 34 (47.9) | 16 (36.4) | |

IQR: interquartile range; SD: standard deviation.

techniques. Countries on the European continent were responsible for 40.8% (58/142) of publications, followed by North America and Asia, with 25% (36/142) each. Furthermore, in Europe, general or breast surgeons published more on the topic than plastic surgeons, with significant statistical difference ($p=0.007$).

In Canada, oncoplastic surgery is not traditionally a part of the formal training of general or oncology surgeons³. In this country, there is a greater interaction between breast surgeons and plastic surgeons regarding an integrated model of surgical care. The most complex volume replacement techniques are always performed by plastic surgeons; surgeons who intend to perform this type of reconstruction should receive formal specialized training in plastic surgery. Even the procedures for volume repositioning are more commonly performed in collaboration with a plastic surgeon^{14,22}.

Brazil has a history of excellence in plastic surgery, and this was reflected in Brazilian oncoplastic surgery, performed predominantly by plastic surgeons. In 2010, 75% of these procedures in Brazil were performed by plastic surgeons^{22,24}. The technical development in oncoplastic surgery in Brazil took place mainly in large, specialized centers, with teams of plastic surgeons and breast surgeons working together²⁴.

A national survey with surgeons from the American Society of Breast Surgeons and the American Society of Plastic Surgeons showed that the majority (69.7%) of breast surgeons reported no limitations for performing oncoplastic surgery in their practice, and 50% of plastic surgeons reported that partial breast reconstruction was limited in their practice because they were not getting the referrals. Surgeons from both specialties agreed that the most complex reconstructions are best performed using the team approach, gathering both types of specialist⁷.

A similar survey was conducted in the UK, with members of the British Association of Plastic, Reconstructive and Aesthetic Surgeons and the Association of Breast Surgery. Surgeons were contacted in two moments, 2010 and 5 years later. They found that, in 2015, the majority (75%) of breast surgeons remained interested in additional training in oncoplastic techniques, while the interest rate of plastic surgeons in additional training in oncoplastic surgery dropped from 62–27%²⁰.

The results of the present study corroborate this tendency to increase the performance of general or breast surgeons in oncoplastic surgery, not only with oncological results but also with patients' satisfaction and quality of life.

There are many reasons why plastic surgeons may not be available to join the team in oncoplastic surgery. There may be a less number of plastic surgeons in specific geographical area or the available plastic surgeon may not be interested in breast reconstruction. The compensation for the plastic surgeon may also be inadequate, incompatible with their level of specialization, and the complexity of the procedure to be performed. Although teamwork is possible in many places, the existence of areas with limited resources and without available plastic surgeons has encouraged breast surgeons to seek training in oncoplastic techniques¹⁸.

Our study has limitations. A major one is the limited inclusion of studies (only those indexed at MEDLINE, in a period of five years, and written in English, Spanish, or Portuguese languages). Our results demonstrate the growing concern of general and breast surgeons with quality of life and patient's satisfaction with the results of oncoplastic surgery, outcomes that have always been part of the primary vocation of plastic surgery. However, despite the majority (83%) of the publications having been carried out in the university services, most studies are still published in journals with a relatively low impact factor (global median=1.85).

CONCLUSIONS

In the previous years, surgeons from specialties other than plastic surgery published more on PRO in oncoplastic surgery, but there was no statistical difference between the groups regarding the impact factor of the journals. Our study does not intend answer the question of who should undergo oncoplastic surgery since we recognized the complexity of this subject. The fact is that, whether a plastic surgeon or a breast surgeon, the major concern must be the patients to remain cancer free and satisfied with the aesthetics of the breast.

AUTHORS' CONTRIBUTIONS

RSA: Conceptualization, Data Curation, Formal Analysis, Writing – Original Draft, Writing – Review & Editing. **CVL:** Conceptualization, Data Curation, Formal Analysis, Writing – Original Draft, Writing – Review & Editing. **PGD:** Conceptualization, Data Curation, Formal Analysis, Writing – Original Draft, Writing – Review & Editing. **LMF:** Conceptualization, Data Curation, Formal Analysis, Writing – Review & Editing. **DFV:** Conceptualization, Data Curation, Formal Analysis, Writing – Original Draft, Writing – Review & Editing.

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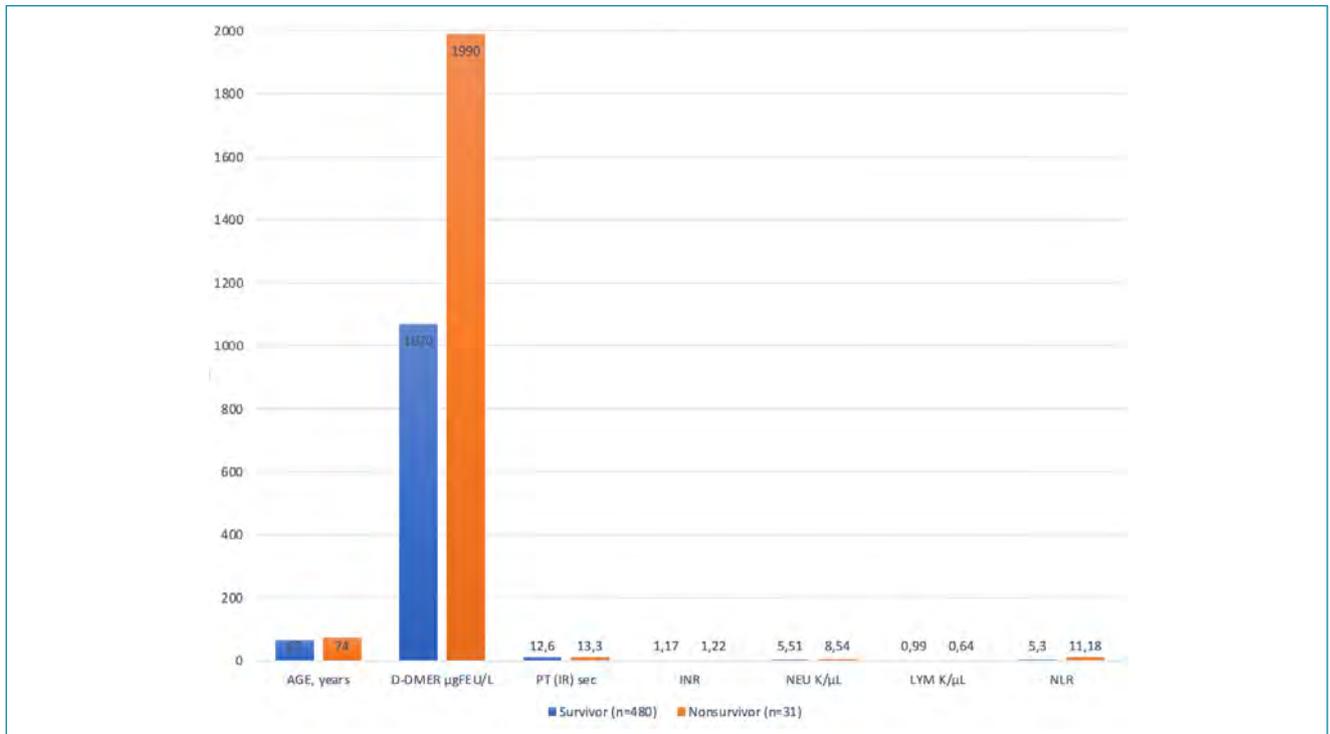


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<https://doi.org/10.1590/1806-9282.67.Suppl1.20200848ERRATUM>

In the manuscript “Evaluation of cardiac parameters between survivors and nonsurvivors of COVID-19 patients”, <https://doi.org/10.1590/1806-9282.67.Suppl1.20200848>, published in the Rev Assoc Med Bras. 2021;67(Suppl 1):80-5, on page 83 Figure 1:

Where it reads:



It should read:

