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Lithiasis in transplant kidney: what to do?

Pedro Francisco Ferraz de Arruda[1*], Luisa Ferraz de Arruda[2], Ricardo Henrique De Rizzo[3], Lara Ferraz de Arruda[4]

Renal lithiasis in a harvested kidney offered for transplant is uncommon (incidence: 0.02–3.4%)[1,2]. However, some calculi can be transferred with the graft to the recipient or can form after the transplant.

In our 30 years of experience at a kidney transplant unit, cases of lithiasis in transplant kidneys are common. Transplant patients with lithiasis may not have any pain symptoms due to the denervation of the transplanted kidney. Moreover, an increase in serum levels of creatinine may occur, which should be analyzed with caution, as there is a risk of ureteral obstruction due to the migration of the calculus.

For cases in which the diagnosis of lithiasis is associated with urinary infection, the transplant should be canceled. On the other hand, renal lithiasis does not necessarily imply the cancellation of surgery, as a postoperative follow-up can help define the best therapeutic option (clinical or surgical). Surgical removal of diagnosed calculi can be performed preoperatively, during surgery, or in the postoperative period. If the therapeutic option is "wait-and-see," follow-up must be rigorous.

As calculi diagnosed in the perioperative period can be transferred to the transplant recipient, ultrasound is encouraged before nephrectomy. Besides the low cost, this examination enables the diagnosis and removal of the calculus during transplant surgery, consequently diminishing possible complications, such as ureteral obstruction and infection after transplantation[3].

The inclusion of imaging examinations in the examination protocol of donors of multiple organs is also important to indicate harvesting or not, and the transplant team should be made aware of the results. From the ethical standpoint, although donation is a morally good act, there should be trust between the health professional and the patient regarding fair, equitable access, informed consent, and respect to the autonomy of the will, dignity, and rights of all involved in the process to avoid the subsequent civil/penal liability of the physician[4].

AUTHORS' CONTRIBUTIONS

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

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Brazilian pulmonology guidelines on Delphi panel for post-coronavirus disease 2019: reflections on persons deprived of liberty

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A guideline on focus published in the *Journal of the Brazilian Medical Association* showed the need for a continuous medical education program offered by different institutions to increase the knowledge of COVID-19; nevertheless, there are institutions that were not included in the discussion of this study[1]. A Delphi study[1] on COVID-19 should comprehensively discuss the subject, but the authors[1] did not address the strategies used in the health of Brazilians deprived of liberty during the COVID-19 pandemic. Therefore, as a contribution to the literature, we summarize the main findings on this topic.

In March 2020, the World Health Organization declared a pandemic due to the discovery of the respiratory disease caused by the new coronavirus (SARS-CoV-2). As a measure to prevent the disease (COVID-19), the use of masks and social isolation were decreed due to the high transmission of the virus through talking, sneezing, and coughing[2]. People deprived of liberty suffer from numerous health problems, especially those of the respiratory system such as asthma and tuberculosis, due to the lack of structures in the penitentiary units, such as overcrowding in cells, unhealthy conditions, and climate control. Although the Brazilian penitentiary system is governed by laws that guarantee the health of those who are deprived of liberty, the execution of such laws and the preparation of health teams are flawed[3].

The national policy for comprehensive health care for people deprived of liberty in the prison system of 2014 aims to guarantee the health of this population; however, in most protocols issued by the government regarding the confrontation of the pandemic, the prison population was rarely mentioned[4]. It is evidenced by the high potential for transmission of the virus in closed environments and with agglomerations, and in the conditions in which Brazilian prisons are found, the possibility of transmission of the coronavirus in penitentiary units is high. As it is already an environment of social isolation, the isolation measure results in a new term called super-isolation[2]. Being characterized as a place of extreme social vulnerability, prisons worldwide have an overrepresentation of certain demographic groups, such as the black population, and the COVID-19 pandemic will disproportionately impact these specific communities[5].

After a preliminary search of Medline, Cochrane, and JBI Evidence Synthesis, we noticed that there was a gap in the literature on this topic. In this sense, it becomes valid to build a discussion covering this topic, since the health of people deprived of liberty in Brazil is unassisted, and public policy aimed at this population is recent. In this view, the research question can be defined as: which are the main strategies and measures implemented in the health of the Brazilian population deprived of liberty during the COVID-19 pandemic? Therefore, we summarized and discuss the main strategies used in the health of people deprived of liberty in Brazil during the COVID-19 pandemic.

Original articles, experience reports, and case studies published in English, Portuguese, and Spanish languages that addressed the health of population deprived of liberty in the context of the COVID-19 pandemic were included. Duplicate articles that did not fit the proposed theme were excluded after reading the title/abstract and also after reading them in full text. Since it is a relatively new subject, no time limit was defined. First, the articles were selected by reading

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the title and abstract beforehand, and after going through this selection and fitting them into the review, the articles were read in full (Figure 1).

IMPLEMENTATION OF COVID-19 CONTROL MEASURES

In this category, control measures against the coronavirus in prisons stand out. Considering prisons as a means of facilitating the resurgence of the pandemic, preventive measures must be dealt with rigorously, following the three main principles: the entry of the virus into penitentiary units must be postponed, it must be controlled if it is already in circulation, and it is the sole responsibility of the preparation of penitentiary units to deal with those who develop SARS-CoV-2[2].

In a penitentiary in Rio Grande do Sul, any individual who enters the unit will be screened for flu symptoms by a trained penitentiary agent, who will then answer a questionnaire to assess the symptoms suggestive of the disease, measuring the temperature and oxygen saturation. In cases suggestive of the coronavirus, entry to the unit would not be allowed for at least 14 days, and the individual is advised to seek out a health unit.

Regarding the entry of new people deprived of liberty, screening was adopted as mentioned above. In asymptomatic cases, they would be isolated for 14 days, and after compliance, they would be passed to the prison health team and submitted to the rapid test, if the result was non-reagent, they would be released to join other prisoners; if not, they would spend another 7 days in isolation[6].

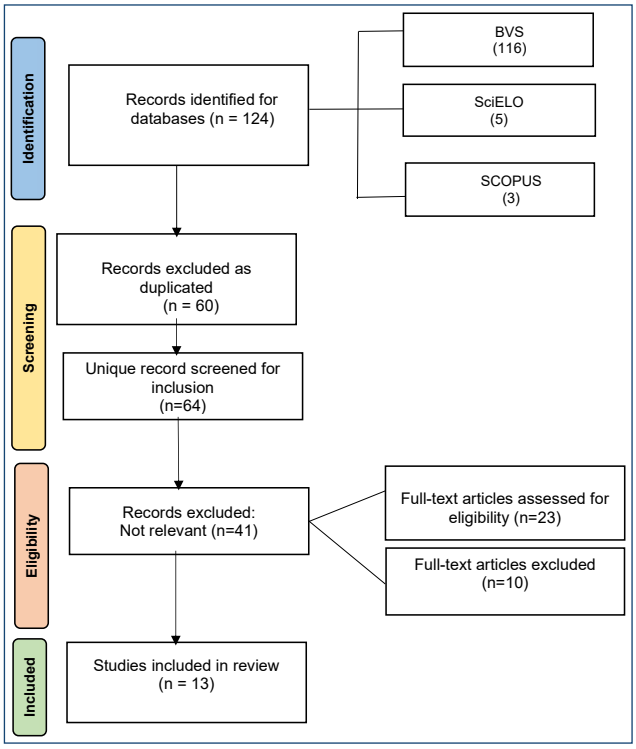

Figure 1. Flowchart.

PRISON TEAM PREPARATION

The category addresses how prison staff were trained and prepared to deal with the virus. At the penitentiary in Rio Grande do Sul, events with servers were used as a strategy to provide the necessary guidance, such as the use of personal protective equipment, correct hand hygiene and disinfection of surfaces, and know what to do if they had symptoms of the coronavirus[6]. In the state of Bahia, government publications were prepared to face the pandemic in this population, with the training of professionals via videoconference, where a questionnaire was carried out about the distribution of hygiene materials to professionals and people deprived of liberty, and guidance on drawing up an internal protocol for coping with COVID-19[7].

POPULATION DEPRIVED OF LIBERTY VACCINATION SCHEDULE

Category brings how the vaccination scheme for the population deprived of liberty was carried out, where the national plan for the operation of vaccination against COVID-19 brought people deprived of liberty as members of phase 4 of the vaccination, but in a new version of the plan, the prison population was no longer treated as a priority group. Finally after much discussion, the plan was revised, and it was decided that vaccination would be articulated with the state, municipal, and justice departments according to the prison system[8]. The Ministry of Health aims to vaccinate 90% of people deprived of liberty against influenza. Vaccination is one of the strategies used to reduce flu conditions, which consequently reduces the number of people tested for COVID-19[6].

AUTHORS' INTERPRETATION

We observed that the studies did not detail how the vaccination schedule of the people deprived of liberty would be carried out and also the great difficulty for the implementation of actions to control the contamination of the virus due to the conditions in which the prisons are found, such as the overcrowding of the cells, lack of ventilation, and unhealthy conditions, which was already a health problem for other infectious diseases but has become an aggravating factor for the coronavirus, which spreads quickly and easily.

The first case of COVID-19 registered in Brazil in the prison system was in the state of Rio de Janeiro, as soon as the pandemic was declared by the World Health Organization in March 2020. Since then, until August 2021, there were already 272 deaths among people deprived of liberty[9]. In the United States of America, the number of COVID cases in the prison system was 5.5 times higher when compared to the general population[10].

Due to the poor governance of the financial resources of Brazilian penitentiary units and the unpreparedness of health teams, it could make it difficult for the population deprived of liberty to access the health care network in cases of extreme need due to COVID-19[2]. In Brazil, the pandemic required not only control measures against the virus but also political positioning, requiring the elaboration of government publications that served this specific population, as occurred in the state of Bahia[3].

The National Council of Justice recommended extrication measures, thus aiming at reducing the overcrowding of cells, with provisional and definitive freedom, as well as house arrest for people deprived of liberty with comorbidities or elderly people, but such measures were rarely applied within units[4]. In Iran, this strategy was used, and there was the release of more than 70,000 people deprived of liberty, which did not occur in Italy and consequently generated riots within penitentiary units, reinforcing the idea that the release of those who apparently would not commit additional crimes could decrease the transmission of COVID-19[11].

The Brazilian Penal Execution Law has the right to ensure visits by family members and spouses of those deprived of their liberty on pre-established days, and this right is often violated, becoming an aggravation in the pandemic, given that during these visits family members also supervise the conditions[12].

Due to the measure to reduce visits by relatives of people deprived of liberty, in Spain, as a form of compensation, an increase in telephone calls and also in videoconferences was allowed, aiming to minimize the negative impacts[13]. Controlling the spread of the virus in prison environments is essential to prevent a larger outbreak of SARS-CoV-2, in view of the health of all those who live and work in this place and also of the general population[14].

In conclusion, prisons favor the transmission and proliferation of the coronavirus, and the main strategies for minimizing the pandemic issued by the World Health Organization were not designed for people deprived of liberty (who already live in a situation of social isolation and vulnerability). Thus, the neglect of the health of this population during the COVID-19 pandemic was evident.

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Postintervention pain levels after elective coronary angiography

Mesut Engin[1*], Ahmet Kagan AS[1], Ufuk Aydın[1], Yusuf Ata[1], Senol Yavuz[1]

Dear Editor,

We have read the article by Kılıç et al.[1] entitled "Comparison of pain levels of traditional radial, distal radial, and transfemoral coronary catheterization" with great interest. First of all, we congratulate the authors for their valuable contribution to the literature. However, we would like to discuss some points about postintervention pain after coronary angiography.

In this study, the authors evaluated post-procedural pain conditions according to different intervention sites in coronary angiography. The study was planned prospectively at three centers, and a total of 540 patients were included in the study (180 patients in each group according to the intervention area)[1]. Were the interventions performed by the same physician in each center? Did each center puncture from only one intervention site? Are groups created like this? Why were 180 patients included in each group in the study? What was the total number of coronary angiographies performed in the centers during this period? The authors stated that "The choice of approach was left to the discretion of the operator". What are their criteria for this choice?

Patients scheduled for non-urgent coronary intervention were included in the study[1]. Did the patient group have a history of analgesic or antipsychotic use in the pre-intervention period? In our country, uncontrolled non-steroidal drug use is quite high. Did the authors think this may affect the study results? It is also known that post-procedural pain levels may be affected by preoperative anxiety[2]. For this reason, pre-procedure anxiety-reducing applications can also be performed[3]. Was a pre-procedural anxiety assessment performed in this study group?

Doppler ultrasonography (DUSG) can be used as an important tool to increase the success of the intervention[4]. Was DUSG used on patients included in the study?

Finally, 40 patients were included in the severe pain group in the study, of whom 32 underwent distal radial artery intervention[1]. When we look at this patient group, the average number of punctures is approximately twice that of the other groups. According to these results, can we attribute the severe pain to the number of punctures performed? Could multivariate logistic regression analysis be done to clarify this situation? We would like to receive the valuable comments of authors on these issues.

AUTHORS' CONTRIBUTIONS

ME: Conceptualization, Data curation, Investigation, Methodology, Supervision, Validation, Visualization, Writing – original draft, Writing – review & editing. **AKA:** Investigation, Methodology, Supervision, Validation, Visualization, Writing – original draft, Writing – review & editing. **UA:** Investigation, Methodology, Supervision, Validation, Visualization, Writing – original draft, Writing – review & editing. **YA:** Investigation, Methodology, Supervision, Validation, Visualization, Writing – original draft, Writing – review & editing. **SY:** Investigation, Methodology, Supervision, Validation, Visualization, Writing – original draft, Writing – review & editing.

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Comment on "A retrospective analysis: the outcome of renal replacement therapies in critically ill children"

Qinqin Zhao[1], Peng Wei[1]*

Dear Editor,

We read with great interest the recent retrospective analysis[1] focusing on the outcomes of renal replacement therapies in critically ill children. The study provides valuable insights into the efficacy and impact of these therapies on a pediatric population facing critical medical conditions. The findings indicate that these interventions play a crucial role in managing renal dysfunction in critically ill children, thereby positively influencing their overall prognosis. Moreover, the study's emphasis on the pediatric population is particularly significant. As renal replacement therapies are often tailored for adult patients, understanding their efficacy and potential challenges in children is of paramount importance. By focusing on this specific demographic, the study contributes to a more targeted approach to treatment strategies, potentially leading to improved outcomes and a better quality of life for critically ill children. However, some of the following concerns deserve further clarification.

First, it is important to mention an issue observed in Table 2 of this study[1]. The table presents the age at admission (months) for both the survivor and nonsurvivor groups. It is noteworthy that the age at admission for survivors is reported as 63 (3–172) months, a value significantly higher than the non-survivors' median age of 6 (5–84) months. While the statistical analysis might suggest no significant difference between the two groups in terms of age at admission (p=0.42), it is important to recognize that relying solely on p-value, especially when dealing with such substantial numerical differences (63 vs. 6 months), might not provide a comprehensive understanding of the actual age-related disparities between the groups. In addition, it is crucial to consider the potential implications of this age discrepancy on the outcomes and interpretations of the study. The fact that such a significant difference in ages between the two groups could have a confounding effect on the study's conclusions, which should be thoroughly addressed in the discussion section. Failing to do so may lead to misinterpretations of the results and the potential misapplication of the findings in clinical practice.

Second, another issue is also observed in Table 2 of this study[1]. The description of some data in Table 2 seems to be inaccurate. Obviously, it is indicated that seven patients in the survivor group received vasoactive inotropic drugs, which would correspond to a usage proportion of 7/28=25%. However, this article erroneously states this proportion as 41.2%. Similarly, in the non-survivor group, where three patients received vasoactive inotropic drugs, the corresponding proportion should be 3/9=33.33% rather than the reported 100%.

Third, we would like to address discrepancies observed in Table 3 of this study[1], which presents data related to systolic blood pressure at admission and its association with mortality, represented by an odds ratio of 0.98 with a 95% confidence interval (CI) of 1.12–1.5. It is evident that the reported odds ratio value of 0.98 lies outside the range of the 95%CI, which is clearly erroneous. Statistically, the value of the odds ratio unequivocally falls within the bounds of the 95%CI. This inconsistency raises concerns about the accuracy of the reported results. Therefore, it is recommended that the authors should carefully review the data presented in this study and ensure that such inconsistencies are addressed and rectified accordingly.

AUTHORS' CONTRIBUTIONS

QZ: Conceptualization, Investigation, Methodology, Writing – original draft, Writing – review & editing. **PW:** Conceptualization, Investigation, Methodology, Supervision, Writing – original draft, Writing – review & editing.

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Investigation of the relationship between fear of birth and prenatal attachment in pregnancy

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SUMMARY

OBJECTIVE: This study was conducted to examine the relationship between the fear of birth and level of prenatal attachment experienced by the pregnant women.

METHODS: In our descriptive and relationship-seeking study conducted between January and March 2020 in Konya, 485 pregnant women who met the inclusion criteria were included in the study. Inclusion criteria for the study were women who were pregnant at the age of 18 years and above, having Turkish literacy, had spontaneous conception were over the 28th gestational week, having a healthy fetus, and not having any existing health problems (based on self-report). The data were collected with an information form, "Prenatal Attachment Inventory" and "Wijma Birth Expectation/Experience (Version A) Scale."

RESULTS: The mean score of the pregnant women from the "Prenatal Attachment Inventory" was 62.44 (21–84), and the mean score of the "Wijma Birth Expectation/Experience Scale/Version A" was found to be 59.45 (0–165). It was concluded that 47.2% of the pregnant women had low, 38.7% had moderate, and 14.1% had high levels of fear of birth. It was determined that there was a negative and weakly significant relationship between "Prenatal Attachment Inventory" and "Wijma Birth Expectation/Experience Scale/Version A" scores of pregnant women (r=-0.11 and p=0.23).

CONCLUSION: In our study, it was determined that as the fear of birth increased, prenatal attachment levels decreased. Initiating and maintaining a healthy mother-infant bond is important for reducing fear of birth.

KEYWORDS: Pregnant women. Birth. Fear. Emotional bonds.

INTRODUCTION

Pregnancy is a natural process that includes biological, cultural, and psychological changes in women's life[1]. In this process, which is full of experiences, negative and permanent changes may occur in the emotional attitudes and behaviors of the expectant mother with the effect of active hormones[2]. The fear of birth, which significantly affects psychosocial health, can also negatively affect the pregnancy and the postpartum period[3]. Not knowing how the birth will take place, feeling ignorant and inadequate about the labor, fear of pain, fear and distrust of health personnel, surgical interventions, thinking that there will be risk to the infant or mother, and death anxiety are the causes of fear of birth[4]. The prevalence of fear of birth detected in pregnant women differs in sociodemographic, obstetric, and cultural terms[5]. In a study conducted in Turkey, it was determined that 62.5% of pregnant women experienced fear of birth[6]. Güleç et al., stated this rate as 46.4% in their study[7]. In a study conducted in Norway, the rate of fear of childbirth experienced by pregnant women was found to be 56.8%, and it was stated that 7.5% of these pregnant women experienced severe fear of childbirth[8]. Toohill et al., found this rate to be 31.4% in their study on nulliparous pregnant women[9]. Fear of childbirth is a problem that can have long-term consequences for the health of women and children, which can be experienced during pregnancy and during and after childbirth[10]. Risky pregnancy history, listening to or watching fearful birth experiences, labor with vacuum or forceps intervention, history of anomaly or stillbirth, history of excessive blood loss during delivery, emergency cesarean section decision, emergencies and experiences during birth, pregnancy and birth, and insufficient social support can trigger the fear of childbirth[11]. In addition, the fear of childbirth can lead the mother to depression[12]. One of the prominent issues in maintaining the psychosocial well-being of pregnant women is prenatal attachment. Prenatal attachment is the first communication established between mother and infant, which provides support for infant development and the emergence of early parenting skills[12,13]. The prenatal period is the period during which the growth and development of the fetus is completed following the onset of pregnancy. In this period, the expectant mother

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adapts to motherhood with the hormonal and physical changes in her body and bonds with her infant. During pregnancy, which is quite active and changing, the first pillars of attachment are to evaluate the emotional and physiological state of the pregnancy, to notice the changes and find solutions if necessary, and to communicate with the fetus with positive emotion[14]. Although it has been determined in the studies that the prenatal attachment level of the pregnant women is good, there are many expectant mothers who have attachment problems[14-18]. Physiological and psychological changes that occur, especially in the expectant mother, are closely related to the prenatal attachment level. Psychiatric problems in pregnancy, prenatal, and postpartum period significantly reduce the level of attachment[19]. Fear experienced in the prenatal period may negatively affect prenatal attachment[20]. The fear of childbirth and attachment problems that can be experienced in the prenatal period can also negatively affect the pregnancy period, birth, and postpartum period, causing psychosocial problems for the mother and the infant. This study was conducted to examine the relationship between the fear of birth and level of prenatal attachment experienced by the pregnant women.

METHODS

Ethical aspect of the study

Before starting the research, the ethics committee approval of Necmettin Erbakan University Meram Faculty of Medicine Non-Pharmaceutical and Medical Device Researches Ethics Committee dated 11.12.2019 and decision number 2019/1759, and for the institution where the research was conducted, the ethics committee approval of Konya Provincial Health Directorate Konya Health Services Unit dated 06.02.2020 and numbered 86737044-806.01.03 were obtained. Also, verbal and written consent was obtained from the participants who met the criteria for being included in the sample and agreed to participate in the research.

Study design

This was designed as a descriptive and relation-seeking study.

Population and sample of the study

The universe of the study consisted of pregnant women who applied to the maternity polyclinics of a training and research hospital in Konya, Turkey, between January 2020 and March 2020. The G*Power 3.1.9.2 package program has been used to determine the sufficient sample size. For the sample of the research, the results of the study conducted by Buko and Özkan were taken as basis. It was decided to include 475 women in the sampling[14]. The data in our study were collected using the face-to-face interview technique from pregnant women, and it takes 15–20 min to complete each questionnaire.

Inclusion criteria of the study

The inclusion criteria of the study were women who were pregnant at the age of 18 and above, over the 28th gestational week, literate in Turkish, conceived spontaneously, had a healthy fetus, and who did not have any existing health problems (based on self-report).

Exclusion criteria of the study

The exclusion criteria were pregnant women who did not want to participate in the study and could not fill in the data collection tool.

Data collection tools

"Personal Information Form", "Prenatal Attachment Inventory (PAI)", and "Wijma Birth Expectation/Experience Scale/Version A (W-DEQ-A)" were used for data collection.

Personal Information Form

The form, which was created as a result of the literature review[14,16,21], consists of questions regarding sociodemographic and obstetric characteristics.

Prenatal Attachment Inventory

Prenatal Attachment Inventory was developed by Mary Muller in 1993 to describe the thoughts, feelings, and situations experienced by women during pregnancy and to determine their level of attachment to the infant during the prenatal period. The Turkish validity-reliability study of the scale was carried out in Turkey by Yılmaz and Beji in 2013. PAI is applied to pregnant women at 20–40 weeks of gestation. In the study by Yılmaz and Beji, the Cronbach's alpha reliability coefficient of the scale was stated as 0.84[21]. In the study, the Cronbach's alpha reliability coefficient of the scale was found to be 0.87.

Wijma Birth Expectation/Experience Scale/Version A

W-DEQ-A was developed by Wijma et al., to measure the fear of birth experienced by women. The Turkish validity and reliability of the scale were performed by Korukcu and Kukulu. The W-DEQ-A scale is applicable to pregnant women at 28–40 weeks of gestation. Korukcu and Kukulu stated the Cronbach's alpha coefficient of the scale as 0.89[22,23]. In the study, the Cronbach's alpha reliability coefficient of the scale was found to be 0.90.

Data analysis

The SPSS (Windows 22.0) software was used for data analysis. Number, percentage, mean, and standard deviation are given in the descriptive statistics of the study. In the comparison of the difference between the mean PAI and W-DEQ-A scores of the pregnant women according to the independent variables, the t-test for the independent groups and the Mann-Whitney U test were used in the two-group variables according to the sample number in the groups. The independent variables that had an effect on the PAI and W-DEQ-A scores of the pregnant women in the primary analyses were evaluated with multiple regression analysis (backward method). The significance level was accepted as $p<0.05$.

RESULTS

When the PAI scores according to the sociodemographic characteristics of the pregnant women were evaluated, it was found that the scores differed according to age, spouse's age, marriage duration, and educational status ($p<0.05$), while the change according to other variables (spouse's education level, employment status, spouse's employment status, family type, house income, and settlement) was insignificant ($p>0.05$) (Table 1). When the mean W-DEQ-A scores of the pregnant women in the study group were analyzed according to their sociodemographic characteristics, it was found that the scale score differed according to the education level and income of the spouse ($p<0.05$), while the change according to other variables (age in years, age of spouse in years, marriage duration in years, education status, employment status, spouse's employment status, family type, and settlement) was insignificant ($p>0.05$) (Table 1).

When the PAI scores according to the obstetric characteristics of the pregnant women were evaluated, it was found that the scale score differed according to the number of pregnancies, the desired pregnancy status, the history of miscarriage and stillbirth, and regular visits to the controls ($p<0.05$). The change according to other variables (gestational period (weeks), duration between current pregnancy and previous pregnancy (years), knowing the gender of the infant, expected gender, relationship with the spouse, and planned method for child feeding) is insignificant ($p>0.05$) (Table 1). When the W-DEQ-A score averages of the pregnant women in the study were examined according to their obstetric characteristics, it was found that the score differed according to the state of wanting pregnancy, going to antenatal care regularly, the bond with their mother and the relationship with their spouse, and the method of feeding the child ($p<0.05$). The change with respect to other variables (parity, gestational period (weeks), duration between current pregnancy and previous pregnancy (years), miscarriage history, still birth, knowing the gender of the infant, expected gender, ties with her own mother, and positive changes in lifestyle) is insignificant ($p>0.05$) (Table 1).

Five independent variables that have a significant effect on the Prenatal Attachment Scale score of the pregnant women, from the most important to the least important, the number of pregnancies ($p<0.001$), regular visits to controls, positive changes in pregnancy lifestyle and health behavior ($p<0.01$), education level, and age ($p<0.05$) explain the change (variance) of the Prenatal Attachment Scale score of pregnant women as 13% (Table 2).

Four independent variables that have a significant effect on the W-DEQ-A Scale score of pregnant women, from the most important to the least important, income evaluation, education level of the spouse, evaluation of the relationship with the spouse ($p<0.01$), and planned method for child feeding ($p<0.05$) explain the change (variance) of the pregnant women in the W-DEQ-A Scale score as 7% (Table 3).

DISCUSSION

According to the results of our study, which was conducted to examine the relationship between the fear of birth experienced by pregnant women and their prenatal attachment status, the scores of the pregnant women in the research group from PBI were in the range of 27–84, and it was determined that the attachment levels of the pregnant women were moderate. In addition to the results similar to our study in the literature[14,16], there are also studies with lower mean PBI scores that are significantly different from our study[15,17,18,24]. It was determined that the mean fear of childbirth score experienced by the pregnant women included in the study was in the range of 0–130 and was at a low level. In addition to moderate birth fear results in the literature[3,25,26] studies with parallel results with our study[8,9,11,27], it has been determined that there is a negative and weakly significant relationship between the PBI scores and W-DEQ-A scores of the pregnant women ($p=0.023$). As the W-DEQ-A scores of pregnant women increase, PBI scores decrease. In line with these findings, it can be said that it was concluded that the fear of childbirth experienced by pregnant women is an important issue that should be evaluated before and during pregnancy.

In this study, the mean attachment score of pregnant women decreases with age. This is an indication that young mothers-to-be are eager during pregnancy and accept their child easily, and their attachment situations are experienced more intensely. There are studies with similar findings in the literature[16,21,28].

Table 1. Comparison of Prenatal Attachment Inventory and Wijma Birth Expectation/Experience Scale/Version A scores according to sociodemographic and obstetric characteristics of pregnant women (n=475).

Characteristics		n	%	PAI			W-DEQ-A		
				$\bar{X}$	SD	p	$\bar{X}$	SD	p
Age in years	18–24[a]	181	38.1	64.0	10.2	**0.000 (a>b)**	59.4	24.7	0.992
	25–34[a]	232	48.8	62.4	10.5		59.3	23.2	
	≥35[b]	62	13.1	57.7	10.9		59.7	23.4	
Age of spouse in years	18–24[a]	57	12.0	64.5	10.6	**0.027 (a>c)**	59.6	25.5	0.678
	25–34[b]	308	64.8	62.8	10.4		58.8	23.7	
	≥35[c]	110	23.2	60.2	11.1		61.1	23.1	
Marriage duration in years	1–2[a]	140	29.5	66.2	10.3	**0.000 (a>b)**	57.7	25.5	0.272
	3–4[b]	113	23.8	61.6	9.8		63.2	23.4	
	5–6[b]	76	16.0	61.9	10.3		58.2	21.7	
	≥7[b]	146	30.7	59.6	10.7		58.8	23.3	
Education status	Primary school[a]	241	50.7	60.7	10.4	**0.000 (a<b)**	60.7	23.5	0.160
	High school[a]	145	30.5	62.6	11.0		59.8	24.1	
	≥University[b]	89	18.7	66.5	9.4		55.	23.8	
Spouse's education level	Primary school[a]	255	53.7	61.6	10.9	0.101	62.6	24.0	**0.001 (a>c)**
	High school[b]	121	25.5	62.5	10.6		58.7	23.6	
	≥University[c]	99	20.8	64.3	9.8		52.1	21.9	
House income	Good[a]	90	18.9	63.1	9.6	0.365	52.1	23.0	**0.000 (a<b<c)**
	Moderate[b]	351	73.9	62.4	10.5		60.2	23.4	
	Low[c]	34	7.2	60.1	13.7		70.2	24.5	
Parity	1st pregnancy	149	31.4	66.9	9.4	**0.000**	56.9	25.1	0.117
	≥2 pregnancy	326	68.6	60.4	10.5		60.6	23.1	
Willing pregnancy?	Willing	436	91.8	62.8	10.4	**0.002**	58.6	23.9	**0.020**
	Non-willing	39	8.2	57.4	12.0		67.9	20.2	
Miscarriage history	Yes	99	20.8	60.1	10.1	**0.014**	59.0	21.4	0.827
	No	376	79.2	63.0	10.7		59.5	24.4	
Still birth	Yes	25	5.3	57.7	11.2	**0.024**	61.6	22.3	0.628
	No	450	94.7	62.7	10.5		59.3	23.9	
Regular obstetrics visits	Yes	444	93.5	62.8	10.6	**0.001**	58.3	23.7	**0.014**
	No	31	6.5	56.2	9.3		66.0	23.0	
Ties with mother	Good	407	85.7	62.8	10.3	**0.029**	57.8	22.5	0.052
	Moderate	68	14.3	59.8	11.8		62.2	25.7	
Relationship with the spouse	Good	421	88.6	62.7	10.5	0.086	57.9	23.6	**0.000**
	Moderate	54	11.4	60.0	10.9		71.2	21.6	
Positive changes in lifestyle	Yes	303	63.8	63.7	10.5	**0.000**	58.5	23.7	0.279
	No	172	36.2	60.1	10.5		61.0	23.9	
Planned method for child feeding	Breast feeding	459	96.6	62.6	10.5	0.061	58.9	23.8	**0.008**
	Ready formula	16	3.4	57.3	12.7		72.9	18.1	

The superscript letters a, b, and c represent subgroups for statistical significance in each line. Statistically significant values are denoted in bold.

Table 2. The effect of independent variables on Prenatal Attachment Scale scores of pregnant women: results of multiple regression analysis (n=475).

Independent variables	B	Se	β	t	p	95% confidence interval for B		Collinearity statistics	
								Tolerance	VIF
(Coefficient)	40.19	4.63		8.678	0.000	31.09	49.29		
Parity	5.11	1.05	0.22	4.882	0.000	3.05	7.16	0.885	1.130
Regular obstetrics visits	5.70	1.85	0.13	3.079	0.002	2.06	9.34	0.996	1.004
Positive changes in lifestyle during pregnancy	2.71	0.96	0.12	2.827	0.005	0.83	4.60	0.979	1.022
Education status	2.72	1.22	0.10	2.232	0.026	0.33	5.12	0.921	1.086
Age in years	-2.81	1.41	-0.09	1.995	0.047	-5.57	-0.04	0.928	1.077

R: 0.37. Adjusted R^2: 0.13. F: 14.88. p: 0.000. Durbin Watson: 1.96.

Table 3. The effect of independent variables on the Wijma Birth Expectation/Experience (Version A) Scale score of pregnant women: results of multiple regression analysis (n=475).

Independent variables	B	Se	β	t	p	95% confidence interval for B		Collinearity statistics	
								Tolerance	VIF
(Coefficient)	29.29	8.32		3.520	0.000	12.94	45.64		
House income	7.03	2.19	0.15	3.206	0.001	2.72	11.34	0.929	1.076
Spouse's education level	-3.89	1.37	-3	2.849	0.005	-6.57	-1.21	0.930	1.075
Relationship with the spouse	9.74	3.46	0.13	2.812	0.005	2.94	16.55	0.914	1.094
Planned method for child feeding	12.17	6.09	0.09	1.998	0.046	0.20	24.14	0.915	1.093

R: 0.29. Adjusted R^2: 0.07. F: 10.48. p: 0.000. Durbin Watson: 2.04.

In our study, it was found that the mean PBI score of the pregnant women with a marriage duration of 1–2 years was significantly higher than those of 3 years or more ($p<0.05$, Table 1). This situation can be explained by the decrease in interest in pregnancy with increasing maternal age, increasing duration of marriage, and number of children. Our study shows that educational status is also an important factor. The attachment status of pregnant women with education level of university and above is found to be higher ($p<0.05$, Table 1). It is thought that the attachment level of pregnant women with a high level of education, willing to be a mother, conscious, researching, and questioning also increases. Parallel results with our study were found in the literature[17,20,29]. In our study, it was concluded that as the number of pregnancies increased, the level of prenatal attachment decreased. Yılmaz and Beji and Elkin reached similar conclusions[21,24]. It is observed that the more eager and excited mothers in the first pregnancies perform increased mother-infant attachment. In our study, when the attachment scores were examined according to the desired state of pregnancy, the difference between the groups was found to be very significant ($p<0.01$, Table 1). Ustunsoz et al., Abasi et al., and Hergüner et al., also concluded in their study that the prenatal attachment status of mothers is high in planned and desired pregnancies[28,30,31]. In our study, the attachment scores of women with a history of miscarriage were found to be low. These expectant mothers have difficulty in attaching to their new infant due to the fear of re-experiencing the negative situations they experienced in their previous pregnancies and losing their infants. In our study, it was found that the mean prenatal attachment score of the pregnant women who received regular health care and experienced positive changes in their health behaviors was also high. These findings show parallelism with the literature[16,17,32]. In our study, it was found that the mean score of the pregnant women who had good ties with their mothers was high, and the difference between the groups was significant ($p<0.05$, Table 1). It is thought that the experiences of pregnant women with their mothers are effective in gaining the role of motherhood.

In this study, it was found that the educational status of pregnant women had no effect on fear of childbirth. This may be due to the fact that more than half of the pregnant women included in the sample are literate/primary school graduates. On the contrary, the average scores of fear of childbirth of pregnant women with high spouse's education level decreases ($p<0.01$, Table 1). It can be said that spouse's education level is an effective variable on fear of childbirth[33,34]. In our study,

income status is also an important variable in terms of fear of childbirth. It was determined that the pregnant women who evaluated their income as bad had a higher level of fear of childbirth compared to the pregnant women who evaluated their income as medium and good. As the income level of pregnant women increases, the level of fear of childbirth decreases and our research findings show parallelism with the literature[7,34]. In our study, it was found that the parity did not affect the fear of birth, but the desire for pregnancy had an increasing effect on the fear of childbirth ($p<0.05$, Table 1). In an unwanted pregnancy, it can be thought that the mother cannot accept her infant and has more fear of birth. In our study, it was found that pregnant women who received regular health care had less fear of childbirth than those who did not. It can be said that pregnant women who receive regular health care have less anxiety and health worries, thus they experience less fear of childbirth.

The important limitation of our study is that the study was conducted in only one hospital institution. In this case, the research data cannot be generalized. The data obtained from the study are limited to the information provided by the women.

CONCLUSION

Prenatal attachment, which facilitates the mother's adaptation to her pregnancy and her infant, is very important. Fear of childbirth is a serious problem that negatively affects both the pregnancy and birth process of the woman. While planning care, health professionals should question the fear of pregnant women, evaluate their attachment status, and take precautions. More detailed studies that examine the demographic characteristics of not only the mother but also the father can be planned.

ETHICAL ASPECT OF THE STUDY

Before starting the research, the ethics committee approval of Necmettin Erbakan University Meram Faculty of Medicine Non-Pharmaceutical and Medical Device Researches Ethics Committee dated 11.12.2019 and decision number 2019/1759, and for the institution where the research was conducted, ethics committee approval of Konya Provincial Health Directorate Konya Health Services Unit dated 06.02.2020 and numbered 86737044-806.01.03 were obtained.

AUTHORS' CONTRIBUTIONS

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

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ORIGINAL ARTICLE

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Do YouTube videos on microscopic varicocelectomy provide reliable information?

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SUMMARY

OBJECTIVE: This study aimed to assess the quality of YouTube videos about microscopic varicocelectomy.

METHODS: On November 20, 2022, a YouTube search for "Microscopic Varicocelectomy" was conducted. Non-English videos uploaded by producers for commercial purposes that lacked audio and subtitles were excluded from the study. A total of 50 videos were evaluated using the *Journal of the American Medical Association Benchmark Score* and the Global Quality Score, both of which are recognized internationally. Additionally, the researcher developed the Microscopic Varicocelectomy Score to evaluate the videos' technical content. The upload source, video length, number of views, likes, dislikes, and video power indexes were evaluated.

RESULTS: The Global Quality Score, *Journal of the American Medical Association Benchmark Score*, and Microscopic Varicocelectomy Score of the academically prepared videos were significantly higher than those of the physician-prepared videos ($p<0.05$). The Global Quality Score, *Journal of the American Medical Association Benchmark Score*, and Microscopic Varicocelectomy Score of uploaded videos with audio, audio, and subtitles were significantly higher than those with only subtitles ($p<0.05$). The video duration was positively correlated with *Journal of the American Medical Association Benchmark Score*, Global Quality Score, and Microscopic Varicocelectomy Score. The video power index had a strong positive correlation with the number of likes. Moreover, a strong positive correlation was observed, indicating that the Global Quality Score and *Journal of the American Medical Association Benchmark Score* increased as the Microscopic Varicocelectomy Score increased.

CONCLUSION: YouTube videos regarding microscopic varicocelectomy were of notably low quality. If the video content created by specialist physicians and academic centers is more meticulously organized, more accurate data can be transmitted. Consequently, viewing video content may not be advised based on the available data.

KEYWORDS: Infertility. Varicocele. Internet. Educational technology. Testis.

INTRODUCTION

Male infertility is a growing issue worldwide, particularly in developed nations.

Varicocele is the most prevalent pathology in male infertility. Although varicocele is seen in 15–22% of the adult male population, it is observed in 30–40% of men who apply for primary infertility and 80% of men who apply for secondary infertility[1,2].

Varicocele is dilatation of the veins of the pampiniform plexus; although many factors are shown as etiological reasons, it is the most known and accepted anatomical factor today. The left spermatic vein is approximately 8–10 cm longer than the right and is opened at a right angle to the left renal vein. The valves in the left spermatic vein are dysfunctional, and the left renal vein is compressed between the aorta and the superior mesenteric artery, which increases the pressure in the internal vein (proximal nutcracker phenomenon) and iliac artery compression on the iliac vein as well as increases the pressure in the external spermatic vein (distal nutcracker phenomenon) and dilatation[3].

Many pathophysiological mechanisms have explained the effect of varicocele on semen parameters and infertility. The majority of these mechanisms include an increase in testicular temperature, a rise in venous pressure, hormonal dysfunction, epididymal dysfunction, autoimmunity, acrosome reaction disorders, renal-adrenal reflux, DNA damage, and oxidative stress. The most studied and accepted mechanism is the increase in testicular temperature[4].

The diagnosis of varicocele is made by physical examination, and additional imaging methods are not needed. However, in conditions that complicate the physical examination, color Doppler ultrasonography may be necessary[5,6].

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Various surgical procedures for the treatment of varicocele have been described. These include percutaneous embolization (interventional radiology), open surgery, laparoscopic, and microsurgical procedures. Compared with conventional varicocelectomy techniques, microsurgical varicocelectomy has been shown to have higher rates of spontaneous pregnancy and lower rates of postoperative recurrence and hydrocele formation in infertile men[7].

YouTube was founded in 2005. The number of YouTube users worldwide in 2021 is approximately 2,240.03 million, and it is anticipated that, by 2025, it will increase to 2,854.14 million[8]. The increased use of social media and the Internet in recent years has also shown itself in health and medicine. However, information pollution is high in all fields, including urology, and it is not easy to obtain accurate and quality information[8,9]. Only one study evaluated the varicocele-related website content published in 2011[10].

Research shows that YouTube is the most widely used platform for information and education by both patients and healthcare professionals[11,12]. Although microscopic varicocelectomy is the most recommended and preferred surgical method in treating varicocele, videos about microscopic varicocelectomy on YouTube have not been evaluated before. YouTube is an excellent opportunity to learn about surgical techniques and develop skills by watching videos. However, as they are not subject to expert review or quality control, YouTube videos' dependability is in doubt. This study aimed to evaluate the quality of microscopic varicocelectomy videos on YouTube with the scoring system prepared with the basic steps of the procedure and current scoring systems.

METHODS

On November 20, 2022, YouTube was searched for videos about "Microscopic Varicocelectomy." Non-English videos that were commercially uploaded by the producers and did not contain audio and subtitles were excluded from the study. A total of 50 videos were evaluated using the internationally recognized *Journal of the American Medical Association Benchmark Score* (JAMAS) and Global Quality Score (GQS). In the JAMAS scoring system, there are four questions with a score of 0–1 each (maximum 4 points) to evaluate the content's validity, effectiveness, and reliability[13]. The GQS, on the contrary, is a scale evaluated on a scale of 1–5 to determine whether the content is understandable for patients[13-15]. The Microscopic Varicocelectomy Score (MVS) was created to evaluate the invasive procedure using 13 criteria, each of which was calculated by the investigator as either 0 or 1 (Table 1). The videos were divided into groups according to the uploaded country, video content (informational, technical), uploading source (academic center, physician), and transmission of information (audio, audio subtitled, and subtitled). Values such as the length of each video, the time spent after uploading, the number of views, the number of likes and dislikes, and the video power index (VPI) were recorded and evaluated[13-15].

The rate of likes (likes/likes+dislikes) and views rate (the number of views/time on YouTube) were calculated. VPI was calculated as like rate×view rate/100. Our study was approved by the Ethics Committee on 01/02/2023 (80576354-050-99/222). All ethical rules in the Declaration of Helsinki were complied with. Data were analyzed with SPSS 22 and GraphPad Prism version 9 (GraphPad Software, CA, USA). The Shapiro-Wilk test was used for normality and regular distribution of variables, and the Mann-Whitney U test was used for categorical variables. The Kruskal-Wallis test was used to compare different score groups, and the Spearman correlation test was used to investigate the relationship between continuous variables. A value of $p<0.05$ was considered statistically significant.

Table 1. Microscopic Varicocelectomy Scoring.

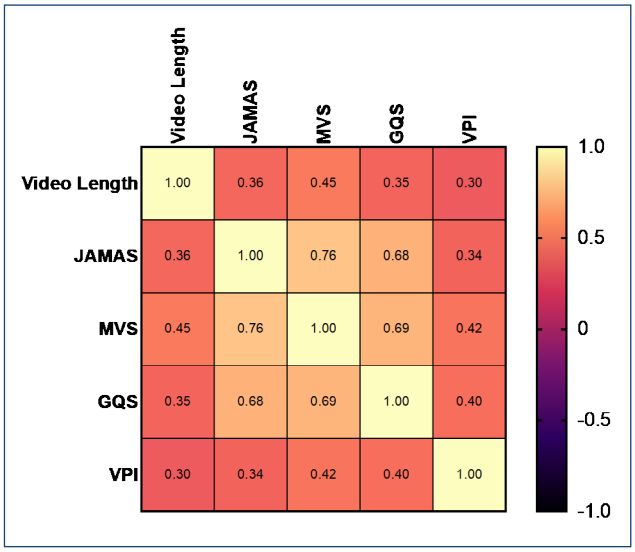
Preoperative evaluation
Are surgical indications stated in the video?
Is there information about spermiogram results in the video?
Is the side to be varicocelectomy indicated in the video?
Is the magnification and brand of the microscope mentioned during the surgery in the video?
Intraoperative evaluation
Is there information about the types of surgical incisions in the video?
Is there information about the use of papaverine in the video?
Is there information about the use of mini-Doppler USG in the video?
Is there information about preserving the vas deferens during the operation in the video?
Is there information about the external spermatic vein during the operation in the video?
Is there any information about the gubernacular vein during the operation in the video?
Postoperative evaluation
Is the length of hospital stay specified in the video?
Is there information about post-op complications in the video?
Is there any information about the postoperative control examinations in the video?

RESULTS

Most of the videos (86.3%) were uploaded by physicians (74.5%) for informational purposes. The videos were uploaded mainly by the individuals living in the Asian countries (64.7%). The average video length was 503 s, and the average time since upload was 1,325 days. The average number of views, likes, and VPI were 34,115, 156, and 0.31. The average GQS, JAMAS, and MVS were 2.1, 1.76, and 4.66, respectively.

The GQS, JAMAS, and MVS scores of academically prepared videos were significantly higher than those of physician-prepared videos ($p<0.05$). The GQS, JAMAS, and MVS scores of uploaded videos with audio, audio, and subtitles were significantly higher than those with only subtitles ($p<0.05$). The GQMS, MAMAS, and MVS scores of videos uploaded with only audio, audio, and subtitles did not differ significantly ($p=0.639$, $p=0.123$, and $p=0.547$, respectively). The length of the video was positively correlated with JAMAS, GQS, and MVS. There was a strong correlation between VPI and the number of likes. In addition, as the MVC score increased, a strong positive correlation was observed, indicating that the GQS and JAMAS scores also increased (Graph 1).

The effect size (Cohen's d) and power value (1–β) for MVS, GQS, and JAMAS scores, compared between the groups of videos, were calculated using the G*Power software (version 3.1.9.2). The alpha level used for this analysis was 0.05. The effect size and power values were 1.78 and 0.98, for MVS, 0.80 and 0.75 for GQS, and 1.53 and 0.98 for JAMAS scores.



Graph 1. Correlation of video length with JAMAS, MVS, GQS, and VPI scores. JAMAS: *Journal of the American Medical Association Benchmark Score*; MVS: Microscopic Varicocelectomy Score; GQS: Global Quality Score; VPI: video power index (like ratio×view ratio/100); Like: like ratio (like/like+dislike).

DISCUSSION

Today, the Internet is an easy-to-access, inexpensive, unrestricted source of information. However, the relevance, accuracy, and completeness of this information are crucial. It is known that 7% of daily Google searches pertain to health[16]. Two out of three adults in the United States regularly search online for health-related information[17]. In Germany, 40% of Internet users search the Internet for health information before and a half after their appointment[18]. However, online sharing about health is done mainly by non-physicians. These posts include patient experiences, advertisements, alternative treatment techniques, and commercial centers. These posts sometimes contain misleading information that puts human health at risk[14].

Varicocele is known as the most common surgically correctable cause of male infertility. Approaches such as retroperitoneal and inguinal open techniques, microsurgical inguinal and subinguinal procedures, laparoscopic repair, and radiological embolization have been reported in the treatment of varicocele. Microscopic varicocelectomy is the gold standard treatment for men with varicocele due to its low rate of complications and high spontaneous pregnancy rate[19]. As microscopic varicocelectomy is a frequently performed surgery, there is much information about this surgery on the Internet and YouTube. Information about varicocele on the Internet has been evaluated before. However, there has been no research in the literature evaluating YouTube videos about microscopic varicocelectomy. Referencing the European Association of Urology Guidelines, they devised a 14-point evaluation scoring system and evaluated 20 different websites. As a result of the evaluation, it was seen that 4 of the 20 sites were established and operated by a urologist, 4 were established and operated by an obstetrician and gynecologist, and 5 of them were commercial sites. It is not clear who founded the remaining seven sites. They found that the sites established by urologists received the highest scores[10].

The purpose of this study was to examine the information, content quality, and trustworthiness of YouTube videos pertaining to "microscopic varicocelectomy," as well as the information, content quality, and trustworthiness of YouTube videos pertaining to "microscopic varicocelectomy." This is the first study in the literature to investigate this issue. Notably, 50 videos with a total duration of approximately 7 h and 1.7 million views were evaluated. It was observed that 88% of the videos were for information purposes, 39% had a voice, and 22% had both voice and subtitles. In three studies examining YouTube video quality related to retrograde inter-renal surgery, percutaneous nephrolithotomy, mini-percutaneous nephrolithotomy, it was

determined that the quality of the audio videos was higher[20-22]. In our study, it was observed that the MVS, JAMAS, and GQS scores of the videos with audio, audio and subtitles were significantly higher than the videos with only subtitles ($p<0.05$, $p<0.05$, and $p<0.05$). This is because giving information by voice is faster and easier than text.

Adorisio et al. evaluated videos on robotic pyeloplasty in children, Yılmaz et al. evaluated mini percutaneous nephrolithotomy videos, and Sogutdelen et al. evaluated videos on holmium laser enucleation of prostate. As a result, they concluded that the quality scores of academically uploaded videos in these three studies were high[22-24]. In our study, it was observed that 24% of the videos were uploaded academically, and the MVS, JAMAS, and GQS scores of the videos uploaded academically were significantly higher than the videos uploaded by physicians ($p<0.05$, $p=0.02$, and $p<0.05$), which is due to the fact that the academically uploaded videos contain more detailed information, as they are uploaded for educational purposes as well as for informing patients.

In addition, Aydogan's study examining the quality of the information in YouTube videos on prostate fusion biopsy and Taş et al.'s study on the quality of the information in testicular cancer self-examination videos found that video quality increased as video duration increased[13,25]. In our study, in parallel with these studies, a low positive correlation was found between video length and MVS, JAMAS, and GQS scores. In other words, as the video length increases, it is seen that the scores increase, which is because the longer the period, the more the time to give information.

Looking at the literature, there are YouTube publications containing more than 90 topics in the Urology section. Most of these publications' video quality and content were inadequate[11]. In our study, it is observed that the scores of the videos were lower than expected. We think that information about human health, especially surgical procedures, should be given by experts and that the level of knowledge should be at a sufficient level and in an orderly manner.

There were some potential limitations to this study. First, videos in the study were watched and scored by a single urologist. In addition, the opinions of the person rating the quality of the video may be subjective. However, we still think that determining the general quality of the existing videos according to the previously validated scoring systems will form the basis for giving readers and video producers an idea.

CONCLUSION

Videos on YouTube providing information about Microscopic Varicocelectomy surgery are of poor quality and they lack content. Advances in technology and the Internet have made it easier for patients and healthcare professionals to access information. However, we think that, to recommend watching Microscopic Varicocelectomy surgery videos, experts should prepare videos with better quality and standardized content. We think that this study can guide content producers who consider publishing new videos in the field of microscopic varicocelectomy.

ETHICAL ASPECTS

Our study was approved by the Ethics Committee on 01/02/2023 (80576354-050-99/222). All ethical rules in the Declaration of Helsinki were complied with.

AUTHORS' CONTRIBUTIONS

MU: Conceptualization, Data curation, Formal Analysis, Funding acquisition, Investigation, Methodology, Project administration, Resources, Software, Supervision, Validation, Writing – original draft, Writing – review & editing. **ME:** Conceptualization, Investigation, Methodology, Writing – original draft, Writing – review & editing. **ÜY:** Conceptualization, Investigation, Methodology, Resources, Writing – review & editing. **BÖ:** Methodology, Software, Supervision, Validation, Visualization.

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ORIGINAL ARTICLE

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The genetic spectrum of polycystic kidney disease in children

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SUMMARY

OBJECTIVE: Autosomal dominant polycystic kidney disease is an inherited kidney disorder with mutations in *polycystin-1* or *polycystin-2*. Autosomal recessive polycystic kidney disease is a severe form of polycystic kidney disease that is characterized by enlarged kidneys and congenital hepatic fibrosis. Mutations at *PKHD1* are responsible for all typical forms of autosomal recessive polycystic kidney disease.

METHODS: We evaluated the children diagnosed with polycystic kidney disease between October 2020 and May 2022. The diagnosis was established by family history, ultrasound findings, and/or genetic analysis. The demographic, clinical, and laboratory findings were evaluated retrospectively.

RESULTS: There were 28 children (male/female: 11:17) evaluated in this study. Genetic analysis was performed in all patients (*polycystin-1* variants in 13, *polycystin-2* variants in 7, and no variants in 8 patients). A total of 18 variants in *polycystin-1* and *polycystin-2* were identified and 9 (50%) of them were not reported before. A total of eight novel variants were identified as definite pathogenic or likely pathogenic mutations. There was no variant detected in the *PKDH1* gene.

CONCLUSION: Our results highlighted molecular features of Turkish children with polycystic kidney disease and demonstrated novel variations that can be utilized in clinical diagnosis and prognosis.

KEYWORDS: Next-generation sequencing. Polycystic kidney disease. Polycystic kidney and hepatic disease 1. PKD1 protein. PKD2 protein.

INTRODUCTION

Autosomal dominant polycystic kidney disease (ADPKD) is the most common inherited renal disorder, with a prevalence between 2.4 and 9.0 per 10,000[1,2]. ADPKD is caused by disease-causing variants in the *polycystin-1* (*PKD1*) and *polycystin-2* (*PKD2*) genes[3]. The clinical diagnosis of ADPKD is based on the patient's age, a positive family history, and the number of kidney cysts on ultrasound imaging[4,5]. Autosomal recessive polycystic kidney disease (ARPKD) is an inherited polycystic kidney disorder characterized by the development of bilateral renal cystic and congenital hepatic fibrosis[6]. ARPKD is associated with pathogenic variants in the *PKHD1* gene. The liver abnormalities consist of hepatomegaly, increased echogenicity, portal hypertension, or dilated intrahepatic bile ducts[7,8]. Genetic tests may be essential to obtain a definitive diagnosis when the diagnosis cannot be established by imaging-based methods[9]. In this study, we evaluated demographic, clinical, and genetic results of children with polycystic kidney disease. However, until now, there has been limited information about the genetic spectrum of Turkish children with ADPKD or ARPKD. In addition, we evaluated the pathogenic effects of novel variants through protein prediction tools.

METHODS

We evaluated 28 children from 26 families with polycystic kidney disease between October 2020 and May 2022. ADPKD was diagnosed by a family history, renal ultrasound findings, and/or genetic results. Demographic, clinical, and laboratory test results were evaluated retrospectively (Table 1). The genetic study was performed after obtaining the informed consent of the parents. The study protocol was approved by the ethics committee of the Eskisehir Osmangazi University (Protocol No: 2022-152). Genomic DNA was obtained from patients' peripheral venous blood using the QIAamp DNA Blood Mini QIAcube Kit (Qiagen, Hilden, Germany) following the manufacturer's instructions. The next-generation sequencing panel provided good coverage of exon-flanking intronic regions of *PKD1* (except for exon 1 of *PKD1*), *PKD2*, and *PKDH1* were analyzed by Illumina NovaSeq platform using the Agilent SureSelect V5 kit. QIAGEN Clinical Insight (QCI) Interpret data analysis platform was used for the analysis of raw data. Several in silico prediction programs were used to evaluate the pathogenic effect of the mutation and its function on the biological processes of the protein such as SIFT, Mutation Taster, and Polyphen2. The American College of Medical Genetics and Genomics (ACMG) guidelines was used

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for variant classification[8]. We evaluated the pathogenicity of the variants taking into account by using the population allele frequency data from different population databases (1000 Genome, gnomAD, and ExAC). The statistical analyses were performed using the SPSS 10.0 software. In this analysis, clinical data were expressed in percentages.

RESULTS

A total of 28 children from 26 families diagnosed with polycystic kidney disease during the period in question were enrolled in the study. Of those patients, 11 (39.3%) were males and 17 (60.7%) were females (Table 1). The mean age of patients was 10.75 (4.85) years ranging from 3 to 18 years. The family history of polycystic kidney disease was discovered in 78.6% of cases (22/28). Notably, 13 patients (46.5%) had a maternal family history, and 9 patients (32.1%) had a paternal family history. Table 1 summarizes the demographic data and clinical outcomes of patients. Renal cysts were bilateral in 18 (67.9%) patients. Only two patients (7.1%) had hepatic cysts, and none of them had hepatic fibrosis. A total of four patients had cardiac findings such as patent foramen ovale (two patients), atrial septal defect (one patient), and ventricular septal defect (one patient). Recurrent urinary tract infections were detected in six (21.4%), hypertension was observed in one (3.6%), urolithiasis was defined in two (7.1%), proteinuria in four (14.3%), pyuria in two (7.1%), and hematuria in five (17.9%) patients. None of them had chronic renal failure during their follow-up. Among 28 children, we identified 18 variants, including 12 *PKD1* (66.7%) variants and six *PKD2* (33.3%) variants (Table 2). The mutation detection rate and PKD1 and PKD2 mutation rates are presented in Table 3. No variant was detected in the *PKDH1* gene in any of the patients. A pathogenic or likely pathogenic variant was determined in 15 patients (11 *PKD1* variants and 3 *PKD2* variants). Among the 12 *PKD1* variants, 7 mutations were novel, including 5 frameshift, 1 nonsense, and 1 missense. Additionally, one novel *PKD1* (c.10364T>G; p.Leu3455Arg) variant of uncertain significance (VUS) was also identified. Among the six *PKD2* variants, two variants were novel. These variants have not been previously found in major variant databases such as ExAc, gnomAD, dbSNP, and ClinVar. Three variants were predicted as pathogenic or likely pathogenic (*PKD2*:c.1180G>C, *PKD2*:c.965G>A, and *PKD2*:c.1906C>T) and three were also predicted as VUS (*PKD2*:c.198C>A, *PKD2*:c.83G>C, and *PKD2*:c.2186T>A) (Table 2).

Table 1. Demographic, clinical, and laboratory findings of patients with polycystic kidney disease.

Characteristics	PKD (28 patients)
Age	Mean±[SD] (min-max) 10.75±[4.85] (3-18)
Sex	Male: 11 (39.3%) Female: 17 (60.7%)
Family history Maternal history Paternal history	22/28 (78.6%) 13 (46.5%) 9 (32.1%)
Renal cyst (bilateral) Renal cyst (unilateral)	19/28 (67.9%) 9/28 (32.1%)
Hepatic cyst	2/28 (7.1%)
Cardiac abnormalities	4/28 (14.3%)
Recurrent urinary tract infections	6/28 (21.4%)
Hypertension	1/28 (3.6%)
Urolithiasis	2/28 (7.1%)
Proteinuria	4/28 (14.3%)
Pyuria	2/28 (7.1%)
Hematuria	5/28 (17.9%)
A positive genetic result	20/28 (71.4%)
A negative genetic result	8/28 (28.6%)

PKD: polycystic kidney disease.

DISCUSSION

ADPKD is the most commonly seen inherited renal disease characterized by the development and progressive enlargement of cysts in the renal, eventually resulting in end-stage renal disease[5]. ADPKD is a monogenic disease caused by mutations in *PKD1* and *PKD2* genes[6]. Mutations in *PKD1* and *PKD2* are not hotspot mutations, suggesting that pathogenic variants of *PKD1* or *PKD2* are often unique[7]. Previous studies showed that *PKD1* and *PKD2* mutations are responsible for 85 and 15% of ADPKD cases, respectively[8,9]. ARPKD is a rare inherited infantile form of polycystic kidney disease, characterized by bilaterally enlarged echogenic kidneys and congenital hepatic fibrosis secondary to malformation of the biliary ducts[10]. The *PKHD1* gene mutations can cause ARPKD[11,12].

In this study, we used a target gene panel search for *PKD1* and *PKD2* (ADPKD) and *PKDH1* (ARPKD) genes in 28 children with a variant detection rate of 71.4% (20/28). However, we could not detect any *PKDH1* gene variant in patients. Kinoshita et al. detected the mutations in 89.1% of the patients[13]. The demographic characteristics of this study group were similar to another Turkish cohort study enrolling 69 ADPKD patients. The mean age of patients in the study was 10.75 years, whereas it was 9.3 years in their Turkish cohort study. In our study, the female to male (17:11) ratio was similar to the other study

Table 2. Details of *polycystin-1* and *polycystin-2* gene variants in this study.

Patient ID	Gene	Exon	cDNA	Protein change	Variant effect	Novelty	ACMG classification	SIFT/Polyphen2/ Mutationtaster
PKD1 gene								
P2	PKD1	10	c.2048G>A	p.Trp683Ter	Nonsense	Reported	PVS1, PM2, and PP5	Pathogenic
P3	PKD1	27	c.9547C>T	p.Arg3183Ter	Nonsense	Reported	PP5, PVS1, and PM2	Pathogenic
P5 and P6	PKD1	46	c.12664dupC	p.Leu4222ProfsTer6	Frameshift	Novel	PM2 and PVS1	Pathogenic
P13	PKD1	11	c.2226C>G	p.Tyr742Ter	Nonsense	Novel	PVS1 and PM2	Pathogenic
P15	PKD1	1	c.165_171del	p.Leu56ArgfsTer15	Frameshift	Reported	PVS1, PP5, and PM2	Pathogenic
P16	PKD1	23	c.8314_8316del	p.Glu2772del	Frameshift	Novel	PM1 and PM2	Pathogenic
P18	PKD1	46	c.12664dup	p.Leu4222ProfsTer6	Frameshift	Novel	PM2 and PVS1	Pathogenic
P19	PKD1	11	c.2534T>C	p.Leu845Ser	Missense	Reported	PP5 and PM2	Pathogenic
P20	PKD1	15	c.6649del	p.Val2217CysfsTer25	Frameshift	Novel	PVS1 and PM2	Likely pathogenic
P21	PKD1	5	c.974A>G	p.Tyr325Cys	Missense	Reported	PM2, PP5, and PP2	Likely pathogenic
P22	PKD1	33	c.10364T>G	p.Leu3455Arg	Missense	Novel	PM2 and PP2	VUS
P25	PKD1	43	c.11716dup	p.Cys3906LeufsTer55	Frameshift	Novel	PVS1 and PM2	Likely pathogenic
PKD2 gene								
P9	PKD2	1	c.198C>A	p.Asp66Glu	Missense	Reported	PP2 and BP4	VUS
P10	PKD2	5	c.1180G>C	p.Asp394His	Missense	Novel	PM2 and PP2	Pathogenic
P11 and P12	PKD2	1	c.83G>C	p.Arg28Pro	Missense	Reported	PP2	VUS
P24	PKD2	4	c.965G>A	p.Arg322Gln	Missense	Reported	PM1, PM2, and PP5	Pathogenic
P27	PKD2	9	c.1906C>T	p.Gln636Ter	Nonsense	Novel	PVS1 and PM2	Likely pathogenic
P28	PKD2	11	c.2186T>A	p.Leu729Gln	Missense	Reported	BS2	VUS

ACMG: American College of Medical Genetics and Genomics; SIFT: Sorting Intolerant From Tolerant.

Table 3. Genetic results of different studies with autosomal dominant polycystic kidney disease cohort.

Authors	Number of patients	Mutation detection rate (%)	PKD1 (%)	PKD2 (%)
Kim et al.[11]	542	81.4	348 (82.3%)	75 (17.7%)
Audrézet et al.[12]	42	90.4	36 (94.7%)	2 (5.3%)
Kinoshita et al.[13]	101	89.1	82 (87.2%)	12 (12.8%)
Tutal et al.[14]	69	66.6	40 (86.9%)	6 (13.1%)
Kasap Demir et al.[15]	29	75.8	22 (95.4%)	1 (4.6%)
Reed et al.[18]	24	58	12 (85.7%)	2 (14.3%)
Audrézet et al.[19]	519	91.6	392 (80.5%)	95 (19.5%)
Carrera et al.[20]	440	80	301 (85.5%)	51 (14.5%)
Eo et al.[21]	188	84.5	131 (69.7%)	57 (30.3%)
Hoefele et al.[22]	93	64.5	52 (86.7%)	8 (13.3%)
Heyer et al.[23]	1,119	92.4	869 (77.7%)	165 (14.7%)
Rossetti et al.[24]	202	89.1	153 (85.0%)	27 (15.0%)
Xu et al.[25]	120	81.7	85 (91.4%)	8 (8.6%)
This study	28	71.4	12 (66.7%)	8 (33.3%)

(38:31)[14]. In a previous study conducted in Turkey, the diagnosis rate was 66.6% with direct sequencing of *PKD1* (86.9%) and *PKD2* (13.1%). The reason of the lower diagnosis yield in their study was the lack of genetic testing in some patients[15]. In our study, the frequencies of mutation in *PKD1* and *PKD2* genes were 66.7 and 33.3%, respectively. Also, the frequency of *PKD1* mutations was higher, the frequency of *PKD2* mutations was lower, and it was compatible with the medical literature (80–90% for *PKD1* and 15–20% for *PKD2*)[16,17]. In another study from Turkey, 3.8% of the patients with ADPKD had *PKD2* gene mutation[18]. The findings show that the main gene responsible for ADPKD in the Turkish population, as in other populations, is the *PKD1* gene. In this study, we found that the mutation rates of *PKD1* and *PKD2* were similar to previous studies (Table 3). A positive family history is not present in approximately 10–20% of individuals with ADPKD[15-18]. Notably, 21.4% of our patients had no family history of the disease, which was consistent with previously reported results. In a recent study on 24 patients suspected of having ADPKD with no apparent family history, 9 patients were retrospectively found to have pathogenic *PKD1* mutations[19]. It should be kept in mind that patients with de novo mutations may develop the disease without a family history. A positive family history should not be necessary for genetic research in patients. Among the 18 variants, we found that in *PKD1* and *PKD2*, 50% (9/18) are novel variants. Genetic analysis results showed that 11 variants in *PKD1* gene and 3 variants in *PKD2* gene were predicted as pathogenic/likely pathogenic. Furthermore, subcategorization of *PKD1* variants showed 6 truncation/frameshift, 3 nonsense, and 3 missense variants. After evaluation of variants for *PKD2*, two missense and one nonsense variants were detected as pathogenic or likely pathogenic. Notably, seven of the *PKD1* variants and two *PKD2* variants were novel. We identified four variants of VUS in *PKD1* (one variant) and *PKD2* (three variants) (Table 2). We identified a novel duplication variant, PKD1:c.12664dupC (p.Leu4222ProfsTer5) in two siblings who suffer from ADPKD. The family history showed a paternal origin. The variant was not identified in the dbSNP, ClinVar, or *PKD1*-LOVD databases. The p.Leu4222ProfsTer5 variant is expected to lead to an early stop codon at position 4222 and it results in a deficient and nonfunctional protein. Loss-of-function variants of the *PKD1* gene are accepted as the type of variant that constitutes the mechanism of the ADPKD. The duplication variant is considered to be the pathogenic factor for ADPKD in that family. We found a novel nonsense mutation c.2048G>A (p.Trp683Ter) was located in the 10th exon of *PKD1*. The variant was not observed in the gnomAD and 1000 genomes. It was predicted to result in a truncated protein with reduced or aberrant function. This variant was predicted to be pathogenic according to the recommendation of the ACMG guidelines. We suggested that the variant could be associated with ADPKD. For the first time, we report two missense variants of the *PKD2* gene, namely, c.198C>A (p.Asp66Glu) and c.1180G>C (p.Asp394His). These variants have not been previously identified in population databases such as 1000 genomes and gnomAD. Fathers of patients carrying these mutations were also diagnosed with ADPKD. Although previous studies have identified other variants of *PKD1* and *PKD2* in the Turkish population, here in this study, we report seven novel variants as follows: c.9547C>T, c.165_171del, c.2534T>C, c.974A>G, and c.974A>G (*PKD1*) and c.83G>C and c.965G>A (*PKD2*). The variants have been previously detected in European, Asian, and Middle Eastern populations[20-25]. *PKD1* or *PKD2* variants were not detected in any of the eight patients with typical features of PKD (8/28; 28.6%). According to the literature, the most common genetic cause of ADPKD is still *PKD1* and *PKD2* gene mutations (18, 19, 20-24). Whole exome sequencing can be used to detect other rare variants that have the potential to contribute to the ADPKD phenotype in patients with a negative result[23,25].

This study has some limitations. First, it was a retrospective, single-center study with a small sample size. In this study, a targeted panel sequence test including *PKD1*, *PKD2*, and *PKDH1* genes was used to identify polycystic kidney disease. Therefore, we could not have the opportunity to examine other genes causative of rarer forms of the disease, including *GANAB*, *DNAJB11*, and *ALG9*.

CONCLUSION

In our study group of patients with polycystic kidney disease, 12 variants were detected in *PKD1* and 6 variants were detected in *PKD2*. Six variants have previously been described in different populations. Notably, 9 out of 18 mutations are not reported before and probably unique. The six frameshift variants detected in the *PKD1* gene are novel and appear to be associated with ADPKD, and two novel missense mutations in *PKD2* can also be associated with ADPKD. This study will enrich the *PKD1* and *PKD2* mutation database and make an important contribution to the genetic counseling of ADPKD patients. Prospective studies are needed in patients with genetically diagnosed ADPKD to detect such a relationship.

AUTHORS' CONTRIBUTIONS

AK: Conceptualization, Investigation, Methodology, Supervision, Validation, Visualization, Writing – original draft, Writing

– review & editing. **YÖA:** Conceptualization, Formal Analysis, Investigation, Writing – original draft, Writing – review & editing. **MS:** Conceptualization, Investigation, Supervision, Writing – review & editing. **TK:** Conceptualization, Formal Analysis, Investigation, Methodology, Project administration, Writing – original draft, Writing – review & editing.

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ORIGINAL ARTICLE

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Sociodemographic characteristics associated with indications for surgical menopause in women: a retrospective study

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SUMMARY

OBJECTIVE: The aim of this study was to evaluate the surgical menopause indications and sociodemographic characteristics of women.

METHODS: In this retrospective study, we analyzed the sociodemographic characteristics of women with indications for surgical menopause in 2010–2020. The R Version 4.1.1 (2021-08-10) software and logistic regression analysis were used to evaluate the data.

RESULTS: A total of 704 women's data were obtained in this study. Surgical menopause indications were found to stem from bleeding (46.0%), cancer (28.3%), cancer risk (18.9%), and other causes (6.8%). Surgical menopause indications originating from cancer were increased by 0.08 times (95%CI 0.01–0.68) due to smoking, 0.45 times (95%CI 0.23–0.88) due to regular drug use, and 0.36 times (95%CI 0.19–0.69) due to the presence of chronic disease ($p<0.05$).

CONCLUSION: More than half of the women with surgical menopause indications were between 41 and 46 years of age. Additionally, 54.9% of the women had a chronic disease. Therefore, it is recommended to plan preventive health services for morbidity and mortality risks that may develop due to surgical menopause.

KEYWORDS: Gynecologic neoplasm. Gynecological surgery. Menopause. Women's health.

INTRODUCTION

Surgical menopause (SM)/bilateral oophorectomy in women has a more adverse effect on vasomotor and cognitive symptoms, mood disorders, genitourinary atrophy[1], dyspareunia[2], loss of libido, osteoporosis and fractures, sleep problems, loss of muscle tone, infertility[3], and anxiety and depression compared to natural menopause[4]. The reason is that changes in circulating sex steroids (a sudden drop in estrogen, progesterone, and testosterone levels) occur more rapidly after SM compared to natural menopause[5]. Hormone therapy can reduce these risks, but it currently has significant limitations[6]. In women with SM who are not treated with hormone therapy, these risks are more pronounced, especially for those under the age of 45 years[7,8].

The age of menopause is an important threshold that can be an indicator of future longevity in women[9]. Although the average age of menopause of women worldwide is 51 years[10,11], the age of menopause due to SM is decreasing[1]. SM causes increased morbidity and mortality rates for both premenopausal and postmenopausal women[4,12]. As the age of menopause decreases, the risk of many chronic diseases, especially cardiovascular diseases (CVD)[7,12] and type II diabetes mellitus[9], increases. Price et al., stated that the obesity rate was higher in women who underwent SM compared to women who underwent natural menopause and that SM increased the risk for higher CVD compared to natural menopause (12.4 vs. 10.8% risk for CVD risk)[7]. Zhu et al., examined 10 observational studies and found that, when compared to women aged 50–54 years who were at natural menopause, women who underwent SM had an increased risk for CVD. Specifically, the risk was 2.55 times higher (CI 2.22, 2.94) for those aged <35 years, 1.91 times higher (CI 1.71, 2.14) for those between the ages of 35 and 39 years, 1.58 times higher (CI 1.44, 1.74) for those between the ages of 40 and 44 years, and 1.20 times higher (CI 1.10, 1.31) for those between the ages of 45 and 59 years[12]. In the cohort study by Zhai et al., the lung health of 1,666 women who had a habit of smoking with a mean age of 59 years was assessed. Of the women involved in the study, 646 (39%) reported early menopause (defined as occurring before the age of 45 years). Out of these, 198 (19.1%) had natural menopause, while 448 (71.3%) had SM. The study found that early menopause is a risk factor for both malignant and non-malignant lung diseases as well as mortality in women smokers[13].

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The reduction of the factors that cause SM is important for public health[14] because the risks that may cause SM in women affect the awareness of these risks and their related health service-seeking behaviors[15]. Therefore, knowing the sociodemographic characteristics of women with SM, such as age, presence of chronic diseases, and smoking may help predict morbidity and mortality risks. It can also guide health professionals (physicians, nurses, etc.) to develop preventive strategies for these morbidity and mortality risks. It would be useful to know the level of sociodemographic characteristics in women with SM to carry out interventions such as prevention of obesity, smoking cessation, and regular follow-up of chronic diseases (diabetes, etc.). Therefore, in this study, we aimed to evaluate the SM indications and sociodemographic characteristics of women.

METHODS

Study design

This retrospective study was conducted by searching past SM participant records between July and October 2021 in the gynecology outpatient clinic of a hospital. We obtained institutional permission from the hospital and received approval from the ethics committee of our institution. All the study data were anonymized before analysis. We performed a power analysis for the sample size of this study using the G-Power 3.0.10 statistical power analysis software. According to our multinominal logistic regression analysis results, the total power of the study was calculated to be 97%.

Participants

The study sample included all women who had SM indications between 2010 and 2020. We obtained the data by searching the archive file records of the participants who were coded as ICD-10, N95,3 (cases with artificial menopause code) from the outpatient clinic records, and we obtained a total of 704 participant records. The inclusion criteria for this study were as follows: age 18 years or above, no occurrence of natural menopause yet, and menopausal conditions that developed as a result of castration of both ovaries with or without the uterus due to a disease. Exclusion criteria included a lack of data on SM indications, premature ovarian insufficiency, and natural menopause processes.

Procedures

We collected research data, which included information about participants with the SM code (ICD-10, N95,3), from the gynecology polyclinic records in the Probel software (hospital information management system). Subsequently, we transferred this data to an Excel file. Then, the researchers transferred the data from the Excel file to the SPSS 24.0 software and prepared them for analysis.

Statistical analysis

We analyzed the research data using SPSS Statistics 24.0. We used multinomial logistic regression analysis and binary logistic regression analysis to evaluate the relationship between the data. We presented differences in these categorical data with an odds ratio with a 95% confidence interval (95%CI). We considered $p<0.05$ to be statistically significant. We used the Plotly 4.10.0 library and ggplot2 3.3.5 graphs on R version 4.1.1 (2021-08-10) to visualize the data.

RESULTS

Table 1 presents data on the sociodemographic characteristics of women.

In Turkey, the average age of menopause is approximately 47 years[16], while it is 51 across the world[10,11]. However, premenopause, which is the transition period before menopause in women, can last for 2–6 years. For this reason, we found it appropriate to examine the age grouping of the sample in four categories. We categorized the groups as 23–40 years, 41–46 years, 47 years, and 48–50 years, respectively.

Figure 1 shows the distribution of women according to the age at which they received an indication for SM.

In Table 2, we performed a logistic regression analysis by grouping SM indications. The first group was "causes related to bleeding" and consisted of AUB and myoma uteri. The second group was "cancer" and consisted of endometrial hyperplasia, elective hysterectomy for breast cancer, endometrial cancer, cervical intraepithelial neoplasia, cervical cancer, and other organ metastases. The third group was "cancer risk" and consisted of adnexal malignant and benign masses. The fourth group was "other indications" and consisted of endometriosis, POP, and tubo-ovarian abscess.

According to the results of the logistic regression analysis, compared to the other SM indication groups, SM indications for cancer increased by 0.08 times due to smoking (95%CI 0.01–0.68; $p<0.021$), 0.45 times (95%CI 0.23–0.88) due to regular drug use, and 0.36 times (95%CI 0.19–0.69) due to chronic diseases. Regular drug use by age increased by 1.81 times (95%CI 1.14–2.89; $p<0.012$) in women aged 41–46 years compared to women aged 23–40 years (Table 2).

Table 1. Sociodemographic characteristics (n=704).

	n	%
Age (43.92±3.56 years)		
23–40 years	95	13.5
41–46 years	450	63.9
47 years	90	12.8
48–50 years	69	9.8
Marital status		
Married	652	92.6
Single	52	7.4
Educational status (n=29)		
Literate	4	13.8
Primary school	9	31.1
Secondary school	11	37.9
University	5	17.2
Family type		
Live alone	34	4.8
With spouse	15	2.1
Nuclear family	655	93.1
Smoking history (n=63)		
Yes	63	8.9
No	641	91.1
Presence of chronic disease (n=387)		
Hypothyroidism	86	22.2
Hypertension	66	17.1
Type II diabetes mellitus	27	7.0
Breast cancer	69	17.8
Asthma-chronic obstructive pulmonary disease	34	8.8
Hypertension and type II diabetes mellitus	41	10.6
Others	64	16.5
Regular drug use (n=284)		
Thyroid hormones	75	26.4
Anti-hypertensive drugs	79	27.9
Antidiabetic drugs	32	11.2
Tamoxifen	57	20.1
Anti-hypertensive and antidiabetic drugs	41	14.4
Mode of delivery (n=594)		
Vaginal delivery	340	57.2
Cesarean section	211	35.5
Vaginal delivery and cesarean section	43	7.3

DISCUSSION

In this study, we evaluated SM indications and sociodemographic characteristics of women between 2010 and 2020. According to the results of this study, the mean age of menopause due to early menopause caused by SM indications was 43.92±3.64 years. According to many researchers, the mean age of SM varies between 44.0 and 48.1 years[1,7]. As the age of menopause decreases, the risk of many diseases, especially CVD[12] and type II diabetes mellitus, increases[9]. Blood pressure is an important indicator of CVD. In the study by Bagnoli et al., it was determined that approximately 30% of 5,027 postmenopausal women with an average age of 51.9 years were obese. In the study, the prevalence of hypertension was higher in overweight (27.62%), obese (40.17%), and morbidly obese (54.55%) patients compared to those with a normal BMI (12.0%), and higher BMI had a significant negative effect on blood pressure[17]. Shen et al., investigated the risks of CVD, cancer, and diabetes in postmenopausal women based on their age at menopause. They found that women with a mean age of menopause of 50 years had mortality rates of 21% due to CVD, 38% due to cancer, and 7% due to diabetes[9]. The age of SM is lower in this study than in other studies, which constitutes an important risk factor for women in terms of CVD and diabetes.

In this study, the rate of indications for SM related to endometrial cancer was 6.1%. As of 2020, corpus uteri cancer is the 19th leading cause of death among women worldwide[18]. Güzel et al., stated that women with a high body mass index have a higher mortality rate from endometrial cancer compared to those with a low body mass index[19]. Zhao et al., evaluated the risk factors for endometrial cancer in patients with endometrial hyperplasia. They found that the incidence of endometrial cancer was 31.58% in a total of 228 patients with endometrial hyperplasia, of whom 72 had endometrial cancer[20]. In this study, the first two SM indications were myoma uteri and AUB, and the fifth SM indication was endometrial hyperplasia. All of these three conditions are among the most common reasons for women to present to the gynecology outpatient clinic with bleeding complaints and are risk factors for endometrial cancer. Compared to women aged 23–40 years in this study, regular drug use in women aged 41–46 years (premenopause) increased by 1.81 times. Regular medication uses increased cancer-related SM indications by 0.45 times and the presence of chronic diseases by 0.36 times (Table 2). Therefore, it is understood that many risk factors for endometrial cancer coexist in our results.

In the findings of this study, other causes of SM included adnexal malignant mass, adnexal benign mass, elective hysterectomy due to breast cancer, endometrial cancer, endometriosis,

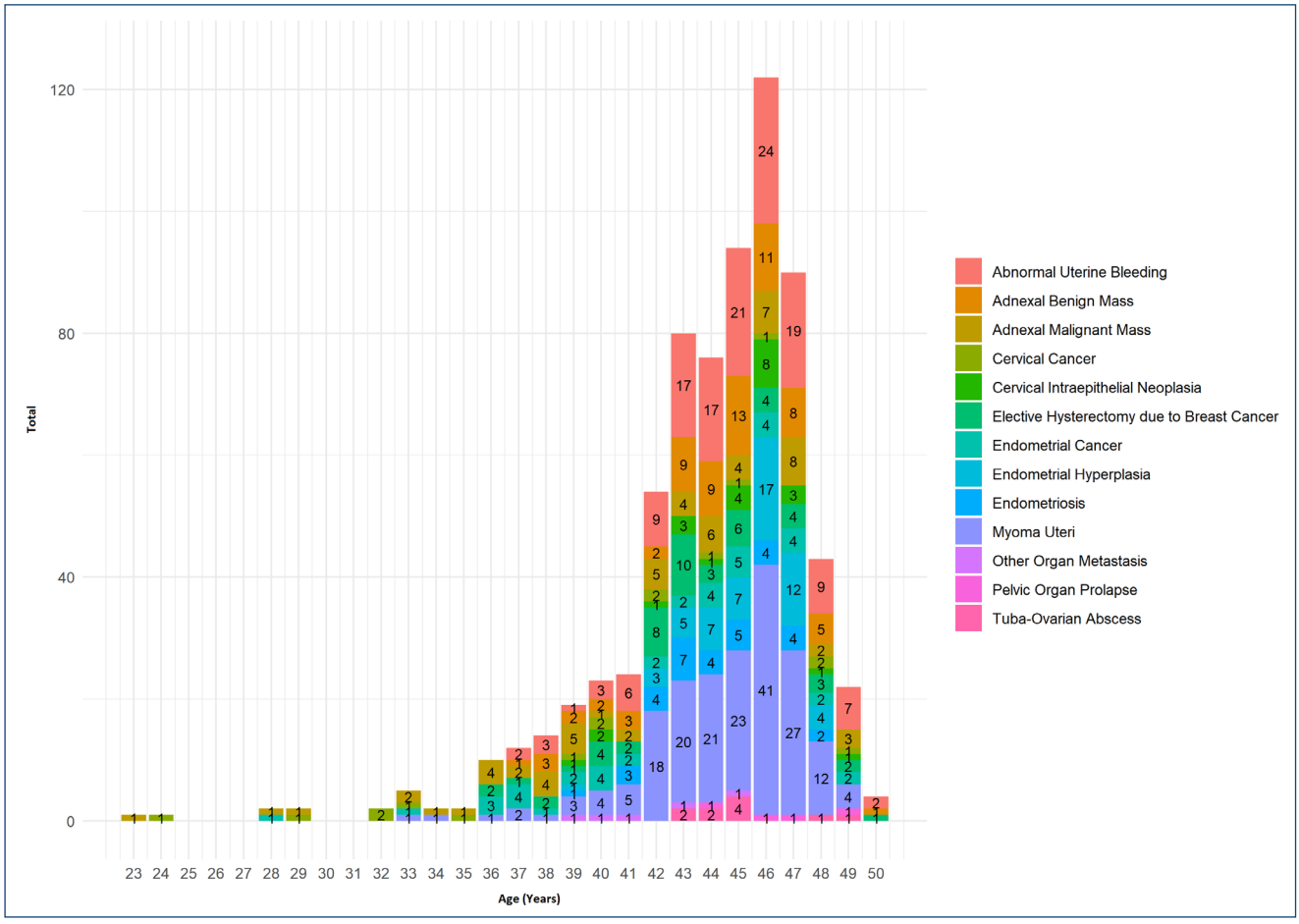

Figure 1. Distribution of women according to age at which they received surgical menopause indication.

Table 2. Associated factors for surgical menopause indication: logistic regression (n=704).

Variable	Surgical menopause indications							
	Causes of bleeding		Cancer		Cancer risk		Other indications	
	n	%	n	%	n	%	n	%
	324	46.0	199	28.3	133	18.9	48	6.8
	Odds ratio (95%CI)	p	Odds ratio (95%CI)	p	Odds ratio (95%CI)	p		
Smoking history[b]	0.17 (0.02–1.34)	0.093	0.08 (0.01–0.68)	**0.021**	0.21 (0.02–1.60)	0.216	1[a]	
Regular drug use[b]	0.76 (0.39–1.46)	0.414	0.45 (0.23–0.88)	**0.020**	0.80 (0.37–1.63)	0.547		
Presence of chronic disease[b]	0.65 (0.35–1.21)	0.177	0.36 (0.19–0.69)	**0.002**	0.72 (0.37–1.41)	0.345		
	Age							
	48–50 years		47 years		41–46 years		23–40 years	
	n	%	n	%	n	%	n	%
	69	9.8	90	12.8	450	63.9	95	13.5
	Odds ratio (95%CI)	p	Odds ratio (95%CI)	p	Odds ratio (95%CI)	p		
Regular drug use[c]	1.16 (0.60–2.25)	0.645	1.48 (0.81–2.71)	0.198	1.81 (1.14–2.89)	**0.012**	1[a]	

[a]1: Reference category, [b]Model chi-square: 83.817; p<0.000, –2 log likelihood: 1309.779, Pseudo R^2 (Nagelkerke): 0.180, [c]Hosmer and Lemeshow test: 0.327, Nagelkerke R square: 0.093, p: 0.003, χ^2: 32.463; df: 9. Bold values indicate data with statistical significance.

CIN, cervical cancer, TOA, other organ metastasis, and POP. Wong et al., stated that 749 of the 2,656 women in their study were applied SM, and 509 had a preoperative SM indication. They found that preoperative SM indications and their rates included malignancy (45%), endometrial hyperplasia (21%), endometriosis (10%), irregular uterine bleeding (9%), pelvic mass (9%), prophylactic bilateral salpingo-oophorectomy (8%), and other indications[21]. In the study by Jain and Somalwar, the causes of benign lesions SM were found to be dysfunctional uterine bleeding, leiomyoma, endometriosis, adenomyosis, and postmenopausal bleeding[8]. There were different rates in terms of administering SM due to the malignancy of its indications, both in these studies and in our study. The mean age of the women in the study of Wong et al., was 55.5 years[21], and it was <45 years in approximately 40% of the women in the study by Jain and Somalwar[8]. However, in this study, 60.1% of the women were under the age of 45 years. Another different result compared to other studies was that the rate of SM originating from the cervix, including 3.6%CIN and 2.4% cervical cancer, was higher in our sample group. There were other significant differences in the studies, such as the inclusion criteria of women in the sample (use of hormone therapy, etc.). Therefore, we thought that there were differences between SM indications in terms of malignancy rates.

The cases coded as malignant adnexal mass in our data were women with ovarian cancer, which accounted for 9.1%. The rate of SM due to elective hysterectomy for breast cancer was 7.5%. In the study by Li et al., SM resulted in a 45% decrease in breast cancer risk in women who had a BRCA1/2 mutation and did not have a history of breast cancer, a 57% decrease in all-cause mortality in breast cancer patients, and a 65% decrease in all-cause mortality related to SM[22]. Reducing the risk of ovarian cancer may continue to be a reasonable target for women undergoing hysterectomy, especially those aged ≥50 years. In our data, the mean age of women who underwent SM due to a benign adnexal mass was 41.7 years. For this reason, we thought that it is an important risk factor for other diseases and fertility loss in women in later life.

The study by Sorpreso et al., identified non-obstetric causes of death in climacteric women in Brazil after "The National Policy for Integral Attention to Women's Health Care (PNAISM)". The PNAISM (launched in 2004 by the Brazilian Health Department) covers a comprehensive area of women's health, including pregnancy, puerperium, prevention, detection and treatment of neoplasms, menopause, etc. The study analyzed data on 2,107,634 women aged 40–64 years between 1996 and 2016. The main causes of death in women were circulatory system diseases (22.47%), neoplasms (19.69%), respiratory system diseases (5.5%), endocrine, nutritional, and metabolic disorders (5.27%) and digestive system diseases (3.74%). After implementation of the PNAISM, the authors observed a downward trend in rates of mortality from diseases of the circulatory and digestive systems and from endocrine, nutritional, and metabolic diseases[23]. As noted in this study, health policies to protect women's health are very important. Therefore, it is important to know the sociodemographic characteristics of women with SM to evaluate women holistically for preventable or controllable risks and to guide health policies. For example, Noll et al., examined 288 postmenopausal women with an average age of 56.23 years, an average menopause duration of 8.15 years, and 48.6% of whom underwent early menopause. In the study, it was determined that 33.4% of the women were obese, 16.7% were smokers, and 54.5% did not engage in physical activity. In the study, the authors reported that obesity was associated with somatic symptoms 1.36 (CI 1.04–1.79), vasomotor symptoms 1.38 (CI 1.01–1.90), and anxiety/fear 1.84 (CI 1.05–3.21)[24]. Also, in this study, 8.8% of the women had a history of smoking, which increased the risk of SM due to cancer by 0.08 (CI 0.01–0.68) times. According to the results of the above studies, the results of this study may contribute to the management of preventable risk factors in women with SM. It is recommended that health professionals (physicians, nurses, etc.) address women's sociodemographic characteristics and perform prospective risk management such as CVD and diabetes after SM.

Limitations

In this study, we were able to obtain data on the education level and contraception methods for a small portion of the women in our study group. Therefore, we were unable to evaluate the effects of educational status and contraception methods.

CONCLUSION

In this study, the age of menopause due to SM in women was found to be below 45 years. The majority of women had chronic diseases, and the prevalence of regular drug use was high. Smoking, the presence of chronic diseases, and regular drug use for chronic diseases increase the rate of SM due to gynecologic cancer. It is recommended that these results can be used to reduce preventable health risks and improve the well-being of post-SM women.

RESEARCH ETHIC

The ethical approval was obtained from the Non-Interventional Ethics Committee of Dokuz Eylul University (date: 28/07/2021, No: 2021/22-31).

AUTHORS' CONTRIBUTIONS

HÖ: Conceptualization, Formal Analysis, Methodology, Supervision, Writing – original draft, Writing – review & editing. **SK:** Conceptualization, Data curation, Supervision, Writing – original draft, Writing – review & editing. **SÖ:** Data curation, Investigation, Writing – original draft. **CTÇ:** Data curation, Investigation, Writing – original draft. **İÖ:** Formal Analysis, Methodology, Visualization, Writing – original draft.

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ORIGINAL ARTICLE

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The effects of adequate dietary calcium intake in patients with hypoparathyroidism non-adherent to treatment: a prospective randomized controlled trial

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SUMMARY

OBJECTIVE: A significant problem that compels clinicians in the conventional treatment of hypoparathyroidism is patients' non-adherence to treatment. This study aimed to evaluate the effects of adequate Ca intake with dietary recommendations among hypoparathyroidism patients who persistently use Ca supplementation irregularly on plasma Ca and phosphate levels.

METHODS: This prospective, randomized, controlled study was conducted on patients diagnosed with chronic hypoparathyroidism who persistently interrupt Ca supplementation therapy and therefore have a hypocalcemic course. Patients with a total daily Ca intake below 800 mg were randomized. All patients were advised to keep the doses of active vitamin D and Ca supplements they were currently using. The patients in the study group (n=32) were advised to consume 1,000–1,200 mg of Ca daily, and the patients in the control group (n=35) were advised to continue their diet according to their daily habits. After 12 weeks of follow-up, the patients' laboratory values were compared between groups to assess treatment goals.

RESULTS: The mean of the total Ca level was 8.56±0.36 mg/dL in the study group and was found to be significantly higher than that in the control group, which was 7.67±0.48 mg/dL ($p<0.001$). The mean serum phosphate and serum Ca-P product levels were significantly higher in the study group ($p<0.001$) but did not exceed the safe upper limits in any patient.

CONCLUSION: A suitable increase in dietary Ca intake could effectively control hypocalcemia in patients with hypoparathyroidism who persistently interrupt the recommended calcium supplementation.

KEYWORDS: Hypoparathyroidism. Dietary calcium. Medication non-adherence.

INTRODUCTION

Hypoparathyroidism (hypoPT) is a mineral metabolism disease characterized by hypocalcemia due to an insufficiency or absence of parathormone (PTH) synthesis[1]. The primary goals of hypoPT treatment are to correct hypocalcemia and prevent disease-related complications[2]. The hypoPT management guidelines recommend conventional therapy as the first-line therapy in hypoPT treatment[2]. Most diseases that develop due to hormone deficiency are usually treated by replacing the missing hormone. However, PTH replacement therapy is recommended for individuals who cannot be adequately controlled using conventional hypoPT therapy[3]. Moreover, it cannot be used widely due to its high cost and lack of long-term safety data[4]. Therefore, most hypoPT patients are treated with the conventional approach.

Oral Ca salts and active vitamin D supplements form the basis of conventional treatment[5]. However, this approach does not always provide adequate or consistent control of the biochemical and clinical aspects of the disease. Adverse short-term and long-term complications include large fluctuations in serum Ca concentrations and risks of calcifications in tissues[6]. Further critical problems that compel clinicians in daily practice related to conventional hypoPT treatment are patients' non-compliance with treatment and irregular use of oral Ca and active vitamin D supplements despite persistent information and warnings[7]. As a result, patients who cannot achieve their treatment goals are frequently encountered. In this patient group, when PTH replacement, which can be an alternative approach, cannot be provided, serious difficulties are experienced in treating this condition.

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The recommended daily Ca intake for hypoPT patients is the same as in the general population[8,9]. In this study, we aimed to examine the effects of adequate Ca intake with dietary recommendations among hypoPT patients who persistently use Ca supplementation therapy irregularly and therefore have low plasma Ca and P levels.

METHODS

Ethical standards

This study was performed in line with the principles of the Declaration of Helsinki. Approval was granted by the Ethics Committee of the University of Health Sciences, Şişli Hamidiye Etfal Training and Research Hospital (Date 28.12.2021/No. 1973). Informed consent was obtained from all individual participants included in the study.

Design and study population

This prospective, randomized, controlled clinical study was conducted with patients who applied to the Endocrinology outpatient clinic in 2022 and received conventional treatment for hypoPT. Patients who came for regular follow-ups at least twice a year, who regularly took the recommended active vitamin D treatment but persistently never or incompletely used Ca supplementation, and whose albumin-corrected plasma total Ca levels were consistently 8 mg/dL and below were identified. Patients who skipped Ca supplementation regularly, at least thrice a week, were defined as non-adherent to Ca supplementation therapy. Patients with chronic kidney disease, a history of urolithiasis, high 24-h urinary Ca excretion (>300 mg/day for males, >250 mg/day for females), serum Ca-P product levels>55 mg^2/dL^2, plasma magnesium (Mg) levels outside the normal reference range, any diagnosed gastrointestinal disease that may affect oral drug or nutrient absorption, and neuropsychiatric disorders that would prevent them from making a food follow-up chart were excluded from the study.

A dietitian contacted the patients for the second screening and informed them of the amounts of Ca in each portion. The patients were trained in preparing a food-tracking chart and asked to keep records for 2 weeks. Patients who did not complete their nutritional follow-up chart, who did not come for control, or whose average daily Ca intake (diet and supplementation) was 800 mg/day and above were excluded from the study.

For randomization, patients were numbered according to their admission order for 2022. Those with odd numbers were classified as the study group, and those with even numbers were classified as the control group. Finally, patients were given nutritional follow-up chart forms and advised not to change their active vitamin D and Ca supplement doses and to keep daily records for 12 weeks. The patients in the control group were advised to continue to eat according to their daily habits. The patients in the study group were advised to consume 1,000–1,200 mg of Ca daily. Furthermore, they were warned that their total daily Ca intake should stay within 800 mg and not exceed 1,500 mg. After 12 weeks, patients in the study group with an average daily Ca consumption below 800 mg and those in the control group with an average daily Ca consumption of 800 mg and above were excluded from the evaluation (Figure 1).

The primary endpoint was the proportion of patients at Week 12 who achieved plasma total Ca levels in the lower limit of or slightly below the normal range (the target range of 8–9.5 mg/dL). The secondary endpoint was that the 24-h urinary Ca excretion, plasma P, and serum Ca-P product levels did not exceed the treatment targets recommended by the hypoPT treatment guidelines. The serum Ca-P product levels were calculated by multiplying plasma calcium and phosphate levels.

Statistical analysis

The conformity of the data to the normal distribution was evaluated using the Shapiro-Wilk test. Mean and standard deviations were used for normally distributed variables. Medians and ranges were used for non-normally distributed variables. Chi-square (χ^2) and Fisher's exact tests were used to compare categorical data. Student's t-test and Mann-Whitney U test were used to compare parametric and nonparametric data, respectively, between the study and control groups. Statistical significance levels were accepted as $p<0.05$.

RESULTS

Overall, 216 patients were screened, and 72 were randomly assigned into two. Notably, 32 patients from the study group and 35 from the control group completed the study (Figure 1). The patients' baseline characteristics, demographic information, and laboratory values were similar between the study and control groups (Table 1).

While the mean prescribed Ca intake per day at baseline was similar between the groups, the dietary and associated total Ca intake were higher in the control group (p-value=0.046 and 0.026, respectively) than in the study group.

Compliance with the dietary recommendations was excellent in the study group (34/36, 94.4%). The data of both groups after 12 weeks of follow-up are shown in Table 1.

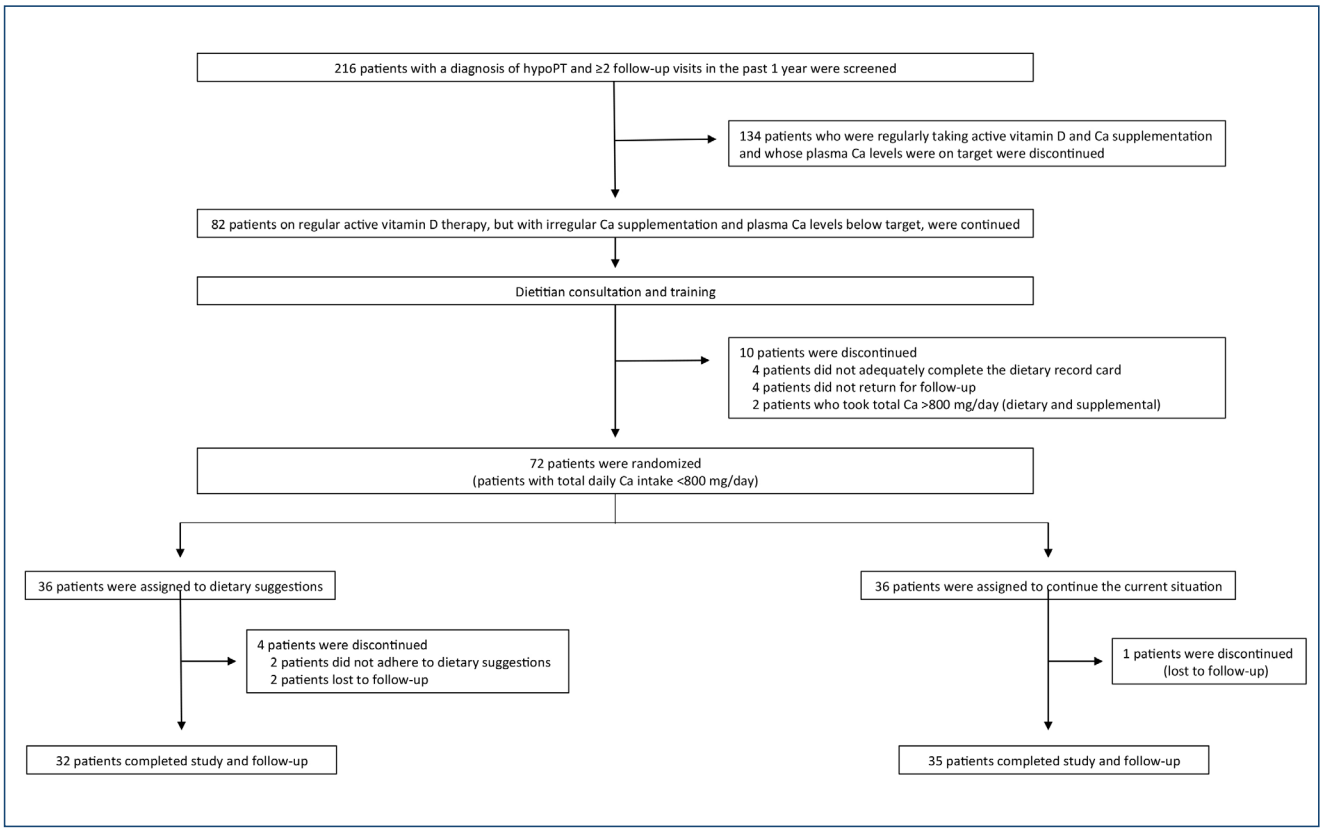

Figure 1. Study protocol.

The mean dietary Ca intake and total daily Ca intake were statistically significantly higher in the study group than in the control group (p<0.001). The mean Ca levels, which was the primary endpoint of the study, was 8.56±0.36 (7.58–9.13) mg/dL in the study group and was significantly higher than that in the control group, which was 7.67±0.48 (6.76–8.78) mg/dL (p<0.001). Furthermore, 87% of patients in the study group attained the target range of serum Ca levels (8–9.5 mg/dL), and the remaining 13% attained very close values (the least was 7.7 mg/dL). In the control group, 3 (8.5%) of the 35 patients attained the target range.

During the follow-up period, no patients in the study group described paresthesia symptoms. The value of mean Ca excretion in 24-h urine in the study group was higher than that of the control group (p<0.001). However, no patient exceeded 250 and 300 mg/day for women and men, respectively. The mean serum P and serum Ca-P product levels were significantly higher in the study group (p<0.001) than in the control group. For the serum P levels, no patient exceeded the upper limit of the reference range (2.5–4.5 mg/dL) by more than 1 mg/dL, and the serum Ca-P product levels did not exceed the safe upper limit of 55 mg^2/dL^2 in any patient.

When the GFR values were compared with the MDRD formulation, it was found to be 98.9 in the study group and 103.3 in the control group (p=0.035). During the follow-ups, nephrocalcinosis, nephrolithiasis, and extraskeletal complications were not observed in the patients.

Table 2 compares the study group values before and after the dietary intervention during the 12-week follow-up period.

Serum Ca levels increased from 7.29 to 8.56, serum P levels increased from 4.43 to 5.21, 24-h urinary Ca excretion increased from 146.5 to 229.6, and serum Ca-P product values increased from 32.35 to 44.59 after dietary changes (p<0.001). Additionally, increased serum creatinine levels (0.75–0.79) and decreased GFR levels (100.9–89.9) were detected.

DISCUSSION

In this observational controlled study, we provide information on the effect and safety of adequate dietary Ca intake in correcting hypocalcemia in hypoPT patients who are incompatible with Ca supplementation and have a hypocalcemic course. Most (87.5%) patients with adequate dietary Ca intake reached the primary endpoint, the target Ca level, compared with only 7.7% in the control group.

Table 1. Patients' baseline and after 12 weeks of follow-up characteristics.

	Study (n=32)	Control (n=35)	p-value *
Baseline characteristics			
Age, years	52.3±8.8 (29–64)	51.2±9.5 (28–64)	0.744
Gender			
°Women	20 (62.5%)	23 (65.7%)	
°Men	12 (37.5%)	12 (34.3%)	0.784
Duration of hypoPT, years			
°≤5 years	2 (6.3%)	2 (5.7%)	
°5–10 years	12 (37.5%)	14 (40%)	
°≥10 years	18 (56.2%)	19 (54.3%)	0.976
Cause of hypoPT			
°Idiopathic, autoimmune disease	10 (31.2%)	12 (34.3%)	
°Post-surgical disease	22 (68.8%)	23 (65.7%)	0.791
Prescribed calcitriol dose, µg/day			
°0.25–0.50	20 (62.5%)	23 (65.7%)	
°>0.50	12 (37.5%)	12 (34.3%)	0.784
Mean prescribed calcitriol dose, µg/day	0.664±0.274	0.650±0.265	0.848
Mean Ca intake, mg/day			
°Prescribed	131.3±252.0 (0–600)	137.1±255.6 (0–600)	0.924
°Dietary	375.8±146.1 (150–750)	475.0±208.1 (150–800)	**0.046**
°Total	504.7±190.3 (250–800)	612.1±165.8 (275–800)	**0.026**
Albumin-corrected total serum Ca (mg/dL)	7.29±0.22 (6.88–7.59)	7.28± 0.31 (6.29–7.59)	0.66
Serum phosphate (mg/dL)	4.43±0.41 (3.48–4.98)	4.58±0.44 (3.68–5.39)	0.14
Serum magnesium (mg/dL)	1.75± 0.12 (1.56–1.97)	1.76±0.13 (1.51–1.96)	0.83
Serum 25 (OH) vitamin D (ng/mL)	19.99±6.56 (5.7–37.1)	18.98±6.55 (6.4–34.9)	0.53
Serum creatinine (mg/dL)	0.75±0.12 (0.43–0.95)	0.74±0.11 (0.50–1.02)	0.71
GFR (mL/min/1.73 m²)	100.97±7.16 (90–115)	102.9±9.66 (90–126)	0.60
Serum Ca-P product (mg²/dL²)	32.35±3.60 (24.3–37.7)	34.07±3.79 (25.3–40.4)	0.06
Urine Ca, mg/24 h	146.5±35.9 (89.3–206.1)	136.3±38.7 (47.5–193.6)	0.27
Data after 12 weeks of follow-up			
Mean Ca intake, mg/day			
°Prescribed	131.3±252.0 (0–600)	137.1±255.6 (0–600)	0.924
°Dietary	1,050.0±179.6 (450–1,350)	510.0±232.3 (150–800)	**<0.001**
°Total	1,185.9±167.8 (1,000–1,650)	647.1±162.7 (300–800)	**<0.001**
Albumin-corrected total serum Ca (mg/dL)	8.56±0.36 (7.58–9.13)	7.67±0.48 (6.76–8.78)	**<0.001**
Number of patients who reached the target Ca value (8–9.5 mg/dL)	28 (87.5%)	3 (8.5%)	
Number of patients with hypocalcemia requiring emergency admission	0	0	
Number of patients with hypocalcemia requiring emergency admission	0	9 (25.7%)	
Urine Ca, mg/24 h	229.6±40.1 (133.6–296.2)	163.1±38.5 (96.3–245.2)	**<0.001**
Serum phosphate (mg/dL)	5.21±0.39 (4.38–5.88)	4.94±0.41 (4.25–5.79)	**0.01**
Serum Ca-P product (mg²/dL²)	44.59±3.97 (36.3–51.5)	34.6±4.9 (28.1–50.8)	**<0.001**
Serum creatinine (mg/dL)	0.79±0.11 (0.57–1.01)	0.74±0.11 (0.50–1.02)	0.11
GFR (mL/min/1.73 m²)	98.9±8.7 (84–114)	103.3±7.9 (87–128)	**0.035**

*Significance level: 0.05. Statistically significant values are indicated in bold.

Table 2. Comparison of the study group values before and after dietary changes.

	Before dietary changes	After dietary changes	p-value*
Mean Ca intake, mg/day			
°Prescribed	131.3±252.0 (0–600)	131.3±252.0 (0–600)	1
°Dietary	375.8±146.1 (150–750)	1,050.0±179.6 (450–1,350)	**<0.001**
°Total	504.7±190.3 (250–800)	1,185.9±167.8 (1,000–1,650)	**<0.001**
Albumin-corrected total serum Ca (mg/dL)	7.29±0.22 (6.88–7.59)	8.56±0.36 (7.58–9.13)	**<0.001**
Serum phosphate (mg/dL)	4.43±0.41 (3.48–4.98)	5.21±0.39 (4.38–5.88)	**<0.001**
Serum creatinine (mg/dL)	0.75±0.12 (0.43–0.95)	0.79±0.11 (0.57–1.01)	**0.001**
GFR (mL/min/1.73 m^2)	100.97±7.16 (90–115)	98.9±8.7 (84–114)	**0.009**
Serum Ca-P product (mg^2/dL^2)	32.35±3.60 (24.3–37.7)	44.59±3.97 (36.3–51.5)	**<0.001**
Urine Ca, mg/24 h	146.5±35.9 (89.3–206.1)	229.6±40.1 (89.3–206.1)	**<0.001**

*Significance level: 0.05. Statistically significant values are indicated in bold.

We observed that all 216 patients diagnosed with hypoPT screened for our study used Ca-gluconate and active vitamin D supplements, so they received conventional treatment. Therefore, the hypoPT treatment guidelines recommend conventional therapy as the first-line therapy for hypoPTH, although new treatment options are available[3,8,10,11]. Conventional treatment is primarily intended to correct hypocalcemia, not as a physiological replacement therapy for PTH deficiency. Therefore, PTH analogs or the administration of recombinant human PTH is recommended for patients unable to achieve treatment goals with conventional therapy[12,13]. PTH analogs limit the need for Ca supplements that are not well tolerated, especially when high doses are required[14]. However, the cost of PTH replacement therapy is considerably higher than that of conventional therapy. In addition, long-term safety data are insufficient, thus limiting its use as a standard replacement therapy for all hypoPT patients[4]. We found that only one of the patients screened within the scope of our study was started on teriparatide (PTH 1-34) treatment 3 years ago. However, after 3 months of use, it was discontinued due to the high cost, and conventional treatment was resumed.

It is nearly impossible to manage hypoPT by ensuring adequate Ca intake through diet alone. Therefore, Ca supplements are necessary. Typically, patients reportedly require 1–2 g of additional Ca, given in divided doses of 500 mg at a time[15,16]. One common problem in daily practice related to conventional treatment is patients' non-compliance. We found that 82 (37.9%) of the 216 patients screened for our study did not use Ca supplementation regularly as recommended. The hypoPT treatment guidelines emphasize the significance of this problem. Reportedly, the numerous pills required daily and the gastrointestinal side effects of Ca preparations contribute to the incompatibility[17]. Unfortunately, the number of studies evaluating drug compliance and related factors in hypoPT patients is limited in the literature. In a study, the rate of non-compliance with $CaCO_3$ treatment was 51.7%, and the rate of non-compliance with calcitriol treatment was 28.3%[7]. Studies on patient compliance with Ca supplementation were mainly conducted in patients diagnosed with osteoporosis. In a study in which 7,624 patients who have prescribed Ca and vitamin D treatment were examined, it was observed that 27.7% of the patients did not continue their Ca supplementary treatment 1 year after starting[18].

Controlling hypocalcemia by providing adequate dietary Ca without Ca supplementation is challenging. A study conducted on subjects without diseases related to Ca metabolism showed a significant correlation between the change in dietary Ca intake and plasma and urinary Ca levels[19]. In addition, dairy products, the primary source of Ca in the diet, are rich in phosphate[20]. Hence, there is concern that overconsumption of dairy products for Ca supplementation may also increase P, thus increasing serum Ca-P product. In the hypoPT treatment guidelines, the recommended dietary Ca intake in hypoPT patients is the same as that recommended for the general population[15]. The daily Ca consumption recommended by the Institute of Medicine for healthy individuals has been accepted by many scientific communities, such as the National Osteoporosis Foundation, and is recommended in exact amounts. According to this recommendation, 1,000 mg/day Ca consumption is recommended for those aged 19–50 years, and 1,200 mg/day Ca consumption is recommended for those aged 50 and above. Ca intake exceeding 1,200–1,500 mg may increase the risk of kidney stones, cardiovascular events, and stroke[9,21].

Managing hypoPT patients who are undergoing conventional treatment but hinder the recommended treatment and therefore develop a hypocalcemic course and cannot be

switched to alternative options due to cost is severely challenging. To date, no study has examined the effects of increasing the amount of Ca in the daily diet of hypoPT patients in a controlled manner. When we examined the daily Ca consumption of the patients who were screened for the study and asked to prepare a nutritional follow-up chart, we observed that their daily Ca intake was well below that of a healthy adult. Daily Ca consumption was 375 mg/day in the study group and 475 mg/day in the control group. In a study, the average Ca intake in adults aged 51 years and older was 674 mg/day, which was significantly less than the adequate daily intake of 1,200 mg[22]. After the patients in the study group were advised to take Ca in the amount recommended by the treatment guidelines[9], it was observed that daily dietary Ca consumption increased from 375 (150–750) mg/day to 1,050 (450–1,350) mg/day and total daily Ca intake increased from 504 (250–800) mg/day to 1,185 (1,000–1,650) mg/day. However, the prescribed Ca amounts for the patients did not change.

Limitations

It is known that the effects of dietary Ca changes on plasma Ca and P levels and urinary Ca excretion occur within a short time, even daily. However, the study period may not be sufficient to achieve the hypoPT treatment goals of these changes and evaluate the safety of complications, such as nephrocalcinosis and nephrolithiasis. Another limitation of the study is that the upper limit of the recommended dietary Ca amount (1,500 mg/day) was not exceeded by any of the patients included in the study; thus, the warnings and the laboratory and clinical implications of exceeding this amount could not be tested.

CONCLUSION

This is the first prospective randomized controlled study to examine the effect of adequate dietary Ca intake in correcting hypocalcemia in patients with hypoPT who are incompatible with Ca supplementation therapy. The recommendation to consume only the amount of Ca a healthy adult should take makes the proposed approach immediately applicable. The results show that a steady increase in dietary Ca intake effectively controls hypocalcemia. Although plasma P and serum Ca-P product increased, they did not exceed the safe upper limit. Additionally, we observed that they did not cause complications during the study by deviating from the treatment targets of hypoPT. Furthermore, patients' compliance was high, and they tolerated the increased Ca consumption well.

AUTHORS' CONTRIBUTIONS

MMC: Investigation, Methodology, Project administration, Writing – original draft. **AB:** Conceptualization, Investigation, Writing – review & editing. **ÇD:** Data curation, Resources. **HK:** Data curation, Visualization. **YA:** Supervision, Validation. **MK:** Formal Analysis, Software. **ZMYK:** Resources. **FYÖ:** Methodology.

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ORIGINAL ARTICLE

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An analysis of lactate/albumin, procalcitonin/albumin, and blood urea nitrogen/albumin ratios as a predictor of mortality in uroseptic patients

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SUMMARY

OBJECTIVE: The aim of this study was to investigate the ratios of lactate/albumin, procalcitonin/albumin, and blood urea nitrogen/albumin to predict 14- and 28-day mortality in uroseptic patients. Urosepsis is a disease with high mortality, and early diagnosis and treatment are important.

METHODS: Patients with urosepsis who were admitted to the intensive care unit between January 2021 and September 2022, had a follow-up of at least 28 days, and met the inclusion criteria were evaluated retrospectively.

RESULTS: The mean age was 70.23 (15.66) years and 84 (53.85%) were males. The number of non-survivors were 75 (48%) in the 14-day mortality group and 97 (62.1%) in the 28-day mortality group. Based on the 14-day mortality data, the blood urea nitrogen/albumin ratio was higher in non-survivors vs. survivors (median, 15.88 vs. 9.62), and the lactate/albumin ratio was higher (median, 0.96 vs. 0.52, p<0.01, all). Based on the 28-day mortality data, the blood urea nitrogen/albumin ratio was higher in non-survivors vs. survivors (median, 14.78 vs. 8.46), and the lactate/albumin ratio was higher (median, 0.90 vs. 0.50, p<0.01, all).

CONCLUSION: It is very difficult to determine the prognosis of patients admitted to the emergency department with the diagnosis of urosepsis. The lactate/albumin ratio and the blood urea nitrogen/albumin ratio can be used as early prognostic markers for both 14-day and 28-day mortality until more reliable markers are identified.

KEYWORDS: Mortality. Blood urea nitrogen. Lactate.

INTRODUCTION

Urosepsis is a serious infection of the urinary tract accompanied by systemic inflammatory response syndrome, which manifests in various forms such as pyelonephritis, cystitis, renal abscess, acute prostatitis, or acute epididymo-orchitis. Urosepsis constitute approximately 30% of all cases of sepsis, which may vary based on geographical regions[1]. It entails a high mortality rate, in the range of 30–40%. Its high mortality rate, its potential to cause sequelae, and the rising cost of hospitalized care warrant rapid and detailed evaluation of patients diagnosed with urosepsis[2].

It should also be remembered that early detection and the therapeutic approach used affect the patient's survey[3]. It is necessary to identify reliable and high-performing clinical indices that can be used in clinical practice to predict development of urosepsis in adults. It will also be useful to have a set of biomarkers that can be reliably used in a clinical setting to estimate prognosis.

Serum lactate (L) is a marker of tissue hypoxia and is associated with mortality in sepsis[4]. Albumin (A), a negative acute phase reactant, is a prognostic indicator of inflammation severity in septic patients[5]. Procalcitonin (PCT) is a peptide precursor of calcitonin. It has been shown that serum PCT levels are notably elevated in bacterial infections[6]. BUN level may be associated with poor prognosis and is a major risk factor indicator in septic patients[7,8].

Therefore, the aim of this single-center, retrospective, observational study was to determine the ratios of lactate/albumin (L/A), procalcitonin/albumin (PCT/A), and blood urea nitrogen/albumin (BUN/A) in evaluating 14- and 28-day mortality and prognosis-relevant factors in uroseptic patients and to investigate the specific L/A, PCT/A, and BUN/A values that may be useful in predicting mortality as a future prognostic factor.

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METHODS

Patients and data collection

A total of 156 patients diagnosed with urosepsis who presented at tertiary-care adult intensive care units at Dr. Ersin Arslan Training and Research Hospital over the period of January 2021 to September 2022 were included in this study. A diagnosis of sepsis was made using the criteria of "Surviving Sepsis Campaign: International guidelines for management of severe sepsis and septic shock: 2012"[9]. The inclusion criteria were the presence of sepsis and a proven diagnosis of urinary infection. The exclusion criteria were as follows:

1. Culture results indicating polymicrobial infection
2. Patients aged less than 18 years
3. Patients not diagnosed with urosepsis
4. Lack of medical documentation precluding inclusion in statistical analysis
5. A negative urine culture.

Data on patients' age, gender, underlying conditions, duration of intensive care unit stay, invasive procedures, clinical particulars, and blood and urine culture evaluations, and prognostic data were collected and analyzed. The 14- and 28-day mortality rates were defined as death within 14 or 28 days, respectively, from the onset date of urosepsis. This study complied with the standards of medical ethics as endorsed by decision 184.22.09, dated 01.26.2023, of the Ethics Committee of Gaziantep Islam Science and Technology University.

Statistical analysis

Descriptive statistics of study data were expressed as mean for numerical variables and as frequency and percentage analysis for standard deviation and categorical variables. The consistency of biochemical and hemogram variables with the normal distribution was evaluated using the Shapiro-Wilk test. It was found that the variables were not consistent with the normal distribution ($p<0.05$). The Mann-Whitney U test was used for comparing the variables on mortality at day 14 vs. day 28. The analytical results for variables outlying the normal distribution were given as median (Q1–Q3). Moreover, the differences between categorical variables were analyzed using the Chi-square test. The receiver operating characteristic (ROC) curve was used for determining the cutoff points for the L/A, BUN/A, C-reactive protein/albumin (CRP/A), PCT/A, and neutrophil/lymphocyte (N/L) ratios. ROC analysis was performed to identify the best cutoff value for mortality prediction. The univariate/multivariate logistic regression analysis was used for evaluating variables which could impact on 14-day and 28-day mortality. Statistical analysis was performed using IBM SPSS 22.0 version (IBM SPSS, Chicago, IL). A significance level of $p<0.05$ was adopted.

RESULTS

Demographic data and clinical characteristics

A total of 156 patients who met the diagnostic criteria of urosepsis at hospitalization were included in the study in a total population of 2,332 patients who had been followed up at the tertiary care adult intensive care unit over the period of January 2021 to September 2022. Patients who were non-uroseptic, aged less than 18 years, or with missing study data were excluded. Notably, 84 (53.85%) of the patients were males, and 72 (46.15%) were females. A statistically significant difference in age or gender was absent between the survivor and the non-survivor groups. A total of 105 (67.31%) of the patients received mechanical ventilation support, and 51 (32.69%) did not need it. The number of non-survivors were 75 (48%) in the 14-day mortality group and 97 (62.1%) in the 28-day mortality group.

Based on the 14-day mortality data, the BUN/A ratio was higher in non-survivors vs. survivors [median, 15.88 (9.06–27.27) vs. 9.62 (5.48–16.50)], and the L/A ratio was higher [median, 0.96 (0.64–1.67) vs. 0.52 (0.39–0.71), $p<0.01$, all]. Similarly, based on the 28-day mortality data, the BUN/A ratio was higher in non-survivors vs. survivors [median, 14.78 (8.28–24.29) vs. 8.46 (5.48–14.58)] and the L/A ratio was higher [median, 0.90 (0.59–1.52) vs. 0.50 (0.37–0.67), $p<0.01$, all].

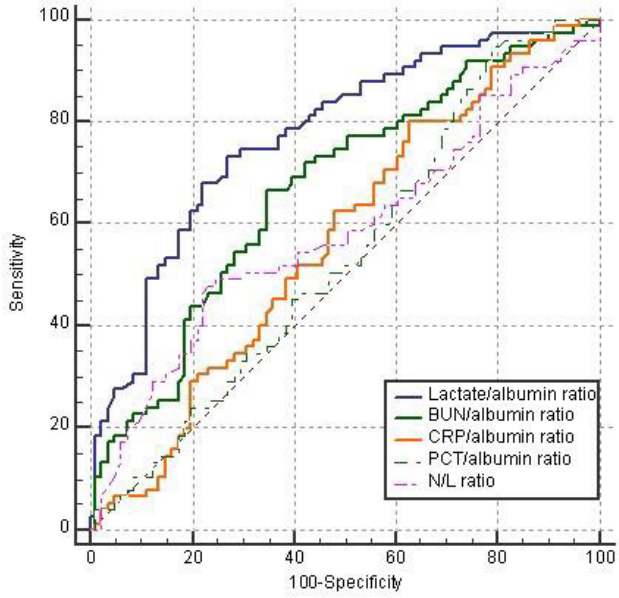
Significant independent risk factors identified by logistic regression analysis in the 14-day mortality data were the L/A ratio, BUN/A ratio, BUN, ferritin, international normalized ratio (INR), protrombin time (PT), D-dimer, platelet, mean corpuscular volume (MCV), and mean platelet volume (MPV). Also, the L/A ratio (OR=7.220, 95%CI 3.249–16.044, $p<0.001$) and the BUN/A ratio (OR=2.672, 95%CI 1.240–5.760, $p=0.012$) were identified as independent risk factors of mortality by multivariate and last model regression analysis (Table 1).

The ROC curves were plotted to predict 14-day mortality using the L/A ratio, BUN/A ratio, CRP/A ratio, PCT/A ratio, and N/L ratio. The area under the curve (AUC) for ROC was 0.771 for the L/A ratio (95%CI 0.697–0.835, $p=0.001$), 0.669 for the BUN/A ratio (95%CI 0.589–0.742, $p=0.001$), 0.567 for the CRP/A ratio (95%CI 0.486–0.646, $p=0.144$), 0.540 for the PCT/A ratio (95%CI 0.459–0.620, $p=0.385$), and 0.584 for the N/L ratio (95%CI 0.502–0.662, $p=0.072$) (Figure 1). For 28-day mortality, AUC for ROC was 0.772 for the L/A ratio (95%CI 0.698–0.835, $p=0.001$), 0.664 for

Table 1. Univariate, multivariate, and last model logistic regression analyses of various features associated with fatal outcomes for 14-day mortality.

Variable	Univariate OR	95%CI	p-value	Multivariate OR	95%CI	p-value	Last model OR	95%CI	p-value
L/A ratio	6.935	3.431–14.016	**<0.001**	6.006	2.488–14.497	**<0.001**	7.220	3.249–16.044	**<0.001**
BUN/A ratio	3.786	1.950–7.350	**<0.001**	2.652	1.196–5.882	**0.016**	2.672	1.240–5.760	**0.012**
BUN	1.020	1.007–1.034	**0.004**						
AST	1.002	0.998–1.005	0.365						
Ferritin	1.001	1.000–1.002	**0.009**	1.000	1.000–1.001	0.324			
INR	2.568	1.025–6.435	**0.044**	1.455	0.104–20.421	0.781			
PT	1.080	1.002–1.164	**0.043**	0.969	0.767–1.224	0.792			
D-dimer	1.096	1.006–1.193	**0.035**	1.047	0.959–1.142	0.303			
Platelet	1.000	1.000–1.000	**0.014**	1.000	1.000–1.000	0.068			
MCV	1.069	1.019–1.120	**0.006**	1.085	1.023–1.150	**0.006**	1.096	1.036–1.159	**0.001**
MPV	1.283	1.012–1.626	**0.039**	1.026	0.756–1.393	0.869			
Neutrophil	1.009	0.985–1.034	0.478						

Statistically significant values are denoted in bold. AST: aspartate aminotransferase.



Variable	AUC	95% CI	p	cutoff
L/A ratio	0.771	0.697 – 0.835	0.001	0.684
BUN/A ratio	0.669	0.589 – 0.742	0.001	12
CRP/A ratio	0.567	0.486 – 0.646	0.144	24.44
PCT/A ratio	0.540	0.459 - 0.620	0.385	0.036
N/L ratio	0.584	0.502 – 0.662	0.072	15.167

Figure 1. Analysis of receiver operating characteristic curve to predict 14-day mortality of uroseptic patients. The area under the curve was 0.771 for lactate/albumin ratio (p=0.001), 0.669 for blood urea nitrogen/albumin ratio (p=0.001), 0.567 for C-reaktive protein/albumin ratio (p=0.144), 0.540 for procalcitonin/albumin ratio (p=0.385), and 0.584 for neutrophil/lymphocyte ratio (p=0.072), respectively. The cutoff point of lactate/albumin ratio to predict 14-day mortality was 0.684 and 12 for blood urea nitrogen/albumin ratio.

the BUN/A ratio (95%CI 0.584–0.738, p=0.001), 0.600 for the CRP/A ratio (95%CI 0.519–0.678, p=0.037), 0.579 for the PCT/A ratio (95%CI 0.497–0.657, p=0.108), and 0.621 for the N/L ratio (95%CI 0.540–0.697, p=0.008) (Figure 2).

A cutoff value of 0.684 was determined for predicting both 14-day and 28-day mortality by L/A, and the survival rates of patients with a value above 0.684 were lower than in those with values below the threshold (p=0.001). Similarly, a cutoff value of 12 was used for predicting 14- and 28-day mortality rates by BUN/A. The survival rates were higher in patients in whom this value was below 12 (p=0.001) (Figures 1 and 2).

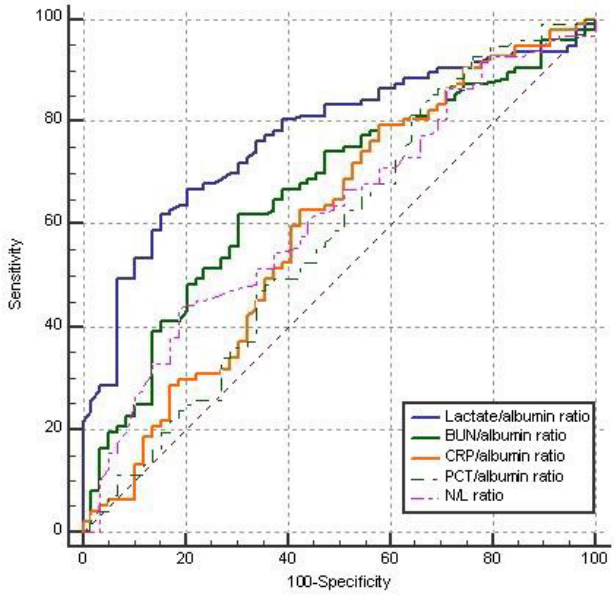
DISCUSSION

Early and accurate identification of sepsis is crucial, particularly in intensive care patients who are at high-risk for mortality. In this study, we investigated the independent risk factors which may potentially impact on prognosis and 14- and 28-day mortality, based on an analysis of clinical characteristics of uroseptic patients.

The 14-day mortality rate was 48% in this study. However, the mortality rate increased with the duration of stay, and the 28-day mortality rate was 62.1%. Our findings were consistent with the mortality rates reported by other studies, ranging from 40–58.3%[10,11].

The L/A ratio is a better prognostic marker of multi-organ failure and mortality in septic patients. Furthermore, a normal or low L/A ratio is associated with better prognosis[12,13]. Some studies have shown the L/A ratio to be a better predictor of mortality in septic patients[14-16].

Moreover, a cutoff value of 0.684 for the L/A ratio was determined for all uroseptic patients to differentiate survivors from non-survivors. In other studies with septic patients, the cutoff



Variable	AUC	95% CI	p	cutoff
L/A ratio	0.772	0.698 – 0.835	0.001	0.684
BUN/A ratio	0.664	0.584 – 0.738	0.001	12
CRP/A ratio	0.600	0.519 – 0.678	0.037	24.44
PCT/A ratio	0.579	0.497 – 0.657	0.108	0.077
N/L ratio	0.621	0.540 – 0.697	0.008	17.8

Figure 2. Analysis of receiver operating characteristic curve to predict 28-day mortality of uroseptic patients. The area under the curve was 0.772 for lactate/albumin ratio (p=0.001), 0.664 for blood urea nitrogen/albumin ratio (p=0.001), 0.600 for C-reaktive protein/albumin ratio (p=0.037), 0.579 for procalcitonin/albumin ratio (p=0.108), and 0.621 for neutrophil/lymphocyte ratio (p=0.008), respectively. The cutoff point of lactate/albumin ratio to predict 28-day mortality was 0.684 and 12 for blood urea nitrogen/albumin ratio.

values used included 1.01, 1.15, and 1.32, respectively[12,17,18]. We believe that the difference originates from the number of included patients. The optimal cutoff values vary between studies, and further investigation is necessary.

Some studies in the literature have suggested that the BUN/A ratio may be inversely related to survival, i.e., survival declines with this ratio increasing[19,20]. In our study, we have also shown that the BUN/A ratio may be used for predicting survey in uroseptic patients. We have determined an optimal cutoff value of 12 for predicting both 14- and 28-day mortality. In a Chinese study on 801 patients, a cutoff threshold of 5.27 was used for predicting 7-day mortality, while in a study on more than 10,000 patients, the cutoff was set to 7.93[19,21]. In a retrospective cohort study of 7,656 patients with sepsis, the cutoff value was 8 to predict 30-day mortality[22]. We believe that this difference between the cutoff values may be due to the differences in population size and the number of days used for mortality assessment.

In our study, in the 14-day mortality evaluation, the PCT/A ratios were higher in non-survivors vs. survivors [median, 0.68 (0.13–3.86) vs. 0.55 (0.6–3.2); p=0.386]. The results were similar for the 28-day mortality evaluation [median, 0.7 (0.14–3.86) vs. 0.36 (0.4–3.2); p=0.1]. Some recent reports in the literature have associated the PCT/A ratio with patient prognosis. A neonatal sepsis study has shown that an increased ratio was predictive of septic shock[23], while another study has suggested that it may be used for differentiating septic and non-septic urinary tract infections[24]. Our study differed from others in that we compared survivors with non-survivors in a population of uroseptic patients. While a statistically significant difference between the two groups was not found, the PCT/A ratios were higher in the non-survivor group.

Compared to the BUN/A ratio, the L/A ratio was a better prognostic marker based on 14-day mortality data (AUC of L/A ratio 0.771, 95%CI 0.697–0.835 vs. BUN/A ratio AUC=0.669, 95%CI 0.589–0.742) (p=0.001) (Figure 1). A similar observation was made in the 28-day mortality data (AUC of L/A ratio 0.772, 95%CI 0.698–0.835 vs. BUN/A ratio AUC=0.664, 95%CI 0.584–0.738) (p=0.001) (Figure 2). Our study has shown that the L/A and BUN/A ratios may be used as prognostic indicators in uroseptic patients. Increases in both of these ratios were independently associated with lower survival.

CONCLUSION

The L/A ratio and the BUN/A ratio may be used as early prognostic markers for both 14-day and 28-day mortality. We recommend using certain ratios as prognostic markers until reliable, affordable, and widely practicable biomarkers, shown to be so in studies, become broadly available.

AUTHORS' CONTRIBUTIONS

AŞ: Conceptualization, Data curation, Formal Analysis, Investigation, Methodology, Project administration, Resources, Writing – original draft, Writing – review & editing. **SB:** Conceptualization, Data curation, Formal Analysis, Supervision, Validation, Writing – original draft, Writing – review & editing. **SA:** Conceptualization, Data curation, Formal Analysis.

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ORIGINAL ARTICLE

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Internal medicine consultation for high-risk surgical patients: reflection on hospital mortality and readmission rates in a low-income country

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SUMMARY

OBJECTIVE: The objective of this study was to assess the impact of internal medicine consultation on mortality, 30-day readmission, and length of stay in surgical patients.

METHODS: This is a retrospective descriptive study developed in a public Brazilian teaching hospital with 850 beds.

RESULTS: A total of 70,245 patients were admitted from 2010 to 2018 to the surgery departments. The main outcomes measured were patients' mortality, 30-day readmission, and length of stay. Mortality of high-risk patients was lower when followed by internal medicine consultation: patients with ASA≥3 (RR 0.89 [95% confidence interval (95%CI) 0.80–0.99], p=0.02), patients with ASA≥3 plus≥65 years (RR 0.88 [95%CI 0.78–0.99], p=0.04), patients with ASA≥3 plus high-risk surgery (RR 0.86 [95%CI 0.77–0.97], p=0.01), and patients with ASA≥4 plus age ≥65 years (RR 0.83 [95%CI 0.72–0.96], p=0.01). The 30-day readmission of high-risk patients was lower when followed by internal medicine consultation: patients with ≥65 years (RR 0.57 [95%CI 0.37–0.89], p=0.01) and patients with high-risk surgery (RR 0.63 [95%CI 0.46–0.57], p=0.005). The Poisson multivariate regression with adjustment in variances showed that all the variables (namely, age, ASA, morbidity index, surgery risk, and internal medicine consultation) were associated with higher mortality of patients; however, internal medicine consultation was associated with a reduction of mortality in high-risk patients (RR 0.72 [95%CI 0.65–0.84], p=0.02) and an increase of mortality in low-risk patients (RR 1.55 [95%CI 1.31–1.67], p=0.01).

CONCLUSION: High-risk surgical patients may benefit from perioperative internal medicine consultations, which probably decrease hospital mortality and 30-day hospital readmission.

KEYWORDS: Hospital medicine. Internal medicine. Perioperative care. Hospital surgery department.

INTRODUCTION

The global burden of diseases is increasing[1], and surgical procedures are expected to have a greater impact on health systems in the coming years[2]. Older subjects, patients with multiple comorbidities, and fragile people will increasingly undergo more complex surgical procedures and will be admitted to receive care as inpatients[3]. Therefore, appropriately designing models of care for this growing population of patients is a part of the current health agenda. Internal medicine consultation (IMC) is mostly requested by surgical services, mainly for the most sick and severe patients[4-6], with the main reasons being medical management/co-management and preoperative evaluation[7].

Surgical co-management is the shared responsibility, authority, and accountability of surgical and medicine teams for patient care[3,8,9]. However, some authors suggest that this model should be adopted selectively and not as a widespread strategy[10,11], showing better inpatient outcomes[12,13], especially in high-risk patients[3,10]. Traditionally, the approach of patients by consultant physicians followed some principles, focusing on the specific requirements of the assisting physician[14]. However, with this paradigm shift, promoted by the advent of co-management by

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hospitalists, the tendency is for IMC teams to address all the patient's complexity and optimize their comorbidities, aiming to improve perioperative outcomes. In the Latin American literature, the hospitalist movement is still incipient, with some references from Cuba[15], Colombia[16], and Chile[17] describing the actuation of IMC departments with generalist practices that assume central roles in their hospitals.

Therefore, the objective of this study was to assess the effect of IMC on surgical patient mortality, 30-day readmission rates, and length of stay (LOS) in a hospital, and our hypothesis was that a greater benefit would be observed in the most severe patients.

METHODS

Internal medicine consultation description

The study was developed in Nossa Senhora da Conceição Hospital (NSCH), which is an 850-bed tertiary center and the largest public hospital in southern Brazil. The Department of Internal Medicine has worked on an expansion project that increased its inpatient responsibility and caused it to assume a central role in hospital dynamics. The team operates with an internist trained in perioperative medicine tutoring second-year and senior internal medicine residents. It provides preoperative evaluation, medical advice, and co-management as requested by the assisting teams. Thus, for the patients cared for under this model, the internal medicine team writes daily notes, orders tests, prescribes medications as appropriate, manages acute decompensations, and, when necessary, proactively participates in ICU transfers.

Characteristics of patients and internal medicine consultations

The following data from all surgical patients admitted to the hospital from 2010 to 2018 were obtained: age, gender, LOS, surgeries performed with the corresponding American Society of Anesthesiologists (ASA) physical status, and Charlson comorbidity index (CCI), which is used in our institution as a measure of patient's level of severity[18].

Patient characteristics were analyzed in three groups: patients who did not receive IMC, defined as the control group; patients who received consultations, defined as the consultation group; and patients who received internal medicine co-management, defined as the co-management group. Each patient was accounted once. Patients receiving co-management and consultation were known to have more complex and severe conditions. Considering that IMC was a growing intervention over the study period, we knew that we would find high-risk patients without this intervention in the cohort. High-risk surgical patients were considered based on the inclusion criteria: (a) patients with ASA≥3, (b) patients aged over 65 years, and (c) patients submitted to a high-risk surgery[19].

Outcomes

The main outcomes evaluated were hospital mortality, hospital LOS, and 30-day readmission in the same hospital. For the outcomes analysis, we considered the consultation and co-management groups to be the IMC group. Our data did not contain other important outcomes such as ICU LOS, mechanical ventilation parameters, percentage of acute kidney injury, or need for renal replacement therapy.

Statistical analysis

Continuous variables were evaluated by the median and interquartile range, as they were all asymmetric. Age was stratified by under 65 or ≥65 years, and ASA physical status was stratified by under 3 or ≥3 and 4 or ≥4. Mortality and 30-day readmission rates were compared using chi-square analysis, for which we defined a relative risk with a 95% confidence interval (95%CI). LOS was compared between groups using the Kruskal-Wallis nonparametric test. Variables associated with perioperative mortality were analyzed using Poisson multivariate analysis with adjustment of variances, and IMC was included as a variable in the model. High-risk patients were predefined, and individual and combined risks were used for analysis, based on (a) ≥65 years, (b) ASA≥3, (c) ASA≥4, (d) high-risk surgery, I ASA≥3 plus≥65 years, (f) ASA≥3 plus high-risk surgery, (g) ASA≥4 plus≥65 years, and (h) ASA≥4 plus high-risk surgery. Other combinations were not possible due to the sample size. The analysis of hospital mortality rate and hospital LOS was adjusted by age, CCI, ASA, and surgery risk. The analysis of the 30-day readmission rate was adjusted by age, CCI, ASA, ICU stay, and surgery risk. Finally, two charts were made comparing the mortality rate in patients with and without IMC. First, we analyzed mortality per ASA physical status classification (from 1 to 5) in patients with and without IMC (patients with both co-management and consultation were in the consultation group). Second, the same data were analyzed but restricted to patients with ICU admission during hospitalization. In all analyses, P-values were considered statistically significant when $p \leq 0.05$.

RESULTS

From 2010 to 2018, 124,666 patients were admitted to the hospital surgical departments. Surgical specialties that received

IMC consultation for ≤2.0% of patients were obstetrics (0.2%), plastic surgery (0.4%), and cardiac surgery (0.5%). Therefore, 70,245 patients were enrolled in the study.

The characteristics of the control and IMC groups are shown in Table 1. Compared with the patients evaluated by the IMC that received only consultation and with the control group, patients evaluated by the IMC that received co-management were older (≥65 years: 55.4, 48.5, and 22.5%, p<0.01), more comorbid (ICC: 4 [3-5], 4 [2-5], and 3 [2-4], p<0.01 and ASA≥3: 65.1, 38.6, and 19.3%, p<0.01), and submitted more frequently to high-risk surgeries (54.0, 39.6, and 16.6%, p<0.01), respectively. Surgical teams that received more consultations were general surgery (20.9%) and urology (32.0%). Vascular surgery patients received co-management for 32.7% of patients.

Outcomes

After adjustments, the mortality of surgical high-risk patients was lower when followed by IMC: patients with ASA≥3 (RR 0.89 [95%CI 0.80–0.99], p=0.02), patients with ASA≥3 plus ≥65 years (RR 0.88 [95%CI 0.78–0.99], p=0.04), patients with ASA≥3 plus high-risk surgery (RR 0.86 [95%CI 0.77–0.97],

Table 1. Characteristics of the patients with and without internal medicine consultation.

	Control group	Internal medicine consultation group		p-value*
		Patients with consultation	Patients with co-management	
Number of patients	65,145	3,507	2,040	–
Age, median	51 [27.2]	64 [18.6]	66 [17.6]	<0.01 ŧ
≥65 years	22.5%	48.5%	55.4%	<0.01 ǂ
Male gender	42.4%	51.2%	54.7%	<0.01 ǂ
Charlson comorbidity index	3 [2–4]	4 [2–5]	4 [3–5]	<0.01 ŧ
Patient risk				
ASA ≥3	19.3%	38.6%	65.1%	<0.01 ǂ
ASA ≥4	1.9%	5.0%	15.0%	<0.01 ǂ
Surgery risk				
Low risk	64.0%	38.4%	30.0%	<0.01 ǂ
Intermediate risk	19.4%	24.7%	16.0%	
High risk	16.6%	39.6%	54.0%	
Surgery department				
General surgery	22,849 (94.6%)	733 (3.0%)	565 (2.3%)	ns
Digestive surgery	786 (66.4%)	357 (30.2%)	41 (3.5%)	
Thoracic surgery	3,036 (89.4%)	248 (7.3%)	111 (3.3%)	
Vascular surgery	8,995 (91.5%)	174 (1.8%)	662 (6.7%)	
Bariatric surgery	550 (96.5%)	7 (1.2%)	13 (2.3%)	
Gynecology	14,797 (96.6%)	390 (2.5%)	125 (0.8%)	
Oncologic surgery	2,992 (93.9%)	51 (1.6%)	142 (4.5%)	
Proctology	2,841 (83.3%)	428 (12.6%)	122 (3.6%)	
Urology	8,299 (85.8%)	1,119 (11.6%)	259 (2.7%)	
Hospital length of stay (days)	4.0 [1.0–11.0]	20.0 [12.0–34.0]	22.0 [13.0–37.0]	<0.01 ŧ
ICU admission need	5.7%	20.1%	40.0%	<0.01 ǂ
Hospital mortality	2.4%	6.9%	18.1%	<0.01 ǂ

ASA: patients with American Society of Anesthesiologists physical status. ICU admission: percentage of patients with intensive care admission during hospitalization. Surgery risk is stratified according to the guidelines. Control group: patients without internal medicine consultation. Continuous variables are all displayed in medians with the interquartile range in brackets. Dichotomous variables are displayed in absolute and relative frequencies. ǂP-value of the chi-square test. ŧP-value of the Kruskal-Wallis test. *Differences between the control and internal medicine consultation groups. No statistical differences were found between patients with consultation and patients with co-management.

p=0.01), and patients with ASA ≥4 plus age ≥65 years (RR 0.83 [95%CI 0.72–0.96], p=0.01). The 30-day readmission of high-risk patients was lower when followed by IMC: patients with ≥65 years (RR 0.57 [95%CI 0.37–0.89], p=0.01) and patients with high-risk surgery (RR 0.63 [95%CI 0.46–0.57], p=0.005) (Table 2). Patients with IMC had a significantly longer hospital LOS (21.0 [12.3–25.8] days vs. 4.0 [1.0–11.0] days, p<0.01), higher ICU need (28.4 vs. 5.7%, p<0.01), and higher crude mortality (11.2 vs. 2.4%, p<0.01) (Table 1).

The Poisson multivariate regression with adjustment in variances showed that all the variables (namely, age, ASA physical status, CCI, surgery risk, and IMC) in the model were positively associated with higher mortality of patients (Table 3). IMC was associated with reduction of mortality in high-risk patients (RR 0.72 [95%CI 0.65–0.84], p=0.02) and increase of mortality in low-risk patients (RR 1.55 [95%CI 1.31–1.67], p=0.01).

DISCUSSION

In this observational study analyzing over 70,000 surgical admissions in the largest-volume tertiary hospital in southern Brazil, we found that high-risk patients can be benefitted from IMC. Depending on the subgroup analyzed, the mortality reduction ranged from 10 to 13%, and the 30-day readmission rate reduction ranged from 37 to 46%. However, a longer hospital LOS was associated with patients receiving medical consultation, as well as an increase of mortality in low-risk surgical patients.

Co-management of surgical patients is a phenomenon that is well described in the literature. By evaluating 694,806 hospital surgical admissions, Sharma et al.[20] showed an increase of 11.4% per year in co-management by generalist physicians (from 33.3% in 1996 to 40.8% in 2006 [p<0.01]), while Chen et al.[21], analyzing fee-for-service Medicare patients, showed variation in medical consultation for patients undergoing colectomy (interquartile range (IQR) 50–91%) and total hip replacement (IQR 36–90%), with greater use for patients with postoperative complications (IQR 90–95%). For patients hospitalized for colorectal surgery, de Vries et al.[22] showed that 27.6% of patients were co-managed, with a great variation between hospitals (1.9–83.2%). As more data on the benefits of co-management for quality of care, postoperative complications, hospital LOS, total care cost reduction, and other outcomes continue to be published, it is rational that hospitals will organize their

Table 2. Evaluation of adjusted hospital mortality*, hospital length of stay**, and 30-day readmission*** in patients of control and internal medicine consultation groups in higher-risk surgical patients.

	Hospital mortality		Hospital length of stay		30-day readmission	
	IMC vs. CG (p-value)	RR (95%CI)	IMC vs. CG	p-value	IMC vs. CG (p-value)	RR (95%CI)
≥65 years	33.3 vs. 37.2% (p=0.06)	0.90 (0.80–1.01)	31 [18–49] vs. 20.5 [11–35]	<0.001	4.5 vs. 8.0% (p=0.01)	0.57 (0.37–0.89)
ASA ≥3	35.0 vs. 39.4% (p=0.02)	0.89 (0.80–0.99)	37 [23–60] vs. 23 [13-38]	<0.001	6.3 vs. 8.8% (p=0.06)	0.7 (0.49–1.03)
ASA ≥4	47.0 vs. 50.5% (p=0.27)	0.93 (0.82–1.96)	35 [22–39] vs. 2 [6–22]	<0.001	8.1 vs. 6.8% (p=0.55)	1.19 (0.67–2.11)
High-risk surgery	29.2 vs. 28.5% (p=0.70)	1.02 (0.91–1.15)	36 [23–56] vs. 22 [12–36]	<0.001	6.1 vs. 9.7% (p=0.005)	0.63 (0.46–0.57)
ASA ≥3 + ≥65 years	41.5 vs. 47.2% (p=0.04)	0.88 (0.78–0.99)	35 [20–55] vs. 21 [12–38]	<0.001	4.2 vs. 7.5% (p=0.07)	0.56 (0.30–1.06)
ASA ≥3 + high-risk surgery	26.6 vs. 19.6% (p<0.001)	1.36 (1.21–1.52)	32 [19–52] vs. 17 [9–28]	<0.001	7.0 vs. 9.0% (p=0.07)	0.78 (0.59–1.02)
ASA ≥4 + >65 years	50.5 vs. 58.3% (p=0.06)	0.87 (0.74–1.01)	33 [18–53] vs. 14 [8–27]	<0.001	5.7 vs. 8.3% (p=0.39)	0.68 (0.28–1.66)
ASA ≥4 + high-risk surgery	51.1 vs. 60.5% (p=0.01)	0.85 (0.74–0.96)	43 [21–63] vs. 20 [10–34]	<0.001	8.5 vs. 5.5% (p=0.26)	1.53 (0.73–3.25)

ASA: patients with American Society of Anesthesiologists physical status. High-risk surgery: patients who underwent high-risk surgery according to the guidelines classification. *The analysis of hospital mortality rate was adjusted by age, Charlson comorbidities index, ASA, and surgery risk. **The analysis of hospital length of stay was adjusted by age, Charlson comorbidities index, ASA, and surgery risk. ***The analysis of hospital 30-day readmission was adjusted by age, Charlson comorbidities index, ASA, ICU stay, and surgery risk. Comparisons of mortality and 30-day readmission are made by the chi-squared test. Comparisons of relative risk, 95% confidence interval in parentheses, and p-values are displayed. Median lengths of stay are compared through the Kruskal-Wallis test and are displayed with the interquartile range in brackets and the p-values.

Table 3. Multivariate analysis for mortality

Variable	Relative risk (95%CI)	p-value
Age (years)	1.03 (1.02–1.03)	<0.001
ASA		
ASA 1	1.00	–
ASA 2	2.11 (1.43–3.15)	<0.001
ASA 3	8.75 (5.83–13.12)	<0.001
ASA 4	22.35 (14.8–33.8)	<0.001
ASA 5	30.91 (19.81–48.17)	<0.001
Charlson comorbidities index		
Charlson comorbidities index <2	1.00	–
Charlson comorbidities index ≥2	6.75 (4.82–10.01)	<0.001
Surgical risk		
Low-risk surgery	1.00	
Intermediate-risk surgery	1.42 (1.22–1.71)	<0.001
High-risk surgery	2.21 (1.93–2.54)	<0.001
Internal medicine consultation	1.11 (1.01–1.21)	0.01
Internal medicine consultation in low-risk patients	1.55 (1.31–1.67)	0.01
Internal medicine consultation in high-risk patients*	0.72 (0.65–0.84)	0.02

ASA: American Society of Anesthesiologists physical status. Surgery risk was analyzed according to the guidelines classification. ICU admission: patients with ICU admission during hospitalization. *High-risk surgical patients were considered: patients with ASA ≥3, patients aged over 65 years, patients submitted to a high-risk surgery, and any combination of these three variables.

services so that a higher proportion of surgical patients receive this care, as it is a cost-effective intervention[13,23,24].

Mortality benefits have been previously shown in cardiothoracic (8.1–2.5% [p=0.01]), vascular (1.56–0.0008% [p=0.003]), and many other surgical patients[21,25]. In one of the first studies on the subject, comparing results with those of a historical cohort, Fisher et al.[25] showed a mortality reduction from 7.7 to 4.7% (p<0.01) for patients aged 60 years or older admitted with hip fracture. Besides that, patients with more complex cases and greater severity of disease tend to receive the most benefit from co-management[3,10].

Consultation is usually requested for the most severe surgical patients. In our study, the median Charlson index of all patients was 3 (IQR 2–4), compared with the median of patients who received IMC, 4 (IQR 2–5), and that of those who received co-management, 4 (IQR 3–5), a statistically significant difference. Because of this, it is expected that those with IMC would probably have worse outcomes for all surgical patients. This finding reinforces the need for high-risk subpopulation analysis in this type of study. In our study, even after adjustment for covariates by regression analysis, IMC was associated with a higher mortality risk, with an RR of 1.12 (95%CI 1.02–1.24; p=0.01). These findings confirm those of previous studies. Wijeysundera et al.[5] found a higher risk of 30-day mortality with an RR of 1.16 (95%CI 1.07–1.25), and Auerbach et al.[6] found a longer adjusted LOS and adjusted costs associated with medical consultation.

Our study has some strengths. First, this is one of the largest studies on co-management and IMC to date. Additionally, as our study had a long period and the intervention was performed in a progressively greater proportion of patients, we found many severe and complex patients without IMC. Finally, the data were derived directly from the hospital's electronic medical records, which decreases the probability of collection bias. However, our study has some weak points that must be addressed. First, it was an observational study, we could not exclude the possibility of unmeasured factors as a potential source of bias, and it is not possible to establish causality. Second, this study utilized the retrospective nature of the data collection. Finally, we did not analyze the medical records individually. Additionally, the generalizability of our findings may interfere with the results of this single-center study. The register bias is another factor to be considered as medical electronic records were the data source.

In summary, IMC for surgical patients is now a current practice and is expected to increase as more sick patients will be eligible for surgical procedures. Our study findings suggest

that, in patients with higher morbidity and hospital complexity admitted by surgical teams, those who received care from internal medicine teams had lower mortality.

AUTHORS' CONTRIBUTIONS

PRMR: Conceptualization, Data curation, Formal Analysis, Investigation, Methodology, Project administration, Supervision, Validation, Visualization, Writing – original draft. **MFS:** Conceptualization, Supervision, Validation, Visualization, Writing – review & editing. **CT:** Conceptualization, Formal Analysis, Investigation, Methodology, Supervision, Validation, Visualization, Writing – review & editing. **LR:** Data curation, Investigation, Writing – review & editing. **MASG:** Data curation, Investigation, Writing – review & editing. **MSB:** Data curation, Investigation, Writing – review & editing.

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ORIGINAL ARTICLE

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Visual or computer-based measurements: Which is important for the interpretation of an athlete's electrocardiography?

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SUMMARY

OBJECTIVE: Preparticipation screening of athletes by electrocardiography is the most crucial step in determining sudden cardiac death risk factors. Several electrocardiography interpretation software programs have been developed for physicians practicing in this field. Our study aimed to assess cardiopoint sudden death screening module by comparing its findings with two cardiologists using Seattle and International criteria.

METHODS: A total of 303 licensed national athletes (37% females) were enrolled. electrocardiographies were examined by the cardiopoint sudden death screening module using Seattle criteria and cardiologists. The consistency between cardiologists and software was compared, and the confidence assessment of the module was tested.

RESULTS: With regard to Seattle criteria, moderate consistency was found between the cardiopoint sudden death screening module and the 1st (κ=0.41) and 2nd cardiologist (κ=0.59). Consistency between two cardiologists was moderate (κ=0.55). When we applied International criteria, there was moderate consistency between the module and the 1st cardiologist (κ=0.42), and good consistency between the module and the 2nd cardiologist (κ=0.63). Consistency between the two cardiologists was good (κ=0.62).

CONCLUSION: The cardiopoint sudden death screening module had similar agreement with cardiologists based on both criteria. However, the software needs to be updated according to International criteria. Using computer-based measurements for preparticipation screening will help to save time and provide standardization of electrocardiography interpretation.

KEYWORDS: Athlete. Electrocardiography. Exercise. Cardiac sudden death.

INTRODUCTION

Sudden cardiac death (SCD) is one of the leading causes of death in sports participants[1,2]. Preparticipation screening, consisting of medical history, physical examination, and a resting 12-lead ECG, aims to identify pre-existing cardiovascular abnormalities that may lead to SCD[3].

ECG interpretation criteria, such as the European Society of Cardiology (ESC) criteria, Seattle criteria, and International criteria, have been developed for preparticipation screening[4-7]. These criteria have clearly and practically delineated normal, borderline, and pathological ECG findings in athletes aged between 12 and 35 years[7]. Each revision of ECG criteria resulted in improved specificity without compromising sensitivity.

Automated ECG interpretation is fast and time-saving; however misdiagnosis is also possible. One such software program is the cardiopoint sudden death screening (SDS) module[8]. This module examines ECGs using Seattle criteria. Slaby et al. reported that the cardiopoint SDS module has a high negative predictive value with variable levels of sensitivity and specificity[9].

The aim of our study was to compare the ECG interpretation of the cardiopoint SDS module to that of two cardiologists in the preparticipation screening of sports participants.

METHODS

Participants

We enrolled 303 licensed national athletes (37% females) from 34 sports disciplines between the ages of 13 and 35 years from October 1, 2017, to April 1, 2018. All athletes underwent cardiovascular screening, including medical histories and physical examination. Morphometric and demographic data were also obtained.

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Ethical approval and consent

Athletes and, if needed, their parents gave informed consent to participate in the study. This study complied with the Declaration of Helsinki, and the research protocol was approved by the local institutional ethics committee.

Electrocardiography

We used a BTL® 08 MT Plus (BTL, United Kingdom) 12-lead ECG tool. All ECGs were automatically sent to the cardiopoint SDS module via Wi-Fi LAN network and were automatically interpreted using Seattle criteria. ECG findings were also analyzed by two cardiologists with different levels of expertise using both Seattle and International criteria.

Statistical analysis

All statistical analyses were performed using SPSS Statistics for Windows, version 22 (IBM Corporation, Armonk, NY). Continuous variables are presented as means±SD and categorical variables are presented as percentages. Values of $p<0.05$ were considered statistically significant. Cohen's kappa (κ) statistics were used to determine the consistency between the cardiopoint SDS module and observers. κ (kappa) scores between 0.01 and 0.20 were classified as none to slight, 0.21 and 0.40 as fair, 0.41 and 0.60 as moderate, 0.61 and 0.80 as good, and 0.81 and 1.00 as almost perfect agreement.

RESULTS

The baseline demographics of athletes are shown in Table 1.

Findings based on Seattle criteria

The cardiopoint SDS module detected 22 (7.3%) ECGs as abnormal. Both cardiologists found 14 (4.6%) ECGs as abnormal. There was moderate consistency between the cardiopoint SDS module and the first cardiologist (κ=0.41), as well as the second cardiologist (κ=0.59). Furthermore, moderate consistency was found between the two cardiologists (κ=0.55) (see Figure 1).

Findings based on International criteria

The ECG findings of the cardiopoint SDS module were also re-evaluated using International criteria. Further examination was suggested in 14 (4.6%) athletes. A total of 7 (2.3%) athletes were suggested for further examination by the first cardiologist, and 12 (4%) athletes were suggested by the second cardiologist. There was moderate consistency between the cardiopoint SDS module and the first cardiologist (κ=0.42), while the kappa statistic between the module and the second cardiologist showed higher consistency (κ=0.63). Likewise, there was good consistency between the two cardiologists (κ=0.62) (see Figure 1).

Table 1. Baseline demographics.

Variables	n=303
Age (years)	18.7±4.1
Height (cm)	173.2±10.0
Weight (kg)	66.9±14.0
Body mass index (kg/m²)	22.1±3.3
Heart rate (beats/min)	75±11.6

Electrocardiographic findings

The ECG parameters for which the cardiopoint SDS module had high sensitivity and specificity, as well as the parameters for which the module had low sensitivity, are shown in Figure 2.

The cardiologists detected 67 early repolarizations and 2 T wave inversions (TWIs); however, these findings were not detected by the module. The module reported one early repolarization and one TWI, which were defined as false positives by the cardiologists. The cardiopoint SDS module found five ECGs with ST segment depression. However, both cardiologists defined these ECG changes as normal findings occurring secondary to right bundle branch block (RBBB). Furthermore, five complete RBBB were detected by the cardiologists; however, none of these were defined by the cardiopoint SDS module.

The cardiopoint SDS module did not report the parameters that were not defined for this software: respiratory sinus arrhythmia and juvenile TWI. The cardiologists found 4 sports participants had juvenile TWI and 29 sports participants had respiratory sinus arrhythmia.

DISCUSSION

In this study, the cardiopoint SDS module provided ECG interpretation results similar to cardiologists. Furthermore,

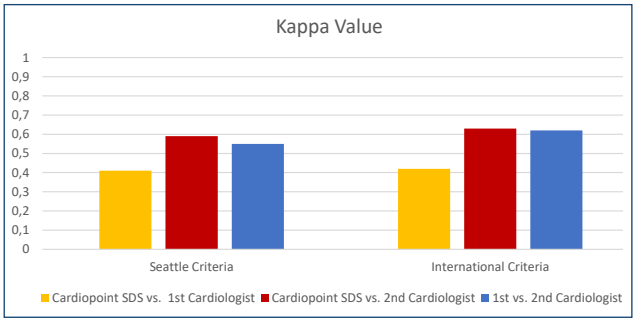

Figure 1. Consistency levels of the cardiopoint sudden death screening module and the 1st and 2nd cardiologists in the evaluation of the Seattle and International criteria.

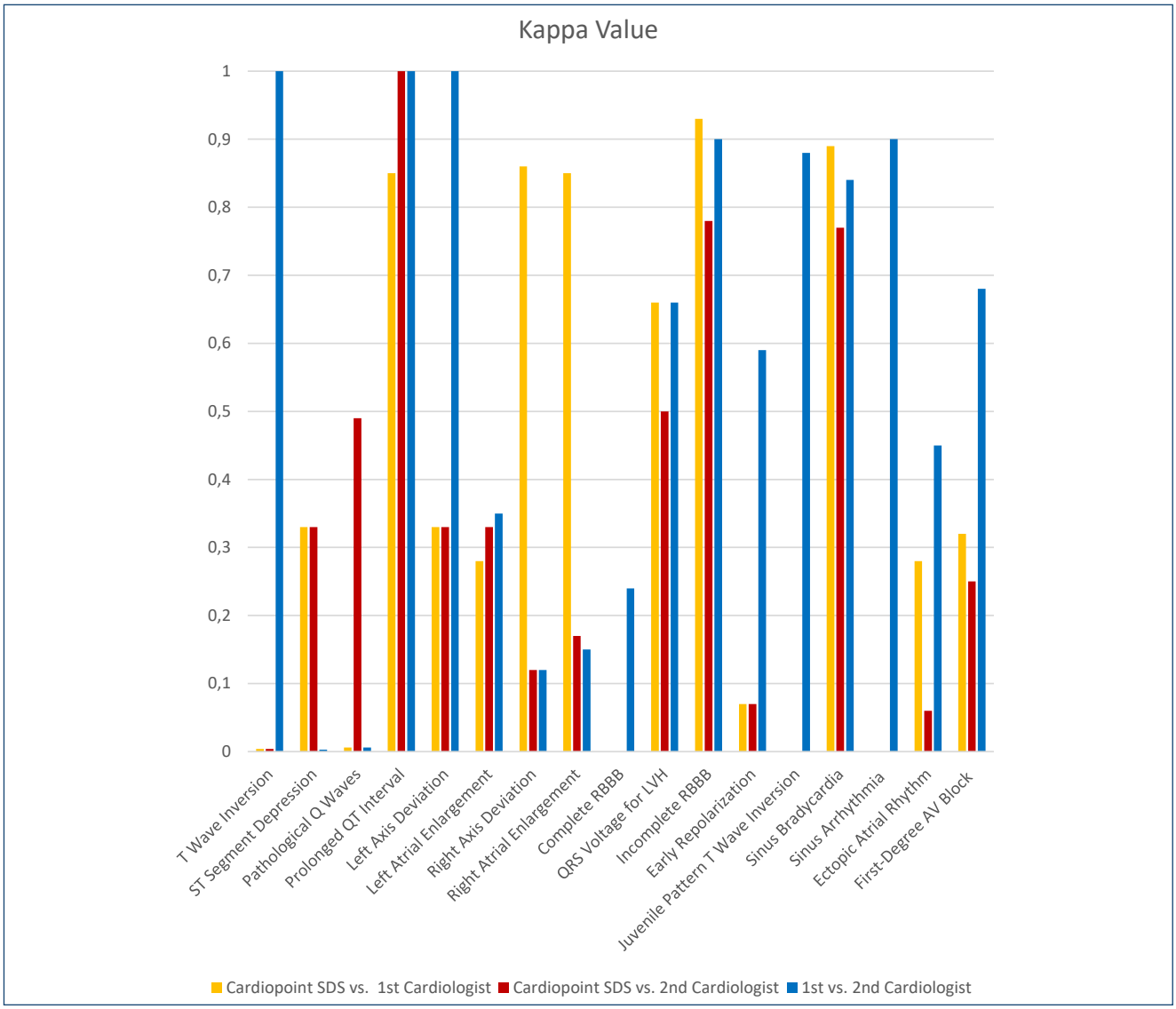

Figure 2. Consistency levels of the cardiopoint sudden death screening module and the 1st and 2nd cardiologists in the evaluation of electrocardiography findings.

when we applied International criteria to the cardiopoint SDS module, the consistency between the module and cardiologists becomes higher.

In preparticipation screening of athletes, strong correlations have been observed between the clinicians and automatic ECG analysis using the Cardea software program with the detailed descriptions of ECG findings[10]. Hyde et al. explained that the difference in pathologic Q wave definition between Seattle criteria and International criteria decreased false positive rates[10]. A new and detailed definition of ECG findings may allow automatic ECG interpretation devices to give more consistent results.

One of the major differences between the Seattle and the International criteria is that some abnormal findings based on the Seattle criteria shifted to the borderline class in the International criteria. Left axis deviation, left atrial enlargement, and complete RBBB were defined as abnormal findings based on the Seattle criteria, while all of these appeared in the borderline class in the International criteria[6,7].

Although previous studies showed no relationship between these abnormal findings in ECG and morphological changes of left or right heart structures[11], these findings may still be abnormal ECG findings as assessed by more sensitive imaging modalities including cardiac magnetic resonance imaging (MRI) due to showing tissue characterization. Therefore, if two or more borderline ECG findings are seen on the surface ECG, it can be useful to lead further evaluation and close follow-up[7]. The other possible factor supporting our

findings was that the age group in which TWI was considered as an abnormal ECG finding. In International criteria, TWI is accepted as a normal ECG finding in athletes below 16 years of age whereas TWI is considered an abnormal ECG finding irrespective of age according to Seattle criteria[6,7]. In our study, athletes below 16 years of age comprised 33% of the study population. So, we can conclude that using International criteria instead of Seattle criteria reduces the rate of abnormal ECG findings.

Importantly, the cardiopoint SDS module had a high sensitivity and specificity for the correct calculation of corrected QT (QTc). Long or short QT is associated with an increased risk of fatal ventricular arrhythmias in young sports participants[12,13], and unfortunately, the QT interval cannot be accurately calculated by clinicians, including experienced cardiologists[14]. Therefore, the evaluation of ECG by clinicians and software together can give more reliable results.

Beyond this accuracy, our study showed that the cardiopoint SDS module did not have the same power as that in a retrospective study by Slaby et al.[9] for the determination of pathological Q wave and left axis deviation. Pathological Q wave and left axis deviation were seen commonly in hypertrophic cardiomyopathy (HCM) subjects[15-17]. HCM is one of the leading causes of SCD in sport participants in the USA[18]. Additionally, silent myocardial infarction can lead to the development of Q wave[19]. Moreover, the software has difficulty identifying myocardial infarction related ECG findings[20]. When all these findings are evaluated together, the cardiopoint SDS module may be insufficient in subjects with a high risk of developing SCD such as HCM. This finding once again demonstrates the importance of ECG analysis with clinicians.

The study by Hyde et al. showed that the Cardea software program had a trend of being more useful in clinical practice with the technological development and standardization of measurements[10]. With more clearly defined ECG parameters, each update of ECG interpretation criteria provided improvement in specificity and decreased false positive results compared to the previous criteria[7]. These findings coupled with the fact that using the International criteria may lead to better consistency between the clinicians in preparticipation screening for young athletes. More consistent results may provide a reduced risk of SCD during exercise and unnecessary disqualification of athletes who do not have cardiovascular disease. In the future, the cardiopoint SDS module may be the recommended software to analyze ECG in sports participants.

LIMITATIONS

Our study included only a small number of athletes. Additional diagnostic tests have not been performed in athletes with ECG changes. Another limitation is that in the evaluation of software-physician consistency, physicians should not be compared with a standard ECG device other than the cardiopoint SDS module.

CONCLUSION

Modern ECG interpretation software analyzes ECGs in a short time with high accuracy. In particular, the cardiopoint SDS module coupled with International criteria may provide more consistent results, and its clinical use may help provide the standardization preparticipation screening for the determination of SCD risk in sports participants.

AUTHORS' CONTRIBUTIONS

ABTK: Data curation, Investigation, Visualization, Writing – original draft. **OY:** Conceptualization, Writing – review & editing. **HD:** Project administration, Writing – review & editing. **İTÇ:** Formal Analysis, Visualization. **TK:** Investigation, Methodology. **DK:** Supervision.

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ORIGINAL ARTICLE

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Accuracy of intrapartum cardiotocography in identifying acidemia at birth by umbilical cord blood gasometry in high-risk pregnancies

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SUMMARY

OBJECTIVE: The aim of this study was to evaluate the accuracy of intrapartum cardiotocography in identifying acidemia at birth by umbilical cord blood gasometry in high-risk pregnancies.

METHODS: This was a retrospective cohort study of singleton high-risk parturients using intrapartum cardiotocography categories I, II, and III. The presence of fetal acidemia at birth was identified by the analysis of umbilical cord arterial blood pH (<7.1). Associations between variables were determined using the chi-square test and Kruskal-Wallis tests.

RESULTS: We included 105 cases of cardiotocography category I, 20 cases of cardiotocography category II, and 10 cases of cardiotocography category III. cardiotocography category III had a higher prevalence of cesarean sections compared to cardiotocography category I (90.0 vs. 42.9%, p<0.006). Venous pH was higher in patients with cardiotocography category I compared to cardiotocography category III (7.32 vs. 7.23, p=0.036). Prevalence of neonatal intensive care unit (NICU) admission was lower in neonates of patients with cardiotocography category I compared to cardiotocography category III (3.8 vs. 30.0%, p=0.014). Prevalence of composite adverse outcomes was lower in neonates of patients with cardiotocography category I compared to cardiotocography category II (9.5 vs. 30.0%, p=0.022) and cardiotocography category III (9.5 vs. 60.0%, p=0.0004). cardiotocography categories II and III had low sensitivity (0.05 and 0.00, respectively) and high negative predictive value (NPV) (0.84 and 0.91, respectively) for identifying fetal acidemia at birth. The three categories of intrapartum cardiotocography showed high specificities (96.0, 99.0, and 99.0%, respectively).

CONCLUSION: All three categories of intrapartum cardiotocography showed low sensitivity and high specificity for identifying acidemia at birth.

KEYWORDS: Pregnancy outcomes. External cardiotocography. Fetal blood. Blood gas analyses. High-risk pregnancy.

INTRODUCTION

Cardiotocography (CTG) is a dynamic intrapartum screening test capable of simultaneously recording fetal heart rate (FHR), fetal movements, and uterine contractions. The objective of this monitoring is to detect early fetal hypoxia and acidemia, analyzing the fetal oxygen reserve to support the stress of labor. CTG is indicated in situations of high risk of fetal acidosis, e.g., in pregnant women with hypertensive disorders, multiple gestations, gestational diabetes mellitus, and preterm birth[1].

However, intrapartum CTG in high-risk pregnancies has shown inconclusive benefits in some studies, not directly affecting perinatal mortality[2]. It is important to highlight that abnormal CTG patterns increase the rate of cesarean sections and instrumental deliveries, since the definitive diagnosis of hypoxia and acidemia depends on fetal blood collection[1].

Thus, to define the best way and time to terminate pregnancy, the CTG category system is used, which is based on baseline FHR, heart rate variability, and the presence or absence of decelerations. This system is divided into normal (category I) and abnormal (category III), both of which facilitate the definition of management. However, when the classification is undetermined (category II), it is indicated that continuous monitoring should be maintained until the category pattern changes, since it is a more challenging interpretation[3].

Although fetal acid-base physiology is similar to that of the newborn, compensatory forms of acidemia are different, and to identify this fetal alteration it is necessary to evaluate arterial and venous pH obtained by gasometry of the umbilical cord blood[4]. At birth, venous umbilical cord blood is rich in oxygen, since it represents the maternal-placental acid-base status, while arterial blood is rich in carbon dioxide, representing

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the neonatal acid-base status[5]. However, there is no consensus on when to perform arterial and venous pH analysis, but the American College of Obstetricians and Gynecologists (ACOG) and the American Academy of Pediatrics advise performing pH analysis after any delivery in which there is a risk of acidemia/hypoxia such as in CTG category III, instrumented vaginal delivery, and low APGAR score[3].

Therefore, the aim of this study was to evaluate the accuracy of intrapartum CTG for detecting fetal acidemia in high-risk pregnancies using arterial and venous umbilical cord blood gasometry.

METHODS

This was a retrospective cohort study conducted at the Mário Palmério University Hospital, University of Uberaba (UNIUBE), through the evaluation of medical records of pregnant women assisted during labor, from November 2019 to November 2022. The study was approved by the Research Ethics Committee of UNIUBE (CAAE: 52299421.7.0000.5145).

Singleton pregnant women with hypertensive disorders, diabetes in pregnancy, collagen diseases, maternal heart disease, decompensated pulmonary disease, epilepsy, hereditary thrombophilia, antiphospholipid antibody syndrome, chronic kidney disease, thyroid disease, moderate/severe maternal anemia, maternal infection (toxoplasmosis, syphilis, cytomegalovirus, parvovirus B19, and HIV), fetal growth restriction, oligohydramnios, fetal malformations, and chromosomal abnormalities were considered high-risk pregnancies[6].

CTG tracings were classified according to ACOG recommendations as follows[1]: Category I—normal tracings predictive of fetuses with normal acid-base status[2], Category II—non-reassuring tracings but not falling into category III and requiring further obstetric monitoring, and[3] Category III—abnormal tracings such as sinusoidal pattern, lack of variability, and frequent type II and III decelerations, among other changes associated with abnormal acid-base status[3].

After fetal expulsion, the umbilical cord was clamped at approximately 20 cm, and 1 mL of arterial and 1 mL of venous blood were collected in a 3 mL heparinized gasometry syringe (BD Luer-Lok, New Jersey, USA). Within 30 min of collection, the blood gas analysis syringes were transported to the hospital's clinical analysis laboratory. A Cobas b 221 gasometer (Roche Diagnostics, Switzerland) was used for cord blood gas analysis. The parameters to be analyzed in cord blood gasometry were arterial and venous pH[7,8]. A practical pH threshold to define pathological fetal acidemia was considered to be umbilical artery pH<7.1 and/or umbilical vein pH<7.2.

The following variables were assessed: age, ethnicity, smoking, number of pregnancies, pre-existing chronic diseases, obstetric risk classification (high-risk or usual-risk), gestational age at delivery, CTG category, type of delivery, time between cord clamping and gas analysis, arterial pH, venous pH, acidemia at birth, APGAR score at 1st min, APGAR score at 5th min, NICU admission, need for neonatal resuscitation, and early neonatal death (first 48 h). The adverse perinatal outcomes were considered to be the presence of fetal acidemia at birth, APGAR score at 1st min<7, NICU admission, need for neonatal resuscitation, and early neonatal death (first 48 h). The presence of at least one adverse perinatal outcome was considered a composite adverse perinatal outcome.

Data were transferred to Excel 2019 (Microsoft Corp., Redmond, WA, USA) and analyzed using the statistical program SPSS version 20.0 (SPSS Inc., Chicago, IL, USA) and Prism GraphPad version 7.0 (GraphPad Software, San Diego, CA, USA). Quantitative variables were first subjected to a normality test (D'Agostino-Pearson), and those with a normal distribution were presented as the mean and standard deviation. Variables with non-normal distribution were presented as median, minimum, and maximum values. Categorical variables were described by absolute and percentage frequencies and presented in tables. The chi-square test was used to examine differences between categorical variables and their proportions. The Kruskal-Wallis test was used to examine differences between continuous variables. Dunn's post hoc test was used to compare pairs. The measurements of the primary endpoints were sensitivity, specificity, false positive rate, false negative rate, positive likelihood ratio, and negative likelihood ratio calculated from cross-reference tables. The significance level for all tests was $p<0.05$.

RESULTS

From November 2019 to November 2022, 2,861 pregnant women were admitted for labor. A total of 1,648 cases were excluded because of no CTG during labor, 899 because of no umbilical cord blood gasometry results in the medical records, 130 because of being classified as low-risk pregnancy, 29 because of inadequate umbilical cord blood conditions for analysis (blood coagulation, time between collection and analysis>30 min), and 20 because of a difference between venous and arterial pH<0.02. For the final statistical analysis, we included 105 cases of CTG category I, 20 cases of CTG category II, and 10 cases of CTG category III.

The clinical characteristics of the study population are shown in Table 1. Patients with CTG category III had a higher

Table 1. Clinical characteristics of the study population.

	CTG category I (105)	CTG category II (20)	CTG category III (10)	p
Age (years)	25 (15–43)	21 (15–35)	23 (16–35)	0.201†
Ethnicity				0.663§
White	47.6% (50/105)	35.0% (7/20)	60.0% (6/10)	
Black	11.4% (12/105)	20.0% (4/20)	10.0% (1/10)	
Mixed	41.0% (43/105)	45.0% (9/20)	30.0% (3/10)	
Smoking	10.5% (11/105)	20.0% (4/20)	0.0% (0/10)	0.235§
Number of pregnancies	1.0 (1.0–9.0)	1.0 (1.0–4.0)	1.0 (1.0–2.0)	0.053†
Number of deliveries				0.074§
Nulliparous	50.5% (53/105)	70.0% (14/20)	80.0% (8/10)	
More than one delivery	49.5% (52/105)	30.0% (6/20)	20.0% (2/10)	
Gestational age (weeks)	39.4 (35–40.9)[A,B]	38.4 (30.6–40.7)	38.4 (33.4–40.0)	0.014†
Type of delivery				0.032§
Vaginal	55.2% (58/105)	35.0% (7/20)	10.0% (1/10)	
Cesarean section	42.9% (45/105)[B]	65.0% (13/20)	90.0% (9/10)	
Forceps	1.9% (2/105)	0.0% (0/20)	0.0% (0/10)	
Time of labor (min)	240.0 (60.0–1,020.0)	240.0 (120.0–240.0)	180.0 (120.0–300.0)	0.358†
Birth weight (g)	3,260.0 (1,975.0–4,485.0)[A]	2,900.0 (1,440.0–3,360.0)[C]	3,280.0 (2,660.0–4,030.0)	<0.001†
APGAR score at 1st min	8 (1–9)[A,B]	7 (2–9)	7 (3–9)	0.006†
APGAR score at 5th min	9 (8–10)[B]	9 (6–10)[C]	8 (8–9)	0.002†
Arterial pH	7.22 (6.86–7.34)[A,B]	7.16 (6.91–7.22)	7.13 (7.01–7.26)	0.002†
Venous pH	7.32 (6.98–7.46)[B]	7.29 (6.99–7.38)	7.22 (7.12–7.35)	0.047†

pH: hydrogen potential; Kruskal-Wallis test†: median (minimum–maximum); Chi-square test§: percentage (n/N); [A]Category I vs. Category II; [B]Category I vs. Category III; [C]Category II vs. Category III; p<0.05.

prevalence of cesarean sections compared to patients with CTG category I (90.0 vs. 42.9%, p<0.006). Gestational age at delivery was significantly higher in CTG category I patients compared to CTG category II (39.4 vs. 38.4 weeks, p=0.002) and CTG category III (39.4 vs. 38.4 weeks, p=0.047). Birth weight was significantly lower in patients with CTG category II compared to CTG category I (2,900.0 vs. 3,260.0 g, p<0.001) and CTG category III (2,900.0 vs. 3,280.0 g, p=0.011). APGAR score at 1st min was higher in patients with CTG category I compared to CTG category II (8.0 vs. 7.0, p=0.012) and CTG category III (8.0 vs. 7.0, p=0.002). APGAR score at 5th min was higher in patients with CTG category I compared to CTG category III (9.0 vs. 8.0, p<0.001). Arterial pH was higher in patients with CTG category I compared to CTG category II (7.22 vs. 7.16, p=0.011) and CTG category III (7.22 vs. 7.13, p=0.005). Venous pH was higher in patients with CTG category I compared to CTG category III (7.32 vs. 7.23, p=0.036).

The association between intrapartum CTG categories and high-risk maternal conditions is shown in Table 2. Patients with gestational arterial hypertension showed lower rates of CTG category I than categories II and III (p=0.002).

A lower prevalence of APGAR score at 1st min<7 was observed in neonates of patients with CTG category I compared to CTG category II (6.7 vs. 25.0%, p=0.024) and CTG category III (6.7 vs. 40.0%, p=0.007). The prevalence of NICU admission was lower in neonates of patients with CTG category I compared to CTG category III (3.8 vs. 30.0%, p=0.014). The prevalence of composite adverse outcomes was lower in neonates of patients with CTG category I compared to CTG category II (9.5 vs. 30.0%, p=0.022) and CTG category III (9.5 vs. 60.0%, p=0.0004) (Table 3).

Patients with CTG category III, compared to those with CTG category I, had an increased risk of APGAR score at 5th min<7 (OR 9.3, 95%CI 2.42–38.77, p=0.007), NICU admission (OR 10.8, 95%CI 2.26–46.76, p=0.014), and composite perinatal outcomes (OR 14.3, 95%CI 3.76–48.69, p=0.004) without increasing the risk of acidemia at birth (OR 0.0, 95%CI 0.0–94.5, p>0.999).

Table 2. Association between intrapartum cardiotocography category and high-risk maternal conditions.

	CTG category I (105)	CTG category II (20)	CTG category III (10)	p
Maternal hemoglobin level <10 g/dL	21.0% (22/105)	25.0% (5/20)	10.0% (1/10)	0.630
Pre-existing and gestational diabetes mellitus	30.5% (32/105)	5.0% (1/20)	20.0% (2/10)	0.066
Gestational arterial hypertension	25.7% (27/105)	65.0% (13/20)	40.0% (4/10)	0.002
Chronic arterial hypertension	13.3% (14/105)	0.0% (0/20)	10.0% (1/10)	0.219
Pre-eclampsia	3.8% (04/105)	5.0% (1/20)	0.0% (0/10)	0.742
Fetal growth restriction	6.7% (07/105)	0.0% (0/20)	20.0% (2/10)	0.117

Chi-square test: percentage (n/N). A: Category I vs. Category II; B: Category I vs. Category III; C: Category II vs. Category III, p<0.05.

Table 3. Association between intrapartum cardiotocography category and adverse perinatal outcomes in high-risk pregnancies.

	CTG category I (105)	CTG category II (20)	CTG category III (10)	p
Acidemia at birth	1.% (1/105)	5.0% (1/20)	0.0% (0/10)	0.359
APGAR score at 1st min <7	6.7% (7/105)[A,B]	25.0% (5/20)	40.0% (4/10)	0.001
NICU admission	3.8% (4/105)[B]	15.0% (3/20)	30.0% (3/10)	0.004
Early neonatal death (first 48 h)	0.0% (0/105)	0.0% (0/20)	0.0% (0/10)	*
Need for neonatal resuscitation	1.0% (1/105)	5.0% (1/20)	10.0% (1/10)	0.118
Composite adverse outcomes	9.5% (10/105)[A,B]	30.0% (6/20)	60.0% (6/10)	<0.001

Chi-square test: percentage (n/N). *Impossible to apply statistical test due to the absence of outcomes. p<0.05. A: Category I vs. Category II; B: Category I vs. Category III.

We observed that intrapartum CTG categories II and III had low sensitivity and high negative predictive value (NPV) for identifying fetal acidemia at birth. CTG category I also showed low positive predictive value (21.0%). The three categories of intrapartum CTG showed high specificities (96.0, 99.0, and 99.0%, respectively). Intrapartum CTG was shown to be rarely useful in improving the ability to identify truly positive (low positive likelihood ratio values) and truly negative (high negative likelihood ratio values) individuals.

DISCUSSION

It is well known that CTG is a continuous and simultaneous recording of FHR, uterine contractility, and fetal movements, and this monitoring aims to identify fetal distress in order to avoid neurological alterations and even fetal death[9].

Previous studies have shown that alterations in intrapartum CTG in high-risk pregnancies contribute to higher rates of cesarean sections and instrumental deliveries[10,11], which is in agreement with this study since patients with CTG category III had a higher prevalence of cesarean sections when compared to CTG category II (90 and 42.9%, respectively). Moreover, this study showed a significant association between CTG and the presence of an APGAR score at 1st min<7, NICU admission, and adverse perinatal outcomes; however, there was no significant association between CTG and acidemia at birth, early neonatal death (first 48 hours), and need for neonatal resuscitation. Weissbach et al.[12], in a retrospective cohort study of 271 patients delivered by cesarean section for non-reassuring FHR, evaluated the duration of CTG category II, variability, tachycardia, and deceleration and correlated them with adverse perinatal outcomes. Patients with reduced FHR had higher rates of pH ≤7.0, and patients with fetal tachycardia had higher rates of APGAR scores at 1st and 5th min<7 and ventilatory support. Longer duration of CTG category II did not result in increased rates of adverse neonatal outcomes.

Intrapartum CTG aims to detect fetal hypoxia related to acute or subacute events during labor that require medical management to reduce the risk of complications such as hypoxic-ischemic encephalopathy, cerebral palsy, and neonatal death[13]. Thus, it is justified that high-risk pregnant women with a CTG category III had a higher prevalence of cesarean section compared to CTG category I (90.0 vs. 42.9%), since in case of alteration in intrapartum fetal monitoring, it is prudent to perform maneuvers to improve maternal-fetal oxygenation, and if monitoring remains inadequate, it is recommended for immediate delivery to avoid metabolic acidemia and tissue injury[14].

APGAR score at 1st min is an important parameter to help in the decision of neonatal resuscitation; however, the APGAR score is not a good predictor of intrapartum acidosis because it is a subjective parameter that depends on the experience of each professional[15]. In this study, APGAR score at 1st min was higher in patients with CTG category I compared to CTG category III, and 40% of patients with CTG category III had APGAR score at 1st min<7, while only 6.7% of patients with CTG category I had this same parameter, however, without observing the association between CTG category and acidemia at birth.

According to the ACOG as well as the International Federation of Gynecology and Obstetrics (FIGO), a normal FHR pattern with accelerations and the absence of decelerations on continuous assessment is predictive of good fetal oxygenation, requiring no additional interventions[16]. However, the presence of late and variable decelerations, bradycardia, and absence of variability may indicate high risk of acidemia at birth, necessitating delivery to avoid future consequences to the newborn[17]. However, a meta-analysis of randomized trials comparing different methods of intrapartum fetal surveillance found that none of them were associated with a reduced risk of neonatal acidemia, NICU admission, APGAR scores, or perinatal death. Compared with other types of fetal surveillance, intermittent auscultation seems to reduce emergency cesarean deliveries in labor without increasing adverse neonatal and maternal outcomes[18].

A study in high-risk pregnancies compared the FIGO 3-tier and 5-tier FHR classification systems to detect acidemia at birth. The 3-tier system showed a greater sensitivity and lower specificity to detect acidemia at birth and severe metabolic acidemia compared with the 5-tier system. The authors concluded that both systems presented a comparable ability to predict acidemia at birth, although the 5-tier system showed a better interobserver agreement identifying pathological tracings[19]. Such results differ from those found in our study, in which all categories of CTG showed low sensitivity to identify acidemia at birth, as well as high NPV. In addition, CTG category I showed low NPV and all CTG categories showed high specificity, indicating that CTG is rarely helpful to identify acidemia at birth.

CONCLUSION

All three categories of intrapartum CTG showed low sensitivity and high specificity for identifying acidemia at birth. Also, CTG category II and category III showed a high NPV for identifying acidemia at birth.

AUTHORS' CONTRIBUTIONS

ABP: Conceptualization, Data curation, Project administration, Visualization. **RSL:** Data curation, Visualization, Writing – original draft. **MFT:** Data curation, Visualization. **CGP:** Investigation, Validation, Visualization. **PTM:** Investigation, Validation, Visualization. **EAJ:** Methodology, Visualization, Writing – review & editing.

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ORIGINAL ARTICLE

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Role of simple inflammatory parameters in predicting the severity of coronary artery disease

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SUMMARY

OBJECTIVE: In our study, we aimed to find simple, useful biomarkers in patients with non-ST elevation myocardial infarction to predict coronary artery severity.

METHODS: Between May 2022 and December 2022, patients diagnosed with non-ST elevation myocardial infarction according to the European cardiology guidelines were included in our study. The Synergy between PCI with Taxus and Cardiac Surgery score was calculated to determine the severity of coronary artery disease. These patients were classified into two groups according to Synergy between PCI with Taxus and Cardiac Surgery≥23 and Synergy between PCI with Taxus and Cardiac Surgery<23 scores. Biochemical markers such as platelet-to-lymphocyte ratio and neutrophil-to-lymphocyte ratio were studied in blood tests taken before coronary angiography in patients diagnosed with non-ST elevation myocardial infarction according to current guidelines. These two groups were compared in terms of the data obtained.

RESULTS: There were 281 patients in group 1 and 67 patients in group 2. There was no significant difference between the two groups in terms of demographic data such as age and gender. Platelet-to-lymphocyte ratio [group 1=125 (26–134) and group 2=156 (73–293); p=0.001] and neutrophil-to-lymphocyte ratio [group 1=2.71 (1.3–30.2) and group 2=3.2 (2.1–32.1); p=0.002] were higher in the group of patients with a Synergy between PCI with Taxus and Cardiac Surgery score of <23, while lymphocyte-to-monocyte ratio [group 1=3.6 (0.56–11) and group 2=3.4 (0.64–5.75); p=0.017] was lower in group 2.

CONCLUSION: We observed that elevated platelet-to-lymphocyte and neutrophil-to-lymphocyte ratios showed coronary artery severity. Multivessel disease and chronic total occlusion rates were observed to be higher in patients with high platelet-to-lymphocyte and neutrophil-to-lymphocyte ratios.

KEYWORDS: Non-ST elevated myocardial infarction. Coronary artery disease. Inflammation. Blood platelets.

INTRODUCTION

The Synergy between PCI with Taxus and Cardiac Surgery (SYNTAX) score is an indicator of the complexity of coronary artery disease. Various clinical outcomes in non-ST elevation myocardial infarction (NSTEMI) patients have been extensively studied using the SYNTAX score II, and this score is a reliable indicator of mortality in patients with acute coronary syndrome (ACS) who underwent PCI[1]. However, the SYNTAX score is an angiographic scoring system. Coronary angiography may be delayed in patients presenting with NSTEMI. Easy, practical, noninvasive, and faster markers are needed to predict the complexity of coronary artery disease. For complicated lesions, arterial sclerosis is in an advanced state. Atherosclerosis is recognized as a continuous, dynamic, and inflammatory process in the circulatory system, in addition to being a cholesterol problem that builds up on the arterial walls in the subintimal region[2]. The immune system and coagulation cells have important roles in the development and complications of atherosclerotic plaque. Many illnesses, including chronic heart failure, cancer, metabolic problems, and cardiovascular disease, have been related to inflammation[3]. For individuals with coronary artery disease, the platelet-to-lymphocyte ratio (PLR) and the neutrophil-to-lymphocyte ratio (NLR) have both offered valuable data for predicting future outcomes. Inflammation that is linked to adverse outcomes in individuals with ACS is shown by low lymphocyte numbers[4]. In the study of Kurtul et al., in patients with ACS, the platelet-lymphocyte ratio was significantly higher in patients with a high SYNTAX score; these patients also had significantly higher in-hospital mortality[5]. Cardiovascular diseases such as stable coronary heart disease, ACS, and non-ST elevation MI are associated with inflammation[6]. NLR is a novel marker of inflammation in various conditions including inflammatory bowel disease, diabetes mellitus, gastrointestinal conditions, thyroiditis, and

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SARS-CoV-2 infection[7]. In addition, it is associated with cardiac conditions[8]. On the contrary, elevated PLR has been reported in thyroid conditions, gastrointestinal diseases, thyroiditis, cancer, diabetes mellitus, irritable bowel disease, and COVID-19 infection[9,10]. Therefore, studying PLR and NLR as predictors of heart disease makes sense. By evaluating these biochemical values in NSTEMI, we may predict the high SYNTAX score, and these biochemical values may guide us in the classification of high-risk patients.

METHODS

Study population

Patients diagnosed with NSTEMI according to the European cardiology guidelines were included in our study. Patients who were referred to the emergency department with chest pain and had a change in electrocardiography and a significant increase in high-sensitive Troponin T levels between May 2022 and December 2022 were included. Patients with severe renal failure (creatinine>2 mg/dL), active infection, age <18 years, and patients with active inflammatory disease and malignancy were excluded from the study. We were able to ascertain the essential clinical characteristics of the patients by looking through the hospital's database. Blood samples were collected at the first arrival. An automated device was used to measure biochemical values and perform a complete blood count from the blood. Being treated for high cholesterol or having a total cholesterol level over 220 mg/dL were defined as signs of hyperlipidemia. Hypertension was defined as blood pressure exceeding 140/90 mmHg or the use of an antihypertensive medication. Glycated hemoglobin A1c values of 6.5%, usage of antidiabetic medicines, or fasting plasma glucose levels of 7.0 mmol/L (126 mg/dL) were all regarded as signs of diabetes mellitus. The study, which was conducted in compliance with the Declaration of Helsinki, was approved by the local ethics committee.

Coronary angiography

Antiplatelet and anticoagulant therapy was started in all patients as soon as the diagnosis of NSTEMI was made in the emergency department. The analysis of coronary angiograms was performed by two independent cardiologists who were unaware of the patient's information. A major coronary artery with a stenosis of 50% or more was considered to be significant. SYNTAX (SYNergy between PCI with TAXUS and Cardiac Surgery) scores II were calculated for all patients after the angiography procedure[11]. Patients were classified into two groups with a SYNTAX score of ≥23 and a SYNTAX score of <23.

Statistical analysis

The statistical analysis was carried out using the statistical software SPSS 22.0 (SPSS Inc., Chicago, IL). Continuous variables were expressed as mean±standard deviation (SD) or median (minimum-maximum). Categorical variables were expressed as percentages and compared using chi-square or Fischer's exact tests. The normality of data distributions was evaluated using the Kolmogorov-Smirnov test. An independent samples t-test was used for continuously distributed data with a normal distribution. Non-normally distributed data were examined using the Mann-Whitney U test. The PLR, LMR, and NLR ratio cutoff values were determined using receiver-operating characteristic analyses (ROC) to predict the degree and complexity of coronary artery disease in individuals with NSTEMI. We used Youden's J statistic for finding the best cutoff values. Univariate and multivariate regression analyses were performed for independent parameters in predicting the severity and complexity of coronary artery disease in patients with NSTEMI. The relationship between the PLR, LMR, and NLR ratios and the severity of the coronary arteries was examined using the Spearman correlation test. For $p<0.05$, statistics were deemed significant.

RESULTS

In total, the data of 432 patients were analyzed. Two groups were formed in which basic clinical and biochemical parameters were similar. Notably, 84 patients were excluded from the study. As a result, 348 patients were included in the study. Group I includes patients with a SYNTAX score of <23, and group II includes patients with a SYNTAX score of ≥23. Table 1 shows the basic characteristics and laboratory findings. There was no difference between the two groups in terms of demographic characteristics. Multi-vessel disease and chronic total occlusion rates were higher in group I. Left ventricular ejection fraction rates were lower in group II. Regarding the medical treatment given to the study's participants, there was no difference between the two groups. The NLR, PLR, and Troponin T levels were statistically high in Group II [NLR 3.2 (2.1–32.1) and 2.71 (1.3–30.2), p=0.002; PLR 156 (73–293) and 125 (26–134), p=0.001; Troponin T 424 (9–2836) and 265 (6–3501), p=0.003]. LMR and lymphocyte counts were statistically lower in Group II. [LMR 3.6 (0.56–11) and 3.4 (0.64–5.75), p=0.017; lymphocyte count 2.4±1 and 2±1.2, p=0.008].

The ROC analysis of PLR, NLR, and LMR values for predicting the severity and complexity of coronary artery disease in patients with NSTEMI were as follows: PLR cutoff value of ≥117, AUC: 0.634; 95%CI (0.558–0.710) with 64.2% sensitivity and 63.3% specificity, p=0.001, NLR cutoff value of

≥3.5, AUC: 0.407; 95%CI (0.332–0.482) with 44.8% sensitivity and 45.2% specificity, p=0.018, LMR cutoff value of ≤2.8, AUC: 0.622; 95%CI (0.544–0.701) with 62.7% sensitivity and 61.9% specificity, p=0.002 (Figure 1). A moderately positive correlation between PLR, NLR, and SYNTAX score II was found using Spearman correlation analysis, respectively (PLR r=0.55, p<0.001, and NLR r=0.51, p=0.002). A moderately negative correlation was found between LMR and

Table 1. Baseline clinical and angiographic characteristics of the study population according to the Synergy between PCI with Taxus and Cardiac Surgery score II.

Variables	Group I n=281	Group II n=67	p-value
Male, n (%)	185 (65.8%)	37 (55.2%)	0.104
Age (years)	61±12.7	62±11.2	0.212
Weight (kg)	78±14.6	77±15.8	0.582
Height (cm)	166±9.1	165±10.4	0.478
Body mass index (kg/m^2)	28.5±4.9	28.3±5.2	0.826
Hypertension, n (%)	142 (50.5%)	39 (58.2%)	0.258
Diabetes mellitus, n (%)	91 (32.4%)	30 (44.8%)	0.056
Hypercholesterolemia, n (%)	90 (32%)	21 (31.3%)	0.914
Smoking, n (%)	20 (7.1%)	5 (7.4%)	0.896
Stroke, n (%)	6 (2.1%)	2 (3%)	0.677
Prior CABG history, n (%)	10 (3.6%)	4 (6%)	0.367
Prior myocardial infarction, n (%)	21 (7.5%)	7 (10.4%)	0.421
Left ventricular ejection fraction	53±9	45±12	**<0.001**
Multi-vessel disease, n (%)	135 (48%)	65 (97%)	**<0.001**
Chronic total occlusion, n (%)	29 (10.3%)	27 (40.2%)	**<0.001**
Biochemical and hematological measurements of the study population			
Hemoglobin (g/dL)	14.1±1.9	14.3±1.9	0.798
WBC (×10^9/L)	9.8±3.2	9.7±3.3	0.784
Neutrophil (×10^9/L)	6.4±2.8	6.8±3	0.303
Lymphocyte (×10^9/L)	2.4±1	2±1.2	**0.008**
Monocyte (×10^9/L)	0.67±0.27	0.62±0.23	0.190
Platelet (×10^9/L)	246.3±78.3	244.3±73	0.850
NLR	2.71 (1.3–30.2)	3.2 (2.1–32.1)	**0.002**
PLR	125 (26–134)	156 (73–293)	**0.001**
LMR	3.6 (0.56–11)	3.4 (0.64–5.75)	**0.017**
Glucose (mg/dL)	156±18	159±72	0.241
Creatinine (mg/dL)	1±0.3	1.1±0.3	0.052
Total cholesterol (mg/dL)	209±63	201±44	0.541
Triglycerides (mg/dL)	156±87	159±71	0.802
LDL-C (mg/dL)	125±42	120±38	0.386
HDL-C (mg/dL)	42±11	43±9.4	0.406
Hs-CRP (mg/L)	7.2 (0.6–9.9)	8.1 (0.9–10.9)	0.081
Uric acid (mg/L)	5.7±1.5	5.9±1.5	0.494
High sensitivity Troponin T (ng/mL)	265 (6–3501)	424 (9–2836)	**0.003**
CK-MB (ng/mL)	14 (0.78–281)	20 (2.91–105)	0.059
GFR (mL/min/1.73 m^2)	70±24	68±20	0.320

CABG: coronary artery bypass graft; NLR: neutrophil-to-lymphocyte ratio; PLR: platelet-to-lymphocyte ratio; LMR: lymphocyte-to-monocyte ratio. Bold values indicate statistical significance at the p<0.05 level.

SYNTAX score II (r=-0.52, p<0.001). In univariate and multivariate logistic regression analysis, a high PLR ratio was an independent predictor of a high SYNTAX score II (OR: 1003; 95%CI (0.998–1.009), p=0.019) (Table 2).

DISCUSSION

To the best of our knowledge, this is the first study to investigate the association between composite inflammatory ratios and angiographic severity of coronary artery disease in patients presenting with NSTEMI. In this observational study, we found NLR, PLR, and LMR were associated with high SYNTAX scores. PLR, NLR, and LMR may be capable of predicting the severity and complexity of coronary artery disease. Moreover, a high PLR ratio was an independent predictor of a high SYNTAX score.

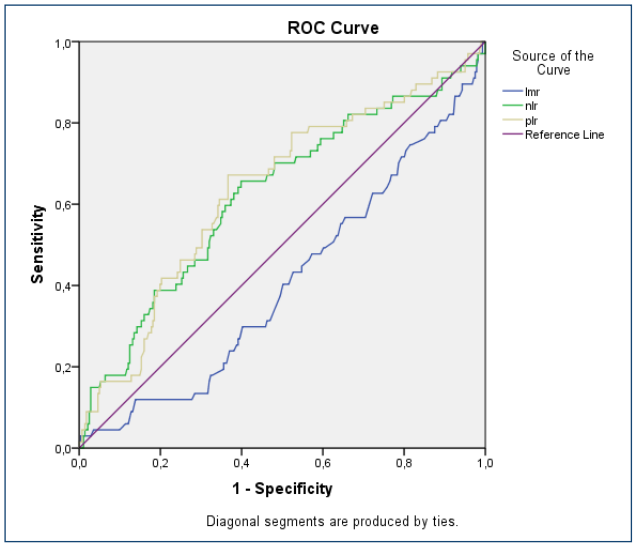

Figure 1. The receiver operating characteristic curve analysis for the cutoff values of platelet-to-lymphocyte ratio, neutrophil-to-lymphocyte ratio, and lymphocyte-to-monocyte ratio for predicting a high Synergy between PCI with Taxus and Cardiac Surgery score II. NLR: neutrophil-to-lymphocyte ratio; PLR: platelet-to-lymphocyte ratio; LMR: lymphocyte-to-monocyte ratio.

It is not unexpected that individuals with coronary artery disease have elevated levels of inflammatory indicators such as neutrophil and platelet counts, red blood cell distribution width, NLR, and PLR. At the onset of atherosclerosis, platelets are crucial. They release inflammatory immunomodulatory molecules such as prostaglandin E2 and platelet-activating factor. Inflammation related to adverse outcomes in patients with ACS is demonstrated by low lymphocyte counts[12,13]. There is a complex relationship between innate immunity and adaptive immunity during the rupture of atherosclerotic plaque. Neutrophils that are attempting suicide may release pro-oxidant and pro-inflammatory mediators and form neutrophil extracellular traps. Neutrophil extracellular traps may cause the development of atherosclerotic plaque and increase thrombus stability[14]. NLR is regarded as a sign of subclinical inflammation. NLR is an independent predictor of cardiovascular events and mortality in ST-segment elevation myocardial infarction[15]. Blood components, such as platelets, neutrophils, and lymphocytes, are included in the systemic immune inflammation index, a novel inflammation marker. In previous studies, systemic immune inflammation index was related to an increased risk of cardiac death, nonfatal MI, nonfatal stroke, and heart failure[16].

In many previous studies and meta-analyses, high PLR rates were found in individuals with stable coronary artery disease as a prognostic marker[17]. In clinical practice, PLR, a systematic inflammatory maker, was used to predict the outcome of oncologic illnesses[18]. PLR has also been used as a prognostic marker in coronary slow flow, coronary collateral circulation, atrial fibrillation, and heart failure[19]. PLR was also a good indicator of atherosclerotic plaque burden. In patients with ACS before the primary percutaneous coronary intervention, Yayla et al., observed that a higher PLR was an independent predictor of the patency of the infarct-related artery[20]. In previous

Table 2. Univariate and multivariate regression analysis of independent variables in predicting a high Synergy between PCI with Taxus and Cardiac Surgery score.

Variables	Univariate analysis			Multivariate analysis		
	OR	95%CI	p-value	OR	95%CI	p-value
Gender (male)	0.640	0.373–1.099	0.106	–	–	–
Hypertension	1.363	0.795–2.337	0.260	–	–	–
Diabetes mellitus	1.693	0.984–2.912	0.057	–	–	–
PLR	1.006	1.002–1.010	**0.001**	1.003	0.998–1.009	**0.019**
LMR	0.847	0.709–1.011	0.065	–	–	–
NLR	1.100	1.026–1.180	**0.008**	1.020	0.927–1.124	0.680

NLR: neutrophil-to-lymphocyte ratio; PLR: platelet-to-lymphocyte ratio; LMR: lymphocyte-to-monocyte ratio. Bold values indicate statistical significance at the p<0.05 level.

studies, high PLR levels have been observed to be associated with in-stent restenosis, saphenous vein graft disease, slow coronary flow, and poor coronary collateral circulation[21].

Atherosclerosis can be slowed down and cardiovascular events can be decreased by reducing the inflammatory response through the management of hyperlipidemia and thrombosis. According to the Canakinumab Anti-Inflammatory Thrombosis Outcomes Study, interleukin-1 beta-targeted anti-inflammatory medication may lower levels of high-sensitivity C-reactive protein and reduce the frequency of recurrent cardiovascular events[22].

The fact that the PLR, NLR, and Troponin T levels increased more in the group with NSTEMI and a high SYNTAX score in our study supports previous studies. Examining these biomarkers in patients diagnosed with ACS in the emergency department will help us both in predicting the prognosis of the patient and in diagnosing complex coronary artery disease. We found that patients with NSTEMI had higher PLR and NLR levels, which indicated the severity of their coronary arteries. Furthermore, it was found that the rates of multivessel disease and chronic complete occlusion were higher in these patients. As a result, coronary angiography is required to calculate the SYNTAX score. Coronary angiography may be delayed for many reasons. PLR and NLR may be used for risk stratification before an invasive angiography-based SYNTAX score. PLR and NLR, which are easily obtained from routine blood tests in clinical practice, may be calculated quickly in patients presenting with NSTEMI and may provide information about the SYNTAX score without coronary angiography.

Limitations

The main limitations are as follows. Our study included only a small number of patients, was conducted at a single center, and had a retrospective design. From the patients who participated in our study, more blood samples could be taken. The effect on long-term mortality is not fully understood, as changes in parameters in-hospital or after discharge are not followed. It was not questioned whether patients had previously taken aspirin, statins, beta-blockers, or anti-inflammatory agents that would affect the inflammatory process. To confirm the results of this investigation, larger, multi-center prospective investigations must be carried out.

CONCLUSION

Early risk stratification of NSTEMI is one of the important problems. New biomarkers are practical parameters that can help us in diagnosis and treatment. PLR, NLR, and LMR may be helpful for stratifying high-risk individuals with NSTEMI since they are practical and cost-effective biomarkers.

AUTHORS' CONTRIBUTIONS

CA: Formal Analysis, Supervision, Writing – review & editing. **UU:** Conceptualization, Resources. **MK:** Data curation, Investigation, Methodology. **AD:** Supervision, Visualization, Writing – original draft.

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ORIGINAL ARTICLE

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Intraoperative, sociodemographic, and postoperative parameters in individuals undergoing bariatric surgery

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SUMMARY

OBJECTIVE: This study aimed to comparatively analyze sociodemographic data and postoperative parameters of patients undergoing bypass and sleeve surgeries in a private hospital in São Luís, MA.

METHODS: The study was descriptive, prospective, observational, and comparative, with a quantitative approach between August 2020 and July 2021. We analyzed 74 participants of both genders, aged between 18 and 70 years, with 31 undergoing Roux-en-Y gastric bypass surgery and 43 undergoing sleeve gastrectomy surgery. In the postoperative period, sociodemographic characteristics, surgery and anesthesia duration, pain levels, adverse effects, weight loss, and complications from the surgical procedure were analyzed.

RESULTS: Males predominated in Roux-en-Y gastric bypass and females in sleeve gastrectomy surgery. Clinical characteristics regarding self-declared ethnicity, age and place of birth, education, and marital status were similar between the studied groups. Roux-en-Y gastric bypass had an average surgery time of 112.14±10.06 min and sleeve gastrectomy 91.11±23.69 min, with a significant difference ($p<0.001$). Regarding anesthesia time, gastric bypass averaged 160.36±13.99 min and sleeve gastrectomy 154.88±29.10 min, with no statistical difference between groups ($p=0.335$). Nausea, vomiting, and drowsiness were more common in Sleeve gastrectomy, with no significant difference ($p=0.562$). Roux-en-Y gastric bypass showed a higher rate of weight loss from 1 month after surgery (14.2±4.15) and more variation in body mass index within 3 months after surgery (32.17±4.76). Complications occurred in a small number of patients.

CONCLUSION: The two surgical techniques proved effective in delivering the best results for patients, with the group undergoing bypass showing statistically significant weight loss from 1 month after the surgical procedure.

KEYWORDS: Obesity. Gastric bypass. Gastrectomy.

INTRODUCTION

Obesity, according to the World Health Organization (WHO), is defined as the excessive accumulation of body fat[1]. This condition is commonly associated with an increased risk for chronic diseases, functional disability, and psychosocial harm[2,3]. Furthermore, the WHO estimates that the global obesity epidemic in 2025 will reach approximately 167 million new people, considering there are already more than 600 million obese people[4].

Besides the physical impact, which increases the risk of several chronic diseases, obesity also impacts the psychosocial aspect of individuals, being closely related to several psychiatric disorders, such as depression and anxiety[5].

Therapeutic strategies consist of physical exercises, dietary approaches, and drug use, some of the pillars of clinical treatment. However, although widely used, it has lower success rates than surgical treatment, which has already proven more effective[6-8].

As a result, considering that most morbidly obese patients do not respond satisfactorily to clinical therapy, bariatric and metabolic surgeries have been increasingly indicated as an alternative for treating this morbidity and its associated pathologies[9]. This procedure proved an effective alternative, bringing numerous benefits to patients regarding physical health and psychosocial aspects[10].

The sleeve gastrectomy and Roux-en-Y gastric bypass stand out among the bariatric surgery options. The latter was the most used among the main techniques for a long time. However, sleeve surgery, being more pragmatic and with lower rates of side effects, is already the most commonly performed bariatric surgery in the United States of America[9].

Considering this scenario, this study searched to comparatively analyze sociodemographic data, intraoperative parameters, and postoperative parameters of patients' techniques of bypass and sleeve gastrectomy.

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METHODS

Study design

This is a cross-sectional and comparative study. This study was approved by the Institutional Research Ethics Committee (CAAE 28324720.0.0000.5085/No. 4.364.508).

In convenience sampling, patients aged 18–70 years who underwent Roux-en-Y gastric bypass or sleeve gastrectomy, of both genders, between August 2020 and July 2021, were included in the study. Exclusion criteria included patients using drugs, who had cardiac arrhythmias, dilated cardiomyopathy, and cardiac conduction disorder, or even those who were lost to follow-up in the postoperative period and did not respond to the questionnaires.

Data collection instrument

Data were collected from clinical charts and evaluation sheets of patients undergoing bariatric surgery in a private hospital in the northeastern capital. The sociodemographic variables analyzed were age and gender, self-declared ethnicity, marital status, and education level. Anthropometric measurements analyzed were height, weight, body mass index (BMI), and total weight loss percentage.

The surgical techniques were performed the same way in all patients according to the group to which they belonged. In addition, all surgeries were performed by the same team of digestive system surgeons at the service, ensuring that the surgical procedures were performed homogeneously and ensuring comparability.

Intraoperatively, the beginning and end of the surgery and the time to wake up were evaluated. In the postoperative period, the occurrence of nausea, vomiting, drowsiness, and dizziness from 0 to 24 h and up to 7 days after surgery and pain intensity up to 6 months postoperatively were assessed. Indicators of pain intensity at rest and after movement were measured using a verbal numeric scale from 0 (no pain) to 10 (most intense pain possible).

Data on possible complications in the postoperative period, such as cholelithiasis and dumping syndrome, were also analyzed, as was the comparison between the weight loss of the two groups in an interval extending up to 6 months after surgery.

In the postoperative period, complications were evaluated according to the Clavien-Dindo classification of surgical complications. The following grade I complications, such as nausea, vomiting, drowsiness, and dizziness, were evaluated from 0 to 24 h and up to 7 days after surgery. Pain intensity, also classified as grade I, was evaluated up to 6 months postoperatively, and pain intensity indicators at rest and after movement were measured using a verbal numeric scale from 0 (no pain) to 10 (pain as intense as possible)[11].

In addition, dumping syndrome, also classified as grade I, and cholelithiasis, a complication that can reach grade III, depending on the need for surgical intervention, were analyzed and compared regarding weight loss in these two groups at intervals of up to 6 months after surgery. Also, the main complications, according to other studies, of bariatric surgery were evaluated, such as fistula, classified as grades II or III, depending on the intervention, intestinal obstruction, grade I, and pulmonary thromboembolism, grade III[11].

After approval by the hospital's Research Ethics Committee and signing the Informed Consent Form, patients between 18 and 70 years of age undergoing bariatric surgery were included in the study. Patients using drugs, with cardiac arrhythmias, dilated cardiomyopathy, or cardiac disorder, or who have lost postoperative follow-up and did not reply to the questionnaires were excluded.

Statistical analysis

Data were statistically analyzed using the SPSS 26.0® program. For the analysis of numerical variables, the results are presented with the mean and standard deviation; categorical data show them through absolute (n) and relative (%) frequencies. Normality was verified using the Kolmogorov-Smirnov test. Student's t-test was used to compare numerical variables, while Pearson's chi-square test was used to analyze categorical variables comparatively.

RESULTS

A total of 74 patients were enrolled in the study, of whom 31 were in G1 and 43 were in G2. Regarding the clinical data of the patients, there was a predominance of males in bypass surgery, and females in sleeve surgery, with 79.07% (n=34), with a statistical difference (p=0.005). Concerning anthropometric data, there was a relevant statistical difference (p<0.05): G1 had higher means of weight and BMI (p<0.001 for weight and BMI and p<0.027 for height). Clinical characteristics regarding self-declared ethnicity (p=0.828), age (p=0.893), place of birth (p=0.395), education (p=0.294), and marital status (p=0.779) were similar between the studied groups (Table 1). Data regarding surgery time showed a statistically significant difference between groups (p<0.001): Roux-en-Y gastric bypass had a mean surgery time of 112.1±10.06 min, while the gastrectomy time was 91.1±23.6 min. There was no statistical difference between groups regarding anesthesia

time (p=0.335), with averages of 160.3±13.9 and 154.8±29.1 min, respectively.

When analyzing postoperative pain at rest and during movement at the intervals studied, similar values were observed, although the sleeve group had slightly more severe pain, with a progressive reduction in both groups over time without a statistical difference (p>0.05).

Regarding the evaluation of side effects, nausea, vomiting, and drowsiness have occurred more frequently in the group that underwent the sleeve. On average, about 60% of patients reported some of these symptoms within 7 days after surgery, with no statistical difference (p=0.562). Concerning dizziness, a more significant occurrence of these symptoms was observed in the group submitted to bypass at different times of the postoperative period (p<0.001) (Table 2).

Regarding the occurrence of postoperative complications, it was noted that there was no relevant statistical difference regarding the occurrence of postoperative complications between the two techniques in the 6-month interval of the surgical

Table 1. Sociodemographic data.

Variables	Bypass	Sleeve	p-value*
	Mean±SD	Mean±SD	
Age (years)	37.32±10.46	37.02±8.23	0.893
Weight (kg)	116.64±27.56	97.26±13.34	<0.001
Height (cm)	167.97±11.01	162.67±9.12	0.027
Initial BMI (kg/m²)	40.93±5.87	36.70±3.50	<0.001
	n (%)	n (%)	p-value**
Gender			
Male	16 (51.61%)	9 (20.93%)	0.005
Female	15 (48.39%)	34 (79.07%)	
Self-declared ethnicity			
Black	3 (9.68%)	2 (4.65%)	0.828
Brown	17 (54.84%)	26 (60.47%)	
White	10 (32.26%)	13 (30.23%)	
Not registered	1 (3.23%)	2 (4.65%)	
Place of birth			
Maranhão	28 (90.32%)	41 (95.35%)	0.395
Other state	3 (9.68%)	2 (4.65%)	
Marital status			
Married/civil partnership	17 (54.84%)	22 (51.16%)	0.779
Single	9 (29.03%)	11 (25.58%)	
Cohabitation	1 (3.23%)	1 (2.33%)	
Divorced	–	2 (4.65%)	
Not registered	4 (12.90%)	7 (16.28%)	
Education			
Complete middle school	–	1 (2.33%)	0.294
Incomplete high school	–	1 (2.33%)	
Complete high school	10 (32.26%)	6 (13.95%)	
Incomplete higher education	3 (9.68%)	10 (23.26%)	
Complete higher education	15 (48.39%)	21 (48.84%)	
Not registered	3 (9.68%	4 (9.30%)	

*Student's t-test. **Pearson's chi-square test. SD: standard deviation.

procedure. Concerning the rate of total weight loss, a more significant reduction was observed in the group submitted to bypass 1 month after the surgical procedure ($p<0.05$). There was a more significant reduction in BMI over the same period, in which a significant difference was already observed in the first postoperative week ($p<0.001$), which was not reproduced over time since the same finding could not be made, for example, 6 months after the surgical procedure ($p=0.117$) (Table 3).

Table 2. Postoperative adverse effects.

Variables	G1	G2	p-value*
	n (%)	n (%)	
Nausea			
Without	14 (45.16)	17 (39.53)	0.562
0 h	10 (32.26)	12 (27.91)	
2 h	–	2 (4.65)	
6 a.m.	3 (9.68)	6 (13.95)	
6 p.m.	1 (3.23)	1 (2.33)	
24 h	–	3 (6.98)	
7 days	3 (9.68)	2 (4.65)	
Vomiting			
Without	14 (45.16)	17 (39.53)	0.790
0 h	15 (48.39)	21 (48.84)	
2 h	–	1 (2.33)	
6 a.m.	2 (6.45)	2 (4.65)	
6 p.m.	–	1 (2.33)	
24 h	–	1 (2.33)	
Dizziness			
Without	14 (45.16)	17 (39.53)	<0.001
0 h	10 (32.26)	18 (41.86)	
2 h	14 (45.16)	2 (4.65)	
6 a.m.	14 (45.16)	2 (4.65)	
6 p.m.	2 (6.45)	–	
24 h	14 (45.16)	1 (2.33)	
7 days	2 (6.45)	3 (6.98)	
Somnolence			
Without	14 (45.16)	17 (39.53)	0.865
0 h	5 (16.13)	7 (16.28)	
2 h	4 (12.90)	5 (11.63)	
6 a.m.	3 (9.68)	8 (18.60)	
6 p.m.	3 (9.68)	2 (4.65)	
24 h	2 (6.45)	3 (6.98)	
7 days	–	1 (2.33)	

*Pearson's chi-square test.

DISCUSSION

In the present study, it was possible to observe that males predominated in Roux-en-Y gastric bypass and females in sleeve gastrectomy. Roux-en-Y gastric bypass had a longer mean surgery and anesthesia time than sleeve gastrectomy. In weight from 1 month after surgery and more considerable variation in BMI at 3 months after surgery. Nevertheless, these complications occurred in a small number of patients.

Bariatric surgery is a theme constantly analyzed from different perspectives by several studies. Although Roux-en-Y gastric bypass is still the most used technique in Brazil, sleeve gastrectomy, or sleeve, has increased considerably in recent years[12]. The current study covers the comparative analysis of two primary forms of bariatric surgery: bypass and sleeve. It proposes to evaluate different aspects within the postoperative period, such as weight loss, possible postoperative complications, pain intensity, nausea, vomiting, dizziness, and sociodemographic aspects.

From an epidemiological point of view, the Brazilian Society of Bariatric and Metabolic Surgery (BSBMS) shows that about 7 out of 10 patients undergoing bariatric surgery in the country are women[9]. These data are reinforced by the statistics present in the study, in which 66.2% of patients undergoing surgical treatment were female. These significantly higher rates in females, although obesity has no relevant epidemiological difference between both genders, are related to several psychosocial, cultural, and economic factors that influence the substantial search for surgery for weight loss by women[13]. In addition, the mean age of the patients in this study was approximately 37 years old, which is similar to those reported in other studies, which indicate a mean age of 39 years[8].

Among the factors, we can mention the socio-cultural pressure to which women are subjected to seek an ideal lean body, fertility problems resulting from obesity, and an increased risk of complications during pregnancy. Therefore, women who perform bariatric surgery tend to be younger than men since, in this age group, they are more affected by cultural pressure and social problems. For seeking health services later, the male gender has higher rates of comorbidities, such as a history of myocardial infarction and coronary artery disease. Consequently, the surgical treatment in the latter group presents higher rates of morbidity, disability, and mortality and has a higher probability of giving up surgery throughout the process[13].

In the economic aspect, bariatric surgery significantly reduces direct and indirect costs for long-term health. Although the decrease in bariatric surgeries performed by the public system can provide anticipated savings, this would lead to higher health costs later[14].

Table 3. Postoperative complications and weight loss.

Variables	Bypass	Sleeve	p-value*
	Mean±SD	Mean±SD	
Complications			
Until 1 month			
No	31 (100.00)	43 (100.00)	–
In 1–3 months			
Dumping syndrome	1 (3.23)	–	0.235
No	30 (96.77)	43 (100.00)	
In 3–6 months			
No	25 (80.65)	36 (83.72)	0.300
Appendicitis	1 (3.23)	–	
Cholelithiasis	2 (6.45)	6 (13.95)	
Dumping syndrome	1 (3.23)	–	
Nephrolithiasis	1 (3.23)	–	
Intestinal obstruction	–	1 (2.33)	
Ulcer in anastomotic mouth	1 (3.23)	–	
Anthropometry			
Weight total lost (kg)			
In 1 week	6.26±1.98	6.68±2.08	0.384
In 1 month	14.28±4.15	12.40±3.67	0.044
In 3 months	24.40±7.28	19.27±5.68	0.001
In 6 months	27.48±3.77	23.95±5.52	0.003
BMI (kg/m^2)			
In 1 week	38.48±5.79	34.24±3.44	<0.001
In 1 month	35.64±6.05	31.99±3.49	0.002
In 3 months	32.17±4.76	29.43±2.73	0.003
In 6 months	28.98±3.57	27.83±2.65	0.117

BMI: body mass index; *Student's t-test.

Regarding access to the health service for bariatric surgery, there must be well-structured multidisciplinary action to properly manage patient care before and after the procedure to avoid discontinuity of treatment. When it comes to the public system, factors such as the difficulty of accessing the health service, lack of knowledge on the part of the population about the flow of care, and delay in referrals further worsen the patient's biopsychological situation, causing distress, anxiety, weight gain, and deterioration of physical health in the waiting period[15,16].

Previous studies have shown that surgery time averaged 93.7 min[17,18], close to the times found in the present study, which showed 91.1 and 112.1 min in the sleeve gastrectomy and Roux-en-Y gastric bypass groups, respectively. There was divergence regarding the data observed in the literature regarding the duration of anesthesia.

There was divergence concerning the data observed in the literature regarding the time of anesthesia. The duration of anesthesia during bariatric surgery is an essential factor in the perioperative course of patients and is strictly related to the duration of surgery. However, according to previous studies, these times differ substantially between the authors. Therefore, this heterogeneity can be reduced by standardizing surgical procedures and the anesthetic protocol[19].

Already widely discussed, the anesthetic techniques used in surgical procedures have an essential effect on several clinical aspects of patients[20]. In this sense, the half-life of the anesthetics used may be directly related to an anesthesia time of fewer than 100 min, as some studies have shown[18], while in the present study, the average was superior to 150 min in both groups.

Nevertheless, the more intense postoperative pain in the group submitted to the sleeve in the first hours after surgery may be intrinsically related to the anesthetics used intraoperatively, as observed in another study[21], with the choice of anesthetic drugs being a factor that should be taken into account during the intraoperative period of patients undergoing bariatric surgery.

Regarding the side effects, the two surgical techniques are related to adverse effects during the operation, so nausea and vomiting were the most reported follow-up to the study already carried out in the Bariatric Surgery Unit after the Surgical Gastroenterology Service of the Public Server Hospital State[22].

Dumping syndrome is also frequently associated with the late postoperative period of patients undergoing bariatric surgery and is found in up to 50% of patients who underwent gastric bypass[23]. However, it was found at a much lower rate in this study, which can be explained by the limiting factor of the tools used in detecting it, considering that factors such as readmissions and visits to the emergency sector were not evaluated in the patients studied.

As previously discussed, these procedures are consolidated as forms of substantial weight loss. Thus, previous studies[7,24] showed data that coincided with those presented in the present study: the average annual loss of total weight was 31.2% for the group submitted to bypass and 25.2% for the group submitted to sleeve. In the present study, in the 6-month follow-up, weight and BMI showed a reduction without significant differences.

Bariatric surgery is widely available in the public health system; however, the disparity between regions is striking: while the South-Southeast axis realized, respectively, in 2018 the amount of 7.307 and 2.991 bariatric surgeries, the northeast region had only 476 procedures performed[12]. In addition to the different access to bariatric surgery faced by regional disparities, there is unequal access between patients in the public system and those who have health insurance. Data from the Brazilian Society of Bariatric and Metabolic Surgery ratify this information, since in 2017, the private sector performed 105.642 bariatric operations while the single health system performed 10.089[25].

Given this, it is noted that the data obtained correspond mostly to those found in the literature, reinforcing this study's relevance. As for the divergent data, one factor that may explain this occurrence is the length of postoperative follow-up of the patients and the influence of qualitative variables, such as the experience and technical skill of the surgical team.

Therefore, one of the limiting factors of this study was the evaluation of the impact of access to public health services in the perioperative period and socioeconomic aspects, considering that it was performed in a private hospital. Notwithstanding, the small sample size, limited to 74 patients, and the follow-up time, which was 6 months, are worth mentioning.

CONCLUSION

The two surgical techniques proved effective in delivering the best results for patients, with the group undergoing bypass showing statistically significant weight loss from 1 month after the surgical procedure. In addition, there was no statistically significant difference between the two techniques regarding sociodemographic data and adverse effects in the postoperative period. However, given the global scenario pointing to an increasing number of obese people, more studies are needed to elucidate more questions related to this problem.

AUTHORS' CONTRIBUTIONS

LLFL: Conceptualization, Data curation, Formal Analysis, Validation. **KCC:** Conceptualization, Validation, Writing – original draft. **TTF:** Conceptualization, Validation, Writing – original draft. **IMT:** Conceptualization, Validation, Writing – original draft. **CMBO:** Writing – review & editing. **ECRM:** Writing – review & editing. **PCL:** Writing – review & editing.

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ORIGINAL ARTICLE

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Effect of a combination of gliptin and metformin on serum vitamin B12, folic acid, and ferritin levels

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SUMMARY

OBJECTIVE: The primary objective of this study was to explore the impact of metformin and metformin/gliptin combination therapy on the serum concentrations of vitamin B12, ferritin, and folic acid in individuals diagnosed with type 2 diabetes.

METHODS: This study included 118 patients, classified into two groups: 59 patients using only metformin and 59 patients using a combination of metformin/gliptin. Among the latter group, 35 patients used vildagliptin/metformin, and 24 used sitagliptin/metformin. The study recorded the demographic data such as the age and gender of the patients, as well as their initial and 1-year follow-up blood parameters.

RESULTS: Folic acid decreased significantly in the metformin group but not in the metformin/gliptin group. Vitamin B12 and ferritin decreased significantly in both groups. The decrease in vitamin B12 and ferritin was not significantly different between the two groups. The decrease in fasting plasma glucose was more significant in the metformin/gliptin group than in the metformin group.

CONCLUSION: After 1 year, both groups taking metformin and metformin/gliptin showed low serum ferritin and vitamin B12 levels. Therefore, vitamin B12 levels in patients using these drugs should be closely monitored. Ferritin levels can be used to indicate whether glycemic control has been achieved.

KEYWORDS: Diabetes mellitus. Metformin. Folic acid. Gliptin. Ferritin. Vitamin B12.

INTRODUCTION

Metformin is commonly the first choice in monotherapy if there is no contraindication in cases where hyperglycemia cannot be controlled despite lifestyle changes, which is the first step[1].

Intestinal absorption of vitamin B12 is reduced in approximately 30% of patients taking metformin. According to one view, the reason for this decrease is the antagonism of the calcium-dependent channel of vitamin B12 in the ileum. This situation is likely to improve with vitamin B12 and calcium supplementation[2]. This decrease in vitamin B12 absorption begins 4 months after metformin is started[3]. Since vitamin B12 can be stored in the liver, the clinical manifestation of vitamin B12 deficiency may take 3–10 years, but it may cause megaloblastic anemia beforehand[4].

Gliptins function by inhibiting the DPP-4 enzyme. It is OADs that increase the effect of endogenous incretins by this mechanism. Vildagliptin, saxagliptin, sitagliptin, linagliptin, and alogliptin are in the dipeptidyl peptidase-4 inhibitors (DPP4-I) group. Drugs in this group have a low risk of hypoglycemia, a small weight loss effect, and are well tolerated. It is more expensive than sulfonylureas and metformin and is not recommended for use in patients with a history of liver failure, heart failure, or pancreatitis[5].

Vitamin B12

The most common side effect of metformin is gastrointestinal intolerance, such as diarrhea, nausea, flatulence, and indigestion[6]. Vitamin B12 is essential for many systems, such as the nervous and hematopoietic systems. Intestinal B12 absorption is reduced in approximately 30% of patients taking metformin. Serum vitamin B12 levels decrease in 10% of patients. This decrease in vitamin B12 absorption begins 4 months after starting metformin[3].

Folic acid

Inadequate dietary intake, pregnancy, chronic hemolytic anemia, increased folic acid requirements of the body due to hemodialysis, intestinal malabsorption, antibiotics such as methotrexate and trimethoprim, and antiepileptic drugs such as phenytoin, carbamazepine, and valproate may cause folic acid deficiency. There is no generally accepted judgment that metformin can cause folic acid deficiency[7].

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Ferritin

Ferritin is a positive acute-phase reactant and, along with transferrin and its receptor, is a member of a protein family that modulates cellular defenses against inflammation. Its serum levels increase oxidative stress and inflammation[8,9].

Publications have shown a relationship between serum ferritin levels, excessive iron absorption, and type 2 diabetes, but this relationship has not yet been proven[10]. Although diets with low iron content are recommended, publications show that ferritin levels are high in patients whose glycemic control cannot be achieved[11,12].

Aim

This study examines the effects of serum levels of vitamin B12, ferritin, and folic acid at baseline and after 1 year in patients with type 2 diabetes using a combination of metformin and metformin/gliptin.

METHODS

A total of 2,459 patients who applied to our center were examined. According to the ADA guidelines, these patients were diagnosed with type 2 DM, had regular follow-ups, and were using metformin alone or in combination with gliptin. As a result of a retrospective file review, patients who were newly diagnosed with type 2 DM, had complete vitamin B12, folic acid, ferritin, and HbA1c values before and 1 year after medication prescription, had not been prescribed any medication, including proton pump inhibitor for 1 year, did not receive insulin or other oral antidiabetic treatment, did not use alcohol, did not have megaloblastic anemia, did not undergo stomach surgery, did not have gastrointestinal system diseases such as celiac, Crohn's disease, *Helicobacter pylori*, chronic pancreatitis, malabsorption, and did not have any chronic systemic disease other than a new diagnosis of type 2 DM were included in the study.

A total of 118 patients were included in the study, with 59 using only metformin and 59 using metformin/gliptin. Of those who used metformin/gliptin, 35 used metformin/vildagliptin, and 24 used metformin/sitagliptin. Demographics such as patient age and sex, baseline, and 1-year follow-up blood parameters were recorded.

Statistical analysis method

A descriptive analysis was conducted to elucidate the fundamental characteristics of the populations encompassed within our study. In this cross-sectional retrospective study, distribution tests, namely, normality tests, skewness kurtosis assessments, and histogram plots, were employed to scrutinize the distribution of the collected data. Nonparametric tests were used for data sets exhibiting abnormal distributions. Specifically, the Mann-Whitney U test was employed to examine independent numeric variables, while the chi-square test was used for categorical variables. Numeric variables were reported as the median value accompanied by the interquartile range, whereas categorical variables were presented as numerical values and percentages. To compare medians between two related groups, the Wilcoxon's test was employed, and cases with a significance level of $p<0.05$ were deemed statistically significant. All statistical analyses were conducted using IBM SPSS 23. The present study received ethical approval from the Ethics Committee of Sakarya University School of Medicine on October 12, 2020, with the decision number 71522473/050.01.04/553. This approval confirmed that the study adhered to the established ethical guidelines.

RESULTS

Our study population consisted of 118 patients, including 59 patients who were given metformin as the initial treatment and 59 patients who were given metformin/gliptin as the initial treatment for type 2 DM. Baseline laboratory parameters were compared with laboratory values 1 year later.

The study included 118 patients in total, with 59 patients receiving metformin in their initial treatment and 59 receiving metformin/gliptin. The median age [interquartile range] of all patients was 55 [14] years, with the metformin group having a median age of 51 [17] years and the metformin/gliptin group having a median age of 58 [11] years. The higher age in the metformin/gliptin group was statistically significant (p=0.022). Of the patients in the metformin group, 39 (66.1%) were females, while the number of females in the metformin/gliptin group was 20 (33.9%) (p<0.001). When comparing the baseline HbA1c percentages of the two groups, the metformin group had an HbA1c percentage of 6.5% [1.3], while the metformin/gliptin group had an HbA1c percentage of 8.6% [2.4] (p<0.001).

When comparing initial vitamin B12, ferritin, and folic acid levels in patients receiving metformin alone versus the metformin/gliptin combination, vitamin B12 levels did not significantly differ between the two groups (p=0.122). However, the metformin/gliptin combination group had significantly higher ferritin levels (83 [121.4] µg/L) compared to the metformin group (46 [83] µg/L) (p=0.020). Additionally, folic acid levels were significantly higher in the metformin group (8.9 [4.8]

μg/L) compared to the metformin/gliptin combination group (6.9 [3.2] μg/L) (p<0.001) (Table 1).

The group that initiated metformin exhibited a noteworthy reduction in vitamin B12 levels from 275 [178] to 232 [151] ng/L (p<0.001), while the group that began the metformin/gliptin combination also experienced a substantial decrease from 309 [218] to 260 [160] ng/L (p<0.001). Furthermore, the group that commenced metformin demonstrated a significant reduction in ferritin levels from 46 [83] to 38 [60.3] μg/L (p<0.001), and the group that started metformin/gliptin combination also had a substantial decrease from 83 [121] to 66.2 [90] μg/L (p=0.002) (Table 2).

We examined the values that showed a statistically significant decrease after 1 year in the metformin and metformin/gliptin groups. Upon comparing the variances between baseline and 1-year measurements in both groups, no statistically significant differences were observed between the two groups regarding the reduction in vitamin B12 (p=0.346) and ferritin levels (p=0.379). While metformin decreased the fasting plasma glucose (FPG) by 8 [23] mg/dL in 1

Table 1. Comparison of baseline values of patients receiving metformin and metformin/gliptin combination.

Variables	Metformin, n=59	Metformin/gliptin, n=59	Total, n=118	p-value
Age, years	52 [17]	58 [11]	55 [14]	**0.022**
Gender				**0.001***
Female, n (%)	39 (66.1%)	20 (33.9%)	59 (50%)	
Male, n (%)	20 (33.9%)	39 (66.1%)	59 (50%)	
Fasting plasma glucose (FPG), mg/dL	131 [27]	183 [84]	146 [80]	**<0.001**
eGFR	99 [21]	100.7 [14.6]	100 [19]	0.651
Triglyceride, mg/dL	152 [127.5]	140 [97.5]	144 [109]	0.481
Total cholesterol, mg/dL	215 [37]	208.5 [53]	212.5 [43]	0.380
HDL, mg/dL	48 [14]	41.5 [12]	43.5 [15]	**0.005**
LDL, mg/dL	142 [44]	133.5 [36]	139.5 [38.5]	0.318
HbA1c, %	6.5 [1.3]	8.6 [2.4]	7.4 [2.8]	**0.001**
Vitamin B12, ng/L	275 [178]	309 [218]	302 [197]	0.122
Ferritin, μg/L	46 [83]	83 [121.4]	60 [94]	**0.020**
Folic acid, μg/L	8.9 [4.8]	6.9 [3.2]	7.95 [3.2]	**0.001**

Median [interquartile range], Mann-Whitney U test was used to compare numerical parameters, and chi-square test (*) was used to compare categorical parameters. Bold values indicate statistical significance at the p<0.05 level.

Table 2. Comparison of changes values after 1 year in patients who received metformin and metformin/gliptin combination.

Variables	Metformin		p-value	Metformin/gliptin		p-value
	n=59	n=59		n=59	n=59	
	Beginning	1 year later		Beginning	1 year later	
Fasting plasma glucose (FPG), mg/dL	131 [27]	116 [30]	**0.001**	183 [84]	143 [57]	**<0.001**
eGFR	99 [21]	104 [24]	0.737	100.7 [16.1]	102.3 [11.05]	0.208
Triglyceride, mg/dL	152 [132.75]	160.5 [118.5]	0.467	140 [98.25]	144 [119]	0.486
Total cholesterol, mg/dL	215 [37.5]	205 [52]	0.564	208.5 [55]	210.5 [76]	0.866
HDL, mg/dL	48 [14.175]	46.5 [17.75]	0.658	41.5 [12.25]	42 [12]	0.611
LDL, mg/dL	142 [44.75]	136 [47.5]	0.362	133.5 [36.75]	138 [61]	0.721
HbA1c, %	6.5 [1.3]	6.4 [1.3]	0.112	8.6 [2.4]	7.3 [1.2]	**0.001**
Vitamin B12, ng/L	275 [178]	232 [151]	**0.001**	309 [218]	260 [160]	**0.001**
Ferritin, μg/L	46 [83]	38 [60.3]	**0.001**	83 [121.4]	66.2 [99]	**0.002**
Folic acid, μg/L	8.9 [4.8]	8.1 [5.1]	**0.001**	6.9 [3.2]	6.4 [3.4]	0.346

Median [interquartile range], Wilcoxon's test was used to compare numerical parameters. Bold values indicate statistical significance at the p<0.05 level.

year, the metformin/gliptin combination decreased it by 37 [76] mg/dL (p=0.001).

DISCUSSION

Wulffelee et al. tested the effect of metformin on serum homocysteine, vitamin B12, and folic acid levels in a placebo-controlled, randomized study in 12 patients who were started on placebo and 25 metformin in a short period of 16 weeks. After 16 weeks, she found a 4% increase in homocysteine, a 7% decrease in folic acid, and a 14% decrease in vitamin B12, which were statistically significant compared to the placebo. The findings of this study indicate that the administration of metformin to individuals with type 2 DM leads to a reduction in folic acid and vitamin B12 levels, resulting in a slight elevation of homocysteine[13].

Indeed, the effects of metformin are not limited to plasma glucose alone. In an androgenized rat model, metformin demonstrates a significant impact on ovarian follicle dynamics by reducing the proliferation of theca cells and suppressing CYP-17 expression[14]. On the contrary, the combination of oral contraceptives and metformin did not improve insulin resistance in women with polycystic ovary syndrome[15]. The combination of metformin and lifestyle changes has the potential to boost the number of menstrual cycles in individuals with polycystic ovary syndrome[16]. Metformin demonstrated positive effects on glucose levels and the homeostasis model assessment-insulin resistance index in female rats androgenized with testosterone. Additionally, it resulted in a partial reversion of ovarian and uterine morphology in these rats[17].

In a prospective study investigating the tolerability of teneligliptin, a DPP4-I, and its effect on peripheral neuropathy in patients with type 2 DM, 20 mg of teneligliptin was given once a day for 3 months. In addition to the study-specific parameters, the vitamin B12 value at baseline and in the third month was also checked to exclude neuropathy due to vitamin B12 deficiency. The initial vitamin B12 value was 594 units/L; 3 months later, it was found to be 457 units/L (p=0.33). No statistically significant difference was found between the vitamin B12 values initially and after 3 months[18]. When examining the effect of metformin on vitamin B12 in 159 patients, they reported no statistically significant difference in the subgroup analysis when metformin was used with DPP4-I[19]. In our literature review for DPP4-I, studies investigating the effects of DPP4-I drugs alone or in combination on serum vitamin B12, ferritin, and folic acid levels were relatively few compared to metformin. We could not find any study on DPP4-I and its combinations of folic acid, ferritin, and vitamin B12 from the time of diagnosis without diabetes.

When we compared the variances between baseline and first-year measurements in both groups, no significant association was found between the groups in which metformin or metformin/gliptin was started in reducing vitamin B12 and ferritin (p=0.346 for vitamin B12; p=0.379 for ferritin).

In a study conducted in 329 type 2 DM patients versus 269 healthy control groups, Canturk et al. found that serum ferritin increased in poorly controlled DM as long as glycemic control was not provided[20]. Chandrashekhar et al. investigated the effect of glycemic control on serum ferritin value in 100 patients, 50 of whom had an HbA1c of 6.5% and below and 50 well-controlled, versus 50 patients with poorly controlled serum Hba1c of 8% and above. While the mean of ferritin in the uncontrolled group was 392 µg/L, it was 91 µg/L in the group with glycemia under control. It was statistically significant that ferritin was high in the poorly controlled group (p<0.001). No statistically significant correlation was found between ferritin and age in either group[21]. Ferritin was 46 [83] µg/L in the metformin-initiated group and 83 [121.4] µg/L in the combination group, and the ferritin value was statistically higher in the metformin/gliptin combination group (p=0.020). This difference may be because women were more common in the metformin group between the two groups, as well as because of statistically higher levels of HbA1c and FPG in the metformin/gliptin group. In both cases, the proportional data of our study on ferritin are compatible with the literature.

CONCLUSION

After 1 year, both metformin and metformin/gliptin groups had low serum ferritin and vitamin B12. Therefore, vitamin B12 levels should be carefully monitored in patients taking these medications. Ferritin levels can be used to indicate whether glycemic control has been achieved. Further randomized, controlled studies are needed for more reliable results.

AUTHORS' CONTRIBUTIONS

FTG: Formal Analysis, Funding acquisition, Investigation, Methodology, Project administration, Resources, Software, Supervision, Validation, Visualization, Writing – original draft, Writing – review & editing. **AN:** Formal Analysis, Funding acquisition, Investigation, Methodology, Project administration, Software, Supervision, Validation, Writing – original draft, Writing – review & editing. **ACG:** Resources, Software, Supervision, Validation, Visualization, Writing – original draft. **TK:** Methodology, Supervision, Supervision.

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ORIGINAL ARTICLE

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Effectiveness of platelet-rich plasma on post-COVID chronic olfactory dysfunction

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SUMMARY

OBJECTIVE: The aim of this study was to investigate the efficacy of platelet-rich plasma injection on the olfactory cleft of patients with post-COVID olfactory dysfunction lasting over 1 year, who were unresponsive to common treatments.

METHODS: Patients over 18 years of age with post-COVID olfactory dysfunction over 1 year whose complaints did not improve with intranasal steroids and D-panthenol/vitamin A combination nasal sprays with olfactory rehabilitation training for 1 month were prospectively collected and randomized into two groups: intranasal platelet-rich plasma group and control group. At the end of 1 month, Connecticut Chemosensory Clinical Research Center olfaction test scores of smell detection threshold and smell identification test were compared accordingly.

RESULTS: A total of 25 patients were randomized into platelet-rich plasma (n=12) and control (n=13) groups. In the platelet-rich plasma group, the mean smell detection threshold score increased from 5.63 (SD 0.68) to 6.46 (SD 0.45), and the mean smell identification test score increased from 11.42 (SD 1.17) to 15.17 (SD 0.39). In the control group, the mean smell detection threshold score changed from 5.69 (SD 0.66) to 5.77 (SD 0.70), and the mean smell identification test score changed from 11.20 (SD 1.12) to 11.85 (SD 1.57). Post-hoc analysis revealed that similar mean smell detection threshold (mean difference 0.07; p=0.994) and smell identification test (mean difference -0.50; p=0.703) scores were transformed into a significant difference between groups (smell detection threshold mean difference 0.69; p=0.037; smell identification test mean difference 3.32; p<0.001).

CONCLUSION: At the end of the first month, there was a significant improvement in olfactory threshold values in the platelet-rich plasma group compared to the control group. No side effect or adverse event related to platelet-rich plasma injection was observed.

KEYWORDS: COVID-19. Smell dysfunction. Platelet-rich plasma.

INTRODUCTION

As the number of cases of coronavirus disease 2019 (COVID-19) increased worldwide, patients admitting clinics with olfactory dysfunction (OD) had also increased. Up to 85% of patients with COVID-19 present with OD, which makes it one of the major symptoms[1,2]. It has been reported that infection and inflammation caused by viral infections lead to chronic olfactory dysfunction (COD) by affecting the olfactory neuroepithelium. Similarly, it is postulated that persistence of the virus in the olfactory region causing an inflammation might be the reason of prolonged OD in COVID-19[3].

In this study, it is reported that even though during the course of COVID-19 infection, distorted olfactory or gustatory function improved in most cases, symptoms related to smell and taste are still the most common complaints of patients after 1 month of PCR positivity[4]. The prevalence of patient informed persistent OD 1 year after COVID-19 was found as high as 70%[5-8].

Recently, there is no efficient treatment for COD patients. Olfactory training (OT) and some supplements are recommended by some physicians but the effects are still unknown[9,10].

Platelet-rich plasma (PRP) has been used in many different areas of the body due to its regenerative effects. Vocal cord scar treatment, neck fistulas, and tympanic membrane perforation repair are some of the PRP usage areas in otolaryngology[10].

The Connecticut Chemosensory Clinical Research Center olfaction (CCCRC) test is a simple and cost-effective tool for olfactory testing. It consists of smell detection threshold (STC) and smell identification test (SIC)[11]. It is validated and can be easily applied in-office settings.

The aim of our study was to investigate the effectiveness and clinical application of intranasal PRP injection in patients with post-COVID COD, lasting more than 1 year.

METHODS

Patients above the age of 18 years with OD complaints for 1 year or more after a COVID-19 infection confirmed with PCR positivity in the otolaryngology outpatient clinic, from April 2022 to November 2022, were prospectively included in the

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study. All patients were treated with nasal steroids and nasal D-panthenol/vitamin A combination sprays for 1 month, after admission to our clinic. Additionally, all patients were given olfactory rehabilitation training and asked to continue rehabilitation during this 1-month period. Patients unresponsive to the aforementioned treatment were then randomized into two groups: PRP and control.

Turkish validated version of the CCCRC olfaction test was administered to all patients as given in detail in the study by Veyseller et al.[12]. A baseline STC and SIC scores were obtained.

Patients with severe nasal septal deviation, allergic rhinitis, nasal polyposis, a known history of sinonasal surgery, or neurological pathology were excluded from the study.

PRP was prepared with the blood sample taken from patients and centrifuged and a single dose of 1 mL was injected into the olfactory cleft region. Patients in the control group were followed without any additional treatment. At the end of 1 month, the tests were applied again.

Continuous variables were summarized with either their means and standard deviations (SD) or medians and interquartile ranges (IQR) according to their distribution patterns tested with the Shapiro-Wilk test. Categorical variables were reported with counts and percentages. To compare the effect of time and treatment on STC and SIC by controlling for age and sex, a mixed-repeated-measures ANOVA modeling was used. Friedman test revealed similar results, which assured that the mixed-repeated-measures ANOVA was robust to violation of normality for this dataset. We checked the homogeneity of variances using Levene's test, detected outliers using a box plot, and checked sphericity using Mauchly's test. All p-value in the model were corrected as described by Greenhouse-Geisser. The effect of treatment options on STC and SIC values in time was tested with the mixed-ANOVA model, and interaction was quantified using partial eta-squared. Post-hoc comparisons were reported with p-values corrected as defined by Tukey.

The accepted maximum type I error in this study was 5%. The study protocol was approved by the ethics committee of our institution (prot. No: 2021/514/205/15). The written informed consent was obtained from all patients. Data analysis was conducted using the Jamovi Project Version 2.3.21 (2023) software (retrieved from https://www.jamovi.org).

RESULTS

A total of 32 patients were assessed for eligibility. After exclusions, 25 patients were included in the study. CCCRC test revealed a median STC score of 6 (IQR 5–6) and SIC score of 11 (IQR 10–12) at admission. After 1-month routine treatment, 5 patients were lost at follow-up, 2 patients were excluded, and the remaining 25 patients with persistent OD were randomized into the PRP (n=12) and control (n=13) groups (Figure 1).

In the PRP group 6/12 (50%) patients and in the control group 7/13 (53.8%) patients were females (p=0.848; chi-square test). The mean ages were 31.8 (SD 6.9) years and 33.5 (SD 11.1) years, respectively (p=0.653; t-test).

The change of STC and SIC scores in time was tested by the repeated-measures ANOVA, and the interaction effect of the treatment options was tested with the mixed-ANOVA model. In the PRP group, the mean STC score increased from 5.63 (SD 0.68) to 6.46 (SD 0.45), and the mean SIC score increased from 11.42 (SD 1.17) to 15.17 (SD 0.39). The simple main effect of time on STC and SIC scores in the PRP group was statistically significant (both Greenhouse-Geisser corrected p<0.001; partial eta-squared: STC 0.73 and SIC 0.94). In the control group, the mean STC score also changed from 5.69 (SD 0.66) to 5.77 (SD 0.70), and the mean SIC score changed from 11.20 (SD 1.12) to 11.85 (SD 1.57). The simple main effect of time on STC score in the control group was not statistically significant (Greenhouse-Geisser corrected p= 0.165 and partial eta-squared=0.15). The simple main effect

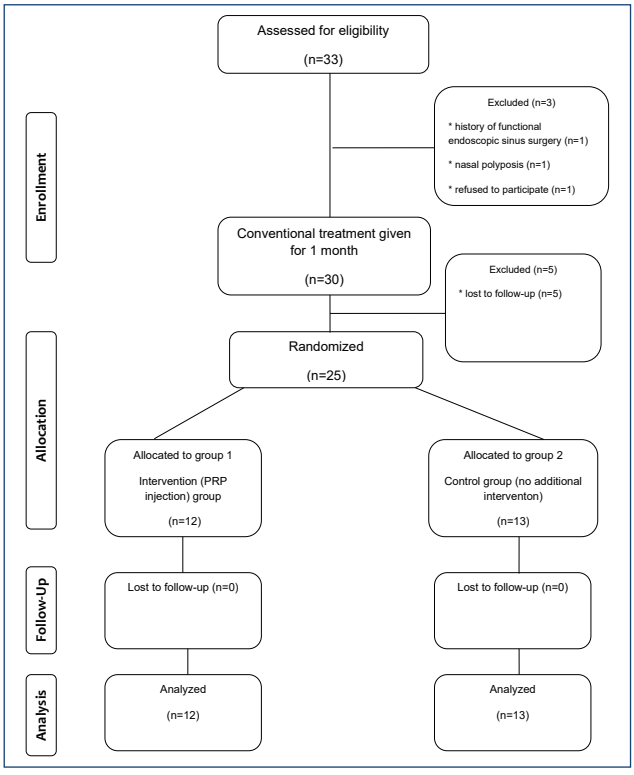

Figure 1. CONSORT flow diagram.

of time on SIC score in the control group was not significant (Greenhouse-Geisser corrected p=0.089 and partial eta-squared=0.69) (Table 1). The interaction effect of treatment options (groups) on the change of both STC and SIC scores in time were statistically significant, i.e., a significant difference was found between treatment groups (STC: Greenhouse-Geisser corrected p<0.001; partial eta-squared=0.50; and SIC: Greenhouse-Geisser corrected p<0.001; partial eta-squared=0.77). Post-hoc analysis revealed that similar mean STC (mean difference 0.07; p=0.994) and SIC (mean difference -0.50; p=0.703) scores were transformed into a significant difference between groups (STC: mean difference 0.69; p=0.037; and SIC: mean difference 3.32; p<0.001; Figure 2).

No adverse effects were reported throughout the study.

DISCUSSION

OD is reported to be the most common clinical symptom of COVID-19 and observed in 30–86% of the infected population. Its pathological mechanism is related to a potential viral invasion of the olfactory bulb and central nervous system through the nasal neuroepithelium[13-15]. Recent studies have shown the efficiency of oral or topical corticosteroids on OD induced by factors other than sinonasal diseases[16,17]. In our clinical practice, we commonly use nasal corticosteroids as the primary treatment for patients admitted to our clinic with OD. Additionally, OT is shown to have positive effects on OD caused by viral infections and is recommended in the treatment of post-COVID OD[9,18,19]. We recommend OT in OD cases, but in our common practice, we have observed that it does not seem practical for our patients since it has to be applied for weeks[20]. Therefore, we believe that there is a need for an alternative treatment method that is more feasible and easily applied.

In our study, all COD patients were given nasal steroids and nasal D-panthenol/vitamin A combination sprays for 1 month, concomitant with OT. The OD did not resolve in any of them, showing the ineffectiveness of steroid treatment in post-COVID COD. When we performed the CCCRC olfaction test after 1 month of treatment, we observed no change in the mean values of SIC and STC.

PRP is an autologous blood product with anti-inflammatory and pro-regenerative features. It has been shown that PRP contains high levels of EGF and PDGF, providing neural and epithelial regeneration. Since it is autologous, risk of rejection or any adverse effects is extremely rare[10].

According to its possible pathophysiology, we aimed to inject PRP directly into the olfactory cleft of the randomized

Table 1. Smell detection threshold measurements and comparison.

	PRP group, n=12 Mean (SD)			Control group, n=13 Mean (SD)		
	Baseline	1st month	Mean difference, p	Baseline	1st month	Mean difference, p
STC	5.63 (0.68)	6.46 (0.45)	0.83 <0.001	5.69 (0.66)	5.77 (0.70)	0.08 0.165
SIC	11.42 (1.17)	15.17 (0.39)	3.75 <0.001	11.20 (1.12)	11.85 (1.57)	0.65 0.089

SD: standard deviation; STC: smell threshold score; SIC: smell identification score. p-value and mean differences were calculated using the mixed-repeated-measures ANOVA.

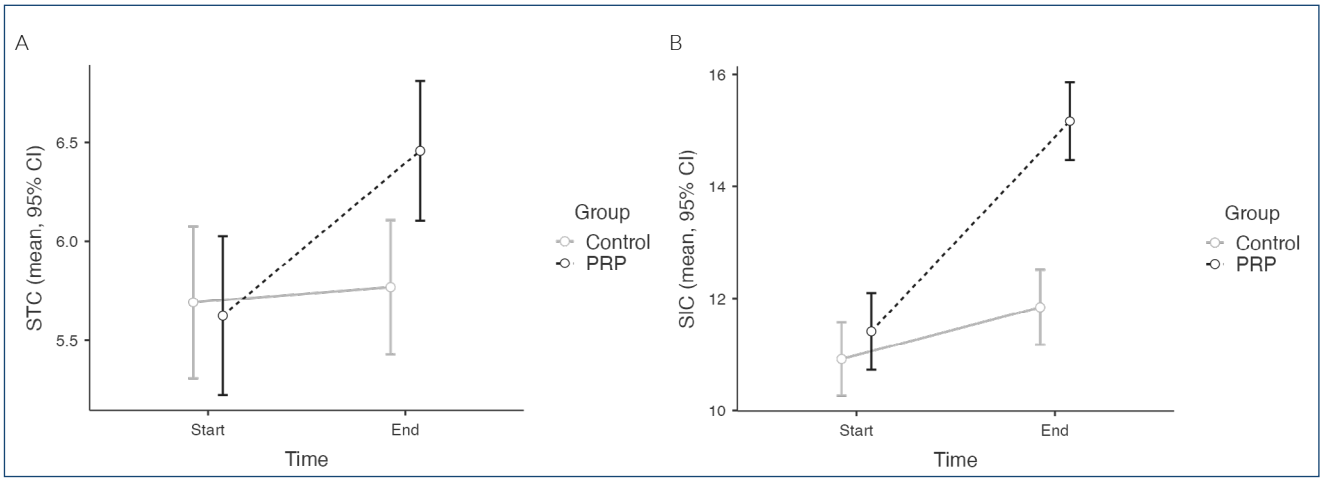

Figure 2. The change of (A) mean smell detection threshold and (B) smell identification test values with 95%CIs in both groups.

post-COVID COD patients to induce neuroepithelial regeneration. Significant improvement was detected on the smell threshold values and smell identification basal values in our PRP group 1 month after injection, whereas no significant improvement was found in the control group. We had similar findings about the efficacy of PRP in post-COVID COD patients with recent studies[10,13,21]. Steffens et al. and Lechien et al. proved the efficacy of PRP 2 months after injection[10,21]. Similarly, Yan et al. reported the continuous effects of PRP 3 months after injection[22]. When compared to aforementioned studies, the duration of the PRP effect could not be reported in our study because the patients did not have a longer follow-up time after PRP injection.

There was no procedure-induced morbidity or adverse event in our group, confirming the feasibility and safety of PRP injection in the treatment for post-COVID COD.

There are some limitations in our study. First, we had small number of patients, and second, the patients were followed up only for 1 month. However, it is thought that the duration of action of PRP and the need for repeated injections can only be understood with larger patient series and longer follow-ups.

CONCLUSION

Our study concludes that injection of PRP directly into the olfactory cleft of patients with post-COVID COD is an effective and easily applied procedure. We believe that the therapeutic effect of PRP injection may depend on timing of OD or effectiveness may change with repetitive doses. Future randomized controlled trials are needed to verify these results and investigate the long-standing effect of this novel approach.

INFORMED CONSENT

Informed written consents were taken from every patient included in the study. The ethical approval was taken from local ethical committee Kartal Dr. Lutfi Kirdar Training and Research Hospital (prot. No: 2021/514/205/15).

AUTHORS' CONTRIBUTIONS

MDE: Conceptualization, Data curation, Investigation, Methodology, Visualization, Writing – original draft. **ZEC:** Data curation, Formal Analysis, Methodology, Visualization, Writing – review & editing.

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ORIGINAL ARTICLE

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Correlation between levels of perceived stress and depressive symptoms in the functional disability of patients with fibromyalgia

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SUMMARY

OBJECTIVE: The aim of this study was to evaluate the factors that are most correlated with the levels of functional disability in patients with fibromyalgia.
METHODS: This is a cross-sectional descriptive study in which 42 patients diagnosed with fibromyalgia according to the criteria of the American College of Rheumatology reported their status using the following questionnaires: the Beck Depression Inventory, the Perceived Stress Scale 14, the Revised Fibromyalgia Impact Questionnaire, the Visual Analog Pain Scale, and the Health Assessment Questionnaire.
RESULTS: Moderate to severe levels of depression (Beck Depression Inventory: 22.35±10.39), moderate to severe functional disability (Health Assessment Questionnaire: 1.28±0.58), and high levels of stress (Perceived Stress Scale 14: 31.59±10.02) were found. The correlation adjusted by multiple regression as a function of the Health Assessment Questionnaire indicated a negligible to weak positive correlation with perceived stress (r=0.11), while a moderately strong positive correlation was observed with the Visual Analog Pain Scale (r=0.55). Regarding physical exercise, one of the pillars of the treatment, a moderate negative correlation was found with the Health Assessment Questionnaire (r=-0.4).
CONCLUSION: The pain levels were moderately influenced by depression severity. The factors most linked to functional disability are due to the pain levels but not to the perception of stress.
KEYWORDS: Fibromyalgia. Stress, psychological. Chronic pain. Depression. Sickness impact profile.

INTRODUCTION

Fibromyalgia is a syndrome characterized by widespread chronic pain, fatigue, sleep disturbances, and functional symptoms[1]. It is associated with other comorbidities such as mood disorders and rheumatic diseases[2,3]. The multiple symptoms and pathologies often associated with fibromyalgia make its diagnosis difficult, promoting underdiagnosis and undertreatment[4]. In Brazil, the prevalence varies between 0.2 and 4.7%, with a higher incidence in women, especially between 45 and 64 years of age[5].

The pathophysiology of fibromyalgia is still not well established. However, the most accepted hypothesis is due to an abnormality in the transmission of painful stimuli, amplifying the pain sensation due to an imbalance in inhibiting afferent and efferent pathways by neurotransmitters and neuropeptides[6-8]. Such dysregulation could be due to psychological stress and genetics, among others[9].

While in 1990, the American College of Rheumatology (ACR) considered generalized pain and the presence of 11 out of 18 tender points as a diagnostic criterion, in 2010, there was a new consensus that gave more prominence to other somatic symptoms and cognitive problems through the Polysymptomatic Distress Scale score (PSD)[9,10].

When assessing the condition of patients with fibromyalgia, the Revised Fibromyalgia Impact Questionnaire (FIQR) is often used in clinical studies and involves questions related to functional capacity, global impact, and physical and psychological symptoms in the last 7 days[11]. Another point of analysis is measuring the level of psychological stress, which can be performed using the Perceived Stress Scale 14 (PSS-14), which

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quantifies the perception of stress in the face of everyday events in the last 4 weeks[12].

Concerning the emotional nature of fibromyalgia, the Beck Depression Inventory (BDI) is universally used to assess the levels of depression in this group of patients[13]. In addition, another tool with high applicability in assessing patients with the disease is the Health Assessment Questionnaire (HAQ), which determines the functional capacity of various activities performed in the last week[14,15].

Given the above, this study sought to measure the levels of perceived stress, pain, and depression, in addition to correlating them with each other, to identify the factors most related to functional disability.

METHODS

This is a cross-sectional descriptive study, approved by the Research Ethics Committee, involving human beings of the State University of Ponta Grossa, under protocol CAAE 28752514.0.0000.0105, in which patients being followed up at the rheumatology outpatient clinics of the Hospital Universitário Regional dos Campos Gerais (HURCG) and in the private practice of rheumatology, Dr. Carolyn Maria de Geus Wenceslau, who met the modified ACR 2010 Criteria for the diagnosis of fibromyalgia[16], reported their status using five questionnaires, namely, FIQR, HAQ, BDI, PSS-14, and a socioeconomic questionnaire. The Widespread Pain Index (WPI), a component of the modified 2010 ACR Criteria, was also analyzed. Individuals with comorbidities that could explain the pain were excluded from the study. The patients answered the questionnaires during their routine appointments, after completing the free and informed consent form.

The impact of fibromyalgia on the quality of life in patients with fibromyalgia was assessed by the FIQR, which is composed of 21 items that cover functionality, impact of the disease, and psychological and physical symptoms, including the level of pain measured by the Visual Analog Scale (VAS)[11,17].

The level of psychological stress was analyzed using PSS-14, which contains 14 items that quantify the perception of stress in the face of everyday events in the last 4 weeks[12]. The depressive symptoms were analyzed using the BDI, which is composed of 21 questions. Based on the scores, BDI classifies symptoms into four categories: absence (<10); mild to moderate (10–18); moderate to severe (19–29), and severe (30–63)[13].

The level of functional disability was measured using the HAQ questionnaire, which contains 20 questions that determine functional capacity in various activities carried out in the last week[14]. The socioeconomic questionnaire collected demographic and clinical data such as age, gender, income, education, duration of the disease, and the presence of other comorbidities.

The verification of the presence of outliers with consequent exclusion was carried out. The sample was tested for distribution normality by the Shapiro-Wilk test. The correlation coefficient (r) was determined by Pearson's test. Multiple regression was performed to adjust the various variables with the determination index. Tests whose p-value was less than 5% (0.05) were considered statistically significant. Analyses were performed using the statistical program MedCalc 5.1 (Belgium).

RESULTS

A total of 48 patients were interviewed, of whom 5 were excluded due to the presence of comorbidities. Outliers analysis detected one patient, who was also excluded. Thus, data from 42 patients were evaluated.

There were 40 females (95%) and 2 males (5%), with a mean age of 50.25 (±9.41) years. It was observed that 79% were economically active, and there was a predominance of individuals with the completion of secondary education (24%). Regarding family income, 98% received less than six minimum wages.

The mean age at diagnosis was 45.61±9.67 years, with a disease progression time of 4.66±4.36 years (Table 1). It was found that most patients had moderate to severe depression, with a mean BDI score of 22.35±10.39.

The FIQR indicated an average of 64.12±19.05 with a VAS index of 7.69±2.42. The WPI revealed an average of 13.93±3.99, and the PSD average value was 22.59±5.11.

Table 1. Mean, standard deviation, and range of analyzed variables (n=42).

	Mean (SD)	Range
Age (years)	50.28 (±9.41)	20–70
Age at diagnosis (years)	45.61 (±9.67)	18–70
Disease duration (years)	4.66 (±4.36)	0–16
BDI (0–63)	22.35 (±10.39)	04–42
FIQR (0–100)	64.12 (±19.05)	13–96
HAQ (0–3)	1.28 (±0.58)	0.25–2.75
PSS-14 (0–56)	31.59 (±10.02)	06–47
VAS (0–10)	7.69 (±2.42)	02–10
PSD (0–31)	22.59 (±5.11)	10–30
WPI (0–19)	13.93 (±3.99)	05–19

SD: standard deviation; BDI: Beck Depression Inventory; FIQR: The Revised Fibromyalgia Impact Questionnaire; HAQ: Health Assessment Questionnaire; PSS-14: Perceived Stress Scale 14; VAS: Visual Analog Scale; PSD: Polysymptomatic Distress Scale; WPI: Widespread Pain Index.

As for the HAQ score, a mean of 1.28±0.58 was found, indicating a higher prevalence of individuals with moderate to severe functional disability. The PSS-14 showed a mean value of 31.59±10.02. Only 14 patients (33%) reported practicing regular physical exercise.

Analysis of the questionnaires in pairs (Table 2) indicated a powerful and statistically significant correlation between BDI and PSS-14 (r=0.75), HAQ and FIQR (r=0.75), and VAS and FIQR (r=0.75). We also observed a weak and significant correlation between the PSS-14 and the PSD (r=0.3), in addition to a weak correlation outside of significance between the PSS-14 and the HAQ (r=0.28).

The most used drug class was simple analgesics, with 31 (74%) individuals using it, followed by 28 (67%) using tricyclic antidepressants and 23 (55%) using SSRI (selective serotonin reuptake inhibitors). The most common combination was simple analgesics and tricyclic antidepressants, with 20 (48%) patients using it.

The correlation adjusted by multiple regression as a function of the HAQ (Table 3) indicated a negligible to weak positive correlation for the PSS-14 (r=0.11). At the same time, compared with the VAS, it showed a moderate to strong positive correlation (r=0.55). On the contrary, physical exercise showed a moderate negative correlation (r=-0.4). The coefficient of determination (R^2) calculation for the PSS-14 indicated a rate of 0.01. In contrast, the VAS had a considerable coefficient in the participation of disability with an R^2 of 0.30. The practice of physical exercise had been proved to be a protective factor for the levels of functional disability with an R^2 of 0.16.

DISCUSSION

Few studies correlated stress and depression with the functional impact in patients with fibromyalgia, thus defining their roles in symptomatology[18]. Gorenstein et al.[19] considered scores greater than 16 on the BDI as the threshold for depression. In this perspective, in the present sample, 69% of individuals were depressed, similar to the study by Homann et al.[20], which found around 75%.

The excessive daily consumption of simple analgesics and SSRIs found in this study corroborates the findings of Gormsen

Table 3. Coefficient of correlations between the multiple variables analyzed and the disability measured by the Health Assessment Questionnaire, adjusted by multiple regression (n=42).

	r	p
PSS-14	0.11	0.5
VAS	0.55	0.0002
Physical exercise	-0.4	0.001

PSS 14: Perceived Stress Scale 14; VAS: Visual Analog Scale.

Table 2. Analysis of the questionnaires in pairs (n=42).

	BDI	PSS-14	FIQR	HAQ	VAS	PSD
BDI	–					
PSS-14	r=0.75					
	p<0.0001	–				
	95%CI (0.58–0.86)					
FIQR	r=0.59	r=0.52				
	p<0.0001	p=0.0004	–			
	95%CI (0.35–0.76)	95%CI (0.26–0.71)				
HAQ	r=0.52	r=0.28	r=0.75			
	p=0.0004	p=0.07	p<0.0001	–		
	95%CI (0.26–0.71)	95%CI (-0.02–0.59)	95%CI (0.57–0.86)			
VAS	r=0.38	r=0.35	r=0.75	r=0.58		
	p=0.01	p=0.02	p<0.0001	p=0.0001	–	
	95%CI (0.09–0.61)	95%CI (0.04–0.59)	95%CI (0.58–0.86)	95%CI (0.34–0.75)		
PSD	r=0.49	r=0.3	r=0.6	r=0.55	r=0.5	
	p=0.0009	p=0.04	p<0.0001	p=0.0001	p=0.0009	–
	95%CI (0.22–0.69)	95%CI (0.001–0.55)	95%CI (0.37–0.77)	95%CI (0.3–0.74)	95%CI (0.22–0.69)	

BDI: Beck Depression Inventory; PSS-14: Perceived Stress Scale 14; FIQR: The Revised Fibromyalgia Impact Questionnaire; HAQ: Health Assessment Questionnaire; VAS: Visual Analog Scale; PSD: Polysymptomatic Distress Scale; CI: Confidence interval.

et al.[18], in which it was demonstrated that the high prevalence of depression intensifies fibromyalgia pain. Homann et al.[21] also stated that pain is a debilitating characteristic and can be considered one of the leading causes of functional incapacity. This was corroborated by the strong positive correlation between FIQR and VAS and the moderately high correlation between HAQ and VAS adjusted by multiple regression found in the present study.

Homann et al.[20] identified a greater perception of stress in patients with fibromyalgia compared to healthy individuals. The present study showed a high level of perception of stress and had as a limitation the non-pairing with a control sample.

González-Ramirez et al.[22] related stress to the pathophysiology of fibromyalgia and the severity of symptoms such as pain. In contrast, in this study, the result of the correlation between pain and stress was positive and weakly moderate, indicating a low association between them. Furthermore, the concept of catastrophizing, more present in depressive patients and defined as a tendency to perceive pain as something unbearable[23], was something less observed considering the weakly moderate correlation between BDI and pain levels.

Busch et al.[24], in a systematic review, indicated a great benefit of aerobic exercise in treating fibromyalgia in multiple aspects, such as pain, fatigue, and physical capacity. In this sense, in the present study, a moderate negative correlation was found between exercise and functional disability. Thus, aerobic physical exercise should be encouraged as one of the main therapeutic methods.

A moderately strong positive correlation was found between the VAS and the HAQ and a weak one between the PSS-14 and the HAQ, indicating that functional incapacity is due to the levels of pain but not to the perception of stress. In addition, physical exercise had been proved to be a protective factor against functional disability.

Among the limitations of the present study are the small number of patients in the sample, the lack of pairing with healthy individuals, and the lack of longitudinal follow-up.

CONCLUSION

The following symptoms were found in patients with fibromyalgia: moderate to severe levels of depression, moderate to severe functional disability, and high-stress levels. The severity of depression moderately influences the pain levels, and the factors most linked to functional disability are due to the pain levels but not to the perception of stress. Physical exercise had been proved to be a protective factor against functional disability.

AUTHORS' CONTRIBUTIONS

LGRF: Conceptualization, Data curation, Formal Analysis, Investigation, Methodology, Writing – original draft. **CMGW:** Conceptualization, Data curation, Formal Analysis, Investigation, Methodology, Writing – review & editing. **AAMS:** Writing – review & editing. **LHJD:** Writing – review & editing. **MH:** Writing – review & editing. **DGL:** Data curation, Investigation, Writing – review & editing. **FPM:** Data curation, Writing – review & editing. **MDS:** Conceptualization, Data curation, Formal Analysis, Methodology, Project administration, Supervision, Visualization, Writing – review & editing.

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ORIGINAL ARTICLE

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Evaluation of the combination treatments with intravenous fosfomycin for carbapenem-resistant *Klebsiella pneumoniae*

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SUMMARY

OBJECTIVE: The aim of this study was to evaluate the combination treatments with intravenous fosfomycin for carbapenem-resistant *Klebsiella pneumoniae* infections in a tertiary-care center.

METHODS: Between December 24, 2018 and November 21, 2022, adult patients diagnosed with bloodstream infection or ventilator-associated pneumonia due to culture-confirmed carbapenem-resistant *Klebsiella pneumoniae* in the anesthesiology and reanimation intensive care units were investigated retrospectively.

RESULTS: There were a total of 62 patients fulfilling the study inclusion criteria. No significant difference was recorded in 14- and 30-day mortality among different types of combination regimens such as fosfomycin plus one or two antibiotic combinations. Hypokalemia (OR:5.651, 95%CI 1.019–31.330, p=0.048) was found to be a significant risk factor for 14-day mortality, whereas SOFA score at the time of diagnosis (OR:1.497, 95%CI 1.103–2.032, p=0.010) and CVVHF treatment (OR:6.409, 95%CI 1.395–29.433, p=0.017) were associated with 30-day mortality in multivariate analysis.

CONCLUSION: In our study, high mortality rates were found in patients with bloodstream infection or ventilator-associated pneumonia due to carbapenem-resistant *Klebsiella pneumoniae*, and no significant difference was recorded in 14- and 30-day mortality among different types of combination regimens such as fosfomycin plus one or two antibiotic combinations.

KEYWORDS: Fosfomycin. Bloodstream infection. Ventilator-associated pneumonia. *Klebsiella pneumoniae*.

INTRODUCTION

Antimicrobial resistance is a global threat, and carbapenem-resistant *Klebsiella pneumoniae* (CRKP) represents a significant challenge that has important regional differences in clinical outcomes with limited treatment options[1]. According to the *in vitro* studies, different degrees of synergy or bactericidal activities were recorded with various treatment combinations for the infections due to CRKP[2].

Currently, there are limited data on the efficacy and safety of intravenous fosfomycin in clinical practice among critically ill patients. Therefore, we aimed to evaluate the risk factors for mortality (14 and 30 days) among combination treatments with intravenous fosfomycin for CRKP infections in a tertiary-care center.

METHODS

Between December 24, 2018 and November 21, 2022, adult patients diagnosed with bloodstream infection (BSI) or ventilator-associated pneumonia (VAP) due to culture-confirmed CRKP in the anesthesiology and reanimation intensive care unit (ICU) of a 900-bed tertiary care university hospital were investigated retrospectively. Primary outcomes were defined as 14- and 30-day mortality.

Bloodstream infection was classified as primary (a laboratory-confirmed BSI that is not secondary to another site infection) or secondary, which is thought to be seeded from a site-specific infection at another body site[3]. Pneumonia was defined using the criteria of the presence of new or progressing infiltrates in the chest radiography and at least two of the following: (I) temperature >38°C; (II) leukocytes >10,000/mm^3 or <4,000/mm^3; (III) decline in oxygenation; and (IV) purulent bronchial secretion (leukocytes>25) with the presence of ≤10 epithelial cells in the Gram staining of deep endotracheal aspirate (ETA) (10´), and VAP was defined as pneumonia that developed after more than 48 h intubation and received mechanical ventilation[4]. Immunosuppression was defined as having a congenital condition or transplantation, an illness, or taking medications

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(chemotherapy, corticosteroids as receiving ≥20 mg prednisone or equivalent per day for at least 2 or more weeks, calcineurin inhibitors, and cytotoxic agents)[5]. INCREMENT (5 points for severe sepsis or septic shock, 4 points for Pitt score ≥6, 3 points for Charlson comorbidity index ≥2, and 3 points for source of BSI other than urinary or biliary tract) score was calculated at the diagnosis of infection[6].

Inclusion criteria:

- Patients ≥18 years of age,
- Meeting the diagnostic criteria for BSI or VAP,
- The presence of a positive culture results in CRKP.

Exclusion criteria:

- Colonizations that were not causing clinical signs or symptoms and/or inflammation resulting from tissue response to injury or stimulation by noninfectious agents,
- Rather than intravenous fosfomycin, patients are treated with combinations of ≥3 antimicrobials that can be used for resistant gram-negative pathogens.

Statistical analyses were performed using the SPSS software version 28.0 (IBM Corp., Armonk, NY, United States). The Student's t-test was used for the analysis of parametric variables. In univariate analysis, a p-value below 0.05 was considered to be statistically significant and included in binary logistic regression analysis.

The study was approved by the Uludag University Ethics Committee with a decision number of 2023-4/10 on February 21, 2023.

RESULTS

There were a total of 62 patients fulfilling the study inclusion criteria. The most common comorbidities were recorded as hypertension (51.6%), diabetes mellitus (45.2%), and malignancy (30.6%), respectively. The mean duration of hospitalization in the ICU was found to be 57.35±6.57 days. A total of 33 patients (53.2%) had BSI, and 29 patients (46.8%) had VAP. Overall mortality rates for 14 and 30 days were recorded as 35.5 and 54.8%, respectively. In the subgroup of BSI, the overall mortality rates for 14 and 30 days were recorded at 30.3 and 57.6%. On the contrary, in the subgroup of VAP, overall mortality rates for 14 and 30 days were recorded at 41.4 and 51.7%, respectively. Univariate analysis for 14- and 30-day mortality is summarized in Table 1.

Multivariate regression analysis for 14- and 30-day mortality is shown in Table 2. Hypokalemia was found to be a significant risk factor (odds ratio (OR): 5.651, 95%CI 1.019–31.330, p=0.048) for 14-day mortality. One point increase in SOFA score at the time of diagnosis (OR: 1.497, 95%CI 1.103–2.032, p=0.010) and CVVHF treatment (OR: 6.409, 95%CI 1.395–29.433, p=0.017) were associated with 30-day mortality.

All of the patients received intravenous fosfomycin with a combination treatment. There was no significant difference in 14- and 30-day mortality among different types of combination regimens such as one or two antibiotic combinations, meropenem-containing regimens, colistin/polymyxin B-containing regimens, and aminoglycoside-containing regimens (Tables 1 and 3).

In the subgroup analysis of patients with BSI (n=33), patients with 14- and 30-day mortality had higher INCREMENT scores than the survivors (patients with a 14-day mortality rate of 13.30±0.77 vs. survivors of 10.39±0.74 had a p-value of 0.025, and those with a 30-day mortality rate of 12.47±0.62 vs. survivors of 9.64±1.02 had a p-value of 0.019).

Hypernatremia was recorded in 17 patients (27.4%) as the most common side effect, followed by hypokalemia in 14 patients (22.5%), and hypernatremia was not significantly affected by using either normal saline or 5% dextrose solution (15/17 vs. 2/17, p=0.712).

DISCUSSION

Although new agents such as ceftazidime-avibactam, meropenem-vaborbactam, and cefiderocol were recommended by guidelines for the treatment of carbapenem-resistant enterobacterial infections, these antibiotic options are still not available, especially in most low- and middle-income countries[7]. The potential efficacy of various combination treatments with intravenous fosfomycin for CRKP has been described in a very limited number of studies with a low number of patients;, therefore, our study highlights the efficacy and safety profiles of intravenous fosfomycin treatment for critically ill patients with BSI or VAP due to CRKP.

A multicenter, observational, and prospective study was performed about the outcomes of critically ill patients treated with fosfomycin for infections due to carbapenemase-producing gram-negative bacteria, and fosfomycin was combined (fosfomycin plus one, two, or three antibiotics in 18 (37.5%), 26 (54.2%), and 4 patients (8.3%)) with colistin in 32 patients (66.7%), with tigecycline in 19 patients (39.6%), with gentamicin in 15 patients (31.3%), with meropenem in 12 patients (25.0%), and with piperacillin/tazobactam in 4 patients (8.3%), respectively. Overall, 28-day mortality was found to be 37.5%,

Table 1. Univariate analysis for 14- and 30-day mortality.

Variables		14-day mortality		p-value	OR	95%CI	30-day mortality		p-value	OR	95%CI
		Present	Absent				Present	Absent			
Age	(years)	53.45±4.17	64.10±2.51	**0.029***	0.966	0.937–0.997	56.74±3.13	64.68±3.15	0.087	–	–
Gender	Male Female	12 10	21 19	0.877	–	–	19 15	14 14	0.644	–	–
Hypertension	Present Absent	6 16	26 14	**0.006***	0.202	0.064–0.632	14 20	18 10	0.073	–	–
Malignancy	Present Absent	11 11	8 32	**0.017***	4.000	1.280–12.502	12 22	7 21	0.383	–	–
Immunosuppression	Present Absent	13 9	7 33	**0.001***	6.810	2.097–22.115	15 19	5 23	**0.032***	3.632	1.115–11.824
Bacteremia	Present Absent	10 12	23 17	0.365	–	–	19 15	14 14	0.644	–	–
CVVHF treatment	Present Absent	10 12	11 29	0.157	–	–	17 17	4 24	**0.005***	6.000	1.712–21.025
APACHE-II score (at the diagnosis of infection)	(point)	25.77±1.59	21.10±1.04	**0.021***	1.105	1.015–1.203	24.53±1.20	20.61±1.31	**0.040***	1.091	1.004–1.185
SOFA score (at the diagnosis of infection)	(point)	10.95±0.81	7.90±0.48	**0.004***	1.303	1.091–1.558	10.68±0.61	6.93±0.48	**<0.001***	1.511	1.200–1.902
Hypernatremia	Present Absent	3 19	14 26	0.081	–	–	10 24	7 21	0.699	–	–
Hypokalemia	Present Absent	9 13	5 35	**0.014***	4.846	1.368–17.171	10 24	4 24	0.164	–	–
Daily fosfomycin dose (adjusted for creatinine clearance)	(g/day)	12.86±0.82	11.86±0.74	0.399	–	–	12.08±0.69	12.37±0.92	0.802	–	–

*p<0.05.

Table 2. Multivariate analysis for mortality.

Variables	14-day mortality			30-day mortality		
	p-value	OR	95%CI	p-value	OR	95%CI
Immunosuppression	0.311	–	–	0.075	–	–
SOFA score (1 point increase at the diagnosis of infection)	0.537	–	–	**0.010***	**1.497**	**1.103–2.032**
APACHE-II score (at the diagnosis of infection)	0.181	–	–	0.985	–	–
CVVHF treatment				**0.017***	**6.409**	**1.395–29.433**
Age	0.372	–	–			
Hypertension	0.083	–	–			
Malignancy	0.776	–	–			
Hypokalemia	**0.048***	**5.651**	**1.019–31.330**			

Nagelkerke R^2: 0.498 (14-day mortality); Nagelkerke R^2: 0.497 (30-day mortality). *p<0.05. Bold values were used for mentioning only the statistically significant results.

but in sub-group analysis, 28-day mortality was shown to be 43.5% for the CRKP group (n=23)[8]. Aysert-Yildiz et al., investigated a total number of 94 CRKP-infected patients treated with intravenous fosfomycin, and they revealed that favorable clinical response rates for combination treatments including meropenem and polymyxins as 66.6% (n=9) and 63.6%

Table 3. Combination treatments and mortality.

Combination type	n (%)	14-day mortality	30-day mortality
Combination with one antibiotic	27 (43%)	6 (22.2%)	11 (40.7%)
Fosfomycin plus meropenem	12 (19%)	3 (25%)	5 (41.6%)
Fosfomycin plus colistin/polymyxin B	7 (11%)	2 (28.5%)	4 (57.1%)
Fosfomycin plus amikacin/gentamycin	3 (5%)	1 (33.3%)	1 (33.3%)
Fosfomycin plus others*	5 (8%)	0 (0%)	1 (20%)
Combination with two antibiotics	35 (57%)	16 (45.7%)	23 (65.7%)
Fosfomycin plus meropenem plus colistin/polymyxin B	14 (23%)	7 (50%)	10 (71.4%)
Fosfomycin plus meropenem plus amikacin/gentamycin	9 (15%)	3 (33.3%)	4 (44.4%)
Fosfomycin plus colistin/polymyxin B plus amikacin/gentamycin	2 (3%)	0 (0%)	1 (50%)
Fosfomycin plus others*	10 (16%)	6 (60%)	8 (80%)

*Others: ceftazidim/avibactam, cefoperazone/sulbactam, tigecycline, TMP/SMX, ciprofloxacin, and levofloxacin.

(n=11) for bacteremia; 62.5% (n=16) and 60% (n=15) for pneumonia, respectively. In addition, they showed that all of the combination treatments had a similar clinical response rates for different types of infections except the tigecycline combination for pneumonia[9]. Perdigao Neto et al., described a prospective series of 13 patients (treated with fosfomycin) who had infections (BSI, n=11) due to β-lactams and colistin-resistant gram-negative bacteria (*K. pneumoniae*, n=9), and they showed that meropenem (82% synergism *via* time-kill assay) was the most commonly used antibiotic in combination with fosfomycin (n=10), with a cure rate of 70%[10]. Oliva et al., evaluated the effect of the ceftazidime/avibactam plus fosfomycin combination in the treatment of BSIs caused by CRKP, and although there was no difference in 30-day overall mortality, they showed a lower rate of subsequent CRKP or secondary infections than other ceftazidime/avibactam-based regimens in fosfomycin combination group[11]. In our study, we also found no statistically significant difference in 14- and 30-day mortality among different types of combination regimens such as one or two antibiotic combinations, meropenem-containing regimens, colistin/polymyxin B-containing regimens, and aminoglycoside-containing regimens.

In Turkey, Sengel et al., showed that the combination of fosfomycin with meropenem was found to be more synergistic (15/17 strains, 88%) than amikacin (29%) or colistin (41%) combinations against OXA-48 and/or New Delhi metallo-beta-lactamase (NDM)-producing CRKP for blood isolates despite very higher MICs for meropenem and fosfomycin[12]. On the contrary, another *in vitro* study evaluated 50 CRKP blood culture isolates regarding synergism and showed a synergy for fosfomycin-meropenem and fosfomycin-colistin combinations in 20 and 16% of the isolates, respectively[13]. Although molecular data about carbapenem resistance profiles was not included in our study, Zarakolu et al., investigated 131 CRKP bloodstream isolates collected from patients in three university hospitals, including our center, and they found that OXA-48 was the most prominent carbapenemase type (70.9%), followed by NDM (20.6%) and KPC (15.2%) types[14].

Although intravenous fosfomycin has a good safety profile for the treatment of CRKP infections, Aysert-Yildiz et al., showed common adverse events with intravenous fosfomycin treatment as hypokalemia (37.2%) and hypernatremia (22.3%)[9]. Pontikis et al., also investigated the side effects of parenteral fosfomycin, and they revealed severe hypokalemia in 10 patients (15.2%) as the main adverse event[8]. In our study, we found hypernatremia in 17 patients (27.4%) as the most common side effect, followed by hypokalemia in 14 patients (22.5%). In addition, the hypernatremia side effect was not significantly affected by using either normal saline or 5% dextrose solution (15/17 vs. 2/17, p=0.712). A retrospective cohort study among 309 critically ill patients treated with intravenous fosfomycin showed that hypokalemia was the most observed adverse event in 62.1% of cases, and regarding 30-day mortality, hypokalemia incidence was not significantly different between the survivors and nonsurvivors[15]. Similar to this study, we also found no significant difference for the hypokalemia side effect in terms of 30-day mortality. However, the presence of hypokalemia as a side effect of intravenous fosfomycin treatment was associated with 14-day mortality in our study.

A study among 384 patients with CPKP bacteremia in the ICU reported that an INCREMENT score ≥10 showed a sensitivity of 98.0% and a negative predictive value of 98.7% with an area under curve (0.800) comparable to other scores such as SOFA (0.815)[6]. In our study, we also found higher INCREMENT scores for patients with 14- and 30-day mortality

in the subgroup of BSIs. A prospective and multicentre observational cohort study about BSIs due to CRKP showed that SOFA score and immunosuppression were significant predictors of 30-day mortality (44%)[16]. Similar to these findings, we also found that a higher SOFA score at the time of infection diagnosis was associated with 30-day mortality in multivariate analysis. A study about the concentration-versus-time profile of fosfomycin in CVVHF with 12 anuric intensive care patients revealed that a regimen of 8 g every 12 h should be appropriate for patients undergoing CVVHF with a fosfomycin-susceptible pathogen[17]. In our study, similar to patients with normal renal functions, a daily fosfomycin dose of 16 g (divided into 2 doses) was preferred in patients undergoing CVVHF. In multivariate analysis of our study, CVVHF treatment was significantly associated with 30-day mortality. We believe that renal dose adjustments of the treatments, such as antibiotics used in combination, may have an impact on these results, and measurement of antibiotic serum levels may contribute to the optimal management of critically ill patients with CVVHF treatment.

Our study has several limitations. The main limitation is that this is a retrospective study with a small number of patients in a single center. Therefore, confounding factors for the endpoint to assess the effect of each combination treatment could not be identified. Finally, although the OXA-48 is the most prominent carbapenemase type according to a multicenter study from Turkey, including our hospital data, molecular identification of carbapenemase types could not be performed in our study.

CONCLUSION

In our study, high mortality rates were found in patients with BSI or VAP due to CRKP, and no significant difference was recorded in 14- and 30-day mortality among different types of combination regimens such as fosfomycin plus one or two antibiotic combinations. Multivariate regression analysis showed that a higher SOFA score and CVVHF treatment were associated with 30-day mortality. We believe that our study may support further investigation of parenteral fosfomycin in the target patient population, including patients with BSI and VAP due to CRKP.

AUTHORS' CONTRIBUTIONS

UÖ: Conceptualization, Data curation, Formal Analysis, Investigation, Methodology, Project administration, Resources, Software, Validation, Visualization, Writing – original draft, Writing – review & editing. **HA:** Conceptualization, Data curation, Formal Analysis, Investigation, Methodology, Project administration, Resources, Supervision, Visualization. N**ÜT:** Data curation, Formal Analysis, Investigation, Resources, Validation, Visualization. P**KK:** Data curation, Formal Analysis, Investigation, Resources, Validation, Visualization. **Rİ:** Data curation, Formal Analysis, Investigation, Resources, Validation, Visualization. N**KG:** Data curation, Formal Analysis, Investigation, Resources, Validation, Visualization. **CÖ:** Data curation, Formal Analysis, Investigation, Resources, Validation, Visualization. **FŞK:** Data curation, Formal Analysis, Investigation, Resources, Validation, Visualization.

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ORIGINAL ARTICLE

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Is the neutrophil-to-lymphocyte ratio a marker for differentiating between benign and malignant submandibular gland masses?

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SUMMARY

OBJECTIVE: This study aimed to evaluate the effect of the neutrophil-to-lymphocyte ratio on the differentiation of benign and malignant masses in the submandibular triangle.

METHODS: We retrospectively evaluated 48 patients who underwent surgery for submandibular gland masses between January 2013 and February 2023. The patient's age, gender, preoperative complete blood count and imaging findings, postoperative histopathological diagnosis, and hemogram data were analysed. Patients were evaluated according to their postoperative histopathological diagnoses and categorised into four main groups: sialolithiasis, sialadenitis, benign tumours, and malignant tumours. Benign submandibular gland disease formations were evaluated under group B and malignant tumour formations under group M.

RESULTS: A preoperative fine needle aspiration biopsy was performed on 19 patients due to sialadenitis, pleomorphic adenoma, and malignant diseases other than sialolithiasis. One patient died among the patients with malignant disease and the remaining 7 patients were compared with the benign group of 40 patients regarding preoperative and postoperative neutrophil-to-lymphocyte ratio. In the benign group, the neutrophil-to-lymphocyte ratio was 2.64 preoperatively and decreased to 2.34 in the first postoperative year. The preoperative neutrophil-to-lymphocyte ratio decreased from 4.79 to 1.77 postoperatively in the malignant group. A statistically significant difference was observed ($p<0.05$).

CONCLUSION: This is the first study to demonstrate that the neutrophil-to-lymphocyte ratio can be used as a biomarker in submandibular gland masses and has prognostic significance in malignant masses. In addition to fine needle aspiration biopsy results, neutrophil-to-lymphocyte ratio can be used as a biomarker.

KEYWORDS: Submandibular gland neoplasm. Fine needle biopsy. Blood cell count. Malignancy. Inflammation.

INTRODUCTION

The submandibular triangle is a clinically significant area in head and neck surgery practice, and patients may present with an isolated submandibular mass. The differential diagnosis of submandibular masses includes salivary gland, lymph node, soft tissue, vascular, and neural pathologies. The most common submandibular gland pathologies are sialadenitis, sialolithiasis, benign tumours, and carcinomas. Inflammatory diseases of the salivary glands and sialolithiasis are more commonly observed in the submandibular gland[1]. Salivary gland tumours are rare, and it has been reported that only 10–15% of them are seen in the submandibular gland[2]. The primary approach for submandibular gland tumours is surgery, and the indication for surgery varies based on the tumour's histopathology and local spread. Therefore, differentiating between benign and malignant lesions and distinguishing low-grade from high-grade malignancies during the preoperative period is vital. Fine needle aspiration biopsy (FNAB) is widely performed and is the preferred intervention in the differential diagnosis of salivary gland pathologies[3]. However, considering the wide variety of tumours in the salivary glands, there are many diagnostic challenges in salivary gland cytopathology, including the need for a uniform reporting system. For this purpose, the "Milan Classification System for Reporting Salivary Gland Cytopathology" has been established under the leadership of the American Society of Cytopathology and the International Academy of Cytology. According to the Milan System, cytopathological diagnoses are classified into six main categories: (1) non-diagnostic (insufficient, ordinary salivary gland); (2) non-neoplastic; (3) atypia of undetermined significance; (4) neoplastic group: (a) benign neoplasia and (b) salivary gland neoplasm of uncertain malignant potential; (5) suspicion of malignancy; and (6) malignant cytology[4]. According to the Milan System, 25% of cytopathological diagnoses fall into the first three categories, and a malignancy risk ranging from 10 to 25% has been estimated for these categories[5]. This rate is significant and cannot be ignored.

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Numerous studies have shown that inflammation plays a significant role in cancer prognosis in recent years. Previous studies have shown that high levels of inflammatory biomarkers such as neutrophil-to-lymphocyte ratio (NLR), platelet-to-lymphocyte ratio (PLR), and systemic immune inflammation index are associated with poor prognosis in many types of cancer. Many disorders have inflammation as a key factor in their development. For example, rheumatoid arthritis produces more inflammation, while others produce only less. NLR is an inflammatory marker, and its diagnostic and prognostic role has been shown in irritable bowel disease, COVID-19 infection, diabetes mellitus, gastrointestinal conditions, cardiac conditions, and thyroiditis[6-11]. Moreover, there is a clear link between inflammation and cancer[12]. Thus, it is rational to study NLR in the differentiation of benign and malignant conditions. In recent years, considerable evidence has shown that inflammation plays a significant role in cancer prognosis[13].

In their study in 2016, Damar et al. included major and minor salivary glands and reported that a high NLR and low lymphocyte count could differentiate malignant tumours from benign tumours. They also reported that these parameters significantly predicted low-grade and high-grade malignancies[14]. However, our literature search did not find a specific study that used NLR values as a marker for malignant tumours in cases where submandibular gland excision was performed.

Therefore, this study aimed to evaluate the importance of demographic data, preoperative FNAB results, and NLR values in comparison with postoperative histopathological results in differentiating between benign and malignant submandibular gland masses in cases where submandibular gland excision was performed in a third-level healthcare institution over 10 years.

METHODS

In this study, patients who underwent surgical intervention for submandibular gland mass in the Department of Otorhinolaryngology and Head and Neck Surgery, Faculty of Medicine, Sivas Cumhuriyet University, between the years 2013 and 2023 were retrospective. Inclusion criteria were as follows: having a previous diagnosis of submandibular gland mass, a history of surgical intervention for this diagnosis, and sufficient pre- and postoperative information. Exclusion criteria included cases that underwent submandibular surgery for a different diagnosis or as part of a more extensive resection and had insufficient follow-up data. Additionally, patients with inflammatory, autoimmune, acute or chronic infectious diseases, haematological disorders, diabetes, obese patients (body mass index >30), hypertension, obstructive sleep apnea, a history of corticosteroid treatment, or chronic kidney failure that could affect inflammatory parameters were excluded, except for five patients. Neutrophil and lymphocyte counts were recorded from complete blood count samples obtained approximately 1 week before surgery (venous blood samples taken at 10:00–11:00 in the morning). The NLR was calculated from these values. All sample analyses were performed on automated haematology analysers purchased from Sysmex XN-9100TM (Kobe, Japan).

After obtaining verbal and written consent from all cases accepting to participate in the study according to the Declaration of Helsinki principles, medical history, age, gender, FNAB results, histopathological diagnosis, and hemogram data were retrospectively reviewed. According to the postoperative histopathological diagnoses, patients were evaluated under four main categories: sialolithiasis, sialoadenitis, benign tumours, and malignant tumours. Sialolithiasis, sialoadenitis, and benign tumours were considered benign disease categories (group B), while malignant tumours were evaluated as malignant (group M). Ethical approval for this study was obtained from the Non-Interventional Ethics Committee of Sivas Cumhuriyet University Faculty of Medicine (Date: 22.02.2023; Decision number: 2023-02/04).

Statistical methods

The SPSS (SPSS Inc., Chicago, IL) 23.0 software was used for data evaluation in the study. After necessary corrections, descriptive statistics and frequency tables were used to describe the population's demographic characteristics. The normality of the data was analysed using the Kolmogorov-Smirnov test, and since the normality criterion was not provided, non-parametric tests were performed. Due to the non-normal distribution of scale means, Mann-Whitney U and Wilcoxon rank tests were used to calculate the difference between two categorical variables. Differences between categorical variables were investigated using Chi-square analysis. All analysis results were interpreted at a 95% confidence level.

RESULTS

A total of 48 patients were included in the study, with 35.40% (n=17) females and 66.6% (n=32) males. The mean age of the patients was 50.08±20.46 years (13–94 years). The mean age of female patients was 55.24±20.54 years (13–94 years), and male patients was 47.26±20.18 years (14–89 years), with no significant difference in age between males and females. The mean age of the benign disease group, which consisted of sialolithiasis, sialadenitis, and benign tumours, was 47.88±20.13 years (ranging from 13 to 94 years), while the mean age of the malignant

disease group was 61.12±19.62 years (ranging from 25 to 89 years) (Figure 1A). The youngest patient in the benign disease group underwent surgery at 13 years, who was in the malignant disease group and was operated on for adenocystic carcinoma at 25 years. There was no statistically significant difference in age between benign and malignant diseases.

In group B, 9 (18.80%) patients underwent surgery due to sialolithiasis, 23 (47.90%) patients due to sialadenitis, and 8 (16.70%) patients due to pleomorphic adenoma. On the contrary, 8 (16.70%) patients underwent surgery due to group M (Figure 1B).

The patients who underwent surgery due to malignant diseases were reported as three cases of adenocystic carcinoma, two cases of mucoepidermoid carcinoma, adenocarcinoma, diffuse large B-cell lymphoma, and peripheral T-cell lymphoma, respectively.

In all, 19 patients underwent FNAB preoperatively due to sialoadenitis, pleomorphic adenoma, and malignant diseases, excluding the sialolithiasis group. Among the 13 patients whose preoperative FNAB results were reported as benign cytology, 9 were confirmed as benign and 4 as malignant, according to postoperative histopathology. All three cases with FNAB results reported as insufficient cytology had benign postoperative histopathology. Among the three cases with suspicious malignant cytology in preoperative FNAB, one was reported as benign and two as malignant in postoperative histopathology (Figure 2A).

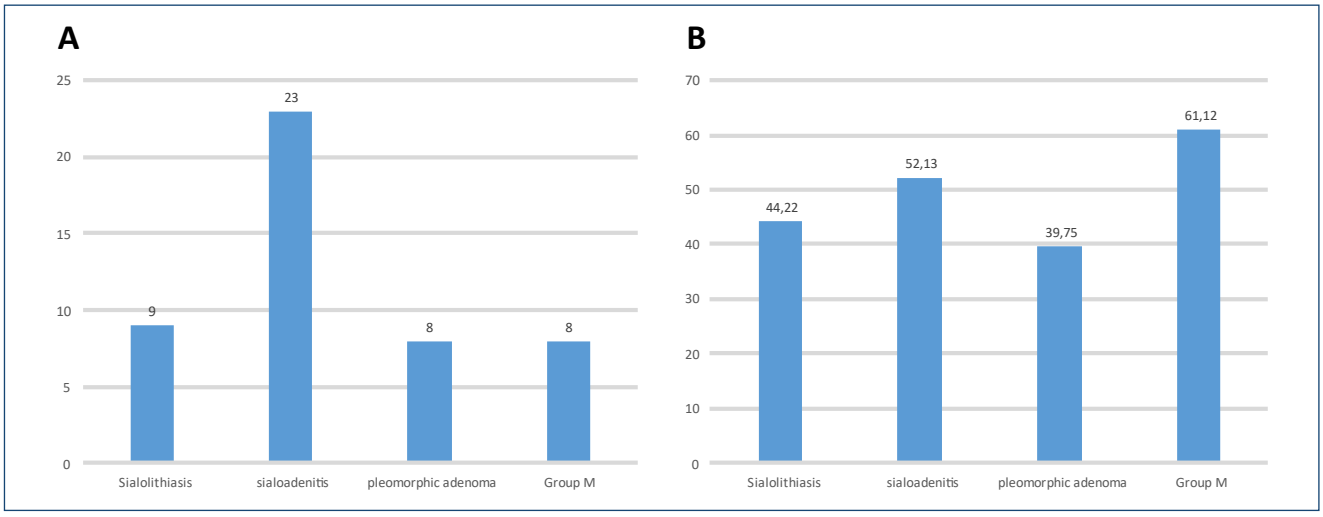

Figure 1. (A) Average age in benign and malignant diseases. (B) Distribution of patients who underwent submandibular gland excision according to the histopathological results.

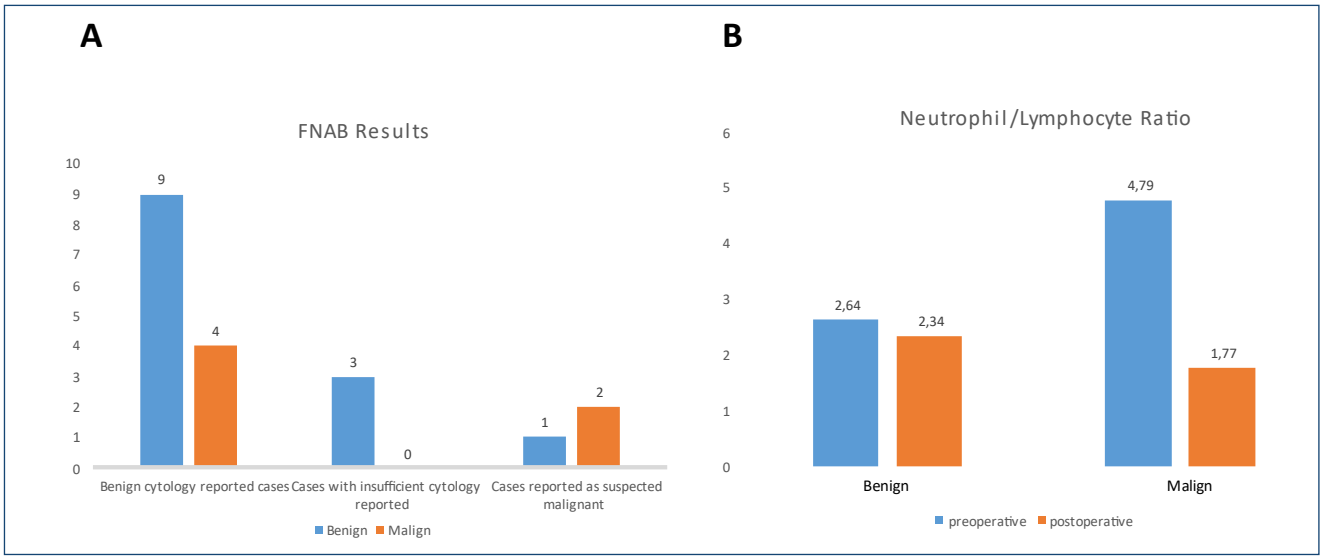

Figure 2. (A) Comparison of preoperative fine needle aspiration biopsy results with postoperative histopathological results. (B) Comparison of the neutrophil-to-lymphocyte ratio of benign and malignant diseases before and after surgery.

One patient has died due to a malignant disease. When the preoperative and postoperative hemogram values of 7 other patients and 40 patients in group B were compared, the preoperative value in group B was 2.64, while it was 2.34 in the first year after surgery. In malignant cases, the preoperative value decreased from 4.79 to 1.77 postoperatively. A statistically significant difference was observed ($p<0.05$) (Figure 2B). The demographic data of the patients along with NLR and histopathological results are summarized in Table 1.

DISCUSSION

Non-neoplastic lesions may resemble neoplastic lesions clinically and pathologically, and their differentiation is significant. The definitive diagnosis is a histopathological evaluation of the surgical material[15]. FNAB is important in the preoperative diagnosis and treatment of patients with submandibular masses[16]. However, due to the high rates of false positives and false negatives in salivary gland pathologies, the predictive value of FNAB is low[17]. In our study, among 13 cases with benign cytology, 4 were reported as malignant and 2 of the cases with suspicious malignant cytology resulted in malignancy. Therefore, due to its misleading outcomes, surgical and medical treatments should not be determined solely based on the FNAB results. The most significant result of our study is that, upon comparing the preoperative and postoperative hemogram values of 7 patients with malignant disease and 40 patients in group B, we observed a decrease in the preoperative value of group B from 2.64 to 2.34 in the first year after surgery. In cases diagnosed with malignancy, the preoperative value decreased significantly from 4.79 to 1.77 after surgery ($p<0.05$). Numerous studies have described the association between malignancy and inflammation[18]. Therefore, we aimed to utilise inflammatory criteria in the differentiation of malignant lesions. NLR values can serve as a dependable indicator of inflammation. Additionally, NLR proves to be valuable in distinguishing between benign and malignant nodules in patients with thyroid nodules. Sit et al. found that the mean NLR of the malignant nodule group (2.1±0.9) was higher compared to both the benign nodule group (1.7±0.9) and the control group (1.7±0.6). The observed difference between the groups was statistically significant ($p=0.002$)[19]. In our study, similar results were obtained, with the additional finding of higher values in malignant patients. This state may be attributed to the assessment based on preoperative values, which differs from the approach taken in the study conducted by Sit et al.[19].

Recently, high preoperative NLR and PLR values have been reported to be associated with increased recurrence risk, tumour aggressiveness, and poor prognosis in various

Table 1. Demographic data, and biochemical and histopathological results of patients with submandibular gland masses.

Age Mean±SD (min–max)		**50.1±20.5 (13–94)**				
Male (n=31)		47.26±20.18 (14–89)				p=0.215
Female (n=17)		55.24±20.54 (13–94)				
Mean age of patients with submandibular gland masses [Mean±SD (min–max)]	Benign diseases	47.88±20.13 (13–94)				p=0.105
	Malignant diseases	61.12±19.62 (25–89)				
Submandibular diagnoses, n (%)	Sialolithiasis	9 (18.8)				
	Sialadenitis	23 (47.9)				
	Pleomorphic adenoma	8 (16.7)				
	Malignant diseases	8 (16.7)				
Fine needle aspiration biopsy results, n (%)		None	Insufficient cytology	Benign	Suspicious malignant	p-value
Sialolithiasis		9 (31)	0 (0)	0 (0)	0 (0)	**0.001**
Sialoadenitis		17 (58.6)	2 (66.7)	3 (23.1)	1 (33.3)	
Pleomorphic adenoma		1 (3.4)	1 (33.3)	6 (46.2)	0 (0)	
Malignant diseases		2 (6.9)	0 (0)	4 (30.8)	2 (66.7)	
Neutrophil-to-lymphocyte ratio	Benign diseases	2.64–2.34 (preoperative–postoperative)				0.387
	Malignant diseases	4.79–1.77 (preoperative–postoperative)				**0.043**

Bold values indicate statistical significance at the $p<0.05$ level.

head and neck malignancies[20]. Kuzucu et al. found a significant difference in the NLR between benign and malignant tumours on parotid gland malignant tumours[21]. The preoperative NLR was significantly different in this study, with an average value of 2.64 in benign tumours and 4.79 in malignant tumours. Similar results were also obtained in our study. Our data showed a very close correlation. We concluded that NLR can be utilised in the discrimination between benign and malignant lesions of submandibular gland tumours. The prevalence of malignancy in submandibular gland tumours varies in the literature. In some series, the prevalence of malignant tumours ranges from 40 to 60%, and this rate is lower in Western populations[22]. In the recent studies, it has been reported that the prevalence of submandibular gland malignancies is approximately 20%[23]. This prevalence rate is also observed in our clinic.

Another important finding of our study is that there was no age-related difference between benign and malignant pathologies. Although the mean age of malignant cases may be slightly higher, the youngest patient with adenocystic carcinoma was 25 years. Therefore, it is necessary to approach every patient presenting with a mass complaint in the submandibular area as a potential malignancy until proven otherwise.

The most common reason for submandibular gland excision in the past was sialolithiasis, but in our study, the most common etiological cause was sialoadenitis[24]. This change is due to the development of new methods, which now allows for the preservation of the gland through endoscopic stone removal and extracorporeal shock wave lithotripsy.

Pleomorphic adenomas are the most common benign submandibular gland tumours, and our study is consistent with the literature[22]. In addition, incomplete resection of pleomorphic adenoma has been reported to result in a high tumour recurrence rate. Therefore, meticulous preservation of the tumour capsule and complete removal of the entire gland are necessary[25]. In our study, we did not have any cases of recurrence due to pleomorphic adenoma.

The limitations of this study include the retrospective study design, single-centre experience, and small sample size (n=48), particularly in histological subtypes and treatment. Survival data should be tested and confirmed in a prospectively designed study.

If there is a mass in the submandibular triangle, careful history-taking, physical examination, and endoscopic examination should be performed first. Ultrasonography is preferred for the initial radiological evaluation. If there is a high suspicion of infection, antibiotic therapy and anti-inflammatory treatment should be initiated while eliminating the submandibular mass. If there is no clinical and radiological improvement with medical treatment, a histopathological examination should be performed to evaluate the risk of malignancy. FNAB is the initial step in histopathological evaluation for submandibular masses. If repeated FNABs are unsuccessful, an excisional biopsy should be performed.

CONCLUSION

This study discussed the demographic data and histopathological evaluation of patients with submandibular masses. Sialadenitis was the most common condition, and benign and malignant tumours were encountered similarly. Although the average age of malignant diseases was slightly higher, no significant difference was observed between benign and malignant tumours based on age. FNAB results for submandibular gland masses can be misleading. Therefore, it is necessary to keep malignancies in mind until proven otherwise in patients presenting with submandibular mass complaints. The NLR and FNAB results may indicate malignant tumours in submandibular gland masses.

ETHICAL APPROVAL AND CONSENT TO PARTICIPATE

The protocol of the study was approved by the Institutional Review and Animal Ethics Use Committee of Sivas Cumhuriyet University School of Medicine, and the study was carried out based on the accepted guidelines on the care and use of laboratory animals (Date: 22.02.2023; Decision number: 2023-02/04).

DATA ACCESSIBILITY

The data that support the findings of this study are available on request from the corresponding author. The data are not publicly available due to privacy or ethical restrictions.

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ORIGINAL ARTICLE

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Aflibercept suppresses ovarian hyperstimulation syndrome: an experimental study in rats

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SUMMARY

OBJECTIVE: In this study, we aimed to determine the impact of the antiangiogenic medications, namely, aflibercept and cabergoline in the prevention and treatment of ovarian hyperstimulation syndrome in a rat model.

METHODS: A total of 36 female Wistar rats were randomly allocated to one of the five groups, including disease-free and ovarian hyperstimulation syndrome controls: Group no OHSS (control, n=6) received saline only intraperitoneally (i.p.); group just OHSS (ovarian hyperstimulation syndrome only, n=6) received 10 IU pregnant mare serum gonadotropin and 30 IU human chorionic gonadotropin subcutaneously to produce ovarian hyperstimulation syndrome; group cabergoline+OHSS (cabergoline+ovarian hyperstimulation syndrome, n=8) received 100 μg/kg oral cabergoline; group aflibercept (12.5 mg/kg)+OHSS (aflibercept+ovarian hyperstimulation syndrome, n=8) received 12.5 mg/kg i.p. aflibercept ; and group aflibercept (25 mg/kg)+OHSS (aflibercept+ovarian hyperstimulation syndrome, n=8) received 25 mg/kg i.p. aflibercept. The groups were compared for ovarian weight, immunohistochemical vascular endothelial growth factor expression, spectrophotometric vascular permeability evaluated with methylene blue solution in peritoneal lavage, and body weight growth.

RESULTS: Vascular endothelial growth factor immunoexpression was substantially greater in the just OHSS group (22.00±10.20%) than in the aflibercept (12.5 mg/kg)+OHSS (7.87±6.13%) and aflibercept (25 mg/kg)+OHSS (5.63±4.53%) groups (p=0.008 and p=0.005, respectively). Post-hoc tests indicated that cabergoline, 12.5 mg/kg aflibercept, and 25 mg/kg aflibercept decreased vascular permeability compared to the untreated ovarian hyperstimulation syndrome group (p=0.003, p=0.003, and p=0.001, respectively). JOH group had the heaviest ovaries, whereas aflibercept (25 mg/kg)+OHSS group had the lightest. In terms of body weight gain, cabergoline+OHSS group was substantially greater than the aflibercept (12.5 mg/kg)+OHSS and aflibercept (25 mg/kg)+OHSS groups (p=0.006 and p=0.007, respectively).

CONCLUSION: Aflibercept, an antiangiogenic medication, decreased ovarian hyperstimulation syndrome by lowering the vascular permeability and vascular endothelial growth factor expression.

KEYWORDS: Aflibercept. Cabergoline. Ovarian hyperstimulation syndrome. Vascular endothelial growth factors.

INTRODUCTION

Ovarian hyperstimulation syndrome (OHSS) is an iatrogenic result of ovarian stimulation that can be potentially fatal. It is characterized by cystic growth of the ovaries and rapid transudation of protein-rich fluid from the vessels into the abdominal cavity. The extra fluid leads to weight gain, abdominal distension, and intravascular depletion. In severe OHSS, this protein-rich fluid may also be detected in the pleural and pericardial cavities[1].

Human chorionic gonadotropin (hCG) used for triggering ovulation in ovulation induction (OI) and IVF cycles is considered to have a pivotal role in the development of this life-threatening disease. After exposure to hCG, there is a strong luteinization of granulosa cells in the corpus luteum of the hyperstimulated ovaries, resulting in OHSS. Vasoactive substances such as vascular endothelial growth factor (VEGF) are produced, which increases vascular permeability, and as a result of the fluid scape from the vessels into the third space, signs and symptoms are related to the consequential edema, ascites, pleural and pleural effusion, and hemoconcentration development[2]. VEGF and VEGF receptor (VEGFR) polymorphisms are reported to be related to the formation of OHSS. IVF recipients who develop OHSS are known to produce less soluble VEGFR1 than OHSS-free recipients, and VEGF concentration has been shown to be directly proportional to the severity of OHSS. Consequently, the pathophysiology of

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OHSS relies on the VEGF/VEGFR system, which has a significant impact on vascular permeability[2,3].

Currently, there are different strategies for prevention of OHSS in clinical practice: primarily, lowering the hCG dose at trigger, using gonadotropin agonist (GnRH-A) for triggering, use of progesterone as luteal phase support rather than hCG, embryo cryopreservation as opposed to immediate fresh embryo transfer, a "freeze-all" technique for patients at high risk of OHSS, and canceling the treatment cycle when abnormally high number of follicles grow and/or there is a dramatic estradiol rise[4]. In addition, cabergoline, an ergot-derived molecule known to be a potent dopamine receptor agonist (DA), is commonly administered by reproductive physicians to treat OHSS[5].

Among VEGFRs, only VEGFR1 and VEGFR2 have been shown to be directly involved in VEGF binding. On the contrary, IVF recipients who develop OHSS are known to produce less soluble VEGFR1 than OHSS-free recipients, and VEGF concentration has been shown to be directly proportional to OHSS. Consequently, the pathophysiology of OHSS relies on this VEGF/VEGFR system, which has a significant impact on vascular permeability[3].

Cabergoline, a D2 receptor agonist, has been shown to have potent inhibitory effects on VEGF by altering both peptide synthesis and secretion[6]. Aflibercept is a recombinant receptor fusion protein that inhibits angiogenesis by combining the second and third domains of human VEGFR1 and VEGFR2[7].

Based on the angiogenic pathophysiology of OHSS, antiangiogenic drugs have a potential in the treatment of this syndrome. We report an experiment in rats comparing aflibercept, whose effect on OHSS has not yet been studied, with cabergoline, which has been extensively studied.

METHODS

Animals and ethical approval

A total of 36 female Wistar albino rats were studied. Notably, 22-day-old rats weighed 35–65 g. Other species, sex, age, weight, mortality during the experiment, and suspected sickness were excluded. Steel cages with a 12-h light-dark cycle held animals in a temperature-controlled room (22±2°C). All animals were free-fed. The Animal Research Ethics Committee of Ankara University approved the Project (16/03/2022-06-32-6-58). The rats were obtained from the Ankara University Animal Laboratory, where the animals were cared for and the experiment was conducted. In all animal experiments, the rules of the Human Care Committee for animal experiments were completely followed.

Experimental concept

The experiment was designed in a randomized controlled manner with five different groups. Randomization was performed using the Microsoft Excel function RAND.

1. The NOH group (no OHSS, control, n=6) received only 0.1 mL of saline intraperitoneally (i.p.) daily for 5 days.
2. To induce OHSS in the JOH group (OHSS only, n=6), 10 IU of pregnant mare serum gonadotropin (PMSG) (Folligon®-Intervet; Schering-Plough Animal Health, Pune, India) was administered subcutaneously (s.c.) for 4 days, followed by 30 IU of hCG (Chorulon®-Intervet, Boxmeer, The Netherlands) on the 5th day.
3. The COH group (cabergoline+OHSS, n=8) received cabergoline (100 µg/kg, Dostinex®-Pharmacia SpA, Ascoli Piceno, Italy) dissolved in 1 mL of tap water, via oral gavage (0.8 mm´45 mm curved delivery cannula), 2 h before each of the 5-day injections required for OHSS stimulation (first 4 days 10 IU PMSG, 5th day 30 IU hCG).
4. The aOH (aflibercept, 12.5 mg/kg+OHSS, n=8) group received i.p. aflibercept (Eylea®; Regeneron, NY, USA) at a dose of 12.5 mg/kg once, 2 h before the first PMSG injection for OHSS stimulation.
5. The AOH group (aflibercept, 25 mg/kg+OHSS, n=8) received aflibercept at a dose of 25 mg/kg once in the same manner. The literature was used to develop the procedure for the OHSS model and the cabergoline doses[1]. The dosage of aflibercept was determined on the basis of previous studies and taking into account the opinion of the pharmacologist[8].

Surgical procedure and vascular permeability determination

All rats (28 days old) were weighed 48 h after hCG administration on the 5th day. The 7-day body weight gains (BWG) were calculated and noted. Then, rats aged 28 days, i.p. 90 mg/kg ketamine hydrochloride (Ketalar®, Eczacıbaşı Warner-Lambert pharmaceutical industry, Levent/Istanbul) and i.p. 10 mg/kg xylazine (Rompun-Bayer®, Şişli/Istanbul) were administered to induce anesthesia. Antisepsis with 10% povidone-iodine solution was performed before surgery. Immediately after confirmation of the depth of anesthesia by skin pinch reaction, 0.2 mL of methylene blue solution (methylene blue solution 1% w/v, Gunduz Chemical®, Umraniye/Istanbul) was administered to the rats through the tail vein via an insulin injector. After a 4 cm vertical incision, the peritoneal cavity was filled with 5 mL of 0.9% NaCl solution. After 30 min, the peritoneal cleansing solutions were extracted using a fertilization

catheter with constant shaking and without tissue damage. These fluids collected for vascular permeability determination were placed in tubes containing 0.05 mL of 0.1 N NaOH and centrifuged (900´g, 30 min).

Methylene blue concentration (MBC) was determined using a spectrophotometer (Thermo Fisher Scientific Inc. Waltham, MA, USA) at 665 nm. The concentration of extravasated dye in the recovered fluid was quantified as micrograms (µg) per 100 g of body weight. The surgical procedure was continued by carefully scraping and excising the bilateral ovaries from the surrounding tissue. The removed bilateral ovaries were weighed (BOW) jointly on a sensitive scale (Radwag© PS 0.6.R2) and then placed in containers that have 10% formolin. Finally, all rats were sacrificed by cervical dislocation while under anesthesia.

Immunohistochemical vascular endothelial growth factor expression

Ovarian tissue samples were embedded in paraffin. Notably, 5 µm sections were made of all paraffin-embedded tissues on the microtome (Leica-RM225 - Thermo HM3555 - Thermo scientific). The Ventana BenchMark XT system (Ventana Medical Systems, Roche, Basel, Switzerland) was used to automatically perform immunohistochemical staining. The universal 3,3'-diaminobenzidine detection kit ultraview (DAB) (Ventana®) was used for automated immunohistochemistry equipment. A positive control for the primary VEGF antibody (Flt-1/VEGFR1, 0.1 mL concentrate 1:501:200 antibody, GenomeME, Richmond BC, Canada) was prepared on each slice. The staining of the cytoplasm was assessed. The number of VEGF-positive cells was determined by counting at least 100 granulosa cells per 10 tissue slices at 100× magnification (Nikon® ECLIPSE 80i, Japan), and cross sections were photographed (NIS -Elements D Ver5.02.03 for 64bit edition software). A pathologist conducted these procedures blindly in a pathology clinic.

Statistical analysis

GPower 3.1 determined the research sample size. Shapiro-Wilk test was used to determine data normality. Continuous variables have mean±standard deviation. One-way analysis of variance (ANOVA) was performed for normal variables and Kruskal-Wallis test was performed for non-normal variables to compare groups. Post-hoc analyses used Bonferroni correction. SPSS.25 was used for analysis, and $p<0.05$ was considered significant.

RESULTS

Body weight development was significantly different across groups, while total bilateral ovary weight was not (Table 1).

The Kruskal-Wallis test revealed a statistically significant difference between groups based on the measured concentrations of methylene blue (µg/100 g) to determine vascular permeability. Post-hoc tests showed that cabergoline (2.85±2.79 µg), 12.5 mg/kg aflibercept (1.93±2.63 µg), and 25 mg/kg aflibercept (0.94±0.89 µg) treatments significantly decreased vascular permeability compared to the untreated OHSS group (9.88±2.73 µg) (p=0.003, p=0.003, p=0.001, respectively). The values and significance levels are shown in Table 1. Figure 1 shows a graphical representation of the MBCs.

The strongest staining in granulosa cells was observed in the untreated OHSS group (Figure 2B). Virtually, no VEGF staining was observed in the control group (Figure 2A). The COH, aOH, and AOH groups showed significantly lower VEGF expression (Figures 2C–E). The Kruskal-Wallis test showed that there was a significant difference in the percentage of VEGF immunoexpression between the groups (p=0.004). According to the post-hoc tests, the percentage of VEGF immunoexpression was significantly higher in the JOH group (22.00±10.20%) than in the aOH group (7.87±6.13%) and the AOH group (5.63±4.53%) (p=0.008 and p=0.005,

Table 1. Comparison of group parameters for body weight gain, bilateral ovarian weight, vascular permeability, and vascular endothelial growth factor expression.

Groups	NOH control (n=6)	JOH OHSS (n=6)	COH OHSS+cabergoline (n=8)	aOH OHSS+aflibercept^{x} (n=8)	AOH OHSS+aflibercept^{y} (n=8)
BWG* (g)	22.00±5.44	23.50±3.51	25.75±2.71	17.13±6.79*	17.25±3.01**
BOW* (mg)	53.50±15.93	66.00±7.51	57.00±12.99	51.12±8.49	48.25±13.78
MBC** (µg/100 g)	2.40±2.33	9.88±2.73^{a}	2.85±2.79^{b}	1.93±2.63^{c}	0.94±0.89^{d}
VEGF** (%)	6.50±3.41	22.00±10.20	9.88±8.59	7.87±6.13^{e}	5.63±4.53^{f}

OHSS: ovarian hyperstimulation syndrome; BWG: body weight gain; BOW: bilateral ovarian weight; MBC: methylene blue concentration; VEGF: percentage of VEGF-positive cells. It was determined by counting at least 100 granulosa cells per 10 tissue slices at 100´ magnification. ^{x}12.5 mg/kg, ^{y}25 mg/kg, *One-way ANOVA analysis, **Kruskal-Wallis test. *p=0.006 COH group and aOH group were compared. **p=0.007 COH group and AOH group were compared. ^{a}p=0.004 JOH group and NOH group were compared. ^{b}p=0.003 JOH group and COH group were compared. ^{c}p=0.003 JOH group and aOH group were compared. ^{d}p=0.001 JOH group and AOH group were compared. ^{e}p=0.008 JOH group and aOH group were compared. ^{f}p=0.005 JOH group and AOH group were compared.

respectively). However, there was no significant difference in the percentage of VEGF immunoexpression between the other groups (Table 1 and Figure 3).

DISCUSSION

This study focused specifically on vascular permeability and VEGF expression. In this study, the antiangiogenic drug aflibercept was used for the first time as a therapy for OHSS. Since this is the first time the drug has been administered in OHSS, the study was organized as an animal experiment. Aflibercept has a preventative effect on two of the most important elements of OHSS: inhibition of vascular permeability and reduction of VEGF expression[1,9].

Daily monitoring of patients' body weight and waist circumference is recommended in the guidelines for the management of OHSS[10]. The importance of measuring the waist circumference of rats in OHSS is not known; therefore, we examined body weight before and after OHSS and compared the amount of weight gain in the different groups. This discrepancy between the final and initial body weight was also used to confirm OHSS induction. The results showed that the aflibercept-treated group gained less weight than the cabergoline-treated group (Table 1). This indicates that aflibercept inhibits OHSS; however, it should be noted that the slower weight gain could be a side effect of aflibercept, as we did not observe similar results in the cabergoline group and 22-day-old rats are normally in a rapid growth phase. In a previous

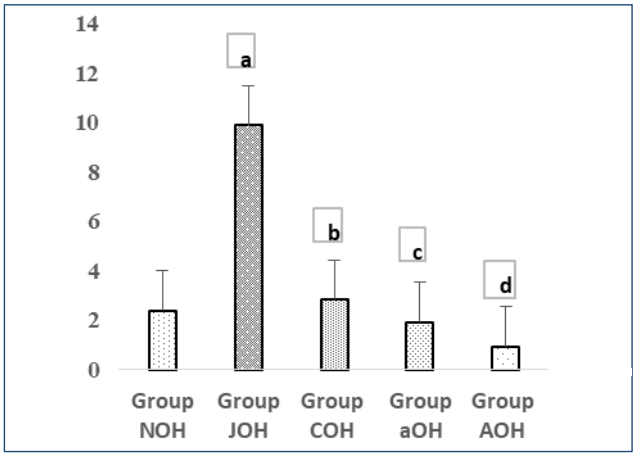

Figure 1. Comparison of vascular permeability between groups. NOH: no OHSS, control; JOH: just OHSS, no treatment; COH: cabergoline+OHSS; aOH: aflibercept (12.5 mg/kg)+OHSS; and AOH: aflibercept (25 mg/kg)+OHSS. Comparison between groups was performed using Kruskal-Wallis test, and in case of significant difference post-hoc analyses with Bonferroni correction were performed. $p<0.05$ were considered significant. [a]$p=0.004$ JOH group and NOH group were compared. [b]$p=0.003$ JOH group and COH group were compared. [c]$p=0.003$ JOH group and aOH group were compared. [d]$p=0.001$ JOH group and AOH group were compared.

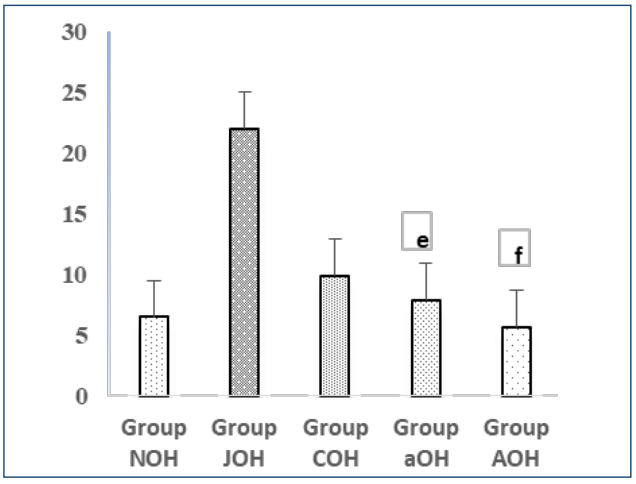

Figure 3. Comparison of vascular endothelial growth factor expression between groups. NOH: no OHSS, control; JOH: just OHSS, no treatment; COH: cabergoline+OHSS; aOH: aflibercept (12.5 mg/kg)+OHSS; AOH: aflibercept (25 mg/kg)+OHSS. Comparison between groups was performed using Kruskal-Wallis test, and in case of significant difference post-hoc analyses with Bonferroni correction were performed. $p<0.05$ were considered significant. [e]$p=0.008$ JOH group and aOH group were compared. [f]$p=0.005$ JOH group and AOH group were compared.

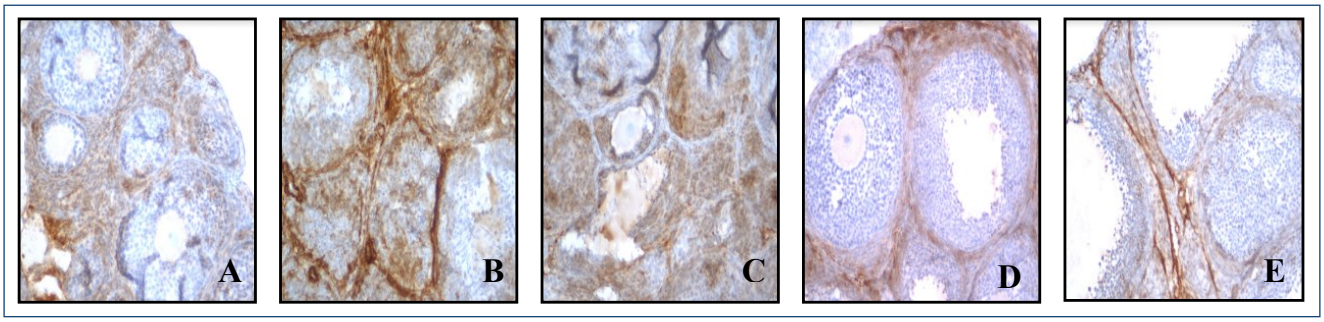

Figure 2. Vascular endothelial growth factor immunoexpression in the ovaries. (A) Control group, less staining; (B) increased expression of vascular endothelial growth factor in granulosa cells in the ovarian hyperstimulation syndrome group; (C) decreased vascular endothelial growth factor expression in the cabergoline group; (D) more decreased vascular endothelial growth factor expression in the 12.5 mg/kg aflibercept group; and (E) much more decreased vascular endothelial growth factor expression in the 25 mg/kg aflibercept group. Magnification 200×.

study, aflibercept was shown to decrease body weight gain[11]. Our study showed that the OHSS group had heavier ovaries than the control group. In the aflibercept-treated groups, ovarian weight decreased proportionally with increasing dose. Although these results are not statistically significant, they are consistent with those of previous studies[1,9].

Ovarian hyperstimulation syndrome's main pathology is capillary permeability. In vulnerable individuals, increased VEGF release in luteinized granulosa cells of the ovary causes symptoms to initiate and develop[12]. Therefore, antiangiogenic drugs are capable of treating OHSS. There are various experiments in the literature for the mechanism of inhibition of angiogenesis: Şanlı et al., focused on oxidative stress sensitive transient receptor potential melastatin 2 (TRPM2) channels that can induce angiogenesis in OHSS. Pala et al., focused on the antiproliferative effect of tamoxifen by blocking the mitogenic effect of estrogen. Zhai et al., focused on the suppression of VEGF expression through the Kisspeptin / KISS1R (KISS1 receptor) system[2,13,14]. In our study, OHSS rats showed higher VEGF levels. Aflibercept reduced VEGF expression and was more effective in treatment than cabergoline.

Early administration of cabergoline is a safe and potentially more effective method for prophylaxis of OHSS in high-risk settings[15]. Our study does not provide information on the clinical safety of aflibercept in OHSS. However, aflibercept is now preferred as first-line therapy for diabetic retinopathy because the risk of complications is lower than with other anti-VEGF drugs[16]. According to ophthalmologists, bevacizumab, another anti-VEGF drug, has a lower success rate in treating retinopathy than aflibercept[17]. It has been shown that another anti-VEGF drug, bevacizumab, was better in treating OHSS than cabergoline when the peritoneal VEGF levels were measured in both groups[18]. On the contrary, we investigated the permeability of peritoneal fluid with methylene blue solution. Our results show that aflibercept is very effective in both inhibiting vascular permeability and reducing VEGF expression, two of the most important indicators of OHSS. The fact that we formed groups that received two different amounts of therapy can be considered a means of validating the results.

Our study has some limitations. Due to its restricted characteristics, this study cannot compare side effects. Ultimately, this is an animal study that is not transferable to humans. Systemic anti-VEGF medicines raise arterial blood pressure, thromboembolic events, left ventricular dilatation, and contractile dysfunction[19]. On the contrary, cabergoline can cause serious side effects such as respiratory problems, complications with heart valves, and risk of addictive behavior, in addition to headache, dizziness, nausea, and constipation[20].Treatments accompanied the OHSS induction. Hence, this study should be viewed more as a preventative measure. Therefore, the acceptance of aflibercept as a treatment option for OHSS depends on further animal studies and clinical trials.

CONCLUSION

Our pioneering study shows that aflibercept, an antiangiogenic drug, effectively reduces OHSS by decreasing vascular permeability and VEGF expression. This study shows that the efficacy of aflibercept in OHSS is significantly more prominent than that of cabergoline.

DATA SHARING STATEMENT

All data from this research, which was planned as an animal study, will be made available upon request. The authors state that the information may be published in the data sharing statement. Data include Excel and/or SPSS version of results obtained for statistical analysis, hematoxylin-eosin stained preparations, immunohistochemistry stained preparations, and any other information obtained.

ETHICAL APPROVAL

The Ankara University Animal Research Ethics Committee approved the project (meeting date: 16/03/2022, meeting number: 2022-06, file number: 2022-32, and decision number: 2022-6-58). The rats were obtained from the animal laboratory of Ankara University, where the animals were cared for and the experiment was conducted. In all animal experiments, the rules of the Human Care Committee for Animal Experiments were completely followed.

AUTHORS' CONTRIBUTIONS

ÇA: Conceptualization, Data curation, Formal Analysis, Funding acquisition, Methodology, Project administration, Resources, Visualization, Writing – original draft. **BD:** Conceptualization, Funding acquisition, Investigation, Project administration, Supervision, Visualization, Writing – review & editing. S**YE:** Data curation, Formal Analysis, Funding acquisition, Resources, Software, Validation, Visualization, Writing – original draft. **FA:** Formal Analysis, Funding acquisition, Methodology, Software, Validation, Visualization, Writing – original draft.

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ORIGINAL ARTICLE

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Should we reconsider high-risk features in thyroid ultrasonography?

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SUMMARY

OBJECTIVE: Round shape is generally considered to reduce the risk of malignancy according to recent guidelines. On the contrary, according to some reports, spherically shaped thyroid nodules are associated with a higher risk of malignancy. Thus, we aimed to evaluate the malignancy risk of solid round isoechoic nodules detected at thyroid ultrasonography and compare it with that of solid ovoid isoechoic nodules.

METHODS: Between 2017 and 2022, solitary solid round isoechoic nodules with diameters ³10 and £25 mm at thyroid ultrasonography were retrospectively selected and enrolled in the study. Age, size, nodule volume, serum thyrotropin levels, thyroid antibody levels, and cytopathological and histopathological results were recorded.

RESULTS: A total of 457 solitary solid isoechoechoic nodules from 457 patients (262 females and 195 males; median age, 59 [31–70] years) were selected, of which 203 were solid round isoechoic nodules, and 254 were solid ovoid isoechoic nodules. A total of 54 surgical operations were performed on 457 nodules, and 31 of them resulted in malignancy. From the 31 malignant results, 25 originated from solid round isoechoic nodules and the remaining 6 originated from solid ovoid isoechoic nodules ($p<0.025$).

CONCLUSION: We found that round nodules have higher malignancy rates than ovoid nodules. We think that ultrasonographic risk stratification systems used to target the most suitable nodules for the necessary biopsies can be dynamically updated, and sphericity can be added as a parameter in patient-based decision-making.

KEYWORDS: Thyroid nodule. Color doppler ultrasonography. Malignancy. Fine needle aspiration.

INTRODUCTION

Thyroid nodules are common in about 50% of the adult population with imaging modalities, and their frequency increases with the age of the population. The risk of malignancy ranges from 7 to 15%, depending on several risk factors[1]. Evaluation of thyroid nodules is mainly based on sonographic assessment and fine needle aspiration biopsy (FNAB). Several sonographic guidelines on thyroid imaging reporting and data systems (TIRADS) employ sonographic criteria to intensify the diagnostic workup and select the suspicious thyroid nodules for FNA. These systems try to establish a standard dictionary of nodule description, define the suspicious characteristics, put the nodule into a risk category, and identify those nodules in which FNA is indicated also by considering the size[2,3].

There are common high-risk sonographic features in different TIRADS, such as marked hypoechogenicity, irregular margins, punctuate echogenities, taller-than-wide shape, and evidence of extrathyroidal growth or pathologic lynphadenopathy. The highest diagnostic accuracy for predicting malignancy was taller-than-wide shape, which reflects a centrifugal pattern of growth[4-8]. Nevertheless, in sonographic classifications, isoechogenicity and round shape are usually among the features that do not affect the risk category of an individual nodule.

Recently, a large prospective cohort study reported that spherically shaped thyroid nodules are associated with a higher risk of malignancy irrespective of age, sex, and nodule size[9]. Thus, we aimed to report our institutional data on relatively small (i.e., 10–25 mm) round isoechoic nodules retrospectively, calculate their spherical shape configuration, and examine their association with malignancy.

METHODS

These retrospective cohort data were collected at our tertiary university hospital in Ankara, from January 2017 to June 2022. Solitary and solid thyroid nodules with the longest diameters of ≥10 and ≤25 mm detected at thyroid ultrasonography (US) were retrospectively selected and enrolled in the study. Age, sex,

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sonographic features, laboratory data, and cytopathological and/or histopathological results were recorded. The study was approved by the local Institutional Research Ethics Committee [Ankara University, 2022000054-1(2022/54)] and certified that the study was performed in accordance with the ethical standards as laid down in the 1964 Declaration of Helsinki.

Thyroid ultrasonography, thyroid nodules, and fine needle aspiration biopsy

Thyroid ultrasonography was performed by 30 and 9-year experienced endocrinologists (MFE and AGC) using a Logiq S6 ultrasound system (GE® Healthcare, Milwaukee, WI) and a 10–13 mHz broadband linear probe. The length, width, and depth of each nodule were reported. The volume of each nodule was calculated using the ellipsoid formula (length×width×depth×π/6)[10]. Nodules were retrospectively classified as ovoid (solid ovoid isoechoic nodule [SOIN]) or round (solid round isoechoic nodule [SRIN]). We determined the round shape of a nodule when the ratio of anteroposterior diameter to either transverse or longitudinal diameter is between 0.9 and 1.1[11]. Oval shape is determined when the anteroposterior diameter of a nodule is less than its transverse diameter on the transverse and longitudinal planes[5]. Nodules with one or more highly suspicious US features (hypoechogenicity, irregular margins, punctuate echogenities, and taller-than-wide shape), hyperechoic/mildly or markedly hypoechoic nodules, and nodules with cystic components were excluded. Patients with a family history of any type of thyroid carcinoma and a history of head and neck irradiation were excluded. Ultrasonography-guided FNAB had been performed by using 22-gauge needles by those endocrinologists with nodules 1 cm or greater in maximal diameter because of the retrospective design of the study[10]. Results were described according to the Bethesda System for Reporting Thyroid Cytopathology[12]. Between 6 and 12 months, periodical sonographical follow-up was performed for all nodules, and repeated FNABs were performed if necessary. For cases of Bethesda 4, 5, and 6 results, the patients underwent either lobectomy or total thyroidectomy, and a subsequent surgical pathological diagnosis was reported[10]. A flow diagram is given for surgical decisions (Figure 1). The nodules that had at least two cytopathological diagnoses of Bethesda category 2 or when histopathological evaluation was benign were accepted as benign[9].

Laboratory evaluation

Serum thyrotropin (TSH), free triiodothyronine (fT3), free thyroxine (fT4), anti-thyroid peroxidase (anti-TPO), and anti-thyroglobulin (anti-Tg) were examined. Normal ranges in our laboratory for TSH, fT3, fT4, anti-TPO, and anti-Tg levels are 0.38–5.33 mIU/mL, 3.99–6.71 pmol/L, 7–15.96 pmol/L, 0–9 IU/mL, and 10–115 IU/mL, respectively. Thyroid autoantibody positivity was determined as values higher than the reference.

Statistical analysis

The Kolmogorov-Smirnov criterion was used for the assessment of normality of diameters and volumes of thyroid nodules. Continuous variables were expressed as a mean±standard deviation or median (minimum and maximum). Discrete variables were expressed as medians with minimum and maximum values instead of interquartile ranges to demonstrate the heterogeneity of the data. Categorical variables, such as age and gender, were summarised as frequencies and percentages. For analysis of categorical variables, the chi-square test or Fisher exact tests were used. The SOIN and SRIN groups were compared with the Mann-Whitney U test for age and laboratory tests.

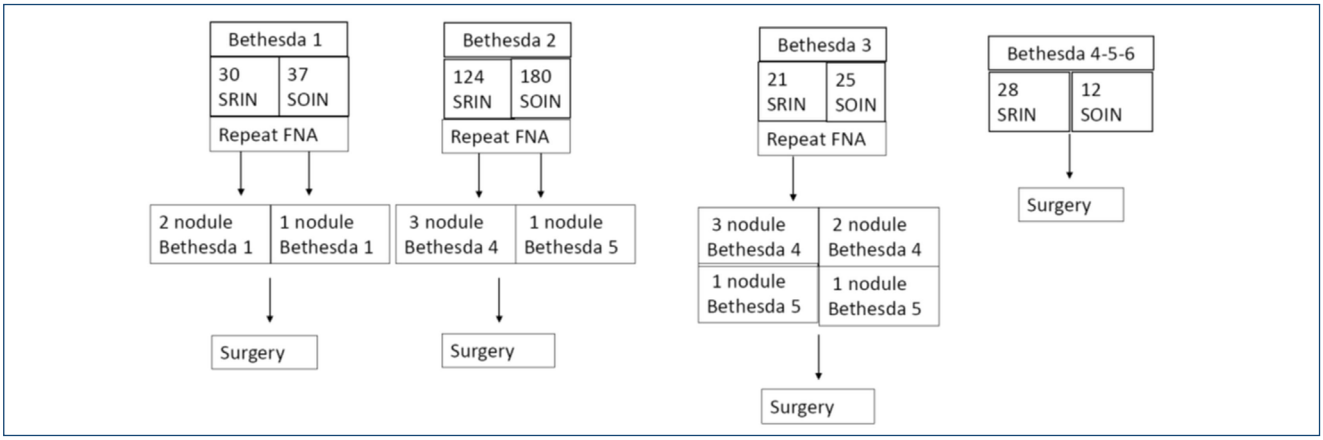

Figure 1. Flow diagram of selection of the nodules according to their Bethesda category for surgery. SRIN: solid round isoechoic nodule; SOIN: solid ovoid isoechoic nodule.

Statistical analyses were performed using the SPSS statistical software (released in 2015, IBM SPSS Statistics for Windows Version 23.0, IBM Corp., Armonk, NY). A two-tailed p<0.05 was determined as statistically significant.

RESULTS

A total of 457 solitary isoechoechoic nodules from 457 patients [262 females and 195 males; median age, 59 (31–70 years)] were selected for the present analysis. The median TSH was 1.16 (0.38–5.33) mIU/mL. The median largest diameter of nodules was 13 mm (10–25 mm), and the median total nodule volume was 0.83 (0.52–4.06) cm^3. In all, 203 of the nodules were SRINs, and 254 of them were SOINs. The median of age, largest diameter, nodule volume, TSH levels, and cytopathological (first fine needle aspiration) and histopathological results of SOINs and SRINs are given in Table 1. Repeated FNAB results were not included in the cytopathology section. Bethesda classes 2 and 6 were significantly different among SRIN and SOIN groups (p-value of 0.003 and 0.001, respectively).

It was observed that a total of 54 surgical operations were performed within 457 nodules, and 31 of them resulted in malignancy. Moreover, we found that out of 31 malignant results, 25 (80.6%) were SRINs and the remaining 6 (19.3%) were SOINs (p=0.025). Out of the 31 malignant nodules, 5 were compatible with follicular variant of papillary thyroid cancer (PTC) (diagnosed from four SRINs and one SOIN), and 26 were compatible with the classical type of PTC (diagnosed from 21 SRINs and 5 SOINs). Cytological distribution of the 31 nodules that were histopathologically proven to be malignant was as follows: 3 Bethesda class 1 (2 SRINs and 1 SOIN), 4 Bethesda class 2 (3 SRINs and 1 SOIN), 6 Bethesda class 3 (no SRIN and 6 SOINs), 4 Bethesda class 4 (4 SRINs and no SOINs), 3 Bethesda class 5 (1 SRIN and 2 SOINs), and 11 Bethesda class 6 (11 SRINs and no SOIN). Overall, Bethesda classifications were similar between the SRIN and SOIN groups. No laboratory or sonographic features could be detected to differentiate between the two groups (Table 2).

Thyroid autoantibody positivity (anti-TPO and/or anti-TG) was higher in SRINs than SOINs (p=0.03), but it was similar between malignant SRINs and malignant SOINs (p=0.94).

DISCUSSION

Several ultrasonographic high-risk features have been identified in the thyroid cancer risk assessment systems at present. Taller-than-wide shape has so far predicted a high risk of malignancy in the guidelines published for risk assessment[13]. Taller-than-wide configuration is reported to be specific but not

Table 1. Comparison of study parameters, and cytological (first fine needle aspiration) and pathological results of solid round isoechoic nodules and solid ovoid isoechoic nodules.

		SRIN (n=203)	SOIN (n=254)	p-value
Age (years)		55 (31–70)	61 (32–70)	**0.003**
Diameter (largest) mm		12 (10–25)	13 (10–25)	0.10
Nodule volume (cm^3)		1.08 (0.52–8.1)	0.70 (0.37–5.2)	**<0.001**
Serum TSH level (mIU/L)		1.2 (0.4–4.3)	1.15 (0.6–4)	0.24
Thyroid autoantibody positivity (anti-TPO and/or anti-TG)		42/203 (20%)	64/254 (25%)	**0.03**
Cytopathological results (initial)	Bethesda classification 1	30 (14.7%)	37 (14.5%)	0.057
	Bethesda classification 2	124 (61%)	180 (70.9%)	**0.003**
	Bethesda classification 3	21 (10.3%)	25 (10%)	0.358
	Bethesda classification 4	9 (4.4%)	10 (3.9%)	0.06
	Bethesda classification 5	8 (4%)	2 (0.8%)	1.000
	Bethesda classification 6	11 (5.4%)	0	**<0.001**
Not operated		166 (81.8%)	237 (93.3%)	0.05
Histopathological results	Malignant	25 (12.3%)	6 (2.4%)	**0.025**
	Benign	12 (5.9%)	11 (4.3%)	

TSH: thyroid stimulating hormone; TPO: thyroid peroxidase; Tg: thyroglobulin; AUS: atypia of undetermined significance; FLUS: follicular lesion of undetermined significance; FN: follicular neoplasia; SFN: suspicious for follicular neoplasia; SM: suspicious for malignancy. Bold values indicate statistical significance at the p<0.05 level.

Table 2. The characteristics of the 31 histopathologically proven solid round isoechoic and solid ovoid isoechoic malignant nodules.

		SRINs (n=25)	SOINs (n=6)	p-value
Age (years)		52 (35–67)	44 (38–63)	0.300
Diameter (largest) mm		12 (10–24)	13 (11–25)	0.691
Nodule volume (cm^3)		0.93 (0.52–3.59)	2.2 (0.6–4)	0.249
Serum TSH level (mIU/L)		1.5 (0.52–4)	1.1 (0.5–2)	0.961
Thyroid autoantibody positivity (anti-TPO and/or anti-TG)		8 (32%)	2 (33%)	0.944
Cytological diagnosis	Bethesda 1	2	1	0.488
	Bethesda 2	3	1	1.000
	Bethesda 3	4	2	0.567
	Bethesda 4	4	0	0.561
	Bethesda 5	1	2	0.087
	Bethesda 6	11	0	0.065
Histopathological diagnosis	FV-PTC	4 (80%)	1 (20%)	1.000
	C-PTC	21 (80.7%)	5 (19.2%)	

TPO: thyroid peroxidase; TG: thyroglobulin; FV-PTC: follicular variant papillary thyroid carcinoma; C-PTC: classical type papillary thyroid carcinoma.

sensitive for malignancy with a false-negative rate of up to 40%[14]. Data have begun to accumulate, suggesting that the spherical shape may also pose a risk[9,11,15].

The growth of a malignant thyroid nodule depends on the sufficient supply of oxygen and nutrients provided by the vessels. Angiogenesis is a requirement for the invasion, progression, and metastasis of tumours[16]. Alexander et al., hypothesised that malignant tumours might configure their shape to maximise exposure and consumption of nutrients and growth. The spherical shape of a tumour maximises the surface area, enabling the maximum number of cells to receive nutrients. Alexander et al., reported that when nodules are classified according to long to short axis ratios (i.e., 1–1.49; 1.5–1.99; ≥2), spherical nodules have a substantially higher malignancy risk when compared to nonspherical ones[15]. Similar results were obtained by Kim et al., who reported that SRINs are associated with a relatively high malignancy rate of 25.9% (7 of 27 SRINs), regardless of their colour Doppler pattern[11]. Recently, in a large prospective study consisting of 4,282 nodules, authors argued that a system used to evaluate three dimensions in both axial and transverse planes is more appropriate than a cross-sectional ratio obtained from the transverse dimension alone. They reported that malignant nodules had a significantly lower long-to-short axis ratio than benign ones, indicating a greater risk of malignancy in more spherical nodules, and the risk continued to increase as the ratio approached a purely spherical ratio of 1.0 (i.e., >2.00, 14.6%; 1.51–2.00, 19.7%; 1.00–1.50, 25.5%; p<0.0001). Aside from the nodule's spherical shape, younger age and male sex were also independently correlated with the risk of cancer in multiple regression analysis, which may contribute to surgical decision-making for indeterminate cytological results[9].

On the contrary, an Italian group, using radiomics analysis of [^{18}F]-fluorodeoxyglucose-avid thyroid incidentalomas, reported that higher values of sphericity are associated with a lower risk of malignancy, with negative predictive values of 82% in a recent study. On the contrary, another Italian group, also using radiomics, reported that spherical configuration had a lower risk of malignancy in cytologically indeterminate thyroid nodules[17,18].

The association between chronic lymphocytic thyroiditis (CLT) and PTC has been investigated for several years. The biological association between CLT and differentiated thyroid cancer (DTC) has not been elucidated yet. In a meta-analysis, both positive thyroglobulin antibody (Tg) and positive thyroid peroxidase (TPO) antibody were found to be associated with an increased risk of DTC[19]. It was hypothesised that the exposure of thyroglobulin antigen during tumour formation could cause an increase in serum TgAb through immune responses[20]. On the contrary, there is an argument that lymphocytic infiltration developed mainly in response to the tumour itself, and lymphocytic infiltration represents a form of immune reaction to control tumour growth and proliferation[21]. In our study, a higher rate of anti-TPO/Tg positivity was obtained in SRINs than SOINs, but thyroid autoimmunity in histopathologically proven malignant nodules was similar between the SRINs and SOINs groups.

In this study, we report a significantly increased malignancy risk in SRIN group. A possible limitation of our study

is that the age was higher in the SOIN group than the SRIN group, but was similar between the SRIN-derived and SOIN-derived malignant populations (median age, 52 vs. 44 years). On the contrary, round nodules were strictly differed from ovoid ones by calculating three-dimensional ratios in the current study. In addition, nodules with cystic components and even those with slight hypoechogenicity or hyperechogenicity were excluded. Moreover, including relatively small- and medium-sized nodules (10–25 mm) in the study enables more precise measurements and avoids irregular-shaped nodules, which are usually more common among larger nodules.

CONCLUSION

We found that SRIN group have significantly higher malignancy rates than SOIN group, which contributed to Kim et al.'s initial findings. This supported the data that being in a round shape rather than ovoid alone poses an extra risk for malignancy in isoechoic nodules. Further studies with isoechogenicity and sphericity are needed to enable the addition of this easy-to-define, and reproducible feature to the risk stratification systems. Since thyroid nodules are quite common in daily practice and thyroid ultrasonography is an affordable, easy-to-use, and accessible technique, usual high-risk sonographic features should be constantly reviewed and revised to reveal a substantial impact on the evaluation of thyroid lesions.

DATA AVAILABILITY STATEMENT

The data that support the findings of this study are available on request from the corresponding author. The data are not publicly available due to privacy or ethical restrictions.

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AUTHORS' CONTRIBUTIONS

AGC: Conceptualization, Data curation, Formal Analysis, Investigation, Methodology, Resources, Software, Writing – original draft. **HYD:** Data curation, Investigation, Methodology. **FNK:** Data curation, Investigation, Methodology. **DGT:** Data curation, Investigation, Methodology. **MFE:** Project administration, Supervision, Writing – review & editing.

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ORIGINAL ARTICLE

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Polycystic ovary syndrome and abdominal fat: is there a relationship?

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SUMMARY

OBJECTIVE: The aim of this study was to compare the distribution of fat tissue in non-obese women with polycystic ovary syndrome and those without the syndrome using dual-energy radiological densitometry.

METHODS: This was a case-control study in which we enrolled women aged 14–39 years with polycystic ovary syndrome according to the Rotterdam criteria with a body mass index between 18.5 and 30 kg/m^2. The control group comprised women with the same profile, but without polycystic ovary syndrome. Patients were treated at the Endocrinological Gynecology Outpatient Clinic of the Department of Obstetrics and Gynecology of the Irmandade da Santa Casa de Misericórdia de São Paulo between 2019 and 2022. Anthropometric measurements were taken and the assessment of body composition was performed using dual-energy radiological densitometry.

RESULTS: The sample comprised 57 women: 37 in the polycystic ovary syndrome group and 20 in the control group. The mean age of the polycystic ovary syndrome group was 24.9 years (±6.9) with a mean body mass index of 60.8 kg/m^2 (±8.5), and for the control group, it was 24.2 years (±6.9) with a mean body mass index of 58 kg/m^2 (±8.4). Body composition was evaluated using dual-energy radiological densitometry and showed a higher value of trunk fat in the polycystic ovary syndrome group (44.1%, ±9.0) compared to the control group (35.2%, ±11.4), which was statistically significant (p=0.002).

CONCLUSION: Our study showed that non-obese polycystic ovary syndrome patients have a higher concentration of abdominal fat, which is a risk factor for increased cardiovascular risk and insulin resistance.

ClinicalTrials.gov ID: NCT02467751.

KEYWORDS: Polycystic ovary syndrome. Body composition. Insulin resistance. Hyperandrogenism. Body mass index.

INTRODUCTION

Polycystic ovary syndrome (PCOS) is a heterogeneous clinical condition characterized by hirsutism, menstrual irregularity, infertility, and endocrine changes such as hyperandrogenism. Its prevalence may vary according to the criteria used for its diagnosis, and it ranges from 9 to 18%. Abdominal obesity is present in approximately 50% of women with PCOS, with onset in late childhood and increasing during puberty. The clinical phenotype and development of PCOS are enhanced by the presence of obesity, especially among those who are prone to genetic disorders[1].

Assessment of body composition by dual-energy radiological densitometry (DEXA) occurs when an X-ray or photon source is placed on one side of the object and the intensity of the beam on the opposite side is related to its thickness, density, and chemical composition. This attenuation phenomenon depends on the energy of the incident photon and is different in bone, lean mass, and fat tissue, reflecting their different densities and chemical composition[2]. DEXA measures visceral and subcutaneous fat accurately and reliably and is a technique that surpasses the accuracy of anthropometric measurements due to its precision in measuring body fat. The software used with DEXA calculates fat in different regions of the body[3]. It is a non-invasive technique that is easy to perform, safe, and low risk. Studies have shown strong correlations in the assessment of body fat with DEXA, indicating that the method can be considered as a reference for measuring adiposity in epidemiological studies. Anthropometric indices, such as body mass index (BMI) and waist circumference, remain the most used parameters to assess adiposity due to their simplicity; however, these indices do not directly measure the amount of adipose tissue and there is no distinction between fat and lean mass, so this raises questions about the validity of anthropometric measures[3-5].

The objective of this study was to compare the distribution of fat tissue using DEXA in non-obese women with PCOS compared to those without the syndrome.

METHODS

This was a case-control study in which we enrolled women aged between 14 and 39 years with PCOS according to the

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Rotterdam criteria[1], with a BMI between 18.5 and 30 kg/m^2 and who were not using contraceptives. The control group comprised women with the same profile but without PCOS. Patients were treated at the Endocrinological Gynecology Outpatient Clinic of the Department of Obstetrics and Gynecology of the Irmandade da Santa Casa de Misericórdia de São Paulo between 2019 and 2022.

The patients were in menacme and they answered questions about the menstrual cycle, acne, hirsutism, and medication use. Body weight (kg) was obtained using an electronic scale (accuracy of 0.1 kg) with an empty bladder and with the woman wearing only underwear. Height (m) was obtained using a wall stadiometer with the woman barefoot and with a precision of 0.5 cm. Thus, we calculated the BMI (BMI=weight/height^2) (kg/m^2), as recommended by the World Health Organization for assessing nutritional status[6]. To measure waist circumference (cm), the tape on the lesser curvature located between the last costal arch and the iliac crest. All anthropometric measurements were performed by a single researcher throughout the entire project.

Clinical hyperandrogenism was evaluated using the modified Ferriman-Gallwey index according to the criteria adopted by Hatch et al.[7], women with a score greater than eight being considered hirsute[8]. In both groups, we evaluated lipoprotein profile [total cholesterol and fractions (mg/dL)], triglycerides (TG) (mg/dL), insulin dosage (μIU/mL), fasting glucose (mg/dL), and classic glycemic curve (2 h) (mg/dL).

Laboratory hyperandrogenism was evaluated through measurements of total testosterone (testosterone T) (ng/dL), dehydroepiandrosterone (DHEA) (ng/dL), dehydroepiandrosterone sulfate (SDHEA) (μg/dL), 17 alpha-hydroxyprogesterone (17OHP) (ng/mL), and sex hormone binding globulin (SHBG) (nmol/L). The following were also measured: thyroid-stimulation hormone (TSH), free tetraiodothyronine (T4l), luteinizing hormone (LH) (mUI/mL), and follicle stimulating hormone (FSH) (mUI/mL).

Hormonal and insulin dosages were performed using the chemiluminescence method with an Immulite 2000 device. Hormonal tests were collected from all women who menstruated in the follicular phase between the third and fifth day. Blood collection occurred after a 12-h fast in the morning. FSH, LH, TSH, free T4, total testosterone, prolactin, classic glycemic curve, and insulin were evaluated by electrochemiluminescence, with a COBAS 6000-ROCHE device. 17OHP was determined by radioimmunoassay. DHEA, S-DHEA, and SHBG were analyzed by electrochemiluminescence in Roche Modular-cobas 601 automation.

Total cholesterol, serum concentrations of high-density lipoprotein, and TG were measured by the enzymatic method using the BT 3000 plus device (Wiener lab®, Rosario, Argentina). The low-density lipoprotein (LDL) value was calculated and obtained using the Friedewald formula (LDLc=TC-HDLc-TG/5)[9]. The homeostatic model for the assessment of insulin resistance (HOMA-IR) was calculated using the formula: {(fasting glucose in mg/dL´0.05551)´fasting insulin in μU/mL}/22.5[10]. All measurements were performed at the Central Laboratory of Santa Casa de São Paulo.

Transvaginal pelvic ultrasound was performed in all women, those menstruating during the follicular phase from the third to the fifth day of the cycle with the Voluson 730 expert machine (GE Medical Systems, ZIPF, Austria). The ovarian volume and the number/size of follicles present in these organs were evaluated. To calculate the ovarian volume, the prolate ellipsoid formula was used (depth´width´length´0.5)[11].

The diagnosis of PCOS was obtained using the Rotterdam criteria, which defines it in the presence of two of the following three criteria: oligomenorrhea or anovulation; clinical or laboratory hyperandrogenism; and ovaries with a polycystic appearance on ultrasound (20 or more follicles measuring between 2 and 9 mm in diameter or increased ovarian volume >10 cm^3). Other causes of menstrual irregularity and hyperandrogenism, such as hyperprolactinemia, hypothyroidism, Cushing's syndrome, non-classical forms of congenital adrenal hyperplasia, and androgen-secreting neoplasms, should also be excluded[1].

Inclusion criteria: PCOS group: Women with PCOS according to the Rotterdam criteria, with a BMI between 18.5 and <30 kg/m^2, and not using contraceptives. Control group: Women without PCOS, with a BMI between 18.5 and <30 kg/m^2, without contraceptive use, with regular cycles, and without medication in the past 3 months.

Exclusion criteria: Women with BMI between 18.5 and >30 kg/m^2, using oral contraceptives in 3 months prior to inclusion in the study, using corticosteroids, antiandrogenic drugs, statins, hyperprolactinemia, congenital adrenal hyperplasia, Cushing's syndrome, history of angina or myocardial infarction, thrombogenic diseases, hematological disease, systemic, vascular, or thyroid disease, infection or inflammation, malignant disease, patients with diabetes or medications that alter insulin resistance in the last 3 months, pregnant women, women with kidney or liver dysfunction, and alcoholics.

The assessment of body composition was performed using DEXA, which is an absorption technique of two low energy beams emitted by RX (DXA-dual x-ray-absorptiometry) in a densitometer of the brand LUNAR – GE of the whole body, being then obtained the corporal composition[12].

The study was approved by the hospital Ethics Committee number 167/10. The statistical tests used were Student's t-test and the Mann-Whitney U test with a significance level of 5%.

RESULTS

We initially selected 102 women who met the inclusion criteria, with 55 volunteers allocated to the PCOS group and 47 to the control group; however, in the PCOS group, 18 did not attend the exams, and in the control group, 27 did not attend (Figure 1). The final sample therefore comprised 57 participants, who were divided into two groups: 37 in the PCOS group and 20 in the control group. The mean age of the PCOS group was 24.9 years (SD ±6.9) with a BMI of 60.8 kg/m^2 (SD ±8.5) and the mean age of the control group was 24.2 years (SD ±6.9) with a BMI of 58 kg/m^2 (SD ±8.4), without any statistically significant differences between the groups (Table 1).

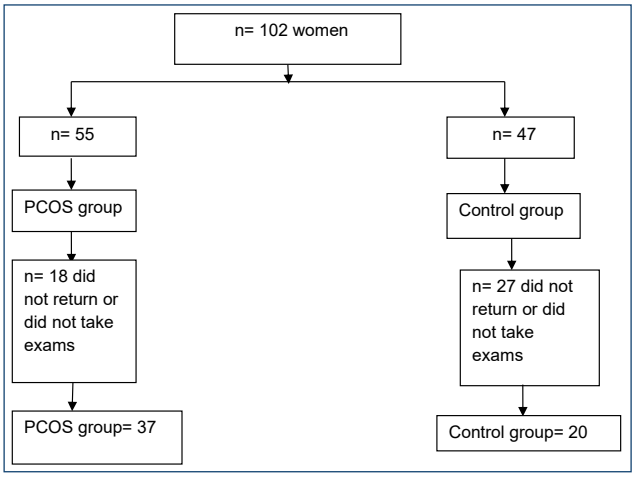

Figure 1. Patient selection flowchart.

There was a significant difference in the following studied parameters: fasting blood glucose (mg/dL) in the PCOS group (88.6±7.9) in relation to the control group (84.2±7.2) (p=0.045) and HOMA-IR in the PCOS group 1.8 (0.4–6.7) and the control group 1.4 (0.7–3.2) (p=0.034). The 2 h blood glucose (mg/dL) (p=0.146), glycated hemoglobin (%) (p=0.056), and insulin (µIU/mL) (p=0.086) had higher values in the PCOS group than in the control group. Total cholesterol (mg/dL), LDL (mg/dL), high-density lipoprotein (HDL) (mg/dL), and TG (mg/dL) did not show significant differences between the studied groups (Table 1).

Serum concentrations of the following analyzed items showed significant differences and were higher in the PCOS group: LH (mIU/mL) 5.4 (0.7–26.4) versus 4 (0.3–7.2) (p=0.026), 17 hydroxyprogesterone (ng/mL) 1.1 (±0.4) versus 0.7 (±0.4) (p=0.005), and total testosterone (ng/dL) 33 (20–109) versus 22.5 (20–55.8) (p=0.003). SHBG values (nmol/L) were higher in the control group than in the PCOS group 89.5 (34–159.8) versus 48.1 (13.3–360) (p=0.004). Serum concentrations of FSH (mIU/mL), DHEA (ng/dL), S-DHEA (µg/dL), and prolactin (ng/mL) were not significant (Table 2).

Body composition was evaluated using DEXA technique and there was a statistically significant (p=0.002) higher value of trunk fat in the PCOS group (44.1%, SD ±9.0) compared to the control group (35.2%, SD ±11.4) (Table 2).

Table 1. Anthropometric characteristics and biochemical parameters of women in the polycystic ovary syndrome group and in the control group.

Variable	PCOS group Median (range)	Control group Median (range)	p
Age (years)	24.9 (±6.9)	24.2 (±6.9)	0.728*
Weight (kg)	60.8 (±8.5)	58.0 (±8.4)	0.242*
BMI (kg/m^2)	23.1 (±3.1)	22.2 (±3.1)	0.311*
Total cholesterol (mg/L)[a]	160.6 (±34.4)	155.3 (±33.8)	0.580*
Low-density lipoprotein (mg/L)	98 (43–143)	90.5 (50–154)	0.694**
High-density lipoprotein (mg/L)	49 (31–115)	51 (36–90)	0.280**
TG (mg/L)	72 (34–173)	57 (35–109)	0.120**
Fasting glucose (mg/L)[a]	88.6 (±7.9)	84.2 (±7.2)	**0.045***
2 h blood glucose (mg/L)	98 (50–240)	89 (69–153)	0.146**
Glycated hemoglobin (%)	5.4 (4–6)	5.1 (5–6)	0.056**
Insulin (uIU/mL)	8.8 (1.9–34.3)	6.8 (3.8–14.4)	0.086**
HOMA-IR	1.8 (0.4–6.7)	1.4 (0.7–3.2)	**0.034****

BMI: body mass index. Statistically significant values are denoted in bold. *Student's t-test; **Mann-Whitney U test; [a]mean±SD; p<0.05.

Table 2. Hormonal parameters and comparison of body composition by in women in the polycystic ovary syndrome group and in the control group.

Variable	PCOS group Median (range)	Control group Median (range)	p
Follicle-stimulating hormone (mUI/mL)	4.3 (2–7.6)	5.6 (0.7–14.2)	0.242*
LH (mUI/mL)	5.4 (0.7–26.4)	4 (0.3–7.2)	**0.026***
17OHP (ng/mL)[a]	1.1 (±0.4)	0.7 (±0.4)	**0.005****
Total testosterone (ng/dL)	33 (20–109)	22.5 (20–55.8)	**0.003***
DHEA (ng/dL)	6.1 (2.1–13.9)	4.7 (1.1–37.1)	0.281*
SDHEA (ug/L)	296 (53–3670)	212.5 (39.3–1390)	0.422*
Prolactin (ng/mL)	10.7 (3.3–47.1)	10.5 (4.9–20)	0.631*
Sex hormone-binding globulin (nmol/L)	48.1 (13.3–360)	89.5 (34–159.8)	**0.004***
Body fat (%)	38.6 (13.3–48.6)	34.0 (16.1–53.4)	0.165*
Truncal fat (%)[a]	44.1 (±9.0)	35.2 (±11.4)	**0.002****
Leg fat (%)[a]	40.1 (±6.4)	37.4 (±9.3)	0.191**

Statistically significant values are denoted in bold. *Mann-Whitney U test; **Student's t-test; [a]mean±SD; p<0.05.

DISCUSSION

We selected women diagnosed with PCOS and with a BMI between 18.5 and <30 for our study. We were interested in this group, as women with PCOS are traditionally obese. However, recent studies have shown that several factors are involved in the pathophysiology of PCOS and that even women with normal or low weight can be carriers of the syndrome.[1]

One of the hallmarks of PCOS is an excess of androgens. In our study, we found an increase in LH, total testosterone, and 17OHP and a decrease in SHBG in the PCOS group, similar to other studies[3,4,5,13]. Increased androgen biosynthesis by the ovaries results in hypothalamic-pituitary-ovarian axis abnormalities. The increase in LH production and the synergistic action with insulin lead to increased androgen production in theca cells. Insulin has a molecular structure similar to insulin-like growth factors and binds to the insulin-like growth factor-1 (IGF-1) receptor, increasing the response of theca cells to LH and, consequently, increasing androgen production[13].

Another issue that caught our attention was the fact that there are controversies in the literature as to which is the best method for measuring the amount of abdominal, trunk, and extremity fat in this group of women. Different methods can be used to assess the amount and distribution of body fat[3,4,14].

In our study, we selected DEXA to assess the amount and distribution of fat. The main advantage of this method is that it allows the direct measurement of the amount of fat in different regions of the body and provides numerical data independent of the operator. In addition, it is a simple method that can be used in population studies. Its main disadvantage is that it is unable to differentiate between subcutaneous and visceral fat[3-5].

However, abdominal fat is metabolically active and linked to insulin resistance and early vascular changes, so the assessment of abdominal fat by DEXA is a good indicator of the metabolic and cardiovascular consequences of obesity and may be a better indicator than a simple determination of visceral fat[15].

In patient with PCOS, excess central fat has been associated with increased insulin resistance. A strong correlation has also been observed using abdominal ultrasound between levels of visceral fat and insulin resistance, as well as metabolic dysfunction[16,17]. In our study, DEXA showed that patients with PCOS had a statistically significant higher concentration of fat in the trunk than the volunteers in the control group.

CONCLUSION

Our study showed that non-obese PCOS patients had a statistically significant higher concentration of abdominal fat than the control group comprising volunteers without PCOS. Increased abdominal fat is probably related to increased cardiovascular risk and insulin resistance.

AUTHORS' CONTRIBUTIONS

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

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