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Actinic cheilitis or squamous cell carcinoma of the lip? Practical recommendations on how to avoid a trap

Hudson Dutra Rezende[1], Daniel Oliveira[2], Marinna Sampaio Campos[1], Loanda Oliveira Fukuma[1], Juliana de Carvalho Delgado[1], Sandra Lopes Mattos Dinato[1]

Actinic cheilitis (AC) is a chronic condition that usually develops in patients with cumulative sun damage[1]. It affects both men and women and is frequently seen in elderly individuals who seek medical help for the treatment of other dermatologic diseases[1-3]. In daily practice, most of these patients complain of signs of photodamage, like dyschromia in photoexposed body areas, telangiectasias, solar lentigines, xerosis, and elastosis, but they hardly ever mention cutaneous alterations of their lips.

The clinical features of AC are mostly seen in the lower lip due to continuous exposition to ultraviolet radiation, which, in turn, allows for a wide range of clinical signs, varying from persistent areas of dryness to overt atrophic changes, ill-defined vermilion border, edema, and focal hyperkeratosis[2]. Advanced lesions of AC may exhibit ulceration and crusting, pointing to a possibly not yet diagnosed skin cancer[4]. In fact, in spite of its premalignant nature, AC still represents a neglected condition in individuals with cutaneous photodamage, both from the patients' and the attending physician's perspectives.

As for any other photoinduced skin disorder, the level of sun exposure during a patient's lifetime may contribute to the development of a skin cancer from preexisting lesions of AC[4,5]. It is especially true for patients who live in tropical global areas, such as in Brazil, where the warm weather encourages people to have outdoor activities during several months of the year, either for leisure or for working needs.

The potential for evolving into invasive squamous cell carcinoma (SCC) is higher for AC than that for classic actinic keratosis[6]. Nonetheless, the investigation of malignant transformation from AC is not standardized and answers to questions such as when a lip biopsy is warranted are incompletely found in the literature.

A better understanding of the indications for surgical approach in patients with AC is also important because malignant transformation may cause textural and color changes in the lips[7]. These changes may ultimately be misinterpreted as being features of alternative conditions, such as lupus erythematosus, oral lichen planus, and even other primary lip diseases like plasma cell cheilitis and cheilitis glandularis[2].

It is unanimous in the literature that every patient who presents with AC that cannot be clinically differentiated from SCC of the lip should have their lips biopsied[2]; however, few authors aimed at putting together such surgical recommendations that would help general practitioners get better decisions in their daily practice.

A lip biopsy should not be routinely performed in patients who display pure signs AC. In contrast, it is not expected from patients with AC to display persistent hyperkeratosis or nodular areas on physical examination, since both represent suspicious signs for SCC[1]. The presence of persistent ulceration, especially if lip hydration and lip sun protection are guaranteed, should also be carefully evaluated and considered for biopsy[6]. A summary of additional indications for lip biopsy, as mentioned by other authors, are displayed in table 1[1,8-10].

Table 1. Clinical recommendation for lip biopsy in patients with the diagnosis of actinic cheilitis.

Vieira et al.[1]	• In the presence of lip textural changes to the touch. • If the semimucosa appears thickened.
Sarmento et al.[8]	• After failure of conservative treatment. • When actinic cheilitis is small and amenable to complete surgical excision. • In the presence of ulcerations, atrophy, or nodules.
Lopes et al.[9]	• After failure of conservative treatment. • If there is clinical suspicion of malignancy. • To determine the degree of epithelial dysplasia with respective follow-up.
Seoane et al.[10]	• When a clinical diagnosis of malignancy is suspicious. • When clinical changes or signs of suspicion for malignant. • Transformation is detected during follow-up (at any time point).

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Another point of discussion for patients with the diagnosis of AC is whether to perform a punch biopsy or an elliptical incision. Even though there is no contraindication for the first, it seems that the latter is more appropriate since microscopic changes that are suggestive of SCC may be unevenly found in different areas of the lips, making a precise diagnosis more complicated from the examination of a little cutaneous specimen[11].

Finally, the diagnosis of AC is made on clinical grounds, but ruling out malignant transformation depends on histopathology. Being aware of early clinical signs of malignant transformation is a key point to the correct diagnosis and management of such patients.

AUTHORS' CONTRIBUTIONS

HDR: Conceptualization, Data curation, Writing – original draft, Writing – review & editing. **MSC:** Conceptualization, Data curation, Writing – original draft, Writing – review & editing. **LOF:** Conceptualization, Data curation, Writing – original draft, Writing – review & editing. **SLMD:** Conceptualization, Data curation, Writing – original draft, Writing – review & editing. **DO:** Data curation, Writing – original draft, Writing – review & editing. **JCD:** Data curation, Writing – original draft, Writing – review & editing.

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Comment on "Are inflammatory and malnutrition markers associated with metabolic syndrome in patients with sarcoidosis?"

Juncai Tu[1], Xiaofei Li[1*]

Dear Editor,

We were very pleased to read the article entitled "Are inflammatory and malnutrition markers associated with metabolic syndrome in patients with sarcoidosis?" by Isik and his colleagues[1]. In this article, the authors revealed that neutrophil-to-lymphocyte ratio and controlling nutritional status are associated with the metabolic syndrome (MetS)+ in sarcoidosis patients. Thus, close monitoring of neutrophil-to-lymphocyte ratio and controlling nutritional status increase in terms of MetS and immune malnutrition may be important in sarcoidosis patients. This study provides very valuable insight for the prevention of sarcoidosis. However, some concerns arise from our point of views.

The main problem of this study was that baseline characteristics differed significantly between the two groups (i.e., the MetS+ sarcoidosis patients vs. sarcoidosis patients). There was a statistically significant difference between the groups in terms of gender and the presence of diabetes mellitus, hypertension, and glucose. In this study, a total of 253 patients, i.e., 94 sarcoidosis with MetS patients and 159 sarcoidosis without MetS patients, were included.

Chronic diseases such as MetS are known to be often accompanied by a low-grade inflammatory response. Changes in neutrophil-to-lymphocyte ratio may be a concomitant phenomenon of MetS.

AUTHORS' CONTRIBUTIONS

JT: Data curation, Formal analysis, Writing – original draft.
XL: Conceptualization, Writing – review & editing.

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Can grading method of BASRI-hip based on X-ray examination better identify hip involvement?

Linyou Wang[1*], Liang Wu[1]

Dear Editor,

We have read the article entitled "Risk factors for radiological hip involvement in patients with ankylosing spondylitis" that analyzes the risk factors of hip involvement in patients with ankylosing spondylitis (AS). In this study, the authors analyzed the clinical characteristics of patients with hip involvement due to AS evaluated by X-ray. From this analysis, it is found that juvenile onset, lower body mass index, and bone mass below the expected range for age were independently associated with radiological hip joint involvement in patients with AS and suggested that the use of nonsteroidal anti-inflammatory drugs can improve the prognosis[1].

However, from our point of view, some information need to be clear in this study.

First, although the grading method of BASRI-hip based on X-ray examination has good reliability, it is not ideal in describing the sensitivity of severe hip involvement[2,3]. We still hope to read the data of morphological and histological changes of hip joint for quantitative evaluation.

Second, in the study design, the inclusion criteria should be included in the latest diagnostic criteria[4]. It is particularly important to identify patients with negative radiological examination and to exclude all hip joint involvements not due to AS, such as hip joint injury caused by trauma, congenital disease, or systemic disease.

Third, the clinical data of this study need to include the treatment factors affecting the hip involvement in the follow-up, such as whether the patient has undergone surgery, physical therapy, or rehabilitation treatment and the work, living environment, and lifestyle of patients[5].

AUTHORS' CONTRIBUTIONS

LW: Conceptualization, Formal analysis, Writing – original draft, Writing – review & editing. **LW:** Conceptualization, Formal analysis, Writing – original draft.

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Comment on: "Relationship of the prenatal psychosocial profile with postpartum maternal duties and newborn care"

Jiannan Jiang[1], Shengxia Ke[1*]

Dear Editor,

We are glad to read an article entitled "Relationship of the prenatal psychosocial profile with postpartum maternal duties and newborn care." This study investigated the relationship between prenatal psychosocial profile (PPP) and postnatal maternal responsibilities and newborn care[1]. In this study, pregnant women were found to have lower levels of stress, higher levels of social support from their husbands and others, and moderate levels of self-esteem. This study provides important evidence for the management of postpartum women. However, the following clarification will help solve the reader's confusion.

First, the purpose of this study[1] was to elucidate the relationship between PPP and postnatal maternal responsibilities and neonatal care. However, the timing of the first assessment of PPP in this study[1] is unclear. Is PPP first evaluated at 3 months, 6 months, or 1 week before delivery? Nevertheless, that important information is not presented in this study, which may lead to potential implementation bias. In addition, were there statistically significant differences in the time of first PPP assessment among all patients? If the timing of the first PPI assessment is different for all patients, it will lead to incomparability of baseline patient characteristics. Therefore, it is essential to provide more detailed information regarding the first PPP assessment.

Second, this study also compared stress as an important parameter. However, there are numerous factors that affect stress during pregnancy, including dietary habit and body mass index (BMI). Evidence from previous study[2] suggests that maternal psychosocial stress, dietary habits, and nutritional status can modulate changes during pregnancy, suggesting that psychosocial stress, dietary habits, and nutritional status are not isolated from each other, but interact with each other. Recent evidence suggests that omega-3 fatty acid intake is important for replenishing the daily loss of DHA in the brain[3,4], thereby maintaining normal neurological function and reducing psychosocial stress during pregnancy. In contrast, in high-stress conditions, a mother's high pre-pregnancy BMI exacerbates unhealthy eating behaviors, which in turn may contribute to increased underlying stress during pregnancy[4].

AUTHORS' CONTRIBUTIONS

JJ: Conceptualization, Investigation, Methodology, Validation, Visualization, Writing – original draft, Writing – review & editing. **SK:** Investigation, Methodology, Supervision, Validation, Visualization, Writing – original draft, Writing – review & editing.

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ORIGINAL ARTICLE

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Prognostic Value of T-wave Positivity in Lead aVR in COVID-19 Pneumonia

Fatih Sivri[1]*, Burcu Özdemir[2], Mehmet Murat Çelik[3], Fatih Aksoy[4], Burakhan Akçay[3]

SUMMARY

OBJECTIVE: T-wave positivity in the lead aVR is a marker of ventricular repolarization abnormality and provides information on short- and long-term cardiovascular mortality in heart failure patients, those with anterior myocardial infarction, and patients who underwent hemodialysis for various reasons. The aim of this study was to investigate the relationship between T-wave positivity in the lead aVR on superficial electrocardiogram and mortality from COVID-19 pneumonia.

METHODS: This study retrospectively included 130 patients who were diagnosed with COVID-19 and treated as an outpatient or in the thoracic diseases ward in a single center between January 2021 and June 2021. All patients included in the study had clinical and radiological features and signs of COVID-19 pneumonia. The COVID-19 diagnosis of all patients was confirmed by polymerase chain reaction detected from an oropharyngeal swab.

RESULTS: A total of 130 patients were included in this study. Patients were divided into two groups: survived and deceased. There were 55 patients (mean age: 64.76–14.93 years, 58.18 male, 41.12% female) in the survived group and 75 patients (mean age: 65–15 years, 58.67 male, 41.33% female) in the deceased group. The univariate and multivariate regression analyses showed that positive *transcatheter aortic valve replacement* (OR 5.151; 95%CI 1.001–26.504; p=0.0012), lactate dehydrogenase (OR 1.006; 95%CI 1.001–1.010; p=0.012), and D-dimer (OR 1.436; 95%CI 1.115–1.848; p=0.005) were independent risk factors for mortality.

CONCLUSION: A positive *transcatheter aortic valve replacement* is useful in risk stratification for mortality from COVID-19 pneumonia.

KEYWORDS: Electrocardiographic. SARS-CoV-2. Mortality

INTRODUCTION

Although the novel coronavirus 2019 (COVID-19) infection primarily affects the lungs and causes pneumonia, acute respiratory distress syndrome, and even death, various cardiovascular complications are also the leading causes of mortality[1]. Numerous studies and case series have reported that COVID-19 causes myocarditis[2-4], tamponade[5], acute heart failure[6], arrhythmia (tachycardia or bradycardia)[7], Brugada-like electrocardiographic (ECG) pattern[8], transient ST elevation, and sudden cardiac death[9,10].

Cardiac involvement is associated with a poor prognostic outcome, independent of other causes, with an incidence rate of 22–44% in cases of advanced and severe COVID-19 infection[11,12]. Cardiovascular damage can occur through a diverse range of pathways. In addition to the direct cardiotoxic effect, cardiovascular damage may be caused by inhibition of ACE-2 receptors, cytokine storm, coronary plaque rupture, coronary spasm, and microthromboembolism[13,14].

On a superficial ECG, the lead aVR is usually neglected. However, it provides prognostic information on many cardiovascular diseases. A positive T-wave amplitude in the lead aVR gives prognostic information on repolarization abnormality and provides diagnostic and prognostic information on many cardiovascular diseases such as in heart failure[15-17]. However, there is no information regarding its relationship with COVID-19 pneumonia. The aim of this study was to investigate the relationship between T-wave positivity in the lead aVR on superficial ECG and mortality from COVID-19 pneumonia.

METHODS

This study retrospectively included 130 patients who were diagnosed with COVID-19 and treated as an outpatient or in the thoracic diseases ward in a single center between January 2021 and June 2021 after the approval of the local ethics committee (permission dated October 21, 2021, and numbered

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2021/67) and the Ministry of Health of the Republic of Turkey. The study was conducted in accordance with the principles of the Declaration of Helsinki.

All patients included in the study had clinical and radiological features and signs of COVID-19 pneumonia. The COVID-19 diagnosis of all patients was confirmed by polymerase chain reaction (PCR) detected from an oropharyngeal swab. All patients were treated with hydroxychloroquine, azithromycin, and favipiravir. Patients with chronic kidney or liver failure; those with history of anti-arrhythmic drugs use; those living with pacemaker; and those with atrial fibrillation, coronary artery disease, heart failure (with preserved systolic function or systolic heart failure), and abnormal serum electrolyte values were not included in the study.

All patients were questioned in detail for hypertension, hyperlipidemia, diabetes mellitus, tobacco use, asthma, COPD (chronic obstructive pulmonary disease), and the drugs used. Hematological, biochemical, and serological values were obtained from the peripheral blood samples taken following 12 h of fasting and recorded. A troponin value above the 99th percentile upper reference limit value or newly developed ECG and echocardiographic change was considered myocardial damage. Chronic renal failure was defined as a glomerular filtration rate less than 60 mL/min/1.73 m^2, persisting for 3 months. The diagnosis of hypertension was defined as receiving antihypertensive therapy or having a systolic blood pressure above160 mmHg and diastolic blood pressure above 90 mmHg in at least three measurements. Diabetes was defined as the use of anti-diabetic drugs and having at least two postprandial blood glucose measurements above 126 mg/dL or an HbA1c level >6.5. The diagnosis of hyperlipidemia was considered as having a low-density lipoprotein (LDL) level >160 mg/dL or the use of statins.

Electrocardiographic evaluation

Superficial 12-lead ECGs of all patients (Nihon Kohden Cardiofix V Model ECG-1550K device 25 mm/s and standard 1 mV/10 mm) were recorded before the treatment of COVID-19 infection and were evaluated by two independent cardiologists who were blinded to the characteristics of the patients. Heart rate, P-R interval, QT and QTc intervals, and QRS duration were recorded. The P-R interval was measured as the time from the beginning of the P wave to the beginning of the QRS complex in milliseconds. The QRS duration was measured from the beginning of the Q or R wave to the end of the R or S wave in milliseconds. The QT interval was measured from the beginning of the QRS complex to the end of the T wave in milliseconds. The QT-corrected distance was measured using Bazett's formula. The depression or elevation of the ST segment in the lead aVR from the isoelectric line was measured numerically (STaVR). According to the T-wave amplitude in the lead aVR, patients with a positive peak (>0 mV) from the isoelectric line were recorded as positive (positive TAVR), while patients with a negative peak (<0 mV) from the isovolumetric line were recorded as negative (negative TAVR). The amplitude of the T wave (TPaVR) was recorded by calculating its negative or positive deflection from the isoelectric line. The TPaVR/STaVR ratio was obtained by dividing whichever value is greater by the other (large value/small value).

Statistical analysis

The study data were evaluated using the SPSS version 21.0 statistical software. Normality distribution of continuous variables was investigated using visual (histogram and probability charts) and analytical methods (Kolmogorov-Smirnov/Shapiro-Wilk tests). The descriptive statistics of the study were presented as mean and standard deviation for normally distributed data and as median, minimum, and maximum for non-normally distributed data. The chi-square test was used to show whether there was a difference between categorical variables. The Student's t-test was used to compare the continuous variables with parametric properties in independent groups, while the Mann-Whitney U test was used to compare continuous variables with non-parametric properties in independent groups. The level of statistical significance was set at a p-value less than 0.05. There was no study that could be referenced in the sample calculation when the literature was searched; medium-effect size of the chi-square test was taken in the calculation and it was decided to recruit 117 participants in 90% power, 0.05 margin of error, 1 degree of freedom, and 129 participants with 10% reserve.

RESULTS

A total of 130 patients were included in this study. Patients were divided into tw o groups: survived and deceased. There were 55 patients (mean age 64.76–14.93 years, 58.18 male, 41.12% female) in the survived group and 75 patients (mean age 65–15 years, 58.67 male, 41.33% female) in the deceased group. There was no difference between the groups in terms of age and gender. The baseline clinical and laboratory characteristics of the groups are shown in Table 1.

The comparison of laboratory characteristics showed that the deceased group had higher CK-MB (60.88±46.99 vs. 30.55±21.77, p=0.000), troponin (106±64.02 vs. 39.87±14.36, p=0.000), lactate dehydrogenase (LDH) (554.61±209.22 vs. 365.2±155.47 p=0.000), C-reactive protein (CRP) (127±75.32 vs. 87.4±68.24,

Table 1. Baseline characteristics and electrocardiographic findings.

		Group				p
		Deceased		Living		
		n	%	n	%	
Sex	Male	44	58.67	32	58.18	0.956
	Female	31	41.33	23	41.82	
Hypertension	No	28	37.33	15	27.27	0.228
	Yes	47	62.67	40	72.73	
DM	No	52	69.33	38	69.09	0.976
	Yes	23	30.67	17	30.91	
Cerebrovascular disease	No	75	100.00	52	94.55	0.073
	Yes	0	0.00	3	5.45	
COPD	No	41	54.67	44	80.00	0.003
	Yes	34	45.33	11	20.00	
TAVR positive	No	47	62.67	50	90.91	0.000
	Yes	28	37.33	5	9.09	
TAVR negative	No	29	38.67	18	32.73	0.486
	Yes	46	61.33	37	67.27	

DM: diabetes mellitus; COPD: chronic obstructive pulmonary disease; TAVR: T-wave amplitude in the lead aVR.

p=0.001), leukocyte (13.01±4.87 vs. 8.82±4.84, p=0.000), and D-dimer values (25.29±23.09 vs. 1.18±1.06, p=0.000).

The laboratory, ECG, and echocardiographic characteristics are shown in Table 2. Positive TAVR (p=0.000) and STaVR (0.15±0.6 vs. 0.19±0.12, p=0.002) were statistically significant in the deceased group. The univariate and multivariate regression analyses showed that positive TAVR (OR 5.151; 95%CI 1.001–26.504, p=0.0012), LDH (OR 1.006; 95%CI 1.001–1.010, p=0.012), and D-dimer (OR=1.436, 95%CI 1.115–1.848, p=0.005) were independent risk factors for mortality (Table 3).

DISCUSSION

This study has examined the effects of superficial ECG and laboratory findings on mortality in patients with SARS-CoV-2 infection and found several important results. First, the positive T wave in lead aVR is an independent risk factor for mortality. Second, D-dimer and LDH values are also independent risk factors for mortality.

Although SARS-CoV-2 infection primarily affects the lungs and causes pneumonia and/or acute respiratory distress syndrome, it leads to complications such as myocarditis, cardiac tamponade, transit ST elevation, acute heart failure, arrhythmia (tachycardia or bradycardia), and sudden cardiac death[18].

Cardiac damage can occur through a diverse range of pathways. While it may be directly related to cardiac damage, it may cause myocardial inflammation and edema by inhibiting ACE-2 receptors and impairing the cellular defense mechanism. Another mechanism of action is the cytokine storm, which results from excessive cytokine release from type 1 and type 2 T-helper cells and leads to immunopathological events. These factors may cause direct myocyte damage as well as coronary spasm, plaque rupture, and microthromboembolism, leading to vascular inflammation and hypercoagulopathy[19].

Although the lead aVR is often neglected on a superficial 12-lead ECG, it provides diagnostic and prognostic information for many cardiovascular diseases. Lead aVR is a unique superficial ECG lead derived from near leads V1 and D1, providing information about right heart upper basal and viewing the left ventricle from the full brow. Since the lead aVR is a unipolar right extremity lead, represents the cavity of the heart, and is the opposite of the main cardiac vector, all positive deflection waves are negative in the lead aVR. A positive T wave in the lead aVR is usually an uncommon finding. According to the most common and valid hypothesis, the T wave is thought to be positive after vectorial deviation caused by damage to the left ventricular apical, inferior and inferior lateral wall due to various reasons. In another study, in patients with anterior myocardial infarction, positive T wave in lead aVR showed global left ventricular ischemia. Recent

Table 2. Basıc laboratory parameters and electrocardiographic findings to deceased and living groups.

	Group										p
	Deceased (n=75)					Living (n=55)					
	Mean	SD	Median	Minimum	Maximum	Mean	SD	Median	Minimum	Maximum	
AGE	64.76	14.93	68.00	31.00	98.00	64.31	16.00	65.00	20.00	95.00	0.930*
CREATININE	1.35	0.87	1.06	0.20	4.30	1.30	1.50	0.90	0.38	9.00	0.066*
CK-MB	60.88	46.49	45.00	14.00	300.00	30.50	21.76	23.00	11.00	121.00	0.000*
LDH	554.61	209.02	467.00	172.00	950.00	365.24	155.47	321.00	152.00	1052.00	0.000*
SODIUM	136.25	6.73	137.00	140.00	150.00	133.13	5.60	134.00	116.00	142.00	0.12
POTASSIUM	4.21	0.94	4.10	2.90	4.14	4.34	0.68	4.30	3.10	4.80	0.14
CRP	127.09	75.32	103.00	36.00	390.00	87.21	68.24	77.60	2.30	270.00	0.001*
WBC	13.01	4.87	13.20	4.03	29.70	8.82	4.84	8.30	2.30	26.10	0.000*
Hg	11.47	2.10	12.10	7.80	16.10	12.28	1.67	12.20	8.20	15.40	0.062
D-DIMER	25.29	23.09	9.33	0.28	136.00	1.18	1.06	0.65	0.14	8.60	0.000*
TROPONIN	106.28	64.02	74.00	5.00	1031.00	39.87	14.36	12.60	3.00	527.00	0.000*
TPaVR	-0.07	0.26	-0.21	-0.41	0.29	-0.16	0.12	-0.18	-0.40	0.22	0.06
STaVR	0.15	0.06	0.12	0.10	0.39	0.19	0.12	0.15	0.01	0.50	0.002*
HR	83.21	19.10	88.00	45.00	111.00	86.51	17.06	90.00	55.00	125.00	0.290*
PR INTERVAL	107.51	7.30	110.00	89.00	125.00	109.56	23.42	102.00	80.00	200.00	0.173*
QRS INTERVAL	110.52	5.71	111.00	95.00	125.00	112.15	9.42	112.00	95.00	160.00	0.333*
LVEF	64.77	1.58	65.00	60.00	68.00	64.73	2.02	65.00	50.00	65.00	0.147*
QT INT	393.73	42.85	398.00	320.00	490.00	382.22	27.63	386.00	320.00	440.00	0.101*
QTC INT	439.79	46.14	427.00	349.00	521.00	429.47	43.69	430.00	320.00	513.00	0.388*
TPaVR/STaVR	1.58	0.79	1.60	0.00	3.46	1.62	0.62	1.38	0.00	3.20	0.739*

CK-MB LDH: lactate dehydrogenase; CRP: C-reactive protein; WBC: white blood cell; Hg: hemoglobın; TPaVR: amplitude of the T wave; STaVR: The depression or elevation of the ST segment in the lead aVR from the isoelectric line; HR: heart rate; LVEF: left ventricular ejection fraction; QT INT: QT interval; QTc INT: corrected QT interval. *

Table 3. Effects of various variables on COVID-19 mortality in univariate and multivariate logistic regression analyses.

	Unadjusted OR	95%CI	p-value	Adjusted OR	95%CI	p-value
TAVR positive	5.957	2.124-16.713	0.001	5.151	1.001-26.504	0.0012
COPD	3.317	1.487-7.397	0.003	1.431	0.306-6.696	0.649
Troponin	1.009	1.002-1.016	0.014	1.005	0.997-1.014	0.221
CK-MB	1.040	1.020-1.059	0.000	1.021	0.996-1.047	0.104
LDH	1.006	1.003-1.009	0.000	1.006	1.001-1.010	0.012
CRP	1.008	1.003-1.014	0.004	1.006	0.996-1.017	0.210
WBC	1.211	1.108-1.324	0.000	1.155	0.958-1.392	0.131
D-Dimer	1.647	1.254-2.163	0.000	1.436	1.115-1.848	0.005
STaVR	0.005	0.000-0.422	0.019	0.000	0.000-8.308	0.092

TAVR: T-wave amplitude in the lead aVR; COPD: chronic obstructive pulmonary disease; CK-MB: Creatine kinase and its MB isoenzyme; LDH: lactate dehydrogenase; CRP: C-reactive protein; WBC: white blood cell. STaVR: The depression or elevation of the ST segment in the lead aVR from the isoelectric line. Bold indicates significant p-value.

studies have shown that the T-wave positivity in the lead aVR is a marker of ventricular repolarization abnormality and provides information on short- and long-term cardiovascular mortality in patients with heart failure, patients with anterior myocardial infarction, and those who receive hemodialysis for various reasons[15-17] .In their long-term follow-up study of male individuals, Tan et al. showed that the T-wave positivity is an independent risk factor for cardiovascular events[20]. The 33-month follow-up study of 93 patients with heart failure and narrow QRS ECG by Okuda et al. showed that the T-wave positivity provided long-term prognostic information, independent of other causes[21]. The 31-month follow-up study of 93 patients with ICD (implantable cardioverter defibrillation) and ischemic and non-ischemic cardiomyopathy by Tanaka et al. showed that a positive T wave in the lead aVR was an independent risk factor for long-term mortality[22]. The study of 86 cases by Donmez et al. showed that the occurrence of the T-wave positivity in the lead aVR after transaortic valve implantation (TAVI) procedure was an independent risk factor for postoperative short- and long-term mortality[23]. In our study, the examination of the ECG findings of the lead aVR in patients with COVID-19 infection revealed that positive TAVR alone was an independent indicator for mortality. This suggests that a positive TAVR wave provides information on the entire myocardial tissue rather than the apical, inferior, and inferior lateral wall. Even if ejection fraction is same in the two groups, univariate analysis has showed that troponin values are significantly higher in the deceased group. Thus, there is marked subclinical ischemia of global left ventricle without any effect of ejection fraction. For this reason, T-wave positivity in the lead aVR may occur in the deceased group.

İn our study, higher LDH and D-dimer value are independent risk factors of mortality, as shown in previous study. Recent studies and meta-analysis showed that D-dimer value higher 3–4 times in the early stage of COVID-19 infection associated with independent risk for mortality and higher vascular complications. High LDH levels were found to be 6 times more related to the progression of COVID-19 pneumonia and 16 times to mortality compared to patients with normal LDH levels[24,25].

Limitations of the study

This study has several limitations. First, the sample size was small, and the study had a retrospective design. Second, the values such as CRP and troponin, which are associated with subclinical myocardial damage, were not followed up. Third, ECGs of the patients at initial diagnosis were examined, while positive or negative T wave changes on ECGs were not examined. Finally, the medical treatments of the patients were not questioned in detail and their post-treatment ECG changes were not investigated. A prospective study with a large number of patients is needed to validate the results of this study.

CONCLUSION

This study demonstrated that positive T wave in the lead aVR was a significant and independent risk factor for mortality from COVID-19 infection. This unique ECG parameter, which is often overlooked, provides information on the mortality of patients even when other ECG parameters are normal. We recommend that a positive TAVR wave not be neglected when evaluating high-risk patients.

AUTHORS' CONTRIBUTIONS

FS: Conceptualization, Data curation, Formal Analysis, Writing – original draft. **BÖ:** Formal Analysis. **MMÇ:** Formal Analysis. **FA:** Formal Analysis. **BA:** Formal Analysis.

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ORIGINAL ARTICLE

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Diagnostic value of serum levels of galanin and obestatin in patients with gastric cancer

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SUMMARY

OBJECTIVE: Gastric cancer ranks the third among the cancer-related deaths. It is diagnosed at advanced stage in many patients due to malignant proliferation and has a poor prognosis. Currently, no instrument or biomarker has been proven to diagnose the disease before the advanced stages. This study aimed to measure the serum levels of galanin and obestatin, which were examined in various studies including cancer studies, and to discuss their diagnostic value in gastric cancers.

METHODS: In this study, 30 adult patients with gastric cancer and 30 healthy adults in the control group were examined prospectively. The demographic characteristics and serum levels of galanin and obestatin in the patient and control groups were recorded.

RESULTS: The mean serum level of galanin in the patient and control groups was 19.73±5.04 and 35.59±10.94 pg/mL, respectively. The mean serum level of obestatin in the patient and control groups was 40.21±5.82 and 15.15±3.32 ng/mL, respectively. A significant difference was found between the groups ($p<0.001$).

CONCLUSION: Serum levels of galanin were lower and serum levels of obestatin were higher in patients with gastric cancer compared to the healthy individuals. Serum levels of obestatin and galanin can be used as potential biomarkers in the diagnosis of gastric cancer.

KEYWORDS: Obestatin. Galanin. Biomarker. Gastric cancer.

INTRODUCTION

The incidence of gastric cancer varies according to the geographical region; however, it is the fourth most common type of cancer in the world and ranks the third among the deaths associated with cancer[1,2]. Gastric cancer is a type of cancer that is diagnosed at an advanced stage in many patients due to malignant proliferation, and it has a poor prognosis[3].

Many gastric cancers are usually asymptomatic in the early stages; however, they are at an advanced stage or even at a metastatic stage when they show symptoms[4]. Since the gastric cancers at the advanced stage have high rates of recurrence after the operation, they have a poor clinical prognosis[5]. Thus, it is vital that the disease is identified and treated in the early stages. The greatest obstacle to the development of effective treatment modalities is the lack of biomarkers that will monitor the pathological progression of the disease and predict the diagnosis at early stages[6]. Many genes and factors, growth factors, and signaling targets have been indicated to play a key role in identifying the pathogenesis of gastric cancer. Nonetheless, these markers are controversial and have not been fully defied in terms of their prognostic and predictive values[6]. As a result, diagnostic methods of gastric cancer are still suboptimal today, and there is no proven biomarker that can be used in the diagnosis of gastric cancer before the disease reaches advanced levels. It is very important to find biomarkers that can diagnose the disease at the early stage. Well-defined biomarkers will guide the diagnosis and treatment of the disease.

This study aimed to discuss serum levels of galanin and obestatin peptides that can be measured from the serum in the blood, which have been investigated in recent years, particularly in cancer studies, in terms of their diagnostic value in gastric cancers in the light of current literature.

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METHODS

This study was conducted with the adult patients, who were hospitalized due to the diagnosis of gastric cancer at the General Surgery and Internal Medicine Medical Oncology Clinic of Atatürk University Faculty of Medicine Research Hospital between March 2020 and August 2020, and the healthy adults or the adult patients with benign gastric diseases, who presented to the general surgery outpatient clinic. The study included 30 patients aged over 18 years with a histopathologically diagnosed gastric cancer, and a control group of 30 healthy individuals or patients with benign gastric diseases. Cases were selected randomly. To minimize the effects on the serum levels of galanin and obestatin levels, patients with primary tumors other than gastric cancer, pregnant women, patients with significant systemic diseases, and individuals aged under 18 years were excluded from the study. Approval was obtained from the AUFM Clinical Research Ethics Committee for this study (Erzurum/Turkey). All individuals participating in the study were acknowledged about the study, and informed consents were obtained.

RESULTS

In the study, 30 patients, who were histopathologically diagnosed with malignant gastric tumor, and 30 healthy individuals with no diseases or patients who were diagnosed with benign gastric diseases under gastroscopy were examined prospectively in the patient and control groups. In the patient group of 30 patients, 19 (63.33%) were male and 11 (36.67%) were female. In the control group of 30 individuals, 19 (63.33%) were female and 11 (36.67%) were male. Adult patients aged over 18 years were included in the study.

The mean age of the patient group was 62.23±10.47, and the mean age of the control group was 61.23±7.69 (44–86); and there was no significant difference between the groups. Body mass index (BMI) was 23.98±4.7 for the patient group and 23.89±3.98 the control group, and there was no significant difference between the groups ($p>0.05$) (Table 1).

The mean serum levels of galanin was19.73±5.04 pg/mL in the patient group and 35.59±10.94 pg/mL in the control group. There was a highly significant difference between the groups ($p<0.001$) (Table 2 and Figure 1).

The mean serum levels of obestatin was 40.21±582 ng/mL in the patient group and 15.15±3.32 ng/mL in the control group. There was a highly significant difference between the groups ($p<0.001$) (Table 2 and Figure 1).

A statistically significant and negative correlation was found between the measured serum levels of obestatin and galanin ($r= -0.585$ and $p<0.001$) (Figure 1).

DISCUSSION

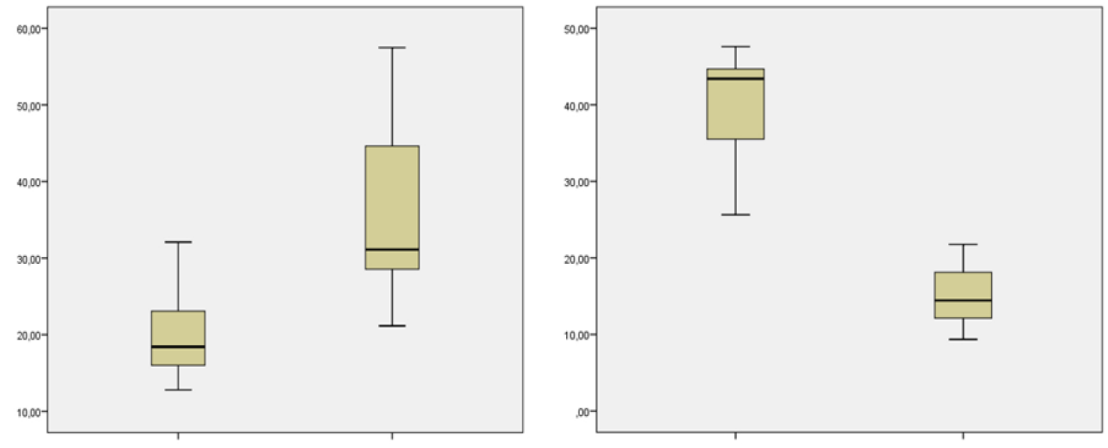
Gastric cancer is the fourth most common cancer in the world, and it has been identified as an international public health issue[7]. Biomarkers are needed for indicating the diagnosis and prognosis of such a disease[8]. In recent years, various hormones have been defined related to the physiology and cancers of the gastrointestinal system. These may be the hormones or markers that can be used in the diagnosis, prognosis, or even treatment of the disease. Galanin is known for its orexigenic effects, and obestatin is known for its anorexigenic effects. They are known as the peptide biomarkers, as proved in one study[9]. The stomach is a tissue that is rich in both of the two hormones and their receptors.

Table 1. Characteristics of the patient and control groups

	Male		Female		Mean age	BMI	Total	
	n	%	n	%	years	kg/m²	n	%
Patients	19	63.33	11	36.67	62.23±10.47	23.98±4.7	30	100
Control	11	36.67	19	63.3	61.23±7.69	23.89±3.98	30	100
Total	30	50	50	50	61.73±9.08	23.93±4.34	60	100

Table 2. Index of variability of obestatin and galanin levels measured in the patient and control groups.

	N	Obestatin (ng/mL) (min–max)	Galanin (pg/mL) (min–max)	p-value
Patient group	30	40.21±5.82 (25.63–47.61)	19.73±5.04 (12.80–32.08)	<0.001
Control group	30	15.15±3.32 (9.36–21.77)	35.59±10.94 (21.15–57.48)	<0.001



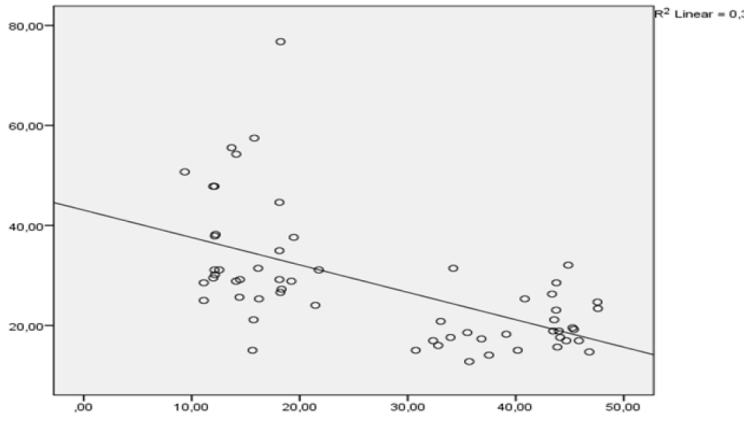


Figure 1. Statistics of galanin and obestatin levels.

The levels of galanin and obestatin in the body are affected by weight[9]. Serum levels of galanin were found to be higher in the obese patients[10]. In contrast, an inverse relationship was found between weight and obestatin in the study on obestatin[11]. The levels of obestatin were found to be higher in individuals with anorexia nervosa compared to the individuals in the healthy group[12].

In terms of weight, no significant difference was observed between the BMI values of the study groups, despite the fact that the patients were selected randomly in our study. Accordingly, investigating the effect of biomarkers used on cancer without being affected by weight contributed to the significance of our study.

Galanin is a neuropeptide with 30 amino acids, which basically isolated in the intestines and has a wide distribution in humans, including enteric nerves in the central nervous system, endocrine system, and autonomic nervous system[13]. Galanin is synthesized in the brain and intestine. It plays a role in the regulation and learning of nutrition, and response to nerve damage and pain. It functions in intestinal contractions, gastric acid secretion, and inhibition of the release of pancreatic peptides in the gastrointestinal system[14,15].

Various studies have been conducted on galanin in patients with cancer[14-17]. In a study conducted on patients with gastric cancer, the levels of galanin measured before the surgery were found to be lower compared to the postoperative levels and the levels of the healthy individuals. In addition, the expression levels of galanin decreased more in the tumor tissue compared to the adjacent tissue without tumor[15].

Although the potential role of galanin in gastric cancer is not fully known, looking at the expression of galanin and its receptors in a series of gastric cancer cell lines, higher expression of galanin initiates apoptosis of the gastric cancer cells. This suggests that galanin may have tumor-suppressing effects in gastric cancer. Thus, a decrease is observed in the expression of galanin in gastric cancers[18].

The most emphasized issue related to the pathophysiology of galanin is that galanin and its receptors play a role in the inhibition of cell proliferation and apoptosis[19,20]. It has been stated that galanin and its receptors play a role in the inactivation of cell proliferation and apoptosis in head and neck cancers[16].

In experiments involving the transplantation of human gastric cancer cells into rats, galanin treatment has been proven to reduce the volume and weight of the tumor; however, it did not change the rates of apoptosis[21].

In addition, the anti-proliferative effects of galanin have been demonstrated in pheochromocytoma and pancreas cancer[17,22].

Despite all these studies, the role of galanin in gastric cancer has not been fully elucidated yet. The BMI values of the groups examined in our study were the same, and the levels of galanin were found to be lower in the patient group. This supports the hypothesis that the expression of galanin decreased and its tumor-suppressing gene characteristics was epigenetically silenced in gastric cancers due to the mechanism of gastric cancers. In addition, due to the anti-proliferative effects, it raises the question of whether galanin and its receptors can be used in cancer treatments. More comprehensive studies are needed on this subject matter.

Obestatin is a peptide with 23 amino acids that is synthesized from preproghrelin, which is a prohormone originated from the stomach and small intestine endocrine cells similar to ghrelin. The stomach tissue, particularly its oxyntic mucosa, is the richest tissue in obestatin[23].

Obestatin is encoded by the same gene as the ghrelin hormone, and it is known to have opposite effects on the energy homeostasis and gastrointestinal functions. It inhibits gastrointestinal motility by stimulating the vagal afferent fibers. It creates a feeling of central satisfaction due to this effect and prevents weight gain. In addition, it causes delay of gastric emptying by inhibiting jejunal contractions[23,24].

The levels of ghrelin, obestatin, and peptide YY3-36, which were measured before and after the subtotal gastrectomy in patients with early gastric cancer, were evaluated. The levels of obestatin in the early postoperative period were observed to decrease compared to the preoperative period. Thus, it is thought that intestinal hormones in the gastrointestinal system may play a role in the pathogenesis during the development of gastric cancer[25].

In our study, similar to the literature, the levels of obestatin were found to be higher in patients with gastric cancer. Since our study was not a genetic analysis study, the pathophysiology was not fully explained. However, the fact that the BMI values of the groups were equal supports the hypothesis that obestatin is more common in tumor environments, and it accelerated the mitogenesis by activating the proliferation of cell line in gastric cancer, rather than supporting the effect of obestatin on motility and appetite.

The most important limitation of this study was the small number of patients due to the expensive tests. Another limitation was the lack of comparison with the serum bloods taken after the resection of the tumor from the same patients diagnosed with gastric cancer as a control group. The other limitations may be the difference in the stages of the gastric cancers, the lack of pathological classification, and the inability of the study to reveal the relationship between the severity of the cancer and the peptide hormones.

CONCLUSION

Although gastric cancer is common among the cancers in the world, the disease is usually diagnosed in advanced stages, and it has a poor prognosis. There are no instruments that have been proven to detect gastric cancer in its early stages. Various biomarkers have been used; however, no biomarker with high diagnostic value has yet been found. Serum levels of galanin were found to be lower and serum levels of obestatin were found to be higher in patients with gastric cancer compared to the healthy individuals. Obestatin and galanin can be used as potential biomarkers in the diagnosis of gastric cancer. Studies on this subject with large patient groups will better explain the effects of these peptide hormones.

AUTHORS' CONTRIBUTIONS

FAU: Conceptualization, Data curation, Formal Analysis, Writing – original draft. **ED:** Conceptualization, Data curation, Project administration, Supervision, Writing – original draft, Writing – review & editing. **RP:** Resources, Formal analysis. **NÖ:** Resources, Formal analysis. **MİY:** Project administration, Supervision, Writing – review & editing. **YA:** Conceptualization, Formal analysis

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ORIGINAL ARTICLE

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Analysis of related factors of behavioral problems in children with congenital pseudarthrosis of tibia

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SUMMARY

OBJECTIVE: This study aimed to investigate the factors associated with behavioral problems in children with congenital pseudarthrosis of the tibia.
METHODS: Random sampling is utilized to obtain a sample of 90 patients. The behavioral problems of the patients are detected by Achenbach Children's Behavior Scale. Parental emotional problems are investigated by the Self-Rating Depression Scale and Self-Rating Anxiety Scale.
RESULTS: The results demonstrate that the detection rate of behavioral problems in children with congenital pseudarthrosis of the tibia is 53.3% (48/90). Among these behavioral problems, an abnormal rate is higher in the four dimensions: thinking, violation of discipline, social interaction, and aggression. The anxiety and depression scores of caregivers are statistically higher in the abnormal group than in the normal group. The results of the multivariate analysis show that the anxiety degree of the parents had a significant impact on the behavior of the children.
CONCLUSIONS: Children with congenital pseudarthrosis of the tibia are facing the issues of high rates of behavioral problems. Parents of children with congenital pseudarthrosis of the tibia had higher levels of anxiety and depression than parents of normal children. The anxiety and depressive state of mind of parents or caregivers had a significant impact on the behavior of children with congenital pseudarthrosis of the tibia.
KEYWORDS: Behavioral problems. Influencing factors. Tibia. Depression. Mental health.

INTRODUCTION

Congenital pseudarthrosis of the tibia (CPT) is a deformity of the tibia caused by dysplasia that is manifested as an angular deformity of the tibia, medullary cavity stenosis, or cyst. It eventually forms a non-union false joint[1-5]. CPT is one of the most challenging and refractory diseases in pediatric orthopedics[6]. Although the surgical treatment of CPT has developed rapidly in recent years, late complications remain, such as ankle valgus, unequal length of limbs, proximal tibial valgus, and re-fractures. Long-term multiple operations and complicated treatment procedures make it easy for the child to develop psychological and behavioral problems[7]. In recent years, more attention has been paid to the psychological and behavioral problems of children caused by CPT. The behavioral problems that appear early in the process of the growth of children are relatively stable. Early detection and early intervention can often get twice the result with half the effort. Some studies have shown that the mental health status of parents or caregivers of children with CPT is generally poor, mainly reflected in obsessive-compulsive disorder, anxiety, fear, psychosis, and so on. However, there are few reports on whether the mental state of the child's parents or caregivers has any influence on the child's mental and behavioral problems.

This study investigated patients over 4 years of age with CPT and explored the relationship between children's psychological behavior problems and parents' or guardians' psychological emotions. It is expected to provide a basis and reference for the early comprehensive intervention of psychological and behavioral problems in children with CPT.

METHODS

Research object

This study selected 90 children with CPT, who were treated in Hunan Children's Hospital from August 2014 to August 2015, and their caregivers, as the research subjects. This study complied with the "Declaration of Helsinki of the World Medical Association" and was approved by the ethics committee of the hospital. All patients or their caregivers signed an informed consent form.

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Inclusion and exclusion criteria

Inclusion criteria of this study were patients who

1. were diagnosed with CPT;
2. aged 4–18 years; and
3. voluntarily signed informed consent,

and exclusion criteria were patients with

1. other chronic diseases;
2. mental illness; and
3. incomplete case data.

Research methods

The general information about the child (gender, age, and course of illness) was collected using self-made questionnaires. The behavioral problems of the children were assessed using the Achenbach Children's Behavior Scale, including social competence and behavioral problems. The scores of each dimension of the children's behavior scale were used in comparison with the national norm. When the score of a certain dimension was greater than the national norm, it was considered an abnormality in that dimension. Children with abnormal scores in any dimension were defined as having behavioral problems. Parents' emotional problems were investigated using the Self-Rating Depression Scale (SDS) and the Self-Rating Anxiety Scale (SAS). The score was compared with the national norm. The anxiety scale was divided into 50 points: 50–59 points indicated mild anxiety, 60–69 points indicated moderate anxiety, and 69 or greater points indicated severe anxiety. The demarcation of the depression scale was divided into 53 points: 53–62 points indicated mild anxiety, 63–72 points indicated moderate anxiety, and 72 or greater points indicated severe anxiety.

Questionnaire survey method

The filling results were screened by the staff, and invalid questionnaires were removed. A total of 90 questionnaires were distributed and 90 were collected, of which 90 were valid questionnaires. The efficiency was 100%.

Statistical processing

After the questionnaires were collected, all raw data were imported into SAS 9.4 for analysis. The measurement data obey normal distribution and are described by mean±standard deviation. The measurement data are described by frequency and constituent ratio. The Student's *t*-test was used for the comparison between groups that satisfied the normal distribution. The non-parametric test was used for the comparison among groups that did not satisfy the normal distribution. Logical regression analysis was used to analyze the influencing factors of behavioral problems in children with CPT. The chi-square test was used for counting data. The p-value <0.05 indicated that the difference was statistically significant.

RESULTS

General

A total of 90 children were enrolled in this study, including 58 male children and 32 female children (aged 4–16 years) with an average age of 7.10±2.58 years, an average treatment course of 5.67±2.47 years, and an average number of operations of 1.68±1.41. The main caregivers were 22–52 years old, with an average age of 33.3±5.1 years. The caregivers enrolled in this study included 33 fathers (36.7%), 55 mothers (61.1%), and 2 other relatives (2.2%). The details are shown in Table 1.

Table 1. General situation of the research subjects.

	n	%
Gender		
Male	58	64.4
Female	32	35.6
Age (years)		
4–7	44	48.9
7–16	46	51.1
Primary caregiver		
Father	33	36.7
Mother	55	61.1
Other	2	2.2
Parental education		
Junior high school and below	38	42.2
High school, technical school	18	20.0
College degree and above	31	34.4
Number of operations		
Have not had surgery	11	12.2
1	62	68.9
≥2	17	18.9
Course of disease (years)		
<4	16	18.2
4–8	47	52.2
>8 years	25	28.4
Guardian anxiety symptoms		
No	12	13.3
Yes	78	86.7
Guardian depressive symptoms		
No	42	46.7
Yes	48	53.3

The current status of behavioral problems of children with congenital pseudarthrosis of the tibia

The results of this study indicate that the detection rate of the behavioral problems of children diagnosed with CPT was 53.3% (48/90). The four areas of problems were thinking (24.4%), violation of discipline (16.7%), social interaction (15.6%), and aggressive (12.2%). The abnormality rate of these four dimensions was high.

Abnormal Self-Rating Anxiety Scale and Self-Rating Depression Scale scores of parents or guardians

The results of this study showed that 41 of the investigated parents had symptoms of depression and 12 had symptoms of anxiety. All had mild-to-moderate anxiety or depression.

Comparison of Self-Rating Depression Scale and Self-Rating Anxiety Scale scores between parents of the abnormal behavior group and the normal behavior group

The results of this study showed that the SDS and SAS scores of the caregivers were 52.73±11.54 and 44.87±9.03, respectively, in the children's abnormal behavior group and 46.85±11.85 and 38.78±5.97, respectively, in the children's normal behavior group. The statistical results showed that the scores for anxiety and depression were statistically higher ($p<0.05$) in the abnormal behavior group than in the normal group. All of the parents of children with behavioral problems had higher levels of anxiety and depression than the parents of children with no behavioral problems.

Single-factor analysis of influencing factors of behavioral problems in children

The results of this study showed that there was no statistically significant difference in the incidence of behavioral problems among different gender, ages, ethnicities, length of illness, number of operations, parental education, monthly family income, and depression scale scores. There was a statistically significant difference in the incidence of abnormal behavioral problems between the abnormal parental anxiety scale group and the normal group. The incidence of abnormal behavior in children in the abnormal score group was higher than that in the normal score group. According to clinical observations and experience, the possible influencing factors for the occurrence of abnormal behavior in children included gender, age, number of operations, duration of illness, parents' educational level, parents' anxiety, and depression. The above variables were taken as independent variables, and whether or not the child had behavioral problems was used as dependent variables. The logistic regression analysis method was set to be Backward, probability for stepwise (Entry 0.05, Removal 0.10). The results showed that none of the variables entered the equation, and the OR value of the two variables (the SAS and SDS scores) tended to be positive infinity, so the model was not stable. Considering that there may be multicollinearity between the two variables, the SDS score was excluded, and the SAS score was successfully introduced into the equation. The results showed that parental anxiety had a significant impact on the behavior of the children. The more anxious the parents were, the more likely children were to have behavioral problems, as presented in Tables 2 and 3.

DISCUSSION

CPT has a long course of the disease, is difficult to treat, requires repeated operations, is of high cost, and patients need to be followed up until the bone is fully mature. Therefore, long-term, multiple operations and complex treatment processes make the family members of children prone to physical and mental health problems. This study found that the total detection rate of behavioral problems in 90 children with CPT was 53.3%. Among these behavioral problems, the abnormal rate in the four dimensions of thinking, violation of discipline, social interaction, and aggression was relatively high. The reasons for this could include three aspects. First, the social aspect: children with CPT had physical disorders with abnormal bones at the prosthetic joints, fractures were easily caused by external forces and were not easy to heal, and the affected limbs needed to be protected by plaster or protective gear for a long period of time during walking until the bones matured. In daily life and at school, they were susceptible to ridicule and rejection from their peers. Studies show that neglected children were less active in all aspects, and rejected children were most likely to have aggressive and disruptive behaviors[8]. Second, the family aspect: overprotection and spoiling were positively correlated with the behavioral problems of children. CPT is a chronic disease. More parents overprotected and took care of their children by ignoring the child's adaptability and need for social skills development. It was easy to make the children infantile, overdependent, and produce an inferiority complex[9]. Third, the child's own aspect: to avoid fractures, children with CPT could not play sports or play games with their partners. Their activities were restricted, and this was not understood by younger children who could only express their inner distress by crying, quarreling, and tantrums.

There was a statistically significant difference in the incidence of abnormal behavior in children between the abnormal anxiety scale score group and the normal group. CPT is a rare, chronic surgical disease that is difficult to treat[7,10-12]. The caregiver needs to take care of the child full time and pay attention to protect the child at all times. The characteristics of this disease, its treatment methods, and the family care methods

Table 2. Multifactor analysis of influencing factors of CPT children's abnormal behavior.

	Behavior problem detection rate (%)	χ^2	p-value
Gender			
Male	50	0.527	0.508
Female	59.4		
Age (years)			
4–7	50	1.875	0.392
7-12	60		
12-16	33.3		
Nationality			
Han nationality	52.4	0.862	0.719
Minority	62.5		
Whether to go to school			
Yes	55.6	0.417	0.339
No	48.1		
Sick time (years)			
0–4 years	50	0.144	0.930
4–8 years	54.2		
8–12 years	56		
Number of operations			
0	54.5	2.650	0.266
1	48.4		
≥2	70.6		
Parents' education			
Elementary to Junior High	44.7	3.15	0.207
High school and equivalent	72.2		
University and above	52.9		
Family monthly income			
1000–3000	51.6	0.325	0.850
3000–8000	52.3		
>8000	60		
Parental anxiety score			
Normal	47.4	8.510	0.014
Abnormal	92.0		
Parent depression scale score			
Normal	44.0	3.451	0.178
Abnormal	62.0		

have a high degree of similarity so that the influences of different genders, ages, lengths of illness, number of operations, family monthly income, parents' education, etc. are concealed.

Previous studies have shown that the psychological response of parents is an important factor affecting the behavior of children with chronic diseases[13-15]. This study used the anxiety scale and the child behavior scale for the first time to verify that caregiver anxiety was a risk factor for behavioral problems in children with CPT. The reason could be that caregivers of children with CPT who were in a state of maladjustment and anxiety lacked confidence in the future of the child, ignored the child's adaptability and advantages, and demonstrated a negative attitude (such as a sad face and a sigh). The anxiety problem had the characteristics of intergenerational transmission, i.e., the parents' anxiety traits affect the anxiety level of the children through parenting methods. In turn, this would make the children feel depressed, cause them to pay too much attention to their own image and appearance, and prevent them from forming a positive self-concept. These children were unable to actively recognize and evaluate their own condition and value, thereby generating more behavioral problems.

In this study, the detection rate of behavioral problems in children was higher. Parents of children with behavioral problems were more anxious and depressed, and children with anxious caregivers were more likely to have behavioral problems. This issue should be taken seriously by medical workers and measures should be implemented. Medical workers themselves should insist on looking at children and their families from the perspective of positive psychology, fully assess the potential advantages of their families, share more cases of good recovery with parents, encourage family members to build confidence, redefine the meaning of illness, and maintain effective communication and close cooperation to help them overcome the difficulty of the impact of illness on the family. Medical workers should also insist the parents to treat their children with an attitude of appreciation, paying attention to their strengths, interests, abilities, and knowledge, and inspiring the confidence of the children to struggle in adversity. In addition, parents of children with CPT should overcome adverse emotions such as anxiety, maintain family unity, and avoid excessive protection. Families with children diagnosed with CPT have high medical expenditures. This may be due to rare diseases and poor treatment effects in the past. At present, they are not included in any assistance. The vast majority of mothers take care of their children full time to protect

Table 3. Logistic regression results.

	Partial regression coefficient	Wald χ^2 value	Degree of freedom	p-value	OR	95%CI
Constant	20.204	3.842	1	0.048	–	–
SAS analysis	2.104	3.770	1	0.052	8.200	0.98–68.59

their children from accidental fractures, so their family income is single. Society should provide more financial support for children with CPT and their families. At the same time, more active attention and publicity should be given to children with CPT. This should include the encouragement of interaction and contact with other children who are also diagnosed with CPT, the presence of a fair and just social environment for children with CPT, and the promotion of mental health for children with CPT.

This is the first study to explore the influence of the mental state of parents or caregivers on the behavior of children with CPT, which is novel and innovative. Moreover, this research has shortcomings and limitations. This study is not a randomized controlled experiment, so there is a certain risk of bias. This study is a single-center clinical study, and subsequent multicenter clinical studies are needed for further discussion. Finally, the sample size included in this study is relatively small; hence, it is necessary to increase the sample size in future research.

CONCLUSION

Children with CPT have psychological and behavioral problems, and their parents' anxiety and depression levels are significantly higher than those of parents with children who do not have CPT. In addition, the anxiety and depressive state of mind of parents or caregivers had a significant impact on the behavior of children with CPT.

AUTHORS' CONTRIBUTIONS

JHX: Conceptualization, Writing – original draft, Writing – review & editing. **HBM:** Data curation, Writing – original draft, Writing – review & editing. **KL:** Data curation, Writing – original draft, Writing – review & editing. **GHZ:** Formal Analysis, Writing – original draft, Writing – review & editing. **YQO:** Formal Analysis, Writing – original draft, Writing – review & editing.

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ORIGINAL ARTICLE

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Premenstrual Syndrome and Childbirth Fear Prior to Pregnancy in Young Women: An Association and Cross-Sectional Study

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SUMMARY

OBJECTIVE: The aim of the study was to determine the association between premenstrual syndrome and the childbirth fear prior to pregnancy.

METHODS: This was an association and cross-sectional study conducted on 327 university students. Data were collected using "Participant Information Form," "Premenstrual Syndrome Scale," and "Childbirth Fear-Prior to Pregnancy Scale."

RESULTS: It was found that the childbirth fear had increased in students with premenstrual syndrome. The Women Childbirth Fear-Prior to Pregnancy Scale score was statistically significantly higher among students who preferred caesarean section than those who preferred vaginal delivery. There was a weak, positive, and statistically significant correlation between the students' depressive sensation, anxiety, fatigue, nervousness, depressive thoughts, pain, appetite changes, sleep pattern changes, and bloating subscales of Premenstrual Syndrome Scale and Women Childbirth Fear-Prior to Pregnancy Scale.

CONCLUSION: The score of the Women Childbirth Fear-Prior to Pregnancy Scale increases with an increase in the score of the Premenstrual Syndrome subscale. It should be evaluated whether or not women experiencing premenstrual syndrome have the childbirth fear prior to pregnancy.

KEYWORDS: Premenstrual syndrome. Childbirth. Fear. Pregnancy.

INTRODUCTION

Premenstrual syndrome (PMS) includes somatic, cognitive, emotional, and behavioral symptoms that occur in the luteal phase of the menstrual cycle in women, disappears with the onset of menstruation, and is frequently experienced during reproductive age[1-3]. In PMS, emotional symptoms such as depression, anger outbursts, irritability, crying spells, anxiety, confusion, social withdrawal, poor concentration, insomnia, increased nap taking, and changes insexual desire as well as physical symptoms such as thirst and appetite changes, breast tenderness, bloating and weight gain, headache, swelling of the hands or feet, aches and pains, fatigue, skin problems, gastrointestinal symptoms, and abdominal pain develop[4].

Childbirth fear is an important factor threatening psychosocial health during pregnancy[5]. The childbirth fear may develop due to reasons such as the fear of hurting herself or baby, inability to cope with pain at birth, loss of control, and distrust to the health care professional[6]. In the adolescence or early adulthood period, the women may avoid pregnancy due to childbirth fear[7]. Young women who plan to become pregnant in the future and who report high levels of childbirth fear tend to prefer obstetric interventions, such as cesarean birth, because they offer the promise to control/avoid pain and bodily damage perceived to be associated with vaginal birth[8].

Determining the factors that cause the childbirth fear before pregnancy makes it possible to enable the fear in early period[6]. Stoll and Hall stated that students with high childbirth fear defined the birth as a frightening and painful distress[9]. In a study conducted in Canada, students with the highest childbirth fear stated that the media shaped their attitudes toward pregnancy and childbirth[10]. Thomson et al. found that 33.3% of the students reported negative birth impressions through direct or indirect resources[11]. Güleç Şatır found that students' fear of birth was high[12].

There are many studies in the literature on PMS and childbirth fear conducted separately. The electronic databases such as PubMed, Google Scholar, Scopus, and EBSCO were searched with appropriate Medical Subject Headings (MeSH) terms (premenstrual syndrome, fear of childbirth). Although there are limited number of studies on the childbirth fear prior to pregnancy, no study was found investigating the association between PMS and the childbirth fear prior to pregnancy. This study was conducted to determine the association between PMS and the childbirth fear prior to pregnancy.

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This study aimed to investigate the following questions:

- What is the PMS prevalence among university students?
- What is the level of the childbirth fear prior to pregnancy among university students?
- Is there an association between PMS and the childbirth fear prior to pregnancy?

METHODS

Study design

This was an association and cross-sectional study.

Population and sample of the study

The population of the study was female students who were continuing their education in the department of nursing and the nursing faculty of two universities located in Istanbul between September 2019 and February 2020.

The sample of the study included the students who did not take any theoretical course about obstetrics and gynecology and did not perform clinical practice on this subject and met the inclusion criteria. The data were collected by the researchers with the face-to-face interview method from the students who were voluntary to participate in the study. The study was completed involving 327 students.

Inclusion criteria of the study

The inclusion criteria were as follows: being over 18 years, being voluntary to participate in the study, having no communication problem, not taking the obstetrics and gynecology courses at both theoretical and practical levels, thinking about having children in the future, not being pregnant during the data collection period, not having a pregnancy experience exceeding 20 weeks, and not having children.

Exclusion criteria of the study

The exclusion criteria were young women who refused to participate in the study and who were unable to complete the data collection instrument.

Data collection tools

Participant Information Form: This form consists of 26 questions in total, which are prepared to determine the students' sociodemographic, menstrual, and childbirth fear-related characteristics.

Premenstrual Syndrome Scale (PMSS): This scale was developed by Gençdoğan[13] in 2006 to measure the severity of premenstrual symptoms. It consists of 44 items, which are marked by the participant considering "the condition of being in the period 1 week before the menstruation." The five-point Likert-type PMSS is composed of nine subscales, namely, depressive sensation, anxiety, fatigue, nervousness, depressive thoughts, pain, appetite changes, sleep pattern changes, and bloating. The lowest score to be obtained is 44 and its highest score is 220. Those with PMSS total score of more than 50% are considered PMS positive. High PMSS score refers to more severe premenstrual symptoms. Cronbach's alpha of the original version of the scale was found as (α)0.75[13]. In this study, the Cronbach's alpha value of the scale was calculated as 0.83.

Childbirth Fear-Prior to Pregnancy Scale: This scale was developed by Stoll et al. in 2016 in order to measure the childbirth fear prior to pregnancy in young men and women. The scale was adapted to Turkish by Uçar and Taşhan in 2018. This scale consists of 10 items, and the responses are measured in a six-point Likert type, ranging from 1 to 6. The minimum score is 10 and the maximum score is 60. High item total score refers to a high level of fear. In the study by Stoll et al., the Cronbach's alpha value is 0.86[6,14]. In the study by Uçar and Taşhan, the female and male forms of the scale were separated, and the validity and reliability analyses were performed separately as the Women Childbirth Fear-Prior to Pregnancy Scale (WCF-PPS) and Men Childbirth Fear-Prior to Pregnancy Scale (MCF-PPS). Cronbach's alpha internal consistency coefficient for WCF-PPS was found to be 0.89[6]. WCF-PPS was used in this study. In this study, the Cronbach's alpha value of the scale was determined as 0.86.

Data analysis

Statistical analysis of the data was performed using the "SPSS" (Statistical Package for Social Sciences) for Windows 16.0 program. In the evaluation of categorical and ordinal variables, nonparametric (chi-square) was used; in the analysis of measurement data, parametric (Student's t-test) showed normal distribution, and in the correlation analysis of data obtained by measurement and normally distributed, data analysis was performed using Pearson's correlation. A $p<0.05$ was accepted as statistically significant.

Ethical considerations

The participants were informed about the purpose of the study before the data collection. Since the data were collected before or after the lesson while the students were in the classroom environment, verbal consent was obtained by informing them about the study. In addition, written information about the

study was given in the data collection form. The data of the study were collected after getting permission from Istanbul Medeniyet University Social and Humanities Research and Publication Ethics Committee. To conduct the study, approval (dated May 8, 2019) and permission were obtained from the Ethics Committee.

RESULTS

The mean age of students was 19.75±1.55 (17–34), their menarche age was 13.20±1.14 (10–16), duration of menstruation was 6.23±1.52 (2–15) days, and menstruation frequency was 29.02±11.51 (11–180) days. It was determined that the menstrual irregularity and pain complaint during menstrual period are more common in those with PMS compared to those who did not have PMS (Table 1).

The prevalence of PMS was 67.6%. The PMSS total mean score of the students was 125.66±35.39 and the highest mean score (21.79±6.77) was determined in depressive sensation subscale among the subscales of the scale. WCF-PPS total mean score was 39.89±10.12.

No difference was found between the students with and without PMS in terms of their characteristics, except for smoking, history of PMS in the family, controlling anger, being diagnosed with anemia, and fear of pregnancy/labur processes. Besides, students experiencing PMS had higher scores in the Childbirth Fear-Prior to Pregnancy Scale compared to those without PMS and the childbirth fear increased in students with PMS (Table 2). Additionally, when the WCF-PPS scores were compared in terms of the delivery method, it was determined that the students who preferred cesarean delivery (43.18±10.93) received statistically significantly higher scores than those who preferred vaginal delivery (39.47±9.95) (t=-2.113; p=0.035).

The students' depressive sensation, anxiety, fatigue, nervousness, depressive thoughts, pain, appetite changes, sleep

Table 1. Comparison of sociodemographic and menstrual characteristics of the students with premenstrual syndrome

	Premenstrual syndrome (-) (n=106)		Premenstrual syndrome (+) (n=221)		t	p
	Mean±SD		Mean±SD			
Age (years)	19.66±1.53		19.79±1.56		-0.735	0.460
Menarche age (years)	13.33±1.05		13.14±1.17		1.449	0.149
Duration of menstruation (day)	5.54±1.23		5.57±1.38		-0.274	0.784
Menstruation frequency (day)	28.35±5.58		29.23±12.50		-0.976	0.330
	n	%	n	%	χ^2	p
Class						
1	38	35.9	72	32.6	2.615	0.271
2	24	22.6	69	31.2		
3	44	41.5	80	36.2		
Family type						
Nuclear family	92	86.8	191	86.4	0.008	0.927
Extended family	14	13.2	30	13.6		
İncome level						
Income less than expense	18	17.0	21	9.5	4.683	0.096
Income equals the expense	80	75.5	174	78.7		
Income more than expense	8	7.5	26	11.8		
Menstrual scheme						
Regular	94	88.7	157	71.0	**12.493**	**0.000**
Irregular	12	11.3	64	29.0		
Pain complaints during menstrual period						
Yes	77	72.6	189	85.5	**7.830**	**0.005**
No	29	27.4	32	14.5		

Bold denotes significant p-value.

Table 2. Comparison of some risk factors in terms of the students' status of experiencing premenstrual syndrome.

	Premenstrual syndrome (–) (n=106)		Premenstrual syndrome (+) (n=221)		t	p
	Mean±SD		Mean±SD			
Women Childbirth Fear-Prior to Pregnancy Scale	35.74±10.02		41.88±9.58		**-5.049**	**0.000**
	n	%	n	%	χ^2	p
Exercising state						
Yes	51	48.1	116	52.5	0.549	0.499
No	55	51.9	105	47.4		
Smoking status						
Yes	3	2.8	25	14.4	**6.583**	**0.010**
No	103	97.2	196	88.7		
Sugary food consumption status						
Yes	98	92.5	204	92.3	0.002	0.963
No	8	7.5	17	7.7		
More than a daily cup of coffee consumption						
Yes	19	17.9	59	26.5	3.035	0.080
No	87	82.1	162	73.3		
Using too much salt						
Yes	14	13.2	49	22.2	3.147	0.076
No	92	86.8	172	77.8		
PMS status in mother or sister						
Yes	48	45.3	149	67.4	**14.656**	**0.000**
No	58	54.7	72	32.6		
Difficulty controlling anger						
Yes	72	67.9	193	87.3	**17.558**	**0.000**
No	34	32.1	28	12.7		
Being diagnosed with anemia						
Yes	20	18.9	72	33.6	**6.661**	**0.010**
No	86	81.1	149	67.4		
Fear of pregnancy/labor processes						
Yes	58	54.7	170	76.9	**16.735**	**0.000**
No	48	45.3	51	66.9		
Delivery method preference						
Vaginal delivery	93	87.7	197	89.1	0.141	0.707
Cesarean delivery	13	12.3	24	10.9		

Bold denotes significant p-value.

pattern changes, and bloating subscales of PMSS had a weak, positive, and statistically significant correlation with WCF-PPS (Table 3). Therefore, it was determined that the students WCF-PPS scores increased as their PMSS subscale scores increased.

DISCUSSION

In this study, it was found that 67.6% of the students experienced PMS. In the literature, there are many studies showing that the prevalence of PMS varies between 16.4 and 80.2%[1,15,16]. From the study results, we can conclude

Table 3. Correlation between the students' Premenstrual Syndrome Scale Subscale Scores and Women Childbirth Fear-Prior to Pregnancy Scale Scores (n=326).

	Depressive affect		Anxiety		Fatigue		Irritability		Depressive thoughts		Ache		Appetite changes		Sleep changes		Swelling	
	r	p	r	p	r	p	r	p	r	p	r	p	r	p	r	p	r	p
WCF-PPS	0.366	**0.000***	0.319	**0.000***	0.256	**0.000***	0.232	**0.000***	0.356	**0.000***	0.185	**0.001***	0.131	**0.018***	0.254	**0.000***	0.191	**0.000***

WCF-PPS: Women Childbirth Fear-Prior to Pregnancy Scale Scores. r: Pearson's correlation; p: p<0.05. *p<0.05. Bold denotes significant p-value.

that PMS is a women's health problem with a wide prevalence range. It is important to identify premenstrual complaints. The health of women in the premenstrual period should be improved by organizing trainings and interventions to reduce/eliminate the complaints and their severity identified.

In this study, the rate of those who were fear of pregnancy and birth processes was higher than those who experienced PMS. The results showed that experiencing complaints specific to PMS may develop the childbirth fear prior to pregnancy in young people who were planning of having children in the future. It was found in the present study that knowing birth history of others, experiencing distress in premenstrual period, and the media were effective in the development of the childbirth fear prior to pregnancy. According to the study by Stoll and Hall, three factors decreasing the childbirth fear were having knowledge about pregnancy and birth, witnessing a delivery, and reporting friends as an information source. Stoll and Hall determined that young women who stated that their attitudes toward pregnancy and birth were affected by media had the highest fear of birth scores[17].Thomson et al. found that witnessing a birth was associated with lower fear scores[11]. Conducting practices to alleviate/eliminate premenstrual complaints and receiving information about pregnancy and birth from health care professionals may prevent the childbirth fear prior to pregnancy.

In addition, high fear in childbirth prior to pregnancy was associated with the preference of cesarean section, which is similar to previous findings[18-20]. Fear of childbirth is a reason for requesting cesarean section.

Comparing the correlation between the PMSS subscale score and the WCF-PSS score, it was determined that the level of the students with childbirth fear prior to pregnancy increases with an increase in their complaints about PMS. With this result, it was determined that experiencing PMS had a role in the development of the childbirth fear prior to pregnancy. It should be evaluated whether or not women experiencing PMS have the childbirth fear prior to pregnancy.

Limitations of the study

This study may not be generalizable to all young women. Since the findings of the study can only be generalized to the research sample, it is recommended to conduct similar studies with larger groups and different samples. Other limitation was that the study was conducted based on questionnaires with closed-ended questions. Qualitative studies or open-ended questions can more deeply examine subject. Therefore, qualitative studies are recommended in this regard.

Strengths and weaknesses of the study

The strength of the study is that it is not single-centered, and its weakness is that it was conducted only on nursing students.

CONCLUSION

Young women who do not have children yet but are planning to have children in the future may be afraid of pregnancy and delivery processes due to premenstrual complaints. Therefore, the elimination of premenstrual complaints and childbirth fear of women who have such complaints should be focused in future studies.

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AUTHORS' CONTRIBUTIONS

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

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Braden scale for predicting pneumonia after spontaneous intracerebral hemorrhage

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SUMMARY

OBJECTIVE: Stroke-associated pneumonia is an infection that commonly occurs in patients with spontaneous intracerebral hemorrhage and causes serious burdens. In this study, we evaluated the validity of the Braden scale for predicting stroke-associated pneumonia after spontaneous intracerebral hemorrhage.

METHODS: Patients with spontaneous intracerebral hemorrhage were retrospectively included and divided into pneumonia and no pneumonia groups. The admission clinical characteristics and Braden scale scores at 24 h after admission were collected and compared between the two groups. Receiver operating characteristic curve analysis was performed to assess the predictive validity of the Braden scale. Multivariable analysis was conducted to identify the independent risk factors associated with pneumonia after intracerebral hemorrhage.

RESULTS: A total of 629 intracerebral hemorrhage patients were included, 150 (23.8%) of whom developed stroke-associated pneumonia. Significant differences were found in age and fasting blood glucose levels between the two groups. The mean score on the Braden scale in the pneumonia group was 14.1±2.4, which was significantly lower than that in the no pneumonia group (16.5±2.6), p<0.001. The area under the curve for the Braden scale for the prediction of pneumonia after intracerebral hemorrhage was 0.760 (95%CI 0.717–0.804). When the cutoff point was 15 points, the sensitivity was 74.3%, the specificity was 64.7%, the accuracy was 72.0%, and the Youden's index was 39.0%. Multivariable analysis showed that a lower Braden scale score (OR 0.696; 95%CI 0.631–0.768; p<0.001) was an independent risk factor associated with stroke-associated pneumonia after intracerebral hemorrhage.

CONCLUSION: The Braden scale, with a cutoff point of 15 points, is moderately valid for predicting stroke-associated pneumonia after spontaneous intracerebral hemorrhage.

KEYWORDS: Intracerebral hemorrhage. Pneumonia. Risk factors.

INTRODUCTION

Nosocomial infections are complications that frequently occur in patients with spontaneous intracerebral hemorrhage (ICH)[1,2]. Stroke-associated pneumonia (SAP) accounts for 18% of all nosocomial infections and is the most common infection in patients with ICH, especially for the elderly[3]. SAP not only increases the length of hospital stay and hospital costs[4,5] but is also an important risk factor for poor outcomes after acute stroke[6,7]. Therefore, it is important to find a scale that is effective in predicting SAP and can help clinicians take early preventative measures to reduce the incidence of SAP[8,9]. The Braden scale is used to assess the risk of pressure ulcers[10,11], and our prior study indicates that the Braden scale is useful for predicting pneumonia after acute ischemic stroke (AIS)[12]. In the clinical use of this scale, we found that the Braden scale might be related to pneumonia after spontaneous ICH. In this study, we aimed to evaluate the validity of the Braden scale in predicting pneumonia after spontaneous ICH.

METHODS

Study participants

We retrospectively included consecutive patients with spontaneous ICH who were admitted to Jingjiang People's Hospital and Zhoukou Central Hospital between January 2015 and August 2018. These two hospitals are the largest tertiary hospitals in the region and are responsible for the treatment of critical illnesses in the area. This study retrospectively

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included ICH patients admitted to the neurology department who did not undergo surgery. The inclusion criteria were patients who

(1) were diagnosed with spontaneous ICH according to the World Health Organization criteria[13];
(2) were confirmed to have ICH by head computed tomography;
(3) did not undergo any surgical procedures to treat or reduce the hematoma, including, but not limited, to minimally invasive hematoma aspiration and craniotomy hematoma removal; and
(4) aged ≥18 years. The exclusion criteria were patients who acquired pneumonia before admission and patients with primary intraventricular hemorrhage.

This study was approved by the Medical Ethics Committee of Jingjiang People's Hospital (ethical application ref: 2019-01-44) and Zhoukou Central Hospital. Because it was a retrospective study and did not include any personal information related to the participants, the need to obtain written informed consent was waived. The treatment of each participant during hospitalization was approved by the patient or their family member, and a written informed consent form was obtained before treatment.

Data collection and variable definitions

Each center selected two senior neurologic physicians to collect information on the included cases. Cases with discrepancies in the data were evaluated by a third senior physician until an agreement was reached. We collected the patients' demographic and clinical characteristics upon admission, including demographic data, risk factors, and laboratory examination results.

Nurses administered the Braden scale at 24 h after admission, which is composed of six subscales: sensory perception, skin moisture, activity, mobility, nutrition, friction, and shear forces. The score for friction and shear forces ranges from 1 (worst) to 3 (best), and the other scores range from 1–4. The sum of the scores ranges from 6–23[14].

Pneumonia after ICH was diagnosed according to the Centers for Disease Control and Prevention criteria[15] for hospital-acquired pneumonia.

Statistical analysis

Statistical analysis was performed using SPSS version 21.0 (SPSS Inc., Chicago, IL, USA). Student's *t*-test was used for normally distributed variables (described as the mean±SD), the Mann-Whitney U test was used for non-normally distributed continuous variables, and Fisher's exact test or the χ^2 test was used for dichotomous variables. A $p<0.05$ was considered statistically significant. Then, receiver operating characteristic (ROC) curve analysis was performed to investigate the predictive validity of the Braden scale for pneumonia after ICH, and the Youden's index was used to determine the diagnostic threshold. An area under the curve (AUC) of 0.97–1.00 indicates excellent accuracy, 0.93–0.96 indicates very good accuracy, 0.75–0.92 indicates good accuracy, <0.75 indicates obvious deficiencies, and an AUC of <0.5 indicates that the test has no predictive ability[16]. Factors with $p<0.10$ and variables of risk factors in the univariate analysis were entered into the multivariate analysis to identify the independent risk factors associated with pneumonia after spontaneous ICH.

RESULTS

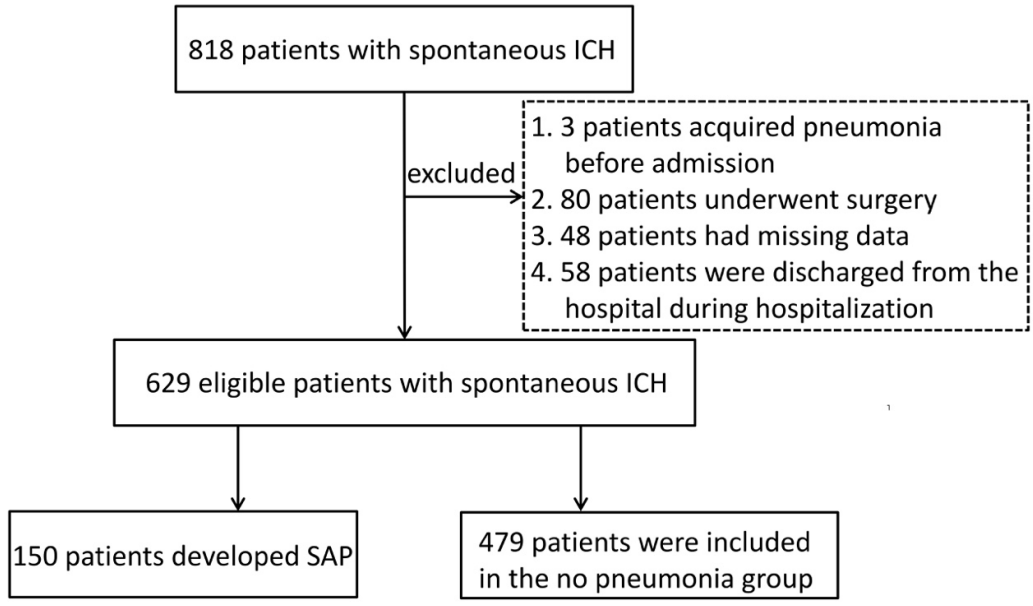
A total of 818 patients with spontaneous ICH were admitted to Jingjiang People's Hospital and Zhoukou Central Hospital between January 2015 and August 2018. Among them, 3 patients acquired pneumonia before admission, 80 patients underwent surgery, 48 patients had missing data, and 58 patients were discharged from the hospital during hospitalization. Ultimately, 629 patients with spontaneous ICH were retrospectively included in this study, of which 150 (23.8%) patients were included in the pneumonia group and 479 (76.2%) patients were included in the no pneumonia group (Figure 1). There were 380 (60.4%) males and 249 (39.6%) females, and their mean age was 66.1±13.4 years.

Demographic and clinical characteristics

There were significant differences in age, history of diabetes, and fasting blood glucose level between the two groups. The other demographic data, risk factors, and laboratory examination results showed no significant differences between the pneumonia and no pneumonia groups. The mean score on the Braden scale in the pneumonia group was 14.1±2.4, which was significantly lower than that in the no pneumonia group (16.5±2.6, $p<0.001$) (Table 1). All six subscale scores on the Braden scale significantly differed between the two groups (Table 2).

Braden scale score and pneumonia after spontaneous ICH

The AUC for the Braden scale for the prediction of pneumonia after spontaneous ICH was 0.760 (95%CI 0.717–0.804). When the cutoff point was 15 points, the sensitivity was 74.3%, the specificity was 64.7%, the accuracy was 72.0%, and the Youden's index was 39.0% (Figure 2).



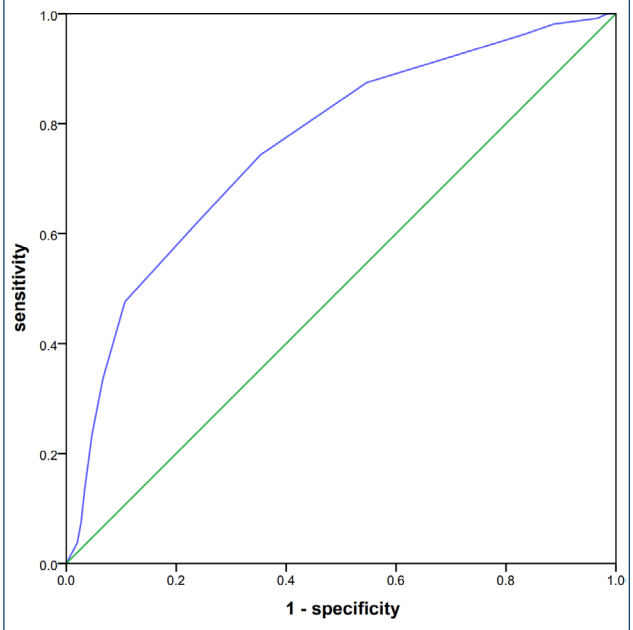
ICH: intracerebral hemorrhage; SAP: stroke-associated pneumonia.

Figure 1. Patient selection flowchart.

Table 1. Demographic and clinical characteristics of the patients in the two groups.

	No pneumonia (n=479)	Pneumonia (n=150)	p-value
Demographic			
Age (years)	64.2±13.0	72.1±12.9	<0.001
Male (case %)	292 (61.0)	88 (58.7)	0.633
Risk factors			
Smoking status (case %)	152 (31.7)	44 (29.3)	0.614
Drinking status (case %)	93 (19.4)	28 (18.7)	0.906
COPD (case %)	6 (1.3)	2 (1.3)	1.000
Hypertension (case %)	333 (69.5)	107 (71.3)	0.760
Diabetes (case %)	142 (29.6)	61 (40.7)	0.009
Hyperlipidemia (case %)	20 (4.2)	6 (4.0)	1.000
Coronary heart disease (case %)	48 (10.0)	19 (12.7)	0.365
AF (case %)	50 (10.4)	12 (8.0)	0.435
Laboratory examination			
INR	1.0±0.3	1.1±0.9	0.154
Serum creatinine (μmol/L)	81.8±58.2	88.7±32.1	0.167
Fasting blood glucose (mmol/L)	6.0±2.2	7.3±3.2	<0.001
TC (mmol/L)	4.3±1.1	4.4±1.6	0.305
TG (mmol/L)	1.5±0.9	1.6±2.5	0.398
HDL (mmol/L)	1.1±0.5	1.2±0.3	0.180
LDL (mmol/L)	2.7±1.0	2.7±1.1	0.834
Scores			
Braden scale	16.5±2.6	14.1±2.4	<0.001

COPD: chronic obstructive pulmonary disease; AF: atrial fibrillation; INR: international normalized ratio; TC: total cholesterol; TG: triacylglycerol; HDL: high-density lipoprotein cholesterol; LDL: low-density lipoprotein cholesterol.



Braden scale for predicting pneumonia after spontaneous intracerebral hemorrhage (Source: Authors.)

Figure 2. Receiver operating characteristic curve for the Braden scale. The area under the curve for the Braden scale for the prediction of pneumonia after spontaneous intracerebral hemorrhage was 0.760 (95%CI 0.717–0.804). When the cutoff point was 15 points, the sensitivity was 74.3%, the specificity was 64.7%, the accuracy was 72.0%, and the Youden's index was 39.0%.

Factors associated with pneumonia after spontaneous ICH

Older age, diabetes, higher fasting blood glucose, and a lower Braden scale score at baseline were associated with pneumonia after spontaneous ICH on univariate analysis. The results of the multivariable analysis are presented in Table 3. After adjusting for confounders, an older age (OR 1.039; 95%CI 1.020–1.058, p<0.001), a higher fasting blood glucose (OR 1.193; 95%CI 1.087–1.309, p<0.001), and a lower Braden scale score (OR 0.696; 95%CI 0.631–0.768, p<0.001) were independent risk factors associated with SAP after ICH (Table 3).

Table 2. Braden scale scores for the two groups (mean±SD).

Braden scale	No pneumonia (n=479)	Pneumonia (n=150)	p-value
Sensory perception	3.4±0.7	2.8±0.7	<0.01
Skin moisture	3.7±0.5	3.5±0.6	<0.01
Activity	1.3±0.8	1.1±0.6	0.001
Mobility	3.0±0.8	2.4±0.8	<0.01
Nutrition	2.9±0.4	2.7±0.6	<0.01
Friction and shear	2.1±0.7	1.7±0.6	<0.01
Sum score	16.5±2.6	14.1±2.4	<0.01

Table 3. Risk factors associated with stroke-associated pneumonia after spontaneous intracerebral hemorrhage.

	B	S.E.	Wals	OR	95%CI	p
Age (years)	0.038	0.009	16.323	1.039	1.020–1.058	<0.001
Female (case %)	-0.356	0.249	2.043	0.701	0.430–1.141	0.153
Smoking status (case %)	0.125	0.260	0.231	1.133	0.681–1.886	0.631
COPD (case %)	0.000	0.939	0.000	1.000	0.159–6.300	1.000
Hypertension (case %)	-0.025	0.239	0.011	0.976	0.611–1.558	0.918
Diabetes (case %)	-0.124	0.266	0.219	0.883	0.524–1.486	0.639
Hyperlipidemia (case %)	-0.214	0.528	0.165	0.807	0.287–2.271	0.685
Coronary heart disease (case %)	-0.202	0.336	0.361	0.817	0.423–1.578	0.548
AF (case %)	-0.659	0.378	3.033	0.518	0.247–1.086	0.082
Serum creatinine (μmol/L)	0.001	0.002	0.416	1.001	0.998–1.005	0.519
Fasting blood glucose	0.176	0.047	13.809	1.193	1.087–1.309	<0.001
Braden Scale	-0.363	0.050	52.272	0.696	0.631–0.768	<0.001

COPD: chronic obstructive pulmonary disease; AF: atrial fibrillation; B: Beta coefficient; S.E.: Standard Error; Wals: Wald χ^2.

DISCUSSION

In this study, we evaluated the correlation between the Braden scale and SAP after ICH. We found that patients with ICH who had a lower Braden scale score were more likely to develop SAP. The AUC for the Braden scale for the prediction of pneumonia after spontaneous ICH was 0.760 (95%CI 0.717–0.804). When the cutoff point was 15 points, the sensitivity was 74.3%, the specificity was 64.7%, the accuracy was 72.0%, and the Youden's index was 39.0%.

SAP is a frequent and often preventable complication of stroke and is one of the major modifiable risk factors for stroke-related in-hospital mortality[17]. In addition, SAP also significantly increases length of stay and hospitalization costs, underscoring the need for screening and preventing poststroke infections[18]. Therefore, knowledge of predictors of SAP is a crucial prerequisite for identifying high-risk patients and taking preventive measures[19]. According to our findings, aggressive measures should be taken to prevent SAP in patients with ICH within 15 points of the Braden scale. This will effectively guide clinical practice and provide a reference for the prevention of ICH complications.

Our previous study verified the correlation between the Braden scale and SAP after AIS. The AUC for the Braden scale for the prediction of pneumonia after AIS was 0.883 (95%CI 0.828–0.937). When the cutoff point was 18 points, the sensitivity was 83.2% and the specificity was 84.2%[12]. This result suggests that the efficacy of the Braden scale in predicting pneumonia after ICH is lower than that in predicting pneumonia after AIS. After we compared the data, we found that the average Braden scale score of all the ICH patients in this study was 15.91±2.77, which was lower than that reported in a previous study of AIS patients (18.96±2.71) and suggests that compared with AIS patients, ICH patients may have poorer mobility and a poorer nutritional status at admission. Therefore, we speculate that ICH patients may have more severe nerve functional impairment at admission, decreasing the sensitivity of the Braden scale in predicting pneumonia after ICH. However, the sensitivity was 74.3% with a cutoff point of 15 points, which still suggests that it is feasible for predicting SAP after ICH.

Risk factors for SAP after stroke include the following[20-22]: age, sex, NIH Stroke Scale (NIHSS) score, dysphagia, current smoking status, Glasgow Coma Scale (GCS) score, and dysphagia. Although the Braden scale does not include these risk factors, the indexes in the Braden scale are associated with some risk factors for SAP. The nutritional indicators are related to the patient's age and dysphagia. Sensory perception and mobility are related to the NIHSS score. Skin moisture and activity are related to the patient's GCS score. This may be the reason why the Braden scale is related to SAP.

Most studies of SAP are based on ischemic stroke, and many scales have been developed to predict SAP after AIS[23-25]. However, the applicability of these scales to ICH needs further exploration. There are studies looking for risk factors for SAP after ICH. Divani et al found that early hospital admission, in-hospital aspiration, intubation, and tracheostomy are risk factors for SAP after ICH[26], which is somewhat different from the SAP risk factors for AIS. Marini et al found that male sex, which is also a risk factor for SAP after AIS, independently increases pneumonia risk and subsequently increases 90-day mortality[27,28]. However, there are few studies on the SAP assessment scale after ICH. Ji et al developed the ICH-APSs scale to predict SAP after ICH[29]. A 23-point ICH-APS-A was developed based on a set of predictors and showed good discrimination in the overall derivation (AUC 0.75; 95%CI 0.72–0.77) and validation (AUC 0.76; 95%CI 0.71–0.79) cohorts. Our study showed that the Braden scale has the same predictive ability, and research can be conducted to evaluate the strengths of different scales in the future.

Unlike AIS patients, we did not observe an association of atrial fibrillation (AF) with SAP after ICH in our multivariate analysis[30]. We speculate that this may be due to the association of AF with the severity of AIS patients. Zhao et al observed a correlation between infarct volume and SAP after AIS[31], whereas patients with cardioembolism tended to have a larger infarct volume[32] and more severe clinical symptoms, which leads to the correlation of AF with SAP. However, in patients with ICH, the severity of symptoms was related to the site and volume of bleeding, which was not directly related to AF, so AF was not an important risk factor when assessing SAP in patients with ICH. In addition, we did not find that chronic obstructive pulmonary disease (COPD) and smoking history affected SAP after ICH, which suggests that factors such as disturbance of consciousness and dysphagia after ICH have a greater impact on SAP than pulmonary adverse factors before admission. The Braden score, which is related to these factors, is indeed an independent risk factor for SAP.

Diabetic patients are more prone to pulmonary infection[33], but we did not observe an association of diabetes with SAP after ICH in the multivariable analysis. However, we found that there is a correlation between fasting blood glucose and SAP, which may suggest that it is the blood sugar control at the onset of ICH rather than the history of diabetes that affects SAP. Therefore, effective blood sugar control for diabetic patients is an important measure to reduce SAP. Another reason for this phenomenon may be stress hyperglycaemia[34]. A previous study

showed that stress hyperglycemia was associated with a high risk of mortality and recurrence after stroke[35] and the excessive release of pro-inflammatory cytokines[35]. These elevated cytokines reduce insulin production in peripheral tissues and further increase blood glucose, resulting in a vicious cycle[36]. Furthermore, the aforementioned pro-inflammatory molecules are significant contributors to SAP[37], and stroke-induced immunosuppression and infection promote and accelerate the occurrence and development of SAP[38]. Thus, stroke patients with a stress hyperglycemia-induced high inflammatory state may be associated with a high risk of SAP. Therefore, for patients with ICH, the history of diabetes should not only be considered, and the blood glucose status at the onset of the disease has a stronger correlation with SAP.

Patients with ICH experience different neurological deficits and levels of consciousness at different times. Therefore, the Braden score, NIHSS score, and GCS score assessed at different time points also differ. We administered the Braden scale at 24 h after admission to evaluate the incidence of SAP after AIS, and we confirmed that the 24-h Braden score can effectively predict poststroke pneumonia. In this study, we also administered the Braden scale to patients at 24 h after admission because cerebral hemorrhage is more likely to progress within 24 h after onset, most patients' conditions tend to stabilize after 24 h of onset, and the possibility of increased bleeding is relatively low. Therefore, the assessments of neurological deficits performed at 24 h are more indicative of the progression of patients' conditions.

Our study did not include patients with ICH who underwent surgery because the purpose of this study was to evaluate the sensitivity of the Braden scale in predicting poststroke pneumonia; the eventual goal was to screen high-risk patients and take effective preventive measures, thereby improving their prognosis. ICH patients undergoing surgery are already at high risk of lung infection due to anesthesia and tracheal intubation[39-41]. These patients need medical staff to take necessary measures to prevent pneumonia after stroke. In addition, there was no correlation between the risk factors for the need for these operations and the Braden scale, but the presence of correlations may increase the incidence of pneumonia and affect the sensitivity of the study. Therefore, we excluded all patients who underwent surgical treatment.

Our study has some limitations. First, our study did not include outpatient clinic patients. Second, there is a possibility that unmeasured confounders might have some impact on the risk of SAP after ICH.

CONCLUSION

The Braden scale, with a cutoff point of 15 points, is a moderately valid clinical grading scale for predicting SAP after spontaneous ICH.

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AUTHORS' CONTRIBUTIONS

YLD: Conceptualization, Data curation, Formal Analysis, Writing – original draft, Writing – review & editing. **ZYJ:** Data curation, Writing - original draft, Writing - review & editing. **YL:** Conceptualization, Data curation, Writing – original draft, Writing – review & editing. **JLN:** Conceptualization, Data curation, Formal Analysis, Writing – original draft, Writing – review & editing.

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ORIGINAL ARTICLE

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The Baecke Habitual Physical Activity Questionnaire (BHPAQ): a valid internal structure of the instrument to assess healthy Brazilian adults

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SUMMARY

OBJECTIVE: This study aimed to validate the internal structure of the Brazilian version of the Baecke Habitual Physical Activity Questionnaire.

METHODS: A cross-sectional study was conducted with individuals over 18 years old of both sexes, with Brazilian Portuguese as their native language. The structure of the Baecke Habitual Physical Activity Questionnaire was tested by confirmatory factor analysis. The model fit was evaluated by the following indices: root mean square error of approximation, comparative fit index, Tucker-Lewis index, standardized root mean square residual, and χ^2/degrees of freedom. We used the Akaike information criterion and Bayesian information criterion to compare different structures of the Baecke Habitual Physical Activity Questionnaire.

RESULTS: A total of 241 individuals participated in this study. The original structure of the Baecke Habitual Physical Activity Questionnaire with 16 items and 3 domains was compared to a structure with 14 items and 3 domains. The internal structure of the Baecke Habitual Physical Activity Questionnaire with 14 items showed better fit indices and lower Akaike information criterion and Bayesian information criterion values.

CONCLUSION: The best internal structure of the Brazilian version of the Baecke Habitual Physical Activity Questionnaire in adults presents 3 domains and 14 items.

KEYWORDS: Physical activity. Factor analysis. Reproducibility of results.

INTRODUCTION

The Baecke Habitual Physical Activity Questionnaire (BHPAQ) is a self-administered and self-evaluating instrument capable of measuring the physical activity of the past 12 months, created in the Netherlands in 1982. The original study initially involved the measurement of construct and content validity, in addition to test-retest reliability. Initially, the BHPAQ had 29 items, reduced to 16 items after principal component analysis (PCA). It included three domains: physical activity in occupation (items 1–8), physical activity in sports in free time (items 9–12), and leisure-time physical activity other than sports (items 13–16). For each domain, the score ranges from 1–5, with higher scores indicating higher physical activity[1].

This instrument has been translated, adapted, and validated for several countries, such as Belgium[2], Portugal[3], and Iran[4]. In Brazil, several validation studies have been conducted. The process of translation and cross-cultural adaptation of the BHPAQ was carried out by Sardinha et al.[5] and Florindo et al.[6], who also determined the internal consistency of the questionnaire to be good when applied to men aged 50 years or older.

Florindo and Latorre[7] validated and investigated the test-retest reliability of the BHPAQ in adult men and concluded that the tool is a good choice for evaluating habitual physical activity in

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Brazilian men. In another study, Guedes et al.[8] verified the validity and reliability of the BHPAQ in adolescents, obtaining satisfactory results regarding its measurement properties. Garcia et al.[9] verified the construct validity of the BHPAQ using the accelerometer as a reference and found acceptable values. In contrast, Carvalho et al.[10] concluded that the construct validity was inadequate when applied to patients with chronic lower back pain.

Despite these scientific initiatives, there are no studies defining the internal structure of the BHPAQ in Brazil considering the three domains defined in the original version, despite the questionnaire being used commonly in the country. Structural validity is useful to measure whether the result obtained reflects the dimensionality of the instrument to be evaluated[11]. Given the importance of this instrument for research and practical applications in healthcare, the objective of this study was to evaluate the internal structure of the Brazilian version of the BHPAQ.

METHODS

Study design

This was a cross-sectional, quantitative study. Data were collected online using the Google Forms platform (Mountain View, CA, USA). After reading the informed consent form, all participants included in the study confirmed their participation ticking the option "I agree to participate" on the first page of the online form. This study was approved by the Research Ethics Committee of the Universidade Ceuma (under number 3.115.347).

Participants

The sample size followed the recommendations of the COnsensus-based Standards for the selection of health Measurement INstruments (COSMIN): seven times the number of items of the questionnaire. Therefore, a minimum of 112 individuals was recommended based on the inclusion of 16 items[11]. The inclusion criteria adopted in this study were as follows: healthy individuals of both sexes, practicing physical activity or not, with Brazilian Portuguese as their native language, and aged 18 years or over. The exclusion criteria for this study were as follows: participants without a fixed profession or unemployed, presence of a medical diagnosis of cognitive alteration, and inability to read or write.

Baecke Habitual Physical Activity Questionnaire

The BHPAQ is a self-applicable, self-report instrument that assesses physical activity over the past 12 months. It consists of 16 items, divided into 3 domains: physical activity in occupation (items 1–8), physical activity in sports in free time (items 9–12), and physical activity during leisure other than sport (items 13–16). There are five Likert scale (1–5) response possibilities[1,6].

The score of the occupational domain is calculated by summing the answers indicated and dividing by 8 (for item 2, the value indicated should be subtracted by 6). The score of the sports domain is calculated by summing the values indicated and dividing by 4. To calculate the leisure domain score, all of the checked answers must be summed and the value must be divided by 4 (for item 13, the indicated value must be subtracted by 6). For each domain, the final score ranges from 1 to 5; the higher the score, the higher the level of physical activity [6].

Statistical analysis

Descriptive statistical analysis was performed, with the presentation of the values as mean and standard deviation for quantitative variables and using absolute number and percentage for qualitative variables. Descriptive analysis was performed using the SPSS software version 17.0 (Chicago, IL, USA).

The validity of the BHPAQ structure was tested by confirmatory factor analysis (CFA), using the R Studio software (Boston, MA, USA) with the lavaan and semPlot packages. CFA was performed with the implementation of a polychoric matrix and the robust extraction method diagonally weighted least squares (RDWLS), as recommended by specialized literature[12]. The model fit was evaluated using the following indices: root mean square error of approximation (RMSEA) with confidence interval (CI) at 90%, comparative fit index (CFI), Tucker-Lewis index (TLI), standardized root mean square residual (SRMR), and chi-square/degrees of freedom (DF)[13,14].

In this study, values >0.90 were considered adequate for CFI and TLI, and values <0.08 were considered adequate for RMSEA and SRMR. Values <3.00 were considered adequate in the interpretation of chi-square/DF[13,15,16]. In CFA, factor loadings ≥0.40 were considered adequate for the domain. The RMSEA and SRMR indices evaluate the model residuals; in the best of conditions, the residual should be equal to 0. In another perspective, CFI and TLI calculate the relative fit of the observed model and compare it with a base model; under the best of conditions, the value should equal 1.

For comparison between the BHPAQ models, i.e., the original version of the questionnaire with 16 items versus 14 items, the Akaike information criterion (AIC) and Bayesian information criterion (BIC) indices were used. The structure with the lowest AIC and BIC values was considered to be the most

parsimonious model, as recommended in the specialized literature[17]. Parsimonious models are simple models that explain the data with a minimum number of parameters.

Criterion validity was assessed by correlating the score of the BHPAQ domains with 14 and 16 items, considering a correlation magnitude >0.70 as adequate[11]. Therefore, normality was verified using the Kolmogorov-Smirnov test and correlations were performed using Spearman's correlation coefficient (rho).

RESULTS

A total of 241 individuals participated in this study. As can be seen in Table 1, most participants were women, young adults, and single adults, with secondary education and who were mildly overweight. Regarding the BHPAQ score, all domains scored slightly higher than 2.50.

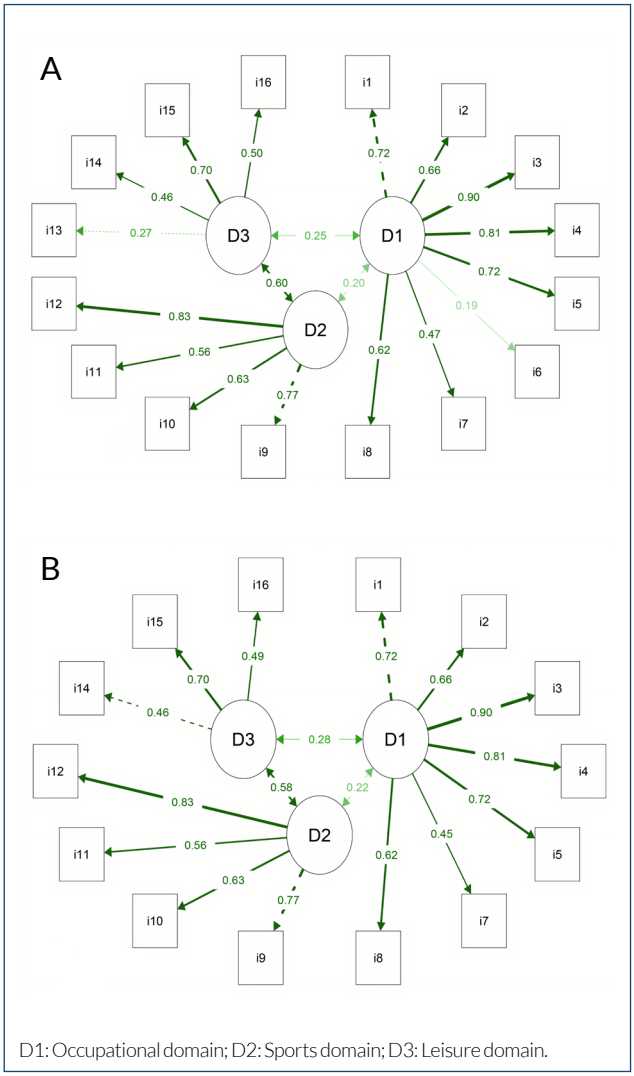
The internal structure of the BHPAQ was evaluated by means of CFA. However, as can be seen in Figure 1, items 6 and 13 had a factor loading below 0.40. Therefore, we compared the original structure of the BHPAQ with 16 items and 3 domains versus the structure with 14 items and 3 domains (excluding items 6 and 13), as given in Table 2. The internal structure with 14 items presented the best fit indices and lowest values of AIC and BIC. In addition, Figure 1 also presents the factor loadings of the BHPAQ with 14 items and 3 domains, and all items have a factorial load >0.40. The Brazilian version of the BHPAQ with 14 items is available on the website: https://questionariosbrasil.blogspot.com

Regarding criterion validity, we observed a satisfactory correlation between the occupational domain with 8 and 7 items (rho=0.985, p<0.001) and between the leisure domain with 4 and 3 items (rho=0.907, p<0.001). As the sport domain did not change in the number of items, the correlation was not performed.

Table 1. Personal characteristics of study participants (n=241).

	Mean (standard deviation) or number (%)
Age (years)	27.73 (9.58)
Gender (female)	130 (53.9)
Marital status	
Single	184 (76.3)
Married	51 (21.2)
Divorced	2 (0.8)
Widower	4 (1.7)
Schooling	
Primary	13 (5.4)
Secondary	150 (62.2)
Superior	78 (32.4)
Mass (kg)	70.57 (16.32)
Height (m)	1.68 (0.10)
Body mass index (kg/m^2)	25.11 (6.64)
BHPAQ (score, 1–5)	
Occupational domain (8 items)	2.71 (0.66)
Occupational domain (7 items)	2.66 (0.71)
Sport domain (4 items)	2.52 (0.81)
Leisure domain (4 items)	2.58 (0.68)
Leisure domain (3 items)	2.51 (0.77)

BHPAQ: Baecke Habitual Physical Activity Questionnaire.



D1: Occupational domain; D2: Sports domain; D3: Leisure domain.

Figure 1. Path diagram of the Baecke Habitual Physical Activity Questionnaire (BHPAQ) with 16 items (A) and 14 items (B).

Table 2. Comparison between the internal structures of the Baecke Habitual Physical Activity Questionnaire (BHPAQ).

Structure	χ^2	DF	χ^2/DF	CFI	TLI	RMSEA (90%CI)	SRMR	AIC	BIC
16 items	230.498	101	2.28	0.935	0.923	0.073 (0.061–0.086)	0.077	10576.960	10698.928
14 items	131.437	74	1.77	0.971	0.964	0.057 (0.041–0.073)	0.061	9192.560	9300.589

DF: degrees of freedom; CFI: comparative fit index; TLI: Tucker-Lewis index; RMSEA: root mean square error of approximation; CI: confidence interval; SRMR: standardized root mean square residual; AIC: Akaike information criterion; BIC: Bayesian information criterion.

DISCUSSION

This study identifies the most appropriate structure for the Brazilian version of the BHPAQ with 3 domains, according to the original article, however, with 14 items: 7 items in the physical activity domain in occupation (items 1–5, 7, 8), 4 in the physical activity domain in sports (items 9–12), and 3 items in the physical activity domain in leisure without sport (items 14–16). Thus, items 6 (occupation domain) and 13 (leisure domain) were excluded. Item 6 refers to how physically tired the individual becomes after work, and item 13 refers to watching television during leisure time.

To the best of our knowledge, only two studies in the literature have verified the internal structure of the BHPAQ. The original version of the questionnaire was carried out by Baecke et al.[1] and used PCA to identify the number of retained factors, finding a structure with 3 dimensions and 16 items. Almeida and Ribeiro[3] evaluated the structure of two of the three domains of the BHPAQ, excluding the occupation domain for methodological reasons. A valid internal structure with two dimensions and eight items was found.

Both studies above did not use the most appropriate analysis method to verify the internal structure of the BHPAQ[11]. According to Tabachnick and Fidell[16], PCA has less adequacy when compared to factor analysis because it considers all variance and is, therefore, contaminated by the variability of error, so it is not recommended to evaluate the internal structure of a questionnaire.

After analysis of the BHPAQ, in this study, items 6 (occupation domain) and 13 (leisure domain) were excluded following the suggestion of the literature regarding items with non-significant factor loading, in this case, <0.40. The low factor load may be due to the following aspects: item 6 asks the respondent to describe physical fatigue after work; however, it may be difficult to differentiate between physical fatigue and mental fatigue. The individual may be mentally tired, but this does not represent their usual physical activity. Item 13 is related to watching television at leisure; however, due to technological changes and the increasing use of modern devices such as mobile phones, it may be that other sedentary habits during leisure time are more important than watching television today.

Our study was carried out in Brazilians and the conclusions must be restricted to this population. However, considering that the BHPAQ was created in 1982[1], it is important that the original version of the questionnaire should be revised in all languages, as society has undergone consistent changes in recent years and physical activity has been considerably affected by these changes. We suggest that consistent factor analyses be considered to suit the ordinal characteristics of the possible responses to the BHPAQ.

CONCLUSION

The structure of the Brazilian version of the BHPAQ with 3 domains and 14 items is the most appropriate based on factor analysis and should be used to investigate physical activity related to occupation, sport, and leisure.

AUTHORS' CONTRIBUTIONS

DSR: Conceptualization, Data curation, Formal Analysis, Methodology, Writing – original draft. **JCS:** Conceptualization, Data curation, Formal Analysis, Methodology, Writing – original draft. **LFSA:** Conceptualization, Data curation, Formal Analysis, Methodology, Writing – original draft. **GNS:** Conceptualization, Data curation, Formal Analysis, Methodology, Writing – original draft. **AVDF:** Conceptualization, Formal Analysis, Methodology, Writing – review & editing. **AF:** Conceptualization, Formal Analysis, Methodology, Writing – review & editing. **RRJT:** Conceptualization, Formal Analysis, Methodology, Writing – review & editing. **ASR:** Conceptualization, Formal Analysis, Methodology, Writing – review & editing. **CAFPG:** Conceptualization, Formal Analysis, Methodology, Writing – review & editing. **DBD:** Conceptualization, Formal Analysis, Methodology, Writing – review & editing.

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ORIGINAL ARTICLE

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Efficacy of fetal left ventricular modified myocardial performance index in predicting adverse perinatal outcomes in intrahepatic cholestasis of pregnancy

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SUMMARY

OBJECTIVE: This study aimed to evaluate the effectiveness of fetal left ventricular modified myocardial performance index in predicting adverse perinatal outcomes for intrahepatic cholestasis of pregnancy.

METHODS: A cross-sectional study was conducted, including 51 women with intrahepatic cholestasis of pregnancy and 80 healthy controls. Using Doppler ultrasonography, E-wave, A-wave, isovolumetric contraction time, isovolumetric relaxation time, and ejection time were recorded and the left ventricular modified myocardial performance index was measured.

RESULTS: Findings showed that the mean left ventricular modified myocardial performance index, isovolumetric contraction time, and isovolumetric relaxation time values were statistically significantly higher while the ejection time and E/A ratios were statistically significantly lower in the intrahepatic cholestasis of pregnancy group than the control group. In the intrahepatic cholestasis of pregnancy group, a statistically significant positive correlation was found between left ventricular modified myocardial performance index and adverse perinatal outcomes in the intrahepatic cholestasis of pregnancy group ($r=0.478$, $p<0.001$), while a statistically significant negative correlation was found between the E/A ratio and adverse perinatal outcomes ($r=-0.701$, $p<0.001$).

CONCLUSIONS: For intrahepatic cholestasis of pregnancy cases, high fetal left ventricular modified myocardial performance index values were an indicator of ventricular dysfunction, and this correlated with negative perinatal outcomes.

KEYWORDS: Fetal heart. Intrahepatic cholestasis of pregnancy. Myocardial performance index. Perinatal outcome.

INTRODUCTION

Intrahepatic cholestasis of pregnancy (ICP) is a disease diagnosed in the late second or third trimester of pregnancy without accompanying hepatobiliary pathology, with a reported incidence of 0.2–2%[1]. ICP is associated with adverse perinatal outcomes such as spontaneous preterm birth, meconium staining of amniotic fluid, fetal distress, respiratory distress syndrome, neonatal intensive care unit admission, and stillbirth[2]. Although factors such as placental microstructure disorders and fetal arrhythmia have been considered, the pathogenesis of these poor obstetric outcomes in ICP, including stillbirth, remains unclear[3-5]. Data from animal studies on rats have indicated that the toxic effects of bile acids may impair cardiomyocyte function and cause arrhythmia in the fetuses of women with ICP, leading to fetal death[6,7].

The myocardial performance index (MPI) is a parameter measuring global myocardial function (both systolic and diastolic)[8]. MPI is considered a reliable marker for fetal cardiac function in assessing cardiac adaptation to various perinatal complications[9].

This study aimed to evaluate the effectiveness of using the fetal left ventricular modified myocardial performance index (LMPI) for women with ICP to predict adverse perinatal outcomes.

METHODS

This study included 51 pregnant women who visited the Perinatology Clinic in the Department of Gynecology and Obstetrics of Sakarya University Training and Research Hospital between April 1, 2018, and March 15, 2021, and

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then followed up due to delivery in this center after being diagnosed with ICP. As a control group, 80 pregnant women who did not have any pregnancy complications and had a completely normal pregnancy were also included. Data from both groups were obtained from medical records. Pregnant women with chronic liver diseases or other chronic diseases, skin diseases, allergic disorders, symptomatic cholelithiasis, or ongoing viral infections affecting the liver (e.g., hepatitis A, B, and C virus, cytomegalovirus, herpes simplex virus, and Epstein-Barr virus), multiple pregnancies, pregnant women with alcohol dependence and smoking, congenital fetal anomalies, evidence of placental insufficiency in Doppler parameters, and pregnant women with sonographic estimated fetal weight <10th percentile were not included in the study. The Institutional Review Board on Human Protection and Research Ethics of the University approved the study.

The diagnosis of ICP was based on characteristic symptoms and elevated serum fasting bile acid level (≥10 µmol/L) in maternal blood, in the absence of other hepatobiliary disease[10]. Those with fasting bile acid levels of 10–40 µmol/L were classified as having mild ICP and those with >40 µmol/L were classified as having severe ICP[11]. When published literature was reviewed in terms of ICP treatment and monitoring, it was seen that various methods existed. In the study clinic, among the approaches mentioned in the literature, patients diagnosed with ICP are routinely treated with ursodeoxycholic acid (UDCA)[12], and birth planning at 37 weeks of gestation is applied for those with improved clinical and laboratory results[13].

All ultrasound examinations were performed by a single sonographer (KG) using Voluson version 730 (GE Medical Systems, Milwaukee, WI, USA) or Voluson version E 6 (GE Healthcare Ultrasound, Milwaukee, WI, USA) ultrasound machine equipped with a 2- to 7-MHz convex transducer. After the assessment of the fetal anatomy, fetal biometry, amniotic fluid index, umbilical artery (UA), middle cerebral artery (MCA), and mean uterine artery (UA), Doppler indices were measured in the absence of fetal movements. The fetal left ventricle Mod-MPI measurement was performed as described initially by Hernandez-Andrade et al.[14]. An apical four-chambered view was obtained. The Doppler sample was opened to 3–4 mm and placed at a location to include both the lateral wall of the ascending aorta and the internal leaflet of the mitral valve, where the clicks corresponding to the opening and closing of the two valves were imaged. The Doppler angle of insonation was <20. The fastest Doppler sweep velocity (15 cm/s) was used, and the wall motion filter was calibrated at 300 Hz. The E-wave (early ventricular filling) and A-wave (active atrial filling) were obtained to calculate the E/A ratio. The isovolumetric contraction time (ICT) was measured from the beginning of the mitral valve closure to the aortic valve opening. The isovolumetric relaxation time (IRT) was measured from the aortic valve closure to the mitral valve opening. The ejection time (ET) was measured from the opening to the closing of the aortic valve. The Mod-MPI was calculated using the following formula: (ICT+IRT)/ET.

In both groups, newborn weight, Apgar scores, and other health information were obtained from medical records. In both groups, negative perinatal outcomes such as non-reassuring fetal heart rate tracing, meconium-stained amniotic fluid, umbilical cord pH <7.20, and neonatal intensive care unit admission were obtained from medical records.

Statistical analyses were performed by using the SPSS version 24.0 package program (SPSS Inc. and Lead Tech. Inc., Chicago, USA). Kolmogorov-Smirnov test was used in compliance with normal distribution. Parametric data were appraised with the independent two-sample t-test, and non-parametric data were compared using the Mann-Whitney U test. Multiple groups were compared with Kruskal-Wallis and Bonferroni's post-hoc correction. Correlations were assessed using Spearman's correlation coefficient. Receiver operating characteristic (ROC) analysis was used to evaluate the predictive performance of LMPI for adverse perinatal outcomes. An alpha <0.05 for Bonferroni correction and a p-value <0.05 for other tests were considered statistically significant.

RESULTS

Patient characteristics, perinatal outcomes, and ultrasound results of groups are shown in Table 1.

A statistically significant positive correlation was found between LMPI and maternal fasting bile acid levels in the ICP group ($r=0.748$, $p<0.001$). The LMPI value was evaluated with the Kruskal-Wallis test between mild ICP, severe ICP, and control groups, and a statistically significant difference was found. As a result of evaluation of the E/A ratio with the Kruskal-Wallis test, a statistically significant difference was found between mild ICP, severe ICP, and control groups (Table 2). As a result of the evaluation of the E/A ratio within the groups with the Mann-Whitney U test, a statistically significantly difference was found higher in the control group than the ICP group ($p<0.001$), while no statistically significant difference was found between mild ICP and severe ICP ($p=0.022$).

A statistically significant positive correlation was found between LMPI and adverse perinatal outcomes in the ICP

Table 1. Patient characteristics, perinatal outcomes, and ultrasound results of groups.

	ICP group (n=51)	Control group (n=80)	p-value
Maternal age (years)	30 (21–39)	30.5 (20–39)	0.226
Gravida (n)	2 (1–5)	4 (1–7)	0.000
Parity (n)	1 (0–4)	2 (0–4)	0.000
Body mass index (kg/m^2)	26.6 (21.2–29.4)	25.8 (22.4–29.1)	0.184
Gestational age at time of study (weeks)	33.9 ± 1.4	34.1 ± 1.3	0.594
Gestational age at birth (weeks)	37.1 (30.4–38.7)	39 (35.2–39.8)	0.000
Birth weight (g)	2913 ± 460	3270 ± 370	0.000
Aspartate aminotransferase (units/L)	56 (17–362)	16.5 (8–27)	0.000
Alanine aminotransferase (units/L)	95 (17–506)	10 (4–19)	0.000
Adverse perinatal outcome	16 (31.4)	3 (3.8)	0.000
Non-reassuring fetal heart rate tracing	8 (15.7)	0 (0)	0.000
Cord pH <7.20	1 (2)	0 (0)	0.210
Meconium strained-amniotic fluid	1 (2)	1 (1.3)	0.747
Neonatal intensive care unit admission	8 (15.7)	2 (2.5)	0.006
Left myocardial performance index	0.49 (0.44–0.56)	0.37 (0.36–0.38)	0.000
isovolumetric contraction time (ms)	34.8 ± 2.8	29.6 ± 1.3	0.000
ejection time (ms)	162.5 ± 4.9	170.5 ± 4.3	0.000
isovolumetric relaxation time (ms)	45.2 (41.8–52.6)	33.9 (31.4–35.8)	0.000
E-wave/A-wave peak velocity ratio	0.62 (0.56–0.75)	0.69 (0.62–0.76)	0.000
Umbilical artery pulsatility index	0.84 (0.74–0.96)	0.86 (0.75–0.94)	0.170
Middle cerebral artery pulsatility index	1.77 (1.61–1.93)	1.73 (1.6–1.93)	0.076
Uterine artery pulsatility index	0.8 (0.67–0.96)	0.77 (0.62–0.97)	0.0146

Data are expressed as mean±standard deviation, median (minimum–maximum), and n (%) where appropriate. p<0.05 indicates significant difference (denoted in bold).

Table 2. Kruskal-Wallis test comparing mild Intrahepatic cholestasis of pregnancy, severe Intrahepatic cholestasis of pregnancy, and control.

	Control group (n=80)	Mild Intrahepatic cholestasis of pregnancy (n=40)	Severe Intrahepatic cholestasis of pregnancy (n=11)	p-value
LMPI	0.37 (0.36–0.38)	0.48 (0.44–0.56)	0.52 (0.49–0.56)	0.000
E/A	0.69 (0.62–0.76)	0.64 (0.56–0.75)	0.60 (0.58–0.62)	0.000

LMPI: left ventricular modified myocardial performance index; E/A: E-wave/A-wave.
Data are expressed as median (minimum–maximum). p<0.05 indicates significant difference (denoted in bold)

group (r=0.478, p<0.001). The LMPI value was statistically significant in predicting adverse perinatal outcomes in the ICP group (p-value 0.001), and the ROC value was found to be 0.796 (Figure 1). When the cutoff value for the LMPI value was accepted as ≥0.495, the sensitivity was 81.3% and the specificity was 65.7%. Again in the ICP group, a statistically significant negative correlation was found between the E/A ratio and adverse perinatal outcomes (r=-0.701, p<0.001). There was no fetal or neonatal death in either group.

DISCUSSION

This study found that fetal LMPI value increased significantly for ICP as the severity of the disease increased, and this value was also positively correlated with fasting bile acid level. In addition, although the E/A ratio did not differ significantly between mild and severe ICP, it was significantly lower when ICP cases were evaluated in general. These results support the idea that the LMPI value and the E/A ratio are effective in predicting adverse perinatal outcomes for ICP.

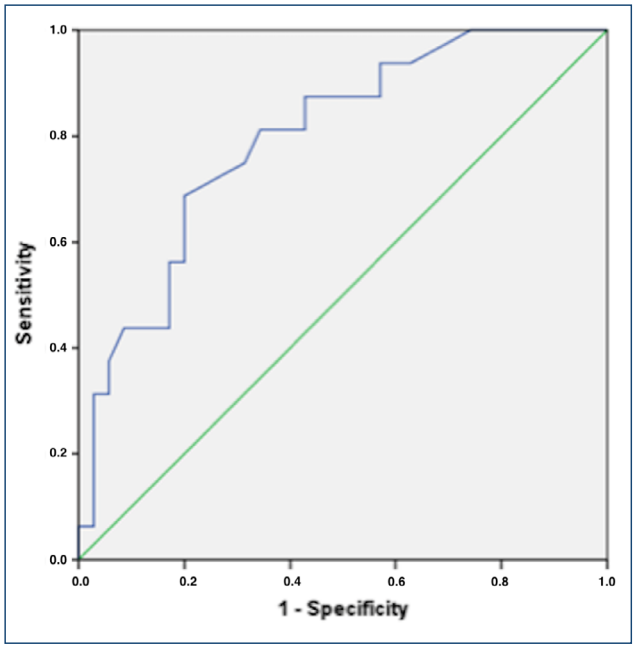

Figure 1. Receiver operating characteristic curve for left ventricular modified myocardial performance index in predicting adverse perinatal outcomes in Intrahepatic cholestasis of pregnancy.

Very few studies investigated the efficacy of LMPI in pregnancy and ICP and determined that the LMPI value increased, similar to this study findings[15-17].

Henry et al. first detected the elevation of LMPI in ICP and reported that there was a significant positive correlation between LMPI and fasting bile acid levels, similar to this study[15]. Another study found that the LMPI value increased as the severity of the disease increased, as shown in our study[16]. Ozel et al. stated that there was no significant difference in LMPI values as the severity of the disease increased and that there was no significant correlation between LMPI and fasting bile acid, which contradicts to this study results[17]. In all these studies, including this study, overt fetal ventricular dysfunction was reported in ICP cases.

Diastolic function for the fetal heart is assessed by IRT and E/A ratio[8,9]. The IRT value becomes abnormal from the early stages of diastolic dysfunction[8]. It has been observed that the E/A ratio increases in the early period to overcome the dysfunction of the fetal heart but decreases in cases where hypoxia becomes chronic and in the late phases of cardiac overload. It has been stated that this decrease in E/A ratio is due to atrial contraction rather than the result of negative pressure during the relaxation phase of the ventricular filling[9]. It has been stated that in fetal arrhythmias, ventricular filling occurs primarily due to atrial contraction and as a result the E/A ratio decreases, while in fetal tachycardias, the gap between E and A waves is shortened and therefore fusion occurs[18]. Ozel et al. found that the E/A ratio increased in ICP cases[17]. However, Sanhal et al. stated that the E/A ratio decreased significantly in ICP cases, the results similar to ours[16]. This difference is thought to be due to the earlier and compensated phase of fetal heart deterioration in the patient group in the study by Ozel et al. and the more advanced and decompensated phase of the disorder in the patient groups of Sanhal et al. and our study.

Although adverse perinatal outcomes are increased in ICP, its relationship with LMPI has been evaluated in only two previous studies. Sanhal et al. reported 81.8% sensitivity and 67.6% specificity when the cutoff value for LMPI was taken to be 0.48 when determining adverse perinatal outcomes in pregnant women complicated with ICP. Again, in this study, it was stated that there was no significant difference in terms of LMPI value and E/A ratio in the group with and without adverse perinatal outcomes, unlike our study[16]. Ozel et al., in contrast, found a significant correlation between the LMPI value and adverse perinatal outcomes, similar to our study, and showed a sensitivity of 85% and a specificity of 61% when the cutoff value for LMPI was taken to be 0.41[17]. The findings of our study and the results of these two studies show that fetal heart dysfunction, manifested by increased LMPI with high sensitivity, causes adverse perinatal outcomes in ICP cases.

Although ICP is a benign obstetric condition for the mother, the most critical fear in antenatal follow-up in these cases is sudden fetal death. Previous study data showed that Doppler parameters were normal, similar to our study, suggesting that the cause of sudden death was not placental[15-17]. Rodríguez et al found that the PR interval, which gives information about atrioventricular conduction, was prolonged when the fetuses of pregnant women complicated by ICP were compared with the fetuses of pregnant women without complications[18]. In the same study, it was mentioned that this situation might lead to the onset of arrhythmias in the fetal heart and eventually lead to fetal death[18]. In animal studies, the toxic effect of bile acids on cardiomyocytes in rats has been demonstrated[6,7]. In the light of this information, it is firmly thought that the cause of sudden death occurs due to disturbances in the electrophysiological conduction in the fetal heart.

The most important strength of this study is that it has been conducted with the largest population in the literature to date. The most important limitations of our study are that it is a retrospective study, and the measurements that may change before and after treatment with UDCA were not evaluated.

CONCLUSION

For ICP cases, high fetal LMPI values were an indicator of ventricular dysfunction, and this correlated with negative perinatal outcomes. Evaluation of the LMPI during routine antenatal follow-up can predict poor fetal outcomes, including stillbirth. Prospective studies with a larger number of patients are needed to prove this situation.

AUTHORS' CONTRIBUTIONS

KG: Conceptualization, Writing – original draft, Writing – review & editing. **BK:** Data curation, Formal Analysis. **MSB:** Data curation, Formal Analysis. **TT:** Writing – review & editing. **OK:** Writing – review & editing. **NT:** Writing – review & editing. **SÖ:** Writing – review & editing.

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ORIGINAL ARTICLE

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Lower urinary system symptoms and affecting factors in female students staying in a dormitory

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SUMMARY

OBJECTIVE: The aim of the study was to determine the lower urinary system symptoms and the factors affecting it among young women living in the dormitory.

METHODS: This is a descriptive and cross-sectional study. A total of 355 women attending education in a public university were interviewed, considering a 95% confidence interval. Data were collected using the descriptive form and the Bristol Female Lower Urinary Tract Symptoms Scale. Necessary permissions were obtained, and appropriate analyses were carried out using the SPSS-22 program.

RESULTS: Findings showed that 71.6% of women have problems with urine storage, 29.7% have urinating disorders, 18.4% have urinary incontinence, 8.8% have sexual life problems, and 37.2% have symptoms related to quality of life. Factors affecting the symptoms include history of chronic disease (such as neurological diseases and depression), smoking, low income, history of urinary incontinence in childhood, the presence of symptoms in the mother or family history, the presence and number of urinary tract infections, chronic constipation, and not paying attention to toilet cleaning.

CONCLUSION: It is recommended to carry out community-based studies to raise awareness of women, support priority risk groups by screening, and increase the number of specialist healthcare personnel for quality care and treatment.

KEYWORDS: Lower urinary tract symptoms. Risk factors. Female.

INTRODUCTION

Lower urinary tract symptoms (LUTS) are characterized by problems with urine storage such as urgency, nocturia, and urinary incontinence (UI); bifurcated-intermittent urine flow; weak urine flow; urination with difficulty; symptoms related to urination such as delayed urination; and post-voiding symptoms such as dripping and incomplete urination[1]. In an average of five women, moderate LUTS is seen, thereby causing disruption in daily activities and discomfort[2]. Although its prevalence is the same as in men, LUTS such as overactive bladder and urine storage are more common in women[3]. The prevalence of LUTS varies in different populations depending on age, gender, symptom types, and cultural characteristics of the population[4]. The prevalence of LUTS among women has been reported to be 40–70% in epidemiological studies[4,5]. The risk factors for LUTS may include vaginal delivery, hysterectomy, more than three deliveries, family history, race, chronic diseases, menopausal period, giving birth to an infant weighing over 4 kg, having episiotomy, chronic constipation, urinary tract infections, genetic structure, and dietary habits[6].

LUTS negatively affects the work efficiency and quality of life of women[7]. Common symptoms affecting women of all ages are not only a medical problem but also the individual's physical, hygienic, psycho-social, economic, and sexual aspects; in short, the quality of life in all its dimensions. LUTS continues as an important health problem for many years[7,8]. LUTS reduces the quality of life, resulting in depression, anxiety, anxiety, and stress and causing a decrease in sexual activity. Despite all these complaints, women are ashamed of their symptoms and do not go to the doctor with feelings such as shyness and embarrassment[9-11].

LUTS is an important public health problem, as it occurs in the majority of women and affects about a quarter of the female population[12]. These complaints, which affect millions of women around the world, affect the quality of life of individuals and society[13,14]. Although its prevalence varies according to age and gender, there are not many studies conducted, especially with young and nulligravida women[9]. Lower urinary symptoms are a condition that causes embarrassment, especially in young people, and prevents them from consulting a

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doctor. It is very important that health personnel should pay close attention to this area and raise awareness of young people. The aim of this planned study was to determine LUTS and the factors affecting it among young women.

METHODS

Research type

This is a descriptive and cross-sectional study.

Study Population and Sample

The population of the study consists of female students who continue their education in a public university (n=4622). The research sample consists of a total of 355 women, calculated at 95% confidence interval, and those who met the study inclusion criteria (http://www.raosoft.com/samplesize.html was taken as reference for sample calculation). Inclusion criteria were female, over 18 years old, who has the ability to speak and understand Turkish, staying in the dormitory, and voluntary to participate in the study.

Data Collection Tools

Individual Information Form: For data collection, a questionnaire form consisting of 35 questions, including sociodemographic characteristics, risk factors, urinary symptoms, genital hygiene, and urinary tract infection, was prepared based on the knowledge of the literature[4,6,8].

The Bristol Female Lower Urinary Tract Symptom Questionnaire (BFLUTS): It is a multidimensional scale developed to determine LUTS, sexual life, and quality of life. The scale consists of 19 items, with a minimum of 0 and a maximum of 71 points. The questionnaire consists of five sub-dimensions: storage (questions 1–4), urination (questions 5–7), incontinence (questions 8–12), sexual life (questions 13–14), and quality of life (questions 15–19). In the question form, the items are scored from 0 to 3 (questions 4, 13, 14, 17, and 19) or from 0 to 4 (questions 1–3, 5–12, 15, and 16). Increase in the score showed that the quality of life and sexual life are negatively affected and the symptoms are more severe. Gökkaya et al. gave validity and reliability of the BFLUTS scale in Turkish[15]. The Cronbach's alpha coefficient of the study was found to be 0.93.

Statistical Evaluation

The data obtained as a result of the research were evaluated using the SPSS-22 program. Error checking, tabulation, and statistical analysis were performed. Data are represented in number and percentage. Statistical significance level was accepted at $p<0.05$.

Ethical dimension of the research

The ethics committee approval of the study was obtained from the Scientific Research and Publication Ethics Committee of X University with the number 95674917-604.01.02-E.824 and the date number January 8, 2019.

RESULTS

The average age of female students participating in the study is 20.21±1.62 (min=18, max=27). The socio-demographic characteristics of the women participating in the study are given in Table 1.

The' average body mass index (BMI) of the students is 21.06±2.90 (min=14.70, max=33.50). The number of students who smoke is 34 (9.6%). The prevalence rates of chronic constipation were 10.1%, depression 8.7%, allergic asthma 5.9%, urinary tract infection 7.6% (seen twice a year or more), gas incontinence 4.5%, neurological diseases 2.5%, and diabetes 1.4%. Notably, 10.4% of students use drugs continuously. It was determined that 13.2% (n=47) of the students had UI complaints in their mothers, 15.2% (n=54) in their families or relatives, and 9.3% (n=33) in their childhood.

In all, 40.8% of female students suffer from frequent urinary tract infections, approximately half of them (50.7%) do not know about urinary tract infections and 66.8% use daily pads.

In this study, the mean LUTS storage symptom was 2.79±2.09 (min=0, max=12), the mean urination symptom was 1.26±1.98 (min=0, max=12), the mean incontinence symptom was 0.75±1.81 (min=0, max=20), mean sexual life symptoms are 0.31±0.95 (min=0, max=6), quality of life symptoms are 1.66±2.37 (min=0, max=11). It is noted that 71.6% of women have problems with urine storage, 29.7% have urinating disorders, 18.4% have incontinence, 8.8% have sexual life problems, and 37.2% have symptoms related to quality of life. The comparison of BFLUTS scores of women with study variables is given in Table 2.

DISCUSSION

LUTS is common among women and negatively affects the quality of life. In a study conducted with women aged 18 years and over in five community-based countries (i.e., Canada, Germany, Italy, Sweden, and the United Kingdom), the overall prevalence of LUTS was reported to be 67%[12]. In our study, storage symptoms were found in 71.6% of young women, urination symptoms in 29.7%, incontinence symptoms in 18.4%, sex life symptoms in 8.8%, and quality of life related symptoms in 37.2%.

Table 1. Assessment of genital hygiene status in female students.

Genital hygiene conditions	n	%
Do you wash your hands when you go to the toilet?		
Before the toilet	25	7.0
After the toilet	235	66.2
Before and after the toilet	95	
Total	355	100.0
How do you clean your toilet?		
Only with water	27	7.6
With toilet paper	64	18.0
With soap	15	4.3
With antiseptic solution	4	1.1
With water and toilet paper	245	69.0
Total	355	100.0
How do you clean the toilet?		
Front to back	204	57.5
From the back to the front	129	36.3
I do not pay attention	22	6.2
Total	355	100.0
How do you prefer your underwear?		
Cotton	238	79.7
Synthetic	18	5.1
I do not pay attention	54	15.2
Total	355	100.0
Do you have frequent urinary tract infections?		
Yes	145	40.8
No	210	59.2
Total	355	100.0
How many times have you had a urinary tract infection in the last year?		
No	17	4.8
1	192	54.1
2	125	35.2
≥3	21	5.9
Total	355	100.0
What do you do when you have a urinary tract infections?		
I will go to doctor	209	58.9
I use medicine	76	21.4
I do not do anything	16	4.5
I use herbal medicine	13	3.7
I drink lots of water	31	8.7
I apply hot	10	2.8
Total	355	100.0
Do you know about urinary tract infections?		
Yes	175	49.3
No	180	49.3
Total	355	100.0
Where did you get information about urinary tract infections?		
TV-netten	100	28.2
From health personnel	114	32.1
From school	39	11.0
I did not take	102	28.7
Total	355	100.0

These problems, which affect millions of women around the world, affect the quality of life of the individual and society[13,16,17]. For example, waking up to urinate two or more times at night significantly reduces the quality of life[18]. Due to the negative effects of UI, it causes a decrease in women's quality of life, social and psychological well-being, increase in urinary tract infections, and skin sensitivity[19]. In our study, it is seen that symptoms are common among women. Coexistence of one or more of the symptoms affects the quality of life more. Approximately one-third of women have symptoms related to quality of life.

In our study, urination symptoms are ranked third in terms of the frequency of symptoms. Wang and Palmer observed 5915 women related to urine excretion and emphasized on the place, time, position, and style of urination and the physical and social environment related to voluntary physiological emptying of the bladder[20]. Another study found that there is a significant relationship between toilet behavior and LUTS[21]. As a result of the study conducted with young and middle-aged women, it was emphasized that there was a lack of knowledge about emptying the bladder normally. It has been reported that there are symptoms of urination, such as avoiding straining during voiding and inability to empty the bladder completely[22]. In this study, it is thought that the reasons for the high urination symptoms are female students, delaying urination, and delaying urination due to physical conditions (e.g., access to the toilet and hygiene conditions).

Ünsal et al. stated that the presence of any chronic disease may be an important risk factor for LUTS[23]. However, according to their logistic model results, the presence of chronic disease was found to be an important risk factor for UI. It has been reported in various studies that some chronic diseases (e.g., diabetes mellitus, hypertension, and chronic obstructive pulmonary disease) are important risk factors for LUTS[3,24]. Some studies stated that chronic constipation is an important risk factor for UI, overactive bladder, and urge UI[6,25]. In our study, it was determined that LUTS was high in patients with depression, chronic constipation, and neurological diseases, as shown in literature.

Urinary tract infection (UTI), one of the most common infections in women, is also a risk factor for LUTS[25,26]. Işıklı et al stated that recurrent urinary tract infections are an important risk factor for LUTS[27]. In our study, LUTS is seen among women with frequent urinary tract infections, except for sexual life symptoms. Storage, incontinence, and total symptom scores were found to be higher among women who had three or more UTIs per year. The results of the study are in line with the literature. Again, one of the factors that cause UTI is genital

Table 2. Comparison status of women's The Bristol Female Lower Urinary Tract Symptom Questionnaire scores.

	Storage symptoms	Urination symptoms	Incontinence symptoms	Sexual symptoms	Symptoms related to quality of life	Total
	Median (95%CI)	Median (95%CI)	Median (95%CI)	Median (95%CI)	Median (95%CI)	Median (95%CI)
Income is less than expense						
Income is equal to expense	4.00 (2.97-3.84)	0.00 (0.90-1.65)	0.00 (0.43-1.00)	0.00 (0.10-0.51)	0.00 (1.25-2.22)	6.00 (6.37-8.59)
Income is more than expense	2.00 (2.24-2.76)	0.00 (0.98-1.53)	0.00 (0.46-0.95)	0.00 (0.19-0.45)	0.00 (1.23-1.87)	5.00 (5.48-7.18)
Income is less than expense	3.00 (2.01-3.80)	1.00 (0.67-1.82)	0.00 (0.22-2.02)	0.00 (0.05-0.36)	2.00 (1.17-2.64)	6.00 (4.60-10.08)
Test value	KW=13.576 p=0.001	KW=0.344 p=0.842	KW=0.297 p=0.862	KW=1.339 p=0.512	KW=2.171 p=0.338	KW=5.688 p=0.058
Smoking status						
Yes	4.00 (2.88-4.62)	0.00 (0.74-2.34)	0.00 (0.64-3.59)	0.00 (0.01-0.59)	0.00 (0.91-3.14)	6.00 (6.12-13.32)
No	3.00 (2.46-2.91)	0 00 (1.01-1.44)	0.00 (0.40-0.75)	0.00 (0.19-0.41)	1.00 (1.34-1.84)	5.00 (5.80-7.06)
Test value	U=3925.50 p=0.006	U=5110.50 p=0.530	U=4026.00 p=0.005	U=5144.50 p=0.632	U=5385.50 p=0.891	U=4461.00 p=0.079
Depressed state						
Yes	3.00 (2.63-4.26)	1.00 (0.81-1.96)	0.00 (0.39-2.12)	0.00 (0.08-0.79)	2.00 (1.30-3.35)	6.00 (6.39-11.28)
No	3.00 (2.49-2.95)	0.00 (1.02-1.47)	0.00 (0.51-0.89)	0.00 (0.19-0.40)	0.00 (1.31-1.82)	5.00 (5.84-7.22)
Test value	U=4124.00 p=0.096	U=4299.00 p=0.159	U=4351.00 p=0.141	U=4969.00 p=0.903	U=4245.00 p=0.122	U=3850.50 p=0.031
Neurological disease state						
Yes	4.00 (1.80-5.08)	3.00 (0.90-4.42)	0.00 (0.54-4.54)	0.00 (0.48-2.93)	1.00 (0.21-5.56)	10.00(4.98-19.46)
No	3.00 (2.55-2.99)	0.00 (1.01-1.43)	0.00 (0.53-0.90)	0.00 (0.18-0.37)	0.00 (1.35-1.85)	5.00 (5.94-7.25)
Test value	U=1224.50 p=0.268	U=894.50 p=0.019	U=1213.00 p=0.167	U=1195.00 p=0.038	U=1264.50 p=0.296	U=945.50 p=0.043
Constipation state						
Yes	3.00 (2.12-3.65)	1.00 (1.21-3.22)	0.00 (0.58-2.02)	0.00 (0.08-0.63)	2.50 (1.74-3.69)	9.00 (7.01-11.81)
No	3.00 (2.54-3.00)	0.00 (0.95-1.35)	0.00 (0.49-0.88)	0.00 (0.20-0.41)	0.00 (1.26-1.76)	5.00 (5.75-7.11)
Test value	U=5645.50 p=0.867	U=4775.50 p=0.020	U=4487.50 p=0.009	U=5643.50 p=0.807	U=4313.50 p=0.008	U=4131.50 p=0.006
Having frequent UTIs						
Yes	4.00 (3.29-5.07)	1.00 (1.34-3.46)	1.00 (0.70-2.84)	0.00 (0.20-1.20)	3.00 (1.79-4.20)	10.00(8.62-15.08)
No	3.00 (2.45-2.89)	0.00 (0.96-1.37)	0.00 (0.48-0.85)	0.00 (0.18-0.37)	0.00 (1.27-1.77)	5.00 (5.66-6.96)
Test value	U=2683.00 p=0.001	U=2759.00 p=0.000	U=2768.50 p=0.000	U=4095.00 p=0.270	U=3163.00 p=0.007	U=2349.00 p=0.000
Number of UTIs in a year						
1	3.00 (2.36-2.93)	0.00 (0.96-1.56)	0.00 (0.36-0.74)	0.00 (0.15-0.43)	0.00 (1.04-1.61)	5.00 (5.29-6.89)
2	3.00 (2.34-3.07)	0.00 (0.77-1.41)	0.00 (0.48-1.25)	0.00 (0.14-0.49)	0.00 (1.40-2.38)	5.00 (5.64-8.09)
3 or more	3.00 (2.71-5.28)	2.00 (1.30-3.36)	1.00 (0.33-2.80)	0.00 (0.01-0.87)	1.00 (0.94-3.34)	10.00(6.75-14.20)
Test value	KW=4.196 p=0.123	KW=9.480 p=0.009	KW=9.049 p=0.011	KW=2.204 p=0.332	KW=4.298 p=0.117	KW=7.759 p=0.021
Urinary incontinence in the mother						
Yes	3.00 (2.35-3.42)	1.00 (0.87-1.78)	1.00 (0.79-1.98)	0.00 (0.19-1.10)	2.00 (1.34-2.69)	7.50 (6.5-10.04)
No	3.00 (2.53-3.01)	0.00 (1.02-1.48)	0.00 (0.45-0.85)	0.00 (0.16-0.34)	0.00 (1.31-1.84)	5.00 (5.79-7.22)
Test value	U=6582.00 p=0.311	U=6241.50 p=0.107	U=4972.50 p=0.000	U=6430.00 p=0.075	U=6252.50 p=0.103	U=5546.50 p=0.010

Continue...

Table 2. Continuation.

	Storage symptoms	Urination symptoms	Incontinence symptoms	Sexual symptoms	Symptoms related to quality of life	Total
	Median (95%CI)	Median (95%CI)	Median (95%CI)	Median (95%CI)	Median (95%CI)	Median (95%CI)
Urinary incontinence in family / relatives						
Yes	3.00 (2.85-4.01)	1.00 (1.00-2.12)	0.00 (0.64-1.46)	0.00 (0.19-0.97)	1.00 (1.26-2.69)	8.00 (6.88-10.31)
No	3.00 (2.44-2.91)	0.00 (0.98-1.43)	0.00 (0.48-0.90)	0.00 (0.16-0.35)	0.00 (1.31-1.84)	5.00 (5.69-7.21)
Test value	U=6216.00 p=0.005	U=6763.00 p=0.037	U=6270.50 p=0.002	U=7453.50 p=0.180	U=7332.00 p=0.214	U=6073.50 p=0.003
Urinary incontinence as a child						
Yes	3.00 (2.21-3.78)	1.00 (0.742.58)	1.00 (0.86-2.28)	0.00 (0.10-1.16)	2.00 (1.40-3.38)	9.00 (6.61-11.93)
No	3.00 (2.53-2.99)	0.00 (1.01-1.43)	0.00 (0.47-0.86)	0.00 (0.17-0.36)	0.00 (1.30-1.81)	5.00 (5.80-7.15)
Test value	U=5008.00 p=0.582	U=4799.00 p=0.336	U=3226.50 p=0.000	U=4750.50 p=0.086	U=4378.50 p=0.071	U=4150.00 p=0.038
How do you clean the toilet?						
Front to back	3.00 (2.38-2.94)	0.00 (0.94-1.46)	0.00 (0.46-0.83)	0.00 (0.23-0.53)	0.00 (1.25-1.86)	5.00 (5.65-7.24)
From the back to the front	3.00 (2.38-3.14)	0.00 (0.98-1.77)	0.00 (0.40-1.24)	0.00 (0.05-0.25)	0.00 (1.21-2.12)	5.00 (5.52-8.08)
I do not pay attention	4.00 (3.35-4.93)	1.00 (0.46-1.72)	0.00 (0.49-2.07)	0.00 (0.09-1.04)	2.00 (1.08-3.20)	9.00 (6.81-11.47)
Test value	KW=11.711 p=0.003	KW=0.068 p=0.967	KW=4.795 p=0.091	KW=2.794 p=0.247	KW=2.227 p=0.328	KW=7.405 p=0.025

CI: Confidence intervals; U: Mann-Whitney U Test; KW: Kruskal Wallis Test. p<0.05 it was considered statistically significant (indicated in bold).

hygiene. Symptoms were also high among women who did not pay attention to toilet cleaning.

Ünsal et al found that the frequency of UI was higher in women with a history of enuresis in childhood. In addition, the history of enuresis has been identified as an important risk factor for UI in the logistic model[17]. In this study, other LUTS were observed together with symptoms of UI among women with incontinence complaints in their childhood, mothers, and relatives. In our study, which is in line with the literature, it is seen that past history and genetic factors are important in the development of LUTS.

CONCLUSION

Studies on LUTS with young women are lacking. As a result of our study, it was found that high rates of LUTS were also observed among young women. Factors affecting the symptoms include history of chronic disease (such as neurological diseases and depression), smoking, low income, history of UI in childhood, the presence of symptoms in the mother or family history, the presence and number of urinary tract infections, chronic constipation, and not paying attention to toilet cleaning.

Limitation of the study

This study was conducted only with young women living in a certain region and cannot be generalized to all young women.

AUTHORS' CONTRIBUTIONS

HÖ: Conceptualization, Formal Analysis, Writing – original draft, Writing – review & editing. **NKB:** Conceptualization, Formal Analysis, Writing – original draft, Writing – review & editing.

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ORIGINAL ARTICLE

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Self-reported symptoms and seroprevalence against SARS-CoV-2 in the population of Mato Grosso: a household-based survey in 2020

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SUMMARY

OBJECTIVE: This study aimed to analyze the association between self-reported symptoms and seroprevalence against severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) in the population of Mato Grosso.

METHODS: A household-based survey was conducted on 4,206 adults from 10 municipalities of Mato Grosso, in the Brazilian Midwest, who were selected by cluster sampling in three stages. Questionnaires were applied between September and October 2020, and chemiluminescence was used for the quantitative determination of immunoglobulin G (IgG) antibodies against the S1 and S2 proteins of SARS-CoV-2.

RESULTS: Approximately half (47.0%) of individuals with SARS-CoV-2 antibodies (12.5%) reported having no symptoms. The most prevalent symptoms among individuals with antibodies were body pain (37.0%), fever (32.9%), and smell and taste change (28.7%). The search for a basic health unit was predominant (45.0%) as the first service, and only 5.3% reported being hospitalized.

CONCLUSION: A high proportion of asymptomatic cases of coronavirus disease 2019 (COVID-19) was identified in the general population, even among older adults and individuals with comorbidities.

KEYWORDS: Coronavirus infections. SARS-CoV-2. COVID-19.

INTRODUCTION

The new coronavirus identified in Wuhan, China, has spread around the world in late 2019 and is currently responsible for the most effective pandemic of the last century[1-3]. Due to the high transmissibility[4], associated with various forms of contagion, such as direct contact with saliva, aerosol, feces, and urine, fomites, and contaminated personal objects that have contact with the mucosa[5-8], its expansion was devastating in populations, totaling 243,354,428 cases and 4,943,926 deaths globally as on October 2021, with 21,723,559 reported cases and 605,457 deaths in Brazil. The state of Mato Grosso had the highest mortality rate from the disease, leading the ranking from April to September 2021[8].

The clinical forms of the coronavirus disease 2019 (COVID-19) are essential because they generate anxiety mainly due to the relationship with the transmission. The incubation time after infection ranges from 2 to 14 days[2] and clinical manifestations can range from mild cases, characterized by mild clinical symptoms, without radiographic findings of pneumonia; common cases, where fever is associated with respiratory symptoms and radiographic manifestations of pneumonia; severe cases, which can lead to respiratory distress and hypoxia; and finally, critical cases, with respiratory failure and the need for mechanical ventilation, shock, and other complications, requiring treatment in intensive care units[9]. Mortality is more prevalent in older adults over 80 years of age[10] and people with comorbidities, such as heart disease, hypertension, diabetes, chronic respiratory diseases, and neoplasms[10].

Thus, symptomatic infections are more prevalent in older individuals, and most young people and children can be asymptomatic carriers[11]. A systematic review[11] described 25 nonspecific symptoms and the most common symptoms are fever, cough, fatigue, and myalgia, which can lead to limitations in the assertive differential diagnosis with other acute febrile

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illnesses endemic in the region. International studies point to the risk of severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) affecting respiratory, neurological, and gastrointestinal systems[2,5].

The number of secondary infections observed in an affected individual with COVID-19 can range from 2–2.5%[12,13], and Xavier et al.[14] highlighted that the spread of the virus occurs more commonly by asymptomatic or symptomatic individuals with mild/moderate conditions. However, the limitation of diagnostic tests hinders the assessment of the actual proportion of asymptomatic among infected cases. The national seroprevalence household-based survey of COVID-19 in Brazil (EPICOVID) showed a prevalence of 12.1% asymptomatic among the positive cases[15]. Thus, it is essential to carry out studies that describe the seroprevalence of SARS-CoV-2 in populations and investigate its clinical characteristics.

In this context, we aimed to analyze the relationship between self-reported symptoms and the seroprevalence of SARS-CoV-2 in the Mato Grosso population by a population-based epidemiological survey.

METHODS

A household-based epidemiological survey was carried out in pole municipalities of the socioeconomic regions of Mato Grosso, a Brazilian Midwestern state, and the main cities include Cuiabá, Várzea Grande, Cáceres, Rondonópolis, Barra do Garças, Tangará da Serra, Alta Floresta, Água Boa, Juína, and Sinop. The state of Mato Grosso has an extension of 903,207.047 km², with 3,567,234 inhabitants as estimated in 2021. According to the last 2010 Census, the population density was 3.36 inhabitants/km² and the Human Development Index (HDI) was 0.725[16].

A three-stage cross-sectional cluster sampling was adopted as follows: census sector (selected with probability proportional to the number of permanent households according to the 2010 Census data); household (selected from a systematic sampling); resident above the age of 18 years (one randomly selected resident). The sample was estimated as 4,530 individuals, proportionally distributed by population size of the municipalities (25,000-65,000 inhabitants; 65,000–150,000 inhabitants; 150,000–300,000 inhabitants; >300,000 inhabitants; >300,000 inhabitants). Further details about the sampling design and the draw of households are available in the study by Oliveira et al[17].

A resident aged above 18 years was randomly selected to answer the questionnaire and submitted to blood sample collection in the residence during data collection from September 16 to October 15, 2020 by professionals after undergoing the training to standardize interviews and blood collection. The questionnaire was applied using the Epi Info™ software, version 7.2, on smartphones (U.S. Department of Health & Human Services – Washington – USA).

The biological samples were submitted to centrifugation in each municipality to obtain the serum, which, in turn, was cryopreserved at -20°C and transported to the Central Public Health Laboratory of Mato Grosso (Laboratório Central de Saúde Pública de *Mato Grosso*, LACEN-MT). The laboratory analysis was conducted using a commercial kit imported by Diasorin (MS Registry: 103.398.40-56) from the Italian company Liaison under batch 354020 and validity till December 15, 2020, through chemiluminescence for the quantitative determination of immunoglobulin G (IgG) antibodies against the S1 and S2 proteins of SARS-CoV-2, with the supplier's report of 97.4% sensitivity (percentage of positive hits) and 98.5% specificity (percentage of negative hits). The authors also performed an internal validation, besides following the LACEN-MT biosafety protocols at all testing stages. This test was chosen after accessing the available commercial kits and internal testing to measure the quality.

In this study, the presence of self-reported symptoms since the onset of the pandemic was evaluated through the question "Did you have signs and symptoms potentially related to COVID-19 since March 2020 (symptoms such as fever, headache, body pain, cough, sore throat, and smell and taste alteration)?" The questionnaire was applied before receiving the test result so that respondents were blind to their serological status. The following symptoms were evaluated: smell or taste change, fever, sore throat, cough, difficulty in breathing, palpitation, tremors or chills, body ache, diarrhea, and vomiting. Symptoms were classified as follows: asymptomatic for no symptoms reported; oligosymptomatic for those who reported one or two symptoms except smell or taste change; and symptomatic for those who reported two or more symptoms and smell and taste change. The number of symptoms and the proportion of asymptomatic individuals were analyzed by the variables such as gender, age group, ethnicity/skin color, schooling, and household income.

The classification of symptoms by search for health services and reported morbidity was also analyzed. Questions include "If you had symptoms, did you seek any health service?" with a yes/no answer, and "Which health service you sought first?" with Basic Health Unit, Polyclinic, UPA, Exclusive COVID-19 Unit, Private Emergency Care, Private Clinic, or Other as answer options. Previous comorbidities were considered:

hypertension, diabetes, asthma or bronchitis, cancer (any type), chronic kidney disease, chronic lung disease, some heart diseases, and some mental disorders such as depression.

All analyses were performed using the Stata software version 12, which allows incorporating weighting factors and considers the complex design of the sample. All ethical aspects in the research were agreed as per Resolution N° 466/2012 of the National Health Council (Conselho Nacional de Saúde), and the project was approved by the Ethics Committee of the University of the State of Mato Grosso on April 23, 2020 (Opinion 3.986.293/2020). All participants signed an informed consent form and were treated at their homes following strict biosafety protocols.

RESULTS

The mean age of the 4,206 (92.8% of the initial sample) analyzed individuals was 46.2 years (SD 16.3), and 53.7% of them were men. The COVID-19 prevalence was estimated as 12.5% (95%CI 10.5–14.7), and 47.0% of the positive cases were asymptomatic. The mean number of symptoms was lower and a higher proportion of asymptomatic was found among the youngest (18–29 years), with no significant differences observed according to gender, ethnicity/skin color, schooling, and household income (Table 1). Approximately half of the individuals in whom antibodies to SARS-CoV-2 were detected reported having no symptoms (47.0%) (Figure 1).

Table 1. Number of symptoms and proportion of asymptomatic patients according to sociodemographic characteristics among patients with antibodies against severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2), Mato Grosso, 2020.

General	Number of symptoms	95%CI	p-value	% of asymptomatic	95%CI	p-value
				47.0	**37.2–57.0**	
Sex			0.14			0.11
Female	2.58	2.03–3.13		38.0	27.6–49.5	
Male	1.83	1.08–2.59		54.0	38.9–68.4	
Age group (years)			0.01			0.03
18–29	1.03	0.38–1.69		67.8	47.0–83.3	
30–49	2.64	2.00–3.27		35.8	24.0–49.6	
50–59	2.05	1.40–2.71		49.1	36.3–62.2	
60 or above	2.25	1.20–3.29		50.6	32.8–68.3	
Race/skin colo[b]			0.92			0.92
White	2.23	1.04–3.43		50.7	27.2–73.9	
Brown	2.24	1.67–2.82		46.4	34.8–58.3	
Black	1.77	0.90–2.67		47.0	23.5–72.0	
Schooling			0.60			0.16
Until complete elementary school	1.80	1.21–2.38		56.8	43.7–68.9	
Incomplete and complete high school	1.96	1.47–2.45		47.1	35.4–59.0	
Undergraduate or more	3.45	2.09–4.81		30.5	11.7–59.3	
Family income			0.36			0.40
Less than one minimum wage (less than R$1,045.00)	1.59	0.78–2.40		41.7	24.2–61.8	
From one to less than three minimum wages (from R$1,045.00–R$3,134.99)	1.95	1.41–2.47		49.8	38.9–60.8	
Three or more minimum wages (BRL 3,135.00 or more)	2.60	1.79–3.41		41.2	26.8–73.2	

CI: confidence interval; R$: Brazilian official currency (Reais, R$); BRL: projection of the value in Brazilian Reais. [b]: Yellow (n=31) and indigenous (n=3) were excluded. Bold indicates statistically significant values.

All 10 symptoms evaluated were significantly more prevalent among individuals with antibodies against SARS-CoV-2, and the most prevalent symptoms were body pain (37.0%), fever (32.9%), smell and taste change (28.7%), and sore throat (25.0%). The most significant differences in prevalence of symptoms between the antibody-positive and antibody-negative groups were loss of smell/taste, palpitation, tremor or chills, and difficulty in breathing (Table 2).

Approximately half (51.3%) of the patients with symptoms reported having sought some health service, which was higher among the symptomatic (71.2%) when compared to the oligosymptomatic (28.8%). Approximately 45% reported seeking a basic health unit as the first service, and 5.3% reported having been hospitalized, with no significant difference observed between those classified as oligosymptomatic and symptomatic. Approximately half of the patients who reported having hypertension, diabetes, asthma, or bronchitis and some mental illnesses were classified as symptomatic, followed by 47.4% of those who reported heart disease and 31.6% of those who reported kidney disease (Table 3).

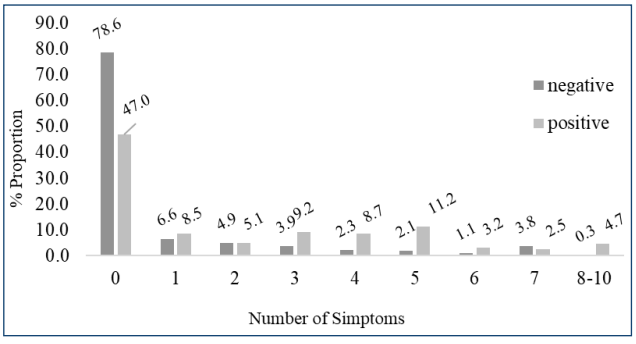

Figure 1. Proportion of serological test for antibodies against severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) according to the number of symptoms. Mato Grosso, 2020.

DISCUSSION

A high proportion of asymptomatic cases were found among individuals with the presence of antibodies to SARS-CoV-2 in the state of Mato Grosso, even among those who reported comorbidities. Furthermore, less than half of those who reported symptoms compatible with COVID-19 sought health services. These results show the importance of asymptomatic carriers in the transmission of COVID-19, as pointed out above,[17-20] also highlighting the critical proportion of people who did not perform diagnosis and isolation measures to prevent transmission between their contacts even with symptoms similar to the disease.

The prevalence of asymptomatic cases was higher than that observed in a nationwide seroprevalence survey conducted in sentinel cities in 26 Brazilian states and the Federal District from May to June 2020 (12.1%)[15] and lower than that observed in systematic review where median asymptomatic prevalence in men and women was 61.1 and 55.7%, respectively[21]. This household-based survey showed no differences between asymptomatic and symptomatic individuals regarding gender, ethnicity/skin color, education, and household income. However, there were higher proportions of asymptomatic young people from Mato Grosso or who had a lower number of symptoms. This result is significant as young people make up most of the active workforce and are more socially active, increasing the likelihood of disease transmission without noticing the infection[20].

Table 2. Proportion of symptoms and prevalence ratio (PR), according to the presence of antibodies against severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2), Mato Grosso, 2020

	Test results		Prevalence Ratio		
	Negative	Positive	PR	95%CI	
Change in smell or taste	3.71	28.70	7.56	5.05	11.32
Fever	8.78	32.92	3.75	2.54	5.54
Sore throat	10.10	25.20	2.49	1.64	4.94
Cough	8.04	28.74	3.42	2.36	4.94
Difficulty in breathing	4.29	16.99	3.96	2.47	6.35
Palpitation	1.80	9.33	5.09	3.06	8.45
Shiver or chills	2.02	11.30	5.58	3.18	9.77
Body ache	11.92	37.04	3.11	2.18	4.43
Diarrhea	5.53	18.57	3.35	1.81	6.22
Vomiting	1.96	6.02	3.06	1.56	6.02

CI: confidence interval; PR: prevalence ratio

Table 3. Search for health services by patients who presented symptoms similar to COVID-19 and classification of symptoms according to the presence of comorbidities among patients with antibodies to COVID-19, Mato Grosso, 2020.

	% weighted	Asymptomatic		Oligosymptomatic		Symptomatic	
		%	95%CI	%	95%CI	%	95%CI
Did you seek health services?							
Yes	51.3	–	–	28.8	19.8–39.8	71.2	60.1–81.1
No	48.6	–	–	55.5	45.2–64.4	45.5	35.5–54.8
Which health service did you seek first?							
Basic Health Unit	45.0	–	–	32.0	18.0–50.1	68.0	49.8–82.0
Polyclinic	4.1	–	–	18.2	7.1–39.3	81.8	60.4–93.0
UPA	13.7	–	–	16.8	8.1–31.5	83.2	68.5–91.8
Exclusive unit for COVID-19	13.3	–	–	29.5	10.0–61.2	70.5	38.8–90.0
Private emergency care	6.2	–	–	29.9	15.6–49.7	70.1	50.3–84.4
Private clinic	5.2	–	–	29.3	9.0–64.3	70.7	36.5–91.0
Other	12.4	–	–	37.8	21.5–57.3	62.2	42.7–78.5
Admitted at health service							
Yes	5.6	–	–	8.4	1.7–32.1	91.6	67.9–98.3
No	94.4	–	–	23.0	14.2–35.0	77.0	65.0–87.8
Comorbidities							
Hypertension or high blood pressure	23.8	39.8	23.3–58.9	9.8	5.0–19.5	50.4	29.6–71.1
Diabetes or blood sugar	7.2	36.2	18.2–59.3	13.4	41.2–35.7	50.4	30.3–70.4
Asthma or bronchitis	1.9	43.7	23.9–65.7	6.3	0.8–35.7	50.0	28.6–71.3
Chronic kidney disease	0.7	22.6	4.1–66.3	45.8	9.0–87.9	31.6	7.6–72.1
Chronic lung disease	0.2	97.4	74.8–99.8	–	–	2.6	0.2–25.2
Some heart diseases	0.2	52.6	24.8–78.6	–	–	47.4	21.2–75.1
Some mental disorders	0.3	21.9	7.0–51.0	23.1	8.7–48.4	55.0	37.9–70.9

CI: confidence interval; Results not shown for cancer due to the low prevalence in the study population (1.3 and 1.1%, respectively).

Undocumented infected cases are estimated as primary source for the geographic spread of COVID[17,22] and the proportion of asymptomatic is considerable, reaching rates ranging from 9.2–69%. However, the range of symptoms produced by COVID-19 is knowingly broad, varying by clinical form of the disease, and may manifest in different systems, with a predominance in the respiratory, neurological, and gastrointestinal systems[2,5,11]. In Mato Grosso, the most prevalent symptoms among individuals with antibodies against SARS-CoV-2 were myalgia, fever, sore throat, and smell and taste change.

Myalgia and fever are described as one of the initial symptoms of COVID-19[12] and were perceived by the population, though they are characterized as nonspecific symptoms of acute febrile illnesses[23], which can often coexist in endemic areas, such as Mato Grosso, and cause confusion in the clinical suspicion. However, other diseases such as hantavirus, malaria, dengue, chikungunya, zika, and influenza must be considered for the differential diagnosis by health professionals in this region[24].

The pain of guaranteeing that it refers more specifically to respiratory infections is also a nonspecific symptom. However, it is easily perceived by the discomfort it causes in the deglutition. Ageusia and anosmia are described by two-thirds of European patients with COVID-19, and are critical symptoms that guide early diagnosis[25].

Besides ageusia and anosmia, palpitation, tremor/chills, and difficulty in breathing were the most prevalent symptoms among SARS-CoV-2-reactive agents in Mato Grosso. The perception of these additional symptoms may be associated with the fact that they are found in more persistent clinical forms

and may predict a clinical evolution to the moderate and severe phases,[9] which drives the search by health services.

The high prevalence of asymptomatic individuals was noteworthy, even among individuals with comorbidities associated with more severe COVID-19. In addition, in our study, 2.9% reported hospitalization due to COVID-19, approximately half of the individuals reported some symptoms, and 45% who sought care accessed primary health care (PHC). In Brazil, which has a robust health system operating universally and characterized by an extensive PHC network, access to these services is facilitated by its high capillarization throughout the national territory and within its reach of expressive segments of the population[26].

Among the limitations of this study is its cross-sectional design, besides self-reported responses about symptoms, which may be subjected to recall bias.

CONCLUSION

A population-based study with a highly accurate diagnostic strategy for identifying antibodies against SARS-CoV-2 showed a high proportion of asymptomatic cases, even among older adults and individuals with comorbidities. The low proportion of individuals who sought health services when they presented symptoms also points to the possible number of cases that were not notified and, therefore, were not considered in the epidemiological surveillance case control and contact monitoring strategies. These results show the difficulty in controlling the transmission of the disease in Mato Grosso.

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AUTHORS' CONTRIBUTIONS

ACPTT: Conceptualization, Writing – original draft, Writing – review & editing. **APM:** Conceptualization, Writing – original draft, Writing – review & editing. **ACSA:** Conceptualization, Writing – original draft, Writing – review & editing. **ECO:** Conceptualization, Writing – original draft, Writing – review & editing.

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ORIGINAL ARTICLE

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Custom-made finger splint versus prefabricated finger splint: finger flexion stabilization

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SUMMARY

OBJECTIVE: Finger splints are used as a treatment option in tendon, bone, and soft tissue injuries. For immobilization, custom-made splints and prefabricated finger splints are used. In splints made for immobilization, it is aimed to limit joint movement. The aim of our study is to reveal how much custom-made splints and prefabricated finger splints limit joint motion (flexion angle in proximal interphalangeal and distal interphalangeal joints).

METHODS: Custom-made splints and prefabricated finger splints were applied to the second fingers of the dominant side in a total of 40 individuals, 20 women and 20 men, not having any health problems. Individuals were asked to flex and joint motion was measured with the iPhone compass application.

RESULTS: The mean distal interphalangeal joint angle values of the participants measured by prefabricated finger splints were found to be 24.27±8.29, and the mean distal interphalangeal joint angle values measured by custom-made splints was 0.52±1.50. There was a difference between the participants' distal interphalangeal joint angle values measured by prefabricated finger splints and custom-made splints ($p<0.001$). distal interphalangeal joint angle values measured with custom-made splints were significantly smaller than those measured with prefabricated finger splint. The mean of the participants' proximal interphalangeal joint angle values measured by prefabricated finger splints was 16.55±7.90, and the proximal interphalangeal joint angle values measured by custom-made splints was "0" for all participants. There was a difference between the participants' proximal interphalangeal joint angle values measured by prefabricated finger splints and custom-made splints ($p<0.001$). Distal interphalangeal joint angle values measured with custom-made splints were significantly smaller than those measured with prefabricated finger splints.

CONCLUSION: According to our study, custom-made splints can significantly reduce the flexion of the finger interphalangeal joints compared to prefabricated finger splints.

KEYWORDS: Finger splint, Orthosis, Prefabricated splint, Custom-made splint.

INTRODUCTION

The metacarpophalangeal (MCP) joint, the proximal interphalangeal (PIP) joint, and the distal interphalangeal (DIP) joint maintain a complementary relationship. Injury to one joint can lead to dysfunction of adjacent joints or fingers. The first reaction in injuries is inflammation that causes edema and pain. Insufficient immobilization may have harmful effects during this period[1]. The injured PIP joint tends to go into a flexed position. In untreated conditions, flexion deformity occurs rapidly[2]. Improper mallet finger splinting causes joint dysfunction, extension lag, and swan neck deformity[3].

Finger splints are a simple immobilization method used in many injuries such as finger fractures, tendon injuries, and soft tissue sprains[4,5], and maintaining the correct and stable position during recovery is part of the treatment[4]. Although injuries are considered simple, delayed treatment and immobilization in inappropriate positions can cause loss of hand function and deformities that cause cosmetic problems[6].

Finger immobilization splints are produced specifically for the patient, which is called custom-made splint (CMS) or prefabricated finger splint (PFS). The advantages of PFS are that they are cheap, practical, and easily accessible. However, as it is not made for the person, adaptation problems and the inability to keep the finger in the desired position are also disadvantages. CMS is more advantageous in that it adapts to the finger. For this reason, it is thought to be more stable in terms of immobilization[7,8]. In a study comparing splints for the DIP joint, it was found that the displacement of the finger with CMS was less than that of PFS[5]. However, it is expected that there will be no joint movement in immobilization splints, especially in mallet finger[9] and fracture cases[10]. The extent to which different splints limit joint motion has been investigated in some studies[11-14]. There are not enough studies in the literature for finger splints. We think that it is important to determine the most effective splint in order to prevent deformities caused

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by inadequate finger immobilization. For this reason, in this article, we aimed to reveal how much the PFS for the finger and the CMS for the patient limits the joint movement (flexion angle in PIP and DIP joints).

METHODS

The sample size of the study was calculated using the G*Power 3.1.9 (G*Power, Universität Düsseldorf, Germany) program. In the study, the amount of type I error was determined as α=0.05, the effect size was medium effect (0.65), the targeted power of the test was 1–β=0.80, whereas the sample size required for statistical analyses was determined as n=39 for group. To reduce the margin of error and increase its generalizability to the population, the study was planned to be completed involving 40 people.

The cases to be included in the study were selected on a voluntary basis among individuals between the ages of 18 and 40 years who did not have any health problems.

Exclusion criteria for the study were as follows: PIP and DIP joint flexion limitation/contracture, presence of rheumatoid disease, or any diagnosed disease that may affect joint movement such as degenerative arthritis, trauma, or diabetes.

Ethical approval for the study was obtained from the Clinical Research Ethics Committee of Sivas Cumhuriyet University on May 26, 2021, with the decision number 2021-05/31. Before the study, the purpose and content of the study were explained to the participants, and an informed consent form was signed, stating that they would participate voluntarily.

First, the participants'age, gender, height, weight, marital status, body mass index, musculoskeletal system problems, and diagnosed disease entities were recorded.

Then, two different types of splints were applied to the second finger of the dominant hand, and the normal joint movement was measured in the DIP and PIP joints.

Finger joint movement measurements are often done using a universal goniometer[15]. Recently, several new smartphone-based apps have been introduced which allow ROM measurement. With the proliferation of smartphones, these applications may offer new ways to provide accurate and reliable ROM measurements, especially in clinical situations where standard goniometers and/or radiographs cannot be used[15]. At present, smart phone applications are preferred because they are practical and easy to apply. In addition, the iPhone Compass application was used in the goniometric measurement of the finger joints, as there may be errors because of deviations that may occur at the pivot point during the measurement by placing the goniometer on the joint with the splint application. In previous studies, the iPhone Compass application has been shown to be reliable[15].

Finger splints, which are CMS, can be made of aluminum material as well as thermoplastic material that can be shaped at low temperatures. As it is easily shaped and practical, thermoplastic material is preferred more[7]. Therefore, in our study, the splint produced specifically for the patient was made of thermoplastic material. When Orfit brand thermoplastic material with a thickness of 2 mm was thrown into water at a temperature of 60–65° and became shaped, it was placed on the finger of the individual to be applied and shaped in the desired position.

Volar splints were performed to keep the DIP and PIP joints at 0° of extension. Two velcro splints were fixed, one over the PIP joint and the other over the DIP joint. Then, the individual was asked to flex the finger, and the range of motion was measured in degrees with the help of iPhone Compass application in the DIP and PIP joints. After the measurement of normal joint motion, the splint was removed and then the PFS was applied. PFS is of the type that fixes aluminum from the volar, distal, and proximal phalanx. After PFS application, normal joint motion was measured using the same method and recorded in degrees.

Statistical Analysis

Mean, standard deviation, median, and minimum and maximum values were given in descriptive statistics for continuous data, and percentage values were given in discrete data. Shapiro-Wilk test was used to examine the conformity of continuous data to normal distribution.

Wilcoxon signed-rank test was used to compare the angle values measured with PFS and CMS of the participants.

The IBM SPSS Statistics 20 program was used in the evaluations and $p<0.05$ was accepted as the statistical significance limit.

RESULTS

The demographic characteristics of the individuals participating in the study are shown in Table 1.

The mean of the DIP joint angle values of the participants measured with the PFS was 24.27±8.29, and the mean of the DIP joint angle values measured with the CMS was 0.52±1.50. There was a significant difference between the DIP joint angle values measured with PFS and CMS ($p<0.001$). The DIP joint angle values measured with the CMS were significantly small compared to the values measured with the PFS.

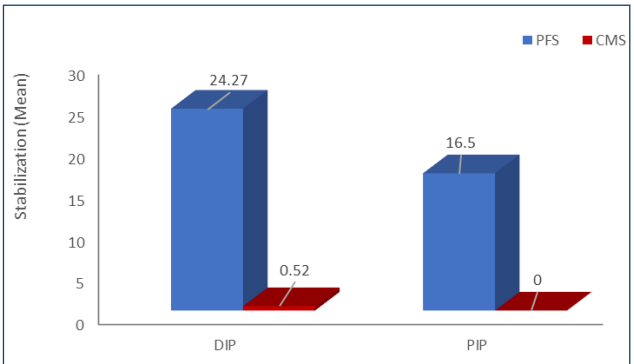
The mean of the PIP joint angle values measured with the PFS of the participants was 16.55±7.90, and the PIP joint

angle values measured with the CMS were measured as "0" in all participants. There was a difference between the participants' PIP joint angle values measured with PFS and CMS ($p<0.001$). The DIP joint angle values measured with the CMS were significantly small compared to the values measured with the PFS (Table 2, Figure 1)

Table 1. Demographic characteristics of the participants.

	Mean±SD Median (Min–Max)
Age (years)	35.52±12.65 35 (20–66)
Body weight (kg)	71.50±12.20 70 (47–140)
Height (cm)	171.27±8.03 171 (156–187)
BMI (kg/m^2)	24.13±4.17 23.19 (18.65–42.27)
Sex, n (%)	
Women	20 (50)
Men	20 (50)

BMI: Body Mass Index; SD: standard deviation.



DIP: distal interphalangeal; PIP: proximal interphalangeal.

Figure 1. Angle values measured with prefabricated finger splint and custom-made splint.

DISCUSSION

In many injuries, especially fractures and tendon injuries, the joint position of the finger splint is important and the recovery is faster in splints that can protect it[16]. Finger flexion and extansion can have an adverse effect on the healing of damaged DIP and PIP joints for several reasons. Finger flexion can cause changes in the lengths of the ligaments, which are considered to be stabilizers of the finger joints.[5] In finger extensor mechanism deformation, changes occur in finger posture with flexion[17]. Although many studies have shown that splint gives good results in mallet finger treatment, they have drawn attention to the importance of splint type and patient compliance[5]. In a study performed on mallet finger, casting and splints made with thermoplastic material were compared and casting was found to be advantageous in terms of extensor lag in only 12 weeks of follow-up. Except this, no difference was observed in the evaluations performed in shorter and longer periods[18]. In a study, the position of the adjustable splint produced with a 3D printer in mallet finger was examined using x-ray and it was found that it was effective in terms of correction[19]. In our results, we found that the finger splint made of thermoplastic material does not allow any flexion in the PIP joint, but there is very less flexion movement in the DIP joint. This movement may be the cause of extensor lag observed in the study by Tocco et al[18].

According to our study, CMS can significantly reduce the flexion of the finger interphalangeal joints compared to PFS.

The facts that the research strategy is comprehensive and that splinting, which is frequently used in the clinic, has been evaluated from a different perspective are considered to contibute to the literature.

This study has several limitations. First, measuring the active flexion motion that a healthy individual can achieve with full effort may not be the same as flexion that can be achieved after an injury. Second, there were no other symptoms such as edema that would affect the splints we applied. The force applied by the subjects was not standardized.

Table 2. Comparison of the angle values of the participants' distal interphalangeal and proximal interphalangeal joints measured with prefabricated finger splint and custom-made splint.

	Prefabricated finger splint	Custom-made splint	Test statistic	p
	Mean±SD Median (Min–Max)	Mean±SD Median (Min–Max)		
distal interphalangeal angle	24.27±8.29 24 (10–42)	0.52±1.50 0 (0–6)	Z= -5.513	0.000*
proximal interphalangeal ANGLE	16.55±7.90 16.5 (4–35)	– 0 (0–0)	Z= -5.514	0.000*

*Wilcoxon test. $p<0.05$.

CONCLUSION

PFS flexion was reduced by more than 70% in PIP and more than 65% in DIP. It should only be used when this limitation of flexion is acceptable during healing of a finger injury. As the result of the present study, CMS can be used in situations where limitation of joint motion is important. The authors suggest that this study be carried out on patients with fracture, tendon injury, and so on.

According to the results of our study, clinicians should prefer CMS if they aim for more restriction and almost complete immobilization in the finger joint. Immobilization success of CMS may be higher.

Ethical approval obtained from Sivas Cumhuriyet University, Non-Interventional Clinical Research Ethics Committee with the decision number 2021-05/11 dated May 26, 2021. This study has been conducted in accordance with the principles set forth in the Helsinki Declaration.

AUTHORS' CONTRIBUTIONS

EG: Conceptualization, Project administration, Formal Analysis, Writing – original draft. **SSK:** Conceptualization, Data curation, Formal Analysis, Writing – original draft.

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ORIGINAL ARTICLE

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Antitumor activity of irinotecan with ellagic acid in C6 glioma cells

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SUMMARY

OBJECTIVE: Irinotecan-based combination chemotherapies in malignant gliomas need to be examined. The aim of this study was to investigate the synergetic effect of ellagic acid, a natural polyphenolic antioxidant compound, with irinotecan, an inhibitor of topoisomerase I enzyme, on the growth, cadherin switch, and angiogenic processes of a glioma cell line.

METHODS: A combination of 100 μM ellagic acid and 100 μM irinotecan was applied to rat C6 glioma cells for 24th, 48th, and 72nd h. The cell proliferation was evaluated by 5-bromo-2′-deoxyuridine immunocytochemistry. The expression levels of vascular endothelial growth factor, E-cadherin, and N-cadherin were measured using real-time polymerase chain reaction and their immunoreactivities using immunocytochemistry.

RESULTS: The treatment of irinotecan with combining ellagic acid enhanced antitumor activity and the synergistic effect of these reduced the cell proliferation of C6 glioma by inhibiting the cadherin switch and promoting the antiangiogenic processes.

CONCLUSIONS: Further research is required to prove a negative relationship between C6 glial cell proliferation and irinotecan with ellagic acid application. Our preliminary data suggest that even with the extremely short-term application, irinotecan with ellagic acid may affect glioma cells at the level of gene and protein expression.

KEYWORDS: Glioblastoma. Ellagic acid. Irinotecan. Cadherin. VEGF.

INTRODUCTION

Malignant glioma is one of the common primary brain tumors detected in the adults. These lesions, highly malignant, easily and diffusely infiltrate the tissues, so that the optimal therapy against these tumors is the combination of surgical resection, radiation therapy, and chemotherapy[1,2].

The successful treatment options are limited for the recurrent gliomas, and progression-free survival is measured as approximately 10 weeks and overall survival as 30 weeks[3]. Therefore, new therapeutic strategies using the combinations of effective compounds with essential chemotherapeutic are essentially required to improve the success of treatments by preventing recurrence and to promote the quality of life of glioma patients[4].

Irinotecan (Ir), an inhibitor of the topoisomerase I enzyme, has a high anticancer effect on the solid tumors in the gastrointestinal tract. This drug, which easily cross the blood-brain barrier, has been proven cytotoxic and antitumor activity of the brain tumors, such as glial neoplasms with multidrug resistance, in preclinical studies[5,6]. Although research has proved the monotherapy of the Ir as efficient, its activity does not have combined effect with other agents[7]. Its combination with other chemotherapeutic agents in the malignant gliomas needs further study[1,7].

Ellagic acid (EA) is a natural polyphenolic compound derived from ellagitannins found in foods with reported antioxidant, anti-inflammatory, and antifibrotic properties[8,9]. However, the potential synergistic effect of Ir with EA, i.e., a common chemotherapeutic agent, is poorly understood for the treatment of gliomas.

The epithelial-to-mesenchymal transition (EMT) provides an aggressive behavior of the tumor cells by reducing the expression or loss of epithelial markers such as adherent junction proteins α-catenin, β-catenin, E-cadherin and by increasing the expression of mesenchymal markers such as vimentin and N-cadherin[10,11].

Glial neoplasms are a highly vascular cancer and also rich in the expression of vascular endothelial growth factor (VEGF) that promotes the process of angiogenesis. Antiangiogenic agents may prevent this process and promote regression of existing vessels[12].

We aimed to demonstrate the antitumor effects of the treatment of Ir with EA in C6 glioma cell line.

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METHODS

Cell culture

C6 glioma cells were purchased from the American Type Culture Collection (Manassas, VA, USA), and all procedures were in accordance with steps described in previous studies[13,14].

Immunocytochemistry

To determine the immunoreactivities of E-cadherin, N-cadherin, and VEGF, all steps of immunocytochemistry (ICC) and H-SCORE analysis described in previous studies were applied in this study[13,14].

Expression analysis

The expression levels of E-cadherin, N-cadherin, and VEGF were determined following all steps of real-time quantitative polymerase chain reaction (qPCR) described in our previous studies[13,14].

5-Bromo-2′-deoxyuridine cell proliferation assay

5-Bromo-2′-deoxyuridine (Br-dU) ICC was used to examine the cell proliferation, and all procedures and scoring were in consistence with steps described in our previous studies[13,14].

Statistical analysis

Semi-quantitative and quantitative data from all groups were statistically analyzed by using GraphPad InStat version 3.06 (GraphPad Software, San Diego, CA, USA). All data were represented as mean±SD. The means of continuous variables were calculated using a one-way analysis of variance, and variations between the groups were compared using a post-hoc Tukey's multiple comparison test. A p-value <0.05 was accepted as statistically significant.

RESULTS

Combined Ellagic acid and Irinotecan suppresses the cell proliferation

To define the efficacy of Ir with or without EA on the cell proliferation of C6 glioma, the Br-dU proliferation assay was performed, and the scores were semi-quantitatively analyzed. Irinotecan treatment alone significantly inhibits the cell proliferation at the 24th (control: 84.87±2.25; Ir: 47.22±1.91, p<0.001), 48th (control: 88.48±2.37; Ir: 47.25±2.63, p<0.001), and 72nd (control: 86.10±1.65; Ir: 35.98±2.24, p<0.001) hours. In contrast, the combination with EA inhibited the proliferation more distinctly compared to the control group at 24th (control: 84.87±2.25, Ir+EA: 5.01±0.52, p<0.001), 48th (control: 88.48±2.37; Ir+EA: 8.45±0.99, p<0.001), and 72nd (control: 86.10±1.65; Ir+EA: 1.52±0.63, p<0.001) hours of incubations.

Combined Ellagic acid and Irinotecan mediates the cadherin switch at the gene and protein levels

The expressions of E-cadherin and N-cadherin were quantified by qPCR. Their protein levels were studied by ICC, as shown in Figures 1 and 2. Treatment with only Ir considerably upregulated the protein levels of E-cadherin expression at all incubation hours in cells compared to the control group at 24th (control: 10; Ir: 45), 48th (control: 8; Ir: 30), and 72nd (control: 5; Ir: 25) hours of incubation (p<0.01) (Figure 1). However, the gene level of E-cadherin was only significantly higher than the control group at 24th incubation time (control: 1.0; Ir: 1.6, p<0.05). In contrast, Ir treatment with EA dramatically increased E-cadherin expression at 24th (control: 1.0; Ir+EA: 3.3, p<0.001), 48th (control: 1.0; Ir+EA: 2.0, p<0.01), and 72nd (control: 1.0; Ir+EA: 1.8, p<0.05) hours of incubation, and protein levels significantly increased at 24th (control: 10; IR+EA: 80), 48th (control: 8; Ir+EA: 55), and 72nd (control: 5; Ir+EA: 45) (p<0.001) hours of incubation (Figure 1).

The treatment of Ir without EA reduced N-cadherin gene levels significantly at 24th hour (control: 7.6; Ir: 4.8, p<0.01), but failed to reduce gene levels at 48th (control: 5.1; Ir: 4.0, p>0.05) and 72nd (control: 5.0; Ir: 3.2, p>0.05) hours of incubation, compared to the control group. Irinotecan without EA significantly reduced the N-cadherin protein level at 24th hour (control: 120; Ir: 55) (p<0.01), but failed to reduce at 48th and 72nd hours of incubation (p>0.05) (Figure 2), as well as Ir with EA significantly decreased the gene levels all the time at 24th (control: 7.6; Ir+EA: 3.0, p<0.001), 48th (control: 5.1; Ir+EA: 2.8, p<0.05), and 72nd (control: 5.0, Ir+EA: 1.9, p<0.01). Irınotecan with EA reduced the protein levels of N-cadherin at 24th (control: 120; Ir+EA: 30, p<0.001) and 72nd (control: 62; Ir+EA: 20, p<0.01) hours of incubation (Figure 2).

Combined Ellagic acid and Irinotecan downregulates the expression of VEGF at the gene and protein levels

The treatment of Ir without EA significantly downregulated the gene levels of VEGF expression at 24th (control: 2.0; Ir: 1.3, p<0.01) hour of incubation compared with the control group, and Ir treatment with EA dramatically downregulated the gene levels of VEGF expression at 24th (control: 2.0; Ir+EA: 1.0, p<0.001), 48th (control: 2.5; Ir+EA: 0.9, p<0.001), and 72nd (control: 1.5; Ir+EA: 0.5, p<0.001) hours. In contrast, Ir

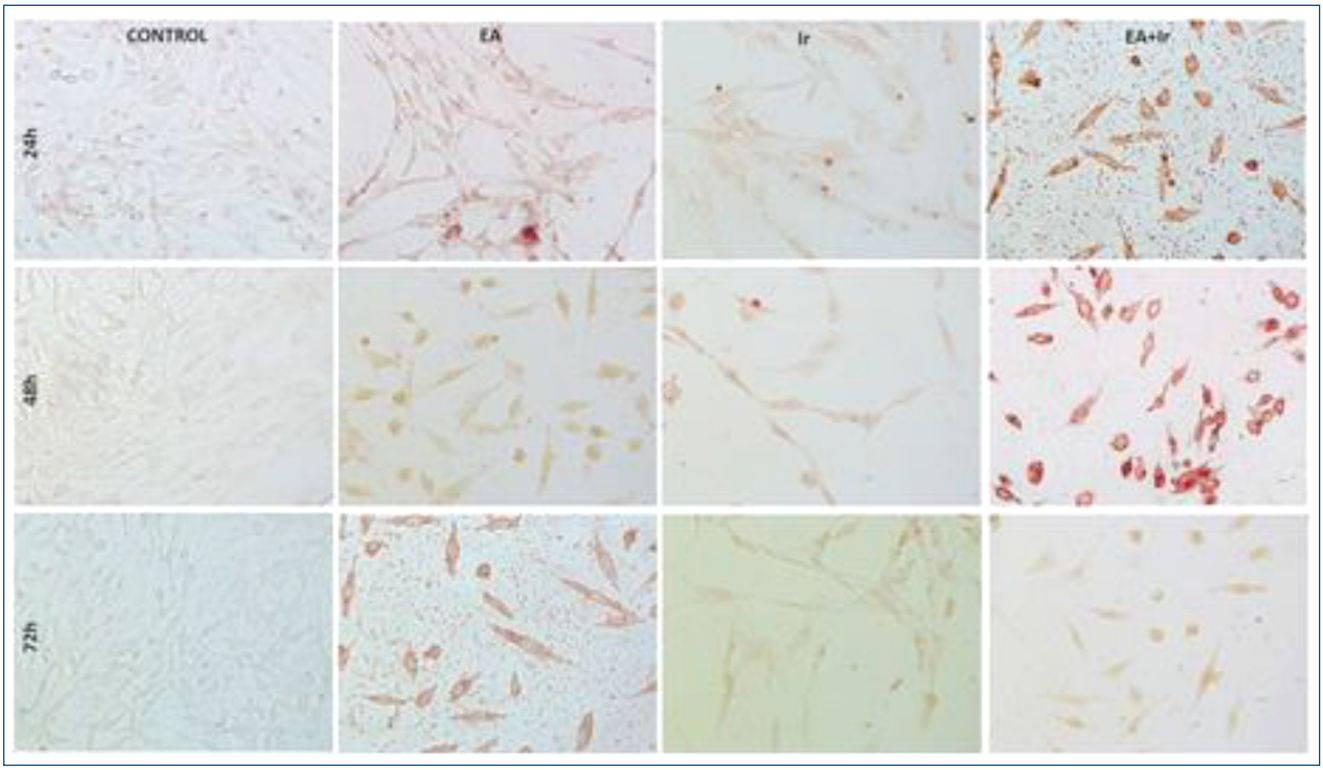

Figure 1. Immunocytoreactivity of E-cadherin in the control (C). EA: ellagic acid; Ir: irinotecan. Combination (ellagic acid+irinotecan) groups, compared with the time of exposure. Magnification: ×400.

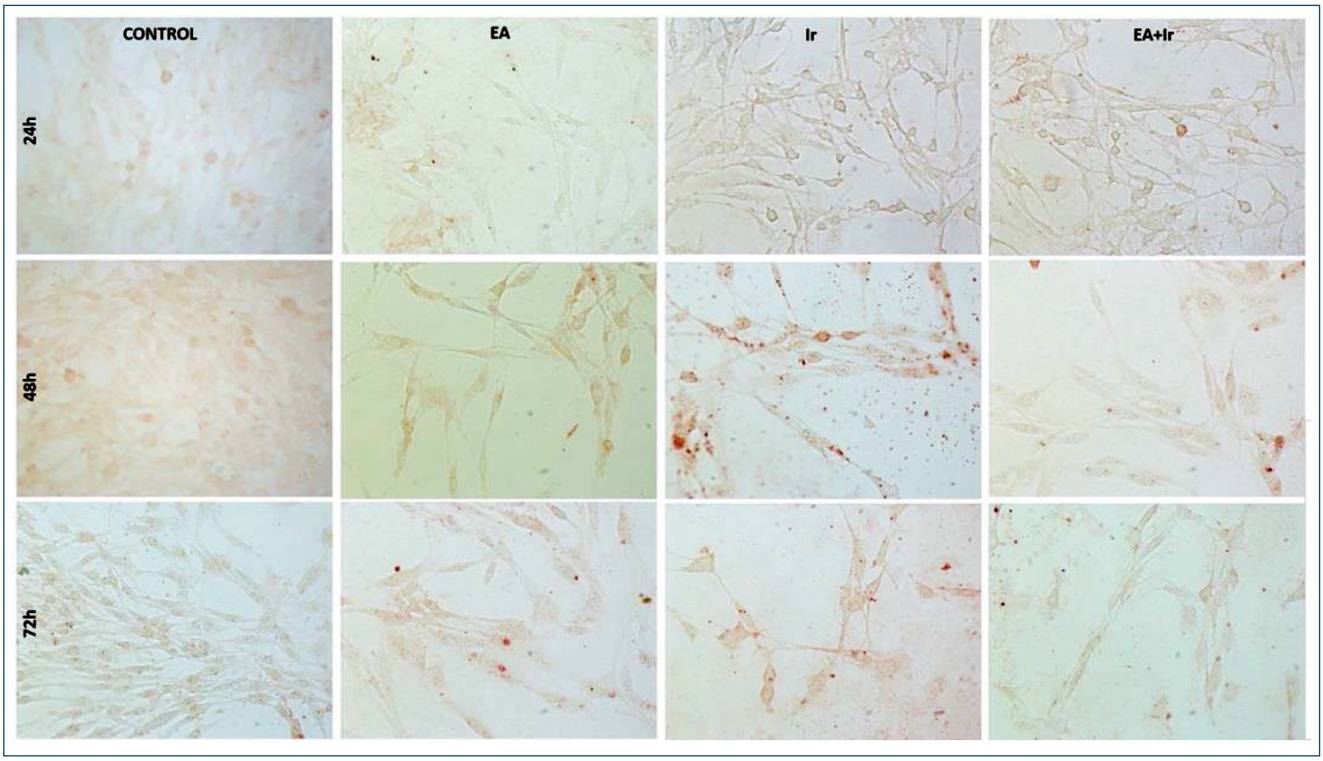

Figure 2. Immunocytoreactivity of N-cadherin in the control (C). EA: ellagic acid; Ir: irinotecan. Combination (ellagic acid+irinotecan) groups, compared with the time of exposure. Magnification: ×400.

without EA significantly decreased the protein levels of VEGF at 48th (control: 42; Ir: 25, p<0.01) and 72nd (control: 22; Ir: 12, p<0.05) hours of incubation, and Ir with EA decreased significantly at 24th (control: 34; Ir+EA: 6), 48th (control: 42; Ir+EA: 5), and 72nd (control: 22; Ir+EA: 4) hours at all incubation times (p<0.001) (Figure 3).

DISCUSSION

There are several modern therapies against glioma cells; however, it is still a fatal malignant disease with extremely poor prognosis[1,2]. Irinotecan, a topoisomerase I inhibitor, has been a new option[6]. The active metabolite of Ir is 7-ethyl-10-hydroxycamptothecin (SN-38), produced by the breakdown of the Ir catalyzed by carboxylesterase enzyme[15]. Irinotecan can be directly converted to SN-38 in glioma cells, resulting in an increase in SN-38 level, a decrease in proliferation, increase in the apoptosis, and induction of morphological changes[16,17]. Coggins et al.[7] demonstrated that Ir was effective in animal models of a variety of CNS tumor xenografts. Nakatsu et al.[16] revealed the antitumor activity of Ir, i.e., multidrug resistance, in human GBM cells. In combination with Ir, the progressive nature and poor prognosis of disease in patients with malignant primary brain tumors compelled the scientists to investigate an alternative agent with novel potent action. Irinotecan, applied as either a monotherapy or a combined therapy with other agents, has been largely studied to treat these malignant and fatal gliomas[15,18].

These combination therapies with Ir targeting the cadherin switch during EMT have been more beneficial than the conventional mono-chemotherapy regimens used against malignant, persistent, or resistant gliomas[16,17]. EMT represents the process in which cells undergo phenotypic changes by losing the cell polarity and cell-cell junctions. EMT results in a transformation from the unipolar and immobile cells into the mobile mesenchymal cells. This transformation of cells plays a fundamental role in the invasion and metastasis of a variety of cancers[10,11]. E-cadherin and N-cadherin are essential players of EMT process in the mechanisms of invasion and metastasis of tumors, resulting in the therapeutic resistance of gliomas. This study showed that the synergistic effects of EA treatment with Ir via altering the expression of E-cadherin and N-cadherin, as well as the expression of VEGF in a model of C6 glioma cells. The combination treatment of the EA with Ir selectively elevated

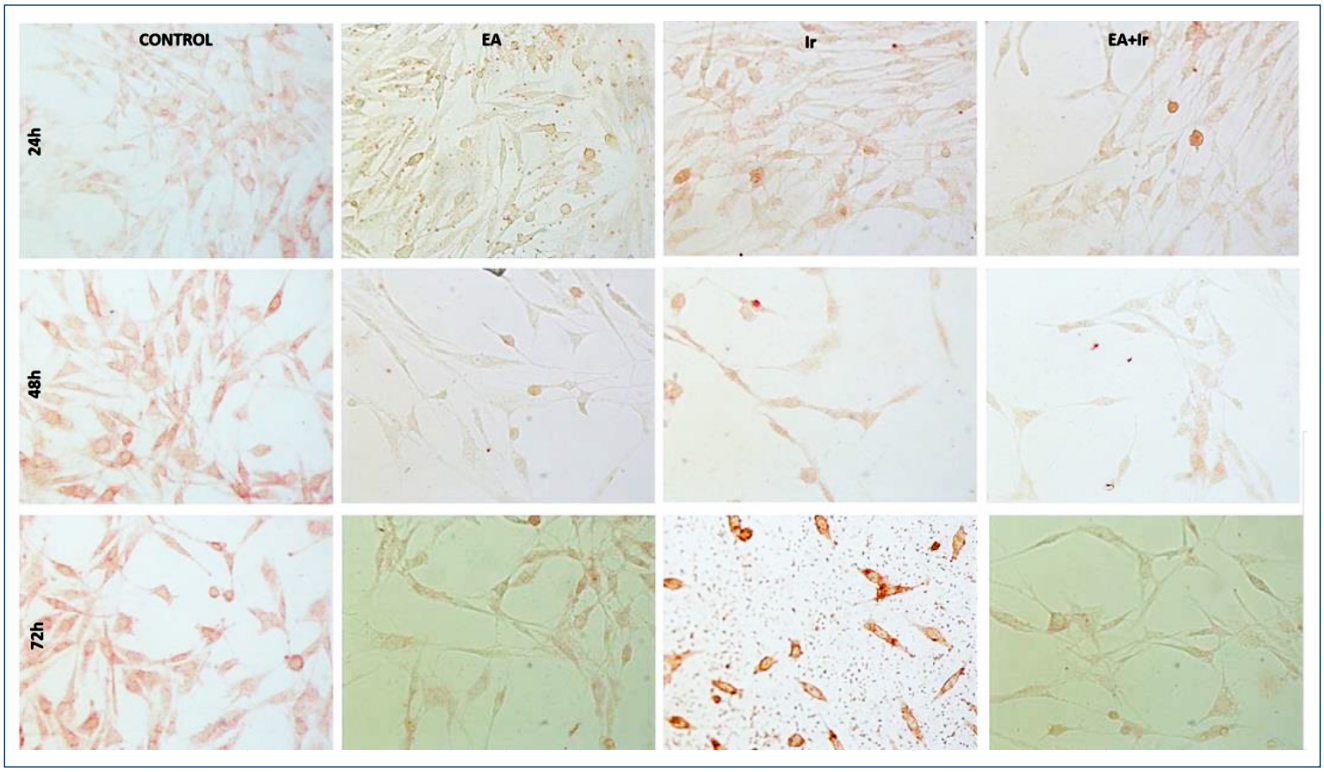

Figure 3. Immunocytoreactivity of vascular endothelial growth factor (VEGF) in the control (C). EA: ellagic acid; Ir: irinotecan. Combination (ellagic acid+irinotecan) groups, compared with the time of exposure. Magnification: ×400.

E-cadherin expression while decreasing N-cadherin expression in a time-independent manner, suggesting a modulatory effect on EMT pathways in GBM cells. Moreover, the treatment EA with Ir decreased the expression of VEGF, regardless of incubation time, suggesting an antiangiogenic effect in glioma cells.

Noronha et al.[10] reported the E-cadherin and N-cadherin in gliomas and suggested that EMT process is compromised by increased N-cadherin expression, causing a poor prognosis, and resistance to the cancer therapies in the patients with glioma. In this study, the EA application with or without Ir considerably reversed the cadherin switch by upregulating E-cadherin expression and downregulating N-cadherin, offering an antitumor activity of EA via interfering with the EMT process in C6 glioma cells.

Angiogenesis plays an essential function in the tumor progression; however, it function is provoked by the altered levels of several proangiogenic factors including VEGF and by the abnormal hypoxic microenvironment of gliomas[19,20]. Therapeutic agents have been developed in combination therapies in order to inhibit this angiogenesis process mostly by targeting the members of the VEGF family, resulting in a decrease in the incidence of gliomas and resultant mortality[14]. Some studies have proposed that EA could inhibit angiogenesis in cancer by decreasing the number of blood vessels[13]. Hosny et al.[21] showed that EA has a significant antiproliferative effect on the in vivo behavior in cancer animal models.

Kamiyama et al.[22] reported that under normoxic and hypoxic conditions, Ir considerably downregulated the expression of VEGF in glioma cells in a time- and dose-dependent manner. Irinotecan has been suggested to inhibit both the endothelial proliferation and vessel formation and the angiogenic pathways in glioma cells. Additionally, the EMT process is predominantly induced by a hypoxia in the microenvironment and the microvascular proliferation via the expression of VEGF in glioma cells[10,22]. This study also supported these in vitro effects of EA on VEGF expression when combined with Ir, indicating the downregulation of its expression and reduction of its immunoreactivity. Therefore, findings showed that the antitumor activity of Ir with EA enhanced the promoting antiangiogenic processes in glioma cells.

CONCLUSION

An in vitro antitumor activity of Ir was exerted by combining with EA in C6 glioma cells. Moreover, in vitro and clinical studies are needed to clarify whether a combined strategy leads to a higher efficacy in the treatment of aggressive cancers than do a chemotherapeutic monotherapy alone, and whether these combinations could reduce the dose of agents and minimize the side effects of cytotoxic therapies.

AUTHORS' CONTRIBUTIONS

AC: Conceptualization, data curation, formal analysis, writing – original draft, Writing – review & editing. **BB:** Conceptualization, data curation, formal analysis, writing – original draft, Writing – review & editing. HO: Conceptualization, data curation, formal analysis, writing – original draft, writing – review & editing.

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ORIGINAL ARTICLE

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Human enteroviral infection in fibromyalgia: a case-control blinded study

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SUMMARY

OBJECTIVE: This study aimed to test the hypothesis that fibromyalgia is associated with a human enteroviral infection.

METHODS: Venous peripheral blood samples from 27 patients fulfilling the American College of Rheumatology revised diagnostic criteria for fibromyalgia and from 26 age- and sex-matched controls, who underwent immunofluorescence assays for coxsackievirus A7 IgG, coxsackievirus B1 IgG, coxsackievirus A7 IgA, coxsackievirus B1 IgA, echovirus IgG, and echovirus IgA. These immunological tests were performed blind to group status.

RESULTS: There were no significant differences between the patient and control groups in respect of positive results for coxsackievirus A7 IgG (p=0.467), coxsackievirus B1 IgG (p=0.491), coxsackievirus A7 IgA (p=0.586), coxsackievirus B1 IgA (p=0.467), echovirus IgG (p=0.236), and echovirus IgA (p=1).

CONCLUSIONS: The results of this systematic study do not support the hypothesis that fibromyalgia is associated with infection by a human enterovirus.

KEYWORDS: Coxsackievirus. Echovirus. Fibromyalgia. Human enterovirus. Immunofluorescence.

INTRODUCTION

Fibromyalgia is a relatively common cause of chronic widespread musculoskeletal pain and tenderness; however, its etiology remains unknown[1]. Since the past century, it has been suggested that infections may trigger this condition[2]. In particular, the possibility has been raised that human enteroviruses may have an etiological role.

The human enteroviruses coxsackie A virus, coxsackie B virus, and echovirus belong to the genus *Enterovirus*, which, in turn, is part of the Picornaviridae family of positive-sense ssRNA viruses[3]. Infection with coxsackieviruses and echoviruses may be associated with myalgia, myocarditis, and central nervous system disorders, possibly including self-limiting meningitis in adults[4-7]. In 1989, Nash and colleagues described the case of a patient with symptoms consistent with primary fibromyalgia who showed evidence of chronic coxsackie B virus infection[8]. Subsequently, Wittrup and colleagues assayed immunoglobulin M (IgM) antibodies to hepatitis C, hepatitis B, cytomegalovirus (CMV), human herpesvirus-6 (HHV-6), rubella, parvovirus B19, and enterovirus in 19 acute-onset fibromyalgia patients compared with 19 healthy controls; IgM antibodies were only found against HHV-6 and enterovirus in the patient group and against CMV, HHV-6, and enterovirus in the control group[9]. A third comparative group, of nonacute-onset patients, also had IgM antibodies against enterovirus. However, no operational criteria were given for classifying patients as being acute onset versus nonacute onset; there was no further classification of the enterovirus; and no IgG or IgA antibody assay results were reported for either the patients or the control subjects[9]. Finally, in their muscle biopsy study, Douche-Aourik and colleagues reported that 4 out of 30 patients diagnosed with either fibromyalgia or chronic fatigue syndrome showed evidence of enteroviral RNA compared with none of 29 controls[10].

We hypothesized that fibromyalgia is associated with infection with one or more of the relatively common human enteroviruses coxsackievirus A7, coxsackievirus B1, and echovirus. To test for evidence of infection by these viruses and the formation of neutralizing antibodies and given the importance of the feco-oral route in the spread of these viruses, we decided to test our hypothesis by assessing the levels of IgG and IgA against each of these viruses in a cohort of well-characterized fibromyalgia patients.

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METHODS

Experimental design and participants

The study was carried out using a cross-sectional, blinded case-control experimental design. Patients were eligible to enter the study if they were aged between 18 and 80 years and fulfilled the revised diagnostic criteria of the American College of Rheumatology, with the diagnostic cutoff threshold employed of ≥13 from the composite painful sites number and symptom severity scale[11]. Healthy volunteers were eligible to enter the study if they were aged between 18 and 80 years and had no history of suffering from a rheumatological disorder (including fibromyalgia) or neurological disorder. Exclusion criteria for the patient group included treatment with antimicrobial/antiviral therapy or corticosteroids; exclusion criteria for the control group included the diagnosis of fibromyalgia in any first-degree relative. This study received ethical approval from a Research Ethics Committee and was carried out according to the Declaration of Helsinki. All participating patients and control subjects gave written informed consent.

Immunofluorescence assays

Notably, 8.5-mL venous peripheral blood was collected from each subject in a labeled sterile serum SST™ II Advance Tube consisting of a plastic (PET) tube with a Hemogard closure incorporating an inert stable gel to aid separation of serum from the blood clot. The labeling consisted of an alphanumeric code which fully anonymized the subsequent laboratory analysis of the serum; no record appeared on each tube of the subject's name, date of birth, sex, or group allocation (patient or control). Following venipuncture, each filled tube was immediately inverted 10 times and then placed vertically at room temperature for 30 min. The tubes were then packed upright and protected from light during transportation, at ambient temperature, to the laboratory where human enterovirus immunofluorescence assays were carried out, blinded to group status, with the following thresholds for positive results: coxsackievirus A7 IgG 1:100, coxsackievirus B1 IgG 1:1000, coxsackievirus A7 IgA 1:10, coxsackievirus B1 IgA 1:10, echovirus IgG 1:1000, and echovirus IgA 1:10.

Statistical analyses

Comparison of the mean age of the two groups was carried out using the Student's t-test, after confirming that there was no significant violation of either normality, using the Shapiro-Wilk test, or equality of variances, using Levene's test. Analysis of two-by-two contingency tables was carried out using the Fisher's exact probability test. All statistical tests were two-tailed. The statistical programs used were R v. 4.1.1 and JASP 0.15[12,13].

RESULTS

There were 27 subjects in the fibromyalgia group (26 females; mean age 49.6 years, standard error [SE] 2.1 years) and 26 subjects in the control group (25 females; mean [SE] age 48.2 [2.4] years). The two groups did not differ significantly in respect of age (p=0.655) or sex (p=1).

The immunofluorescence assay results are given in Table 1. There were no significant differences between the patient and control groups in respect of positive results for coxsackievirus A7 IgG, coxsackievirus B1 IgG, coxsackievirus A7 IgA, coxsackievirus B1 IgA, echovirus IgG, or echovirus IgA.

DISCUSSION

The results of this study did not provide any evidence in favor of the hypothesis.

These results are at variance with expectations, given the muscle biopsy findings by Douche-Aourik and colleagues mentioned above[10]. However, closer examination of those positive muscle biopsy findings reveals that the patient and control groups were not matched for either age or sex. Furthermore, it is not clear how many of the four positive biopsy results were in patients with fibromyalgia and how many in those with a diagnosis of chronic fatigue syndrome; the report simply states that 22 of the patient group were diagnosed with fibromyalgia, and the remainder with chronic fatigue syndrome[10].

As seen in Table 1, relatively high levels of positive results were found in the control group, as follows: coxsackievirus

Table 1. Immunofluorescence assay results.

Immunofluorescence assay	Number positive in fibromyalgia group (n=27)	Number positive in control group (n=26)	p
Coxsackievirus A7 IgG	21	23	0.4672
Coxsackievirus B1 IgG	25	26	0.4906
Coxsackievirus A7 IgA	13	15	0.5857
Coxsackievirus B1 IgA	21	23	0.4672
Echovirus IgG	24	26	0.2358
Echovirus IgA	19	19	1

A7 IgG in 88%, coxsackievirus B1 IgG in 100%, coxsackievirus A7 IgA in 58%, coxsackievirus B1 IgA in 88%, echovirus IgG in 100%, and echovirus IgA in 73%. It is noteworthy that coxsackievirus B1 infection has been found to be associated with a wide range of diseases[14-16]. Coxsackievirus A7 is associated with neurological diseases and can cause paralytic poliomyelitis[17]. In a recently published analysis of 153 worldwide epidemiological studies, the weighted median prevalence in Europe of all enteroviruses examined, which included, but was not limited to, coxsackievirus A7, coxsackievirus B1, and echovirus, was well under 10%, as was the median prevalence of enteroviruses in those at least 18 years of age[18]. The much higher prevalence figures in our cohort of healthy adult volunteers are difficult to explain. All members of the control group were white Caucasian British subjects who lived in the United Kingdom (as indeed were all members of the patient group). It would be interesting to carry out a larger study of the prevalence of enteroviruses in healthy subjects residing in the part of the United Kingdom from which the subjects of this study were recruited.

CONCLUSIONS

The results of this systematic study do not support the hypothesis that fibromyalgia is associated with infection by a human enterovirus.

AUTHORS' CONTRIBUTIONS

BKP: Conceptualization, Data curation, Formal analysis, Investigation, Methodology, Software, Validation, Writing – original draft, Writing – review & editing. **GSL:** Conceptualization, Data curation, Investigation, Methodology, Project administration, Writing – review & editing. **AS:** Conceptualization, Data curation, Investigation, Methodology, Project administration, Supervision, Validation, Writing – review & editing.

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ORIGINAL ARTICLE

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A model for training ultrasound-guided fine-needle punctures

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SUMMARY

OBJECTIVE: To evaluate the efficacy of a training program in ultrasound-guided fine needle puncture using a cost-effective model.

METHODS: We evaluated the training of 20 resident radiology physicians, based on a theoretical course and a practical simulation part with models that focused on the puncture technique of thyroid nodules. The total time to perform the procedure, the number of punctures on the model surface, and the application of a questionnaire were used to assess the performance and confidence of the resident physicians in performing the procedure.

RESULTS: The training model used was easy to reproduce, inexpensive, versatile, and capable of simulating the echotexture of thyroid tissue. There was a significant reduction in the total time needed to perform the procedure with a mean of 173.7 s±91.28 s from R1 and 112.8 s±17.66 s from R2 before the course vs. 19.2 s±112.8 s and 14.3 s±9.36 s, respectively, after the course ($p<0.0001$); as well as the number of superficial punctures, with a mean of 2.2 punctures±0.92 from R1 and 1.5 punctures±0.32 from R2 before the course vs 1.1 punctures±0.71 and 1.0 puncture±0.0, respectively, after the course ($p<0.0001$). There was also a subjective improvement in the performance and confidence in performing this procedure.

CONCLUSIONS: An inexpensive and easy-to-reproduce gelatin-based model enabled adequate training of resident physicians and proved capable of improving their skills and confidence in simulating the procedure, even with a short period of training.

KEYWORDS: Thyroid gland. Biopsy, fine-needle. Ultrasonography. Education, Medical. Simulation Training.

INTRODUCTION

Ultrasound-guided fine-needle aspiration biopsy (FNAB) is a widely available, safe, and accurate procedure, but the effectiveness of the procedure depends on the skill and experience of the professional and requires adequate training[1-3]. FNAB is a technically challenging procedure for inexperienced clinicians with sensitive nearby structures such as the jugular veins, carotid arteries, and trachea.

Practical simulation-based training with models and virtual environments is useful for step-by-step training in a variety of procedures, in addition to improving coarse skills and learning how to handle materials in a controlled environment where specific flaws can be identified and addressed[4-6]. An objective measurement of performance, associated with an analysis of the tests done by the students, allows the assessment of effectiveness of the model and progress of resident physicians[1,4,5].

In this study, we evaluated the training of 20 medical residents in radiology, 10 from the first year and 10 from the second year of residency, based on theoretical classes and practical simulations with a gelatin-based model, focusing on FNAB of thyroid nodules.

The main aim of this study was to create a feasible and inexpensive model for training in ultrasound-guided procedures, with special emphasis on FNAB. The final goal was to determine whether this training could increase the resident doctors' confidence and performance in conducting an FNAB.

METHODS

Subjects

Twenty radiology resident doctors from the Department of Radiology of the University Teaching Hospital at Campinas (UNICAMP) participated in the study after signing an informed consent form. The subjects were divided into 2 groups, one of which consisted of 10 resident physicians from the first year of the course (R1), whereas the other consisted of 10 residents from the second year of the course (R2). None of the participants had any previous experience in ultrasound-guided punctures or training models, although the second-year residents (R2) had more training in nonprocedural diagnostic ultrasound.

Device

The matrix consisted of a reproducible combination of gelatin, Metamucil, *maisena* (cornstarch), and water (Figure 1)[7]. This mixture provided a homogeneous matrix for elastography, with adequate rigidity for puncturing. Additional elements can be added

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to this matrix, depending on the aim of the training. The gelatin is opaque, so the target is not visible through the matrix. The major advantage of this model is its very low final cost (~US$1).

We used a grape as a target because it has the following characteristics:

1. a morphology, echotexture, and dimensions similar to those of a thyroid nodule,
2. a composition that consisted of puncturable material with good resistance, and
3. material that was easy to obtain and inexpensive.

The target was glued to the bottom of the container to prevent it from moving, thus eliminating the need for several phases of matrix layering (Figure 2).

Figure 1. Close-up external view of the model. The target, which consisted of a grape embedded in the red elastic matrix, is not visible in this view.

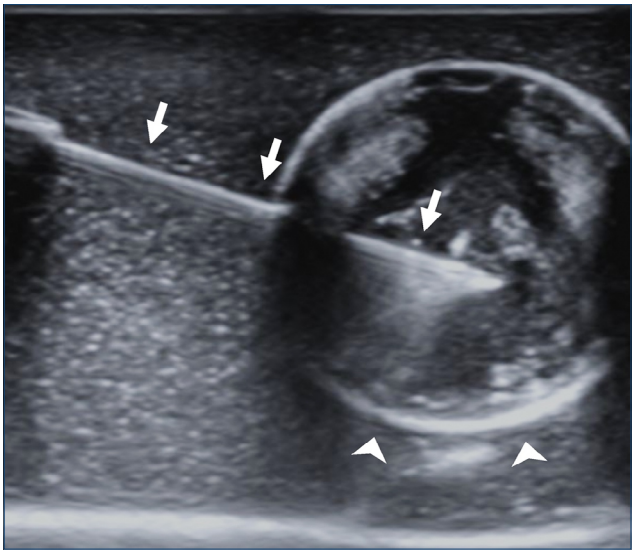


Figure 2. A target (a grape; arrowheads) embedded in the elastic matrix of the model. Note the good contrast between the surrounding "tissue" (matrix) and the target, and the clear visualization of the needle (arrows).

The perishable nature of the grapes meant that the model had a maximum shelf-life of 20 days when stored at ~4°C (39.2°F). In general, the model retained its durability and intactness for up to ~10 punctures.

Recipe for the matrix

Notably, 100 mL of natural spring water, 150 mL of boiling water, 20 g of gelatin, 10 g of Metamucil, and 2 g of cornstarch were mixed, thoroughly stirred for 2 min, and then added to the mold (container) to which the target had already been glued. The mold and its contents were then placed in a refrigerator to cool for 30–60 min. This cooling step is necessary for proper matrix solidification.

Training program

A theoretical and practical course (3 h duration) was offered, with an emphasis on thyroid nodules and FNAB. Theoretical classes were taught by specialist doctors, through an online platform, with each class lasting for 30 min. The classes included the ultrasonographic diagnosis of thyroid nodules, the clinical relevance of thyroid nodules, FNAB technique, and pathological analysis. The practical class was done face-to-face, lasted for 1 h, and was taught by a radiologist; this class provided an opportunity for the resident doctors to review the FNAB technique and train their puncture technique in the model. Each resident received one copy of the model with which to train.

Data acquisition

The resident physicians performed an ultrasound-guided biopsy of a target (grape) embedded in the polymeric matrix, before and after the course. Targets were at the same depth for all residents. For this, a 25-gauge needle was used, without the puncture guide. The time required to initiate puncturing of the matrix surface, the time until ultrasound identification of the needle within the target, and the total time required for the complete procedure were recorded. The training was considered complete when the needle was identified within the target. The number of punctures on the matrix surface (simulating the patient's skin) was also quantified. These data (keeping time and number of punctures) were recorded by a third-year resident physician. After the course, the participants completed a questionnaire that sought to evaluate the usefulness of the model and the course. The replies were scored using Likert's 10-point psychometric response scale (see Appendix).

Statistical methods

A descriptive statistical analysis was applied to the data and involved measures of central tendency (median and mean) and dispersion (standard deviation) for numerical variables. The Mann-Whitney nonparametric test was used to compare

the numerical variables evaluated before the course, and to compare the answers to the questionnaire applied to the two groups (R1 and R2) after the course. Comparisons between intervals (before and after the course) and groups (R1 vs, R2) were done using the analysis of variance (ANOVA) test for repeated measures. A value of $p<0.05$ indicated significance.

This study was conducted after the approval of the local ethics committee of our institution.

RESULTS

Time to perform the procedure

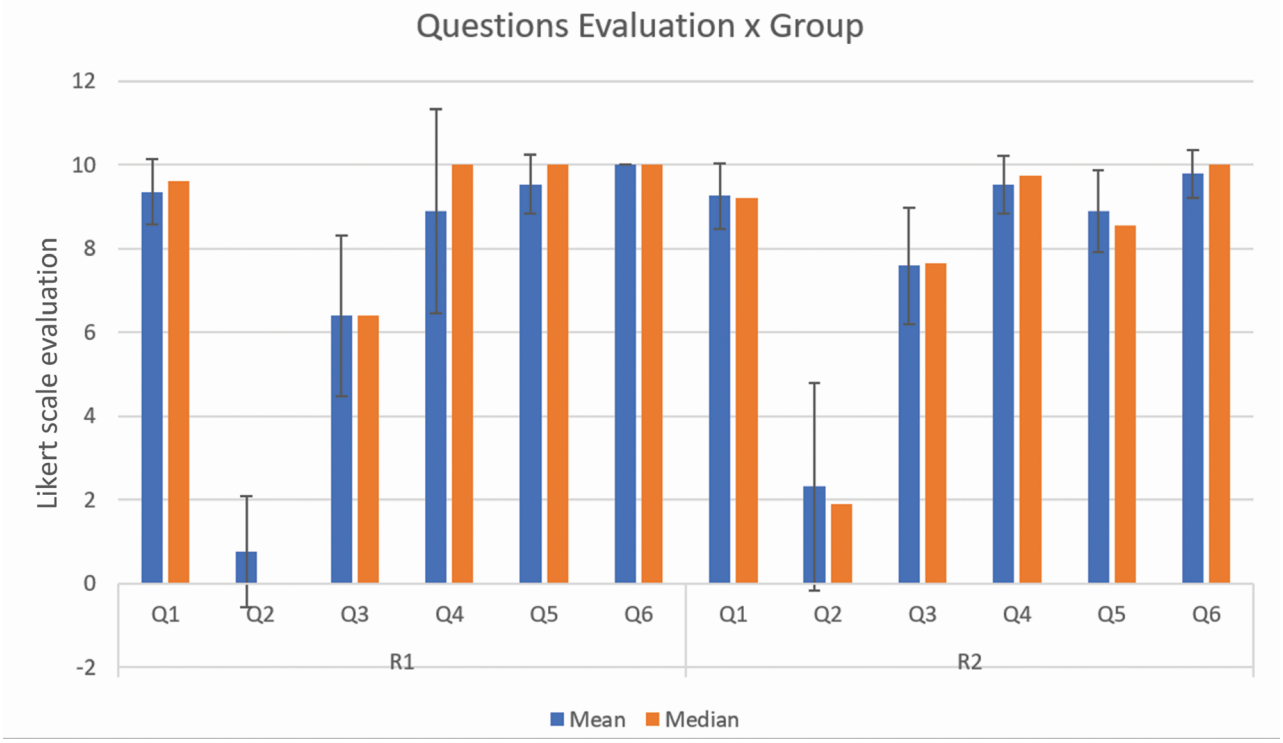
The total time required to perform the procedure after the course was significantly shorter than before the course, regardless of the group of residents ($p<0.0001$). Before the course, R1 had a mean of 173.7 s±91.28 s and R2 had a mean of 112.8 s±17.66 s; after the course, they had a mean of 19.2 s±112.8 s and 14.3 s±9.36 s, respectively. There was no difference between the two groups of residents (R1 vs R2) in the time required to perform the procedure before ($p=0.1617$) or after ($p=0.3133$) the course. There was also no interaction between time and groups ($p=0.2974$), indicating that the training was equally effective in both groups.

Number of punctures on the matrix surface

The number of punctures done after the course was significantly lower than before the course, regardless of the group of residents (R1 vs. R2) ($p<0.0001$). Before the course, R1 had a mean of 2.2 punctures±0.92 and R2 had a mean of 1.5 punctures±0.32; after the course, they had a mean of 1.1 punctures±0.71 and 1.0 puncture±0.0, respectively. There was no difference in the number of punctures done by the two groups of residents (R1 vs R2) before ($p=0.0747$) or after ($p=0.0527$) the course. There was also no interaction between time and groups ($p=0.1368$), indicating that the training was equally effective in both groups.

Questionnaire

Overall, the resident physicians' evaluation of the course was positive. This evaluation included their understanding of the basic, introductory nature of the course, the course workload and methods of assessment, and a subjective analysis of their confidence and improvement in performing the procedures. The model was seen as a useful tool for teaching the basic steps of FNAB and for improving their technique in executing the procedure. There was no significant difference between the two groups of residents in their answers to the questionnaire (Figure 3).



Q: question; R1: first-year residents; R2: second-year residents.

Figure 3. Statistical analysis of residents' responses to each of the questions (Q) based on the Liekert 10-point psychometric scale. Overall, there was a positive response to the course in matters of basic understandings, nature of the course, workload, and methods, with an increase in their confidence. No significant difference was observed between the two groups.

DISCUSSION

There is increasing emphasis on the use of simulation for training of ultrasound-guided procedures in medical education across multiple specialties[8-10], and the use of models is a promising method for improving teaching in interventional radiology as it allows for training before initiating the procedure on patients[1,4,5]. The traditional training for interventional procedures in radiology, in which the trainee performs the procedure first on a live patient, can lead to adverse outcomes and patient dissatisfaction[11].

Homemade and inexpensive models can improve ultrasound-guided procedural skills[11,12]. Studies that developed models focused on training ultrasound-guided procedures for medical residents identified improvement in ultrasound-guided procedural skills[1,11,13] and reported increased comfort and confidence in performing these procedures after training[11,13].

In this study, we used a gelatin-based model that is easy to reproduce, inexpensive, versatile, and capable of simulating the echotexture of thyroid tissue. Our results indicate that even with a short training period, the model significantly reduced the number of punctures done and the total time required to perform the procedure. In addition, there was a subjective improvement in performance and confidence in executing the procedures.

Limitations

Although there was a significant reduction in the number of punctures and the total time required to perform the procedure, these improvements will not necessarily be reproduced in clinical practice. The number of punctures was studied to simulate the number of punctures on the patient's skin, as an indicator of the degree of procedure complexity. However, there is no evidence in the literature that a greater number of punctures leads to or is indicative of worse clinical outcomes.

Another limitation of the study was that completion of the procedure was based on ultrasound identification of the needle within the target (a measure adopted to enhance the lifetime of the model). However, this approach did not include essential FNAB steps that are necessary to acquire an adequate sample and the correct preparation of the blade.

The small sample size of only 20 resident physicians, the fact that the study was done in a single academic center, and the decision not to use the puncture guide during training are other potential limitations of this study.

Future prospects

Our findings, together with the promising results of other investigations in the simulated training of resident physicians in ultrasound-guided procedures[1,2,9,11], as well as the proven benefits in clinical practice of using models for training, such as training in laparoscopic surgery simulators demonstrating improvements in the performance of resident physicians in the operating room procedure[14] and the use of simulation devices for instructing surgical residents and fellows in basic endovascular techniques improving resident performance in a catheter-based intervention[15], indicate that future studies should assess whether training with models directly correlates with better clinical results in interventional radiology.

CONCLUSION

An inexpensive and feasible model enabled the adequate training of resident physicians to perform the punctures, with an improvement in the level of subjective confidence and in objective measures. Future research should assess how these improvements relate to overall competency and safety in the performance of ultrasound-guided FNAB.

AUTHORS' CONTRIBUTIONS

FML: Conceptualization, Data curation, Formal Analysis. **VRDY:** Conceptualization. **KAAS:** Conceptualization, Writing – original draft. **FR:** Writing – review & editing. **SSJD:** Writing – review & editing.

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APPENDIX

QUESTIONNAIRE

1. How effective was the course for your learning?

0 ----------10

2. How safe did you feel in performing the procedures before the course?

0 ----------10

3. How safe do you feel now in performing the procedures after the course?

0 ----------10

4. For a basic introductory course, what did you think of the course load?

0 ----------10

5. Were the methods of evaluation adequate?

0 ----------10

6. How necessary is it for the Department to have a model for biopsy training?

0 ----------10

Note.

Q1: How effective was the course for your learning?
Q2: How safe did you feel in performing the procedures before the course?
Q3: How safe do you feel now in performing the procedures after the course?
Q4: For a basic introductory course, what did you think of the course load?
Q5: Were the methods of evaluation adequate?
Q6: How necessary is it for the Department to have a model for biopsy training?

ORIGINAL ARTICLE

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Continuous clonidine infusion: an alternative for children on mechanical ventilation

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SUMMARY

OBJECTIVE: This study aimed to assess the clonidine infusion rate in the first 6 h, as maintenance dose (first 24 h), and in the pre-extubation period (last 24 h), as well as the cumulative dose of other sedatives and the hemodynamic response.

METHODS: This is a retrospective cohort study.

RESULTS: Children up to the age of 2 years who were admitted to the pediatric intensive care unit of a tertiary referral hospital in the south region of Brazil, between January 2017 and December 2018, were submitted to mechanical ventilation, and received continuous clonidine infusions were included in the study. The initial, maintenance, and pre-extubation doses of clonidine; the vasoactive-inotropic score; heart rate; and systolic and diastolic blood pressure of the study participants were assessed. A total of 66 patients with a median age of 4 months who were receiving clonidine infusions were included. The main indications for mechanical ventilation were acute viral bronchiolitis (56%) and pneumonia associated with acute respiratory distress syndrome (15%). The median of clonidine infusion in the first 6 h (66 patients) was 0.53 μg/kg/h (IQR 0.49–0.88), followed by 0.85 μg/kg/h (IQR 0.53–1.03) during maintenance (57 patients) and 0.63 μg/kg/h (IQR 0.54–1.01) during extubation period (42 patients) (p=0.03). No differences were observed in the doses regarding the indication for mechanical ventilation. Clonidine infusion was not associated with hemodynamic changes and showed no differences when associated with adjuvants.

CONCLUSION: Clonidine demonstrated to be a well-tolerated sedation option in pediatric patients submitted to mechanical ventilation, without relevant influence in hemodynamic variables.

KEYWORDS: Clonidine. Pediatric intensive care unit. Artificial respiration. Sedation, conscious. Analgesia.

INTRODUCTION

Several factors negatively contribute to the physical and emotional status of critically ill children, including the absence of relatives, the high level of noise in pediatric intensive care unit (PICU), and the need of invasive procedures[1-4]. PICU patients often require ventilatory support and are submitted to procedures that can lead to pain; therefore, drugs are used to control anxiety, pain, and discomfort[1,5-7].

Sedation and analgesia goals must be tailored individually. For example, a patient who are submitted to mechanical ventilation (MV) during the acute phase may need sedation and muscle relaxation; however, the same patient during weaning may need comfort and lighter sedation levels to allow spontaneous breathing[1,6,8,9].

Studies suggest that the use of clonidine for long-term sedation is safe, despite the associated occurrence of bradycardia and hypotension[10-12]. In children, such negative hemodynamic effects have not led to an increase in inotropic support[13-16]. In the neonatal population, the use of clonidine continuous infusion was associated with adequate analgesia and sedation, with no discernible risks in the short term[4,16,17].

The primary aim of this study was to describe the clonidine continuous infusion doses, as well as the cumulative doses of adjuvants in three different time periods: (1) initial (hour 6 of clonidine continuous infusion), (2) maintenance (hour 24 of infusion), and (3) pre-extubation (24 h before extubation). The secondary aim was to evaluate the correlation between clonidine dose and the vasoactive-inotropic score (VIS)[18], heart rate (HR), systolic blood pressure (SBP), and diastolic blood pressure (DBP) during the three time periods.

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METHODS

We conducted a retrospective cohort study including all MV children £2 years old who received continuous infusion of clonidine, between January 2017 and December 2018, at the PICU of Hospital de Clínicas de Porto Alegre (HCPA), Brazil. Exclusion criteria included the presence of complex congenital heart disease, use of £2 anticonvulsants or antipsychotics, patients submitted to hemodialysis, use of non-invasive ventilation, patients who progressed to extubation in <6 h, patients with complex chronic diseases hospitalized for >100 days, and patients readmitted to the PICU. This study was approved by the HCPA Research Ethics Board (project 95105718.2.0000.5327).

The HCPA is a university-affiliated hospital in southern Brazil, reference for complex diseases (e.g., genetic disorders), major surgeries, and bone marrow and liver transplant. Its tertiary PICU has 13 beds, with an average of 600 annual admissions; 60% of PICU patients require MV, with a mortality rate close to 7%.

The sedation and analgesia goals for the next 24 h for each patient are decided during the PICU morning round. Sedation targets vary according to individual patient needs and therapeutic goals, and potential contraindications for drugs. Throughout the day, sedation and analgesia doses are monitored by the nursing and medical team and adjusted according to the desired purposes. Two previously trained researchers (CCN and VIF) collected data from medical charts. Study variables included age, weight, sex, hospital and PICU admission date, intubation and extubation date, PICU and hospital discharge date, and hospital mortality. Data on HR, mean arterial pressure (MAP), DBP, and SBP were collected in three time periods: at hour 6 of clonidine infusion, at hour 24 of clonidine infusion, and at 24 h before extubation. Data on the hourly continuous infusion doses of clonidine and other sedatives (continuous infusion and bolus) were collected during the first 24 h of sedation and the 24 h before extubation.

RESULTS

We summarized our results using means (standard deviation [SD]) or medians (interquartile ranges [IQRs]) for continuous variables. Categorical variables were described in absolute and relative frequency (proportions). To assess the continuous variables, we applied the Student's t-test and ANOVA. We compared the median clonidine infusion dose at the three predetermined time points (hour 6 and hour 24 of continuous infusion, and 24 h before extubation) using the Mann-Whitney U test. We applied the Kruskal-Wallis test to compare the clonidine doses used for different patient subgroups and evaluated the correlation between clonidine dose and VIS by applying the Spearman's test. Data were analyzed using Stata Statistics version 13.0.

During the study period, we identified 170 patients who had received clonidine infusion, and 66 of whom fulfilled the inclusion criteria (Figure 1).

The median age was 4 months (IQR 2–10), with 67% (44 patients) being male. The main indications for MV were acute viral bronchiolitis (56%) and pneumonia associated with acute respiratory distress syndrome (ARDS) (15%). The median duration of MV was 6 days (IQR 4–9 days). The medians of length of PICU and hospital stay were 10 days (IQR 8–13 days) and 20 days (IQR 16–42 days), respectively (Table 1). No patient died during the study observation period.

No patient received a bolus dose of clonidine before starting the continuous infusion. The median dose of clonidine infusion at hour 6 was 0.54 µg/kg/h, reaching a median dose infusion of 0.85 µg/kg/h at hour 24 (Figure 2). In the

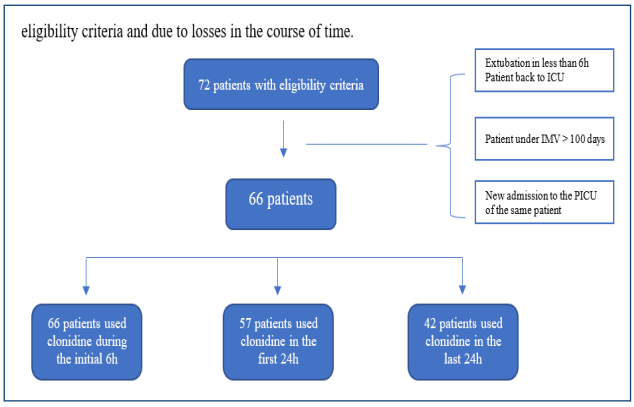

Figure 1. Flowchart of study population.

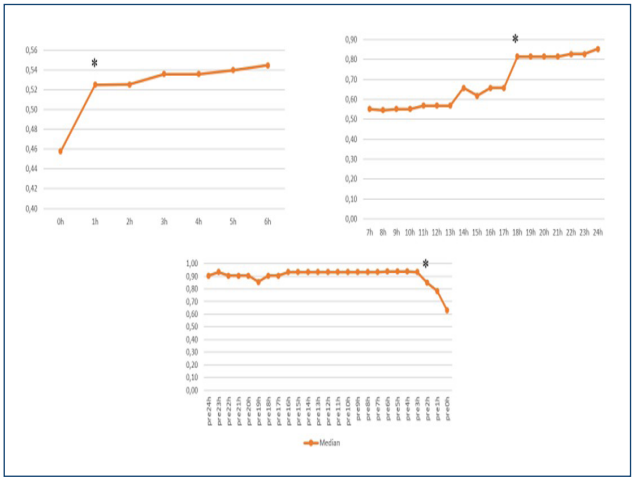

Figure 2. Median of continuous clonidine infusion doses (A: over the first 6 h of mechanical ventilation; B: over the hours 7 and 24; C: over the last 24 h pre-extubation). (*p<0.001).

Table 1. Demographic data and characteristics of 66 patients submitted to mechanical ventilation and using continuous clonidine infusion as an alternative.

Age, n (%)	
Median (IQR), months	4 (2–10)
< 6	38 (58)
6–12	13 (20)
12–24	15 (23)
Sex, n (%)	
Male	44 (67)
Indications for PICU, n (%)	
Bronchiolitis	37 (56)
Pneumonia/ARDS	10 (15)
Postoperative	9 (14)
Others	10 (15)
Duration of MV, median ($IQ_{25-75\%}$), days	6 (4–9)
PICU length of stay, median ($IQ_{25-75\%}$), days	10 (8–13)
Hospital length of stay, median ($IQ_{25-75\%}$), days	20 (16–42)

IQR: interquartile ranger; PICU: pediatric intensive care unit; ARDS: acute respiratory distress syndrome; MV: mechanical ventilation.

pre-extubation period, 24 patients were still receiving clonidine with a median dose of 0.63 µg/kg/h. We did not observe any difference regarding the median dose between the three time points (p>0.4).

When analyzing the temporal evolution of clonidine dose, we observed that the median dose increased in the first hour, from 0.46 to 0.52 µg/kg/h (p<0.001), and in hour 17 of infusion, from 0.66 to 0.82 µg/kg/h (p<0.001). Later, the median clonidine dose remained stable until the end of the 24 h (Figure 2). In the 24 h pre-extubation, continuous infusion dose was kept stable at 0.93 µg/kg/h until hour 3 of pre-extubation. From this period onward, clonidine dose was gradually decreased until it reached a median dose of 0.63 µg/kg/h during extubation (p<0.001) (Figure 2).

We did not find differences between the medians of clonidine doses at the three observed periods when stratified by MV indication.

While evaluating the necessity of adjuvants to the continuous clonidine infusion, we did not observe any differences related to it, except during pre-extubation period, due to the decreased number of associations. Only cases with a cumulative of ketamine were depicted (n=11), perceiving an increase in the rate of clonidine infusion with a median of 1.88 (0.72–2.07) µg/kg/h.

The correlation between clonidine and VIS, HR, SBP, and DBP was poor (r<0.4).

DISCUSSION

Clonidine has been used as a sedative for some time, but literature on it is still scarce[9,16]. Most studies demonstrate the restricted use of dexmedetomidine infusion in children, which were limited to specific populations and conducted in developing countries, where the reasons for MV are different compared to the ones observed in regions with limited resources[8,19].

Clonidine is a good alternative as it acts on the postsynaptic alpha-2-adrenergic receptors, leading to an attenuation of neuronal activation. It is also a partial agonist stimulating alpha-2 receptors in the brain, resulting in a reduction of sympathetic stimulus on the *locus coruleus* which leads to a sedative effect[6,20]. Clonidine also has an antihypertensive effect, possibly leading to hypotension and bradycardia depending on the doses[21]. Despite its potential side effects, studies show that clonidine may have a beneficial effect in critically ill patients by reducing afterload and consequently increasing cardiac output[10,13,22]. Such findings have been confirmed in patients, for whom VIS score remained stable[1,18,21].

In our study, clonidine was not associated with negative hemodynamic effects, neither during MV period nor during extubation. This finding corroborates with others suggesting that continuous infusion of clonidine does not necessarily induce significant negative hemodynamic response. Kleiber et al.[15] used clonidine (0.5–2 µg/kg/h, over 30 h of infusion) in 23 newborn babies submitted to cardiac surgery. Authors reported that, despite a statistically significant reduction in HR (p<0.0001) and DBP (p=0.018), no clinical repercussions were observed. In the Sleeps[16] study, clonidine use was compared to intravenous midazolam in 120 MV children who required sedation for more than 12 h. Authors showed that patients were adequately sedated (medians clonidine 73.8% vs. midazolam 72.8%).

As previously mentioned, the use of dexmedetomidine, an alpha-2 agonist that promotes a "conscious sedation" without respiratory depression, has been better documented in pediatric patients[3,23]. It is known for having greater selectivity for alpha-2-agonist receptors when compared to the clonidine's alpha-1-agonist receptors (1620:1 for dexmedetomidine and 220:1 for clonidine)[19,24]. Despite being a good sedative, dexmedetomidine is significantly more expensive. The cost of using dexmedetomidine can be four times higher than the cost of clonidine. Thus, having clonidine as a sedative option could have major therapeutic and financial implications in low- and middle-income countries.

Our study has limitations. The use of a retrospective design is associated with the absence of a predefined rigid protocol for titrating the doses of clonidine infusion and for reporting the

minor side effects related to the drug. Nevertheless, our results are consistent with similar ones already published[2,16,21]. In contrast, our study also has important strengths. We included a pragmatic sample size of patients and described the adjustment of clonidine continuous infusion doses in daily practice, and to the best of our knowledge, this is the first study to assess the use of clonidine continuous infusion during the extubation period.

CONCLUSION

In this regard, our data suggest that clonidine could be an option to be used during weaning of MV support up to the extubation moment. Another strong point is that our results emphasize the strategy of starting continuous clonidine infusion at a lower dose, without bolus attack, which is frequently associated with cardiovascular side effects. However, more studies are required to confirm and extrapolate these results in other pediatric populations.

AUTHORS' CONTRIBUTIONS

CCN: Conceptualization, Data curation, Formal Analysis, Funding acquisition, Investigation, Methodology, Project administration, Resources, Software, Validation, Visualization, Writing – original draft, Writing – review & editing. **VIF**: Data curation, Investigation. **PSF**: Conceptualization, Data curation, Formal Analysis, Investigation, Methodology, Project administration, Supervision, Validation, Visualization, Writing – review & editing. **JPP**: Conceptualization, Data curation, Formal Analysis, Investigation, Methodology, Project administration, Supervision, Validation, Visualization, Writing – review & editing.

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REVIEW ARTICLE

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Effect of accelerated rehabilitation surgery nursing on laparoscopic radical surgery for elderly patients with colorectal cancer

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INTRODUCTION

Colorectal cancer is a common malignant tumor that seriously threatens human life and health, and its incidence rate ranks third in the world[1] and it is increasing at a rate of 2% per year. Most of the new cases are elderly patients[2]. With the continuous development of laparoscopic and other minimally invasive techniques, laparoscopic surgery has been more and more widely applied in clinic, which can effectively improve the prognosis of patients[3], so laparoscopic surgery is the most ideal radical treatment approach for colorectal cancer[4]. However, elderly patients with colorectal cancer generally have the characteristics of long course of disease, more preoperative complications, and high incidence of postoperative complications. Accelerated rehabilitation surgery care is an important part of the accelerated rehabilitation surgery concept (enhanced recovery after surgery – ERAS). This concept has caused a great change in the clinical care model of many diseases[5]. This nursing model can utilize the perfect, scientific, and timely nursing methods to promote the early recovery of gastrointestinal function of patients after surgery to reduce the hospitalization time and complications[6], thereby providing patients with high-quality, efficient, and safe nursing services. This study explored the effect of accelerated rehabilitation surgical nursing on the perioperative period of laparoscopic radical surgery for elderly patients with colorectal cancer.

PATIENTS AND METHODS

Patients

The elderly patients who underwent laparoscopic colorectal cancer radical surgery in our hospital between September 2018 and March 2020 were included in the study. Inclusion criteria were as follows:

1. all patients were diagnosed with colonoscopy colorectal (straight) bowel cancer and postoperative pathology confirmed as colorectal cancer.
2. Patients aged 60 years or older.
3. After examination, all patients were evaluated in accordance with the indications for surgical treatment and found no contraindications for surgery.
4. Patient signed informed consent.
5. Tumor infiltration depth was T1-T4.
6. After preoperative conversation and education, the patient agreed to perform accelerated rehabilitation surgical nursing.

Finally, a total of 60 patients were included and randomly divided into two groups as follows: accelerated rehabilitation surgery nursing group combined with laparoscopic colorectal cancer radical resection (n=30 cases) (experimental group) and routine nursing group combined with laparoscopic colorectal cancer radical resection (n=30 cases) (control group). This study was approved by the ethnic committee of our hospital, and all participants signed the informed consent.

METHODS

Surgery and nursing were performed by a medical team working in the Department of Oncology Surgery 1 (gastrointestinal) of our hospital. Surgical surgeon has more than 20 years of experience and is skilled in the diagnosis and treatment of colorectal cancer in elderly patients. After professional training, the surgeon can proficiently perform laparoscopic

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surgery for colorectal cancer. Likewise, the nurse team has more than 5 years of experience and is proficient in laparoscopic knots, rectal cancer radical surgery perioperative nursing, and received accelerated rehabilitation surgery nursing knowledge and skills training.

Experimental group:

1. after admission, a comprehensive evaluation and formulation of a nursing plan was conducted.
2. Preoperative education: one-on-one introduction of responsible nurses was made, and the health manuals for routine admission and education were distributed, including familiarization with the department environment, introduction of the medical team, and introduction of relevant systems, safety and protection education, ERAS nursing education, including purpose and significance, the main content of nursing implementation, and benefits and perioperative cooperation matters.
3. Psychological support: the psychological state of the patient was assessed, and patient's doubts were answered to enhance compliance.
4. Preoperative preparation: physical exercise was increased appropriately according to the patient's own situation, and cough training, deep breathing training, bed and toilet training were conducted, and patients were taught how to perform postoperative pain assessment and early bedtime activities; they were advised to quit smoking and alcohol before surgery; in general, mechanical bowel preparation is not recommended, and patients with no obstruction should be given oral laxatives after admission; if patients were preassessed for malnutrition, they should be given enteral nutrition powder or parenteral nutrition; they were allowed to eat solid food 6 h before surgery, and transparent liquid 2 h before surgery; 200 ml of routine oral carbohydrate electrolyte solution should be added before induction of anesthesia; diabetic patients were given the same amount of saline; appropriate elastic stockings were worn 2 h before surgery; gastric tube was not placed routinely before surgery.
5. Laparoscopic colorectal cancer radical surgery was performed.
6. Intraoperative care: specialists are relatively fixed in cooperation with the staff; there are standardized procedures for surgical cooperation; electric surgical adjustment beds, endoscopic and electrosurgical equipment, thermal insulation equipment, etc. have good performance; surgery posture safety management should be strengthened; the patient's core body temperature should be maintained at 36–37°C during operation to prevent intraoperative hypothermia; during the process of gastric bloating or fluid accumulation, the gastric tube was temporarily decompressed, and the gastric tube was removed at the end of the operation.
7. Postoperative care: the patient can leave the bed on the day of operation, 2 h of bedtime activities were recommended on the first day after the operation and 6 h of daily bedtime activities afterward; the urinary catheter can be removed for the first time after the bed, and patients with low rectal surgery can extend the time of indwelling catheter, usually 3–4 days after surgery; patients were encouraged to start oral feeding; after 6 h, they were allowed to eat clear liquid of 50 mL each time for every 4 h, and whether the patient has nausea and vomiting and reflux situation was observed; chewing gum was allowed to stimulate gastrointestinal peristalsis in order to prevent intestinal obstruction; assessment was done and work was recorded.
8. Postoperative pain care: 3 h after surgery, the first pain assessment was performed using a pain assessment ruler as follows: ≥7 points, every hour; between 3 and 7 points, every 4 h; and between 1 and 3 points, when measuring body temperature; on the basis of assessment, the patients were evaluated: for 3 points or higher, the responsible nurse conducted health education and psychological counseling, and for 4 points or higher, the doctor was notified to deal with it in time and make a record; the score was calculated up to the 10th day after the operation. In the process of accelerating the implementation of rehabilitation surgery nursing, the implementation plan was adjusted at any time according to the changes of the patient's condition.

Control group:

1. the patients underwent routine nursing education and psychological nursing.
2. Routine fasting for 24 h and drinking for 4 h were recommended before surgery.
3. Intestinal preparation was performed 3 days before operation using enema.
4. Indwelling gastric tube was inserted before operation.
5. During the operation, no heat preservation measures, and measures for preventing deep vein thrombosis were taken.

6. Indwelling gastric tube and urinary tube were inserted after operation.
7. After the first exhaust, the liquid food was gradually transition to semi-liquid food, i.e., general food.
8. Patient was encouraged to perform bed activity or assist passive activity.
9. Analgesics were applied when the patient had pain.

Observation indicators

1. Comparison of postoperative conditions:
   ① time after bed (h);
   ② exhaust time (h);
   ③ postoperative pain score (0–10 points);
   ④ average hospital stay (days);
   ⑤ hospitalization costs (days) (in Chinese Yuan);
2. Comparison of postoperative complications:
   ① anastomotic leakage;
   ② intestinal obstruction;
   ③ infection, including incision infection, urinary tract infection, and lung infection.
3. Discharge criteria:
   ① normal body temperature;
   ② pain can be controlled by oral pain killers;
   ③ patients have smooth exhaust and defecation;
   ④ patients can move freely.

Statistical Methods

Statistical analysis was performed using the SPSS version 26.0 software. Age, height, BMI, and weight were tested by Student's t-test; gender, ethnicity, and postoperative complications were assessed by chi-square test. Postoperative conditions were tested by rank-sum test. A p-value <0.05 was considered statistical significant.

RESULTS

Basic characteristics of all participants

The mean age was 62±10 years for experimental group and 63±9 years for control group, with no significant difference (p=0.573). Han people accounted for 76.7% in experimental group and 86.7% in control group (p=0.317). The comparison of general information between the two groups showed no significant differences (p>0.05), and the data of two groups were comparable (Table 1).

Comparison of postoperative data

Two groups of patients underwent laparoscopic radical surgery for colorectal cancer. The first postoperative exhaust time was 19.50 h (9–72) in the experimental group and 40 h (11–192) in control group, with a significant difference (p=0.026); the pain score was 3.63 (1–5) points in the experimental group and 4.5 (2–6) points in control group (p=0.004); the total number of hospitalization days and postoperative hospitalization days between two groups showed a significant difference (p<0.05); the average hospitalization cost was 60775.87 Chinese Yuan for experimental group and 77180.17 for control group, with a significant difference between them (p=0.001) (Table 2).

Comparison of complications

Comparison of the occurrence of postoperative complications between the two groups of patients showed that there was one anastomotic leakage in experimental group and six in control group (p=0.044), and two with lung infection in experimental group and nine in the control group, with a statistical difference (p=0.020). The complications of intestinal obstruction, incision infection, and urinary tract infection did not differ significantly between the two groups (Table 3).

Table 1. Comparison of age, sex, weight, height, BMI, and ethnicity of the two groups of patients.

	Experimental group	Control group	$t/z/\chi^2$	p
	n=30	N=30		
Age	63.70 (38–76)	62.13 (47–80)	-0.620	0.573
Gender				
Male (%)	20 (66.7)	17 (56.7)	0.635	0.426
Female (%)	10 (33.3)	13 (43.3)		
Weight (kg)	64.57 (42–90.5)	63.47 (43–82)	-0.385	0.702
Height (cm)	165.53 (150–177)	164.73 (150–180)	-0.435	0.665
BMI	23.50 (16.82–33.30)	23.38 (15.79–29.69)	-0.140	0.889
Nationality				
Han (%)	23 (76.7)	26 (86.7)	1.002	0.317
Others (%)	7 (23.3)	4 (13.3)		

Table 2. Comparison of the time of getting out of bed, time of first exhaustion, pain score, total days of hospitalization, and total hospitalization costs.

	Experimental group	Control group	t/z/χ^2	p
	n=30	n=30		
Time of getting out of bed (h)	46.2 (8–120)	36.77 (9–136)	-1.524	0.127
First exhaust time (h)	19.50 (9–72)	40 (11–192)	-2.227	0.026
Pain score	3.63 (1–5)	4.5 (2–6)	-2.878	0.004
Total days of hospitalization (days)	23.83 (9–44)	30.70 (13–59)	-2.561	0.010
Postoperative hospital stay (days)	8.5 (5–16)	12.83 (7–30)	-2.748	0.006
Total hospitalization expenses (Chinese Yuan)	60775.87	77180.17	3.668	0.001

Table 3. Comparison of the postoperative anastomotic leakage, intestinal obstruction, incision infection, urinary tract infection, lung infection, and complications.

	Experimental group	Control group	t/z/χ^2	p
	n=30	n=30		
Anastomotic fistula (%)	1 (3.3)	6 (20.0)	4.043	0.044
Intestinal obstruction (%)	1 (3.3)	1 (3.3)	0.000	1.000
Incisional infection (%)	3 (10)	7 (23.3)	1.920	0.166
Urinary tract infection (%)	1 (3.3)	4 (13.3)	1.964	0.161
Lung infection (%)	2 (6.7)	9 (30)	5.455	0.020

DISCUSSION

The nursing team is the most solid force in the implementation of ERAS and has undertaken the most tedious work[7]. Compared with traditional nursing methods, accelerated rehabilitation surgery nursing is more humanized and individualized and focuses on the perioperative evaluation and rehabilitation of patients. The clinical application effect has been confirmed by several studies[8-11]. Through preoperative education and psychological care, patients had the relevant knowledge of laparoscopic surgery and can overcome psychological fear. A volume of 200 mL of oral carbohydrate electrolyte solution before surgery avoids the occurrence of hypoglycemia in elderly patients and avoids clean enema before surgery to prevent the occurrence of dehydration in elderly patients. Maintaining the patient's body temperature during surgery effectively reduced the incidence of surgical infection, intraoperative bleeding, and postoperative complications.

Since laparoscopic surgery has the advantages of avoiding large wounds and decreasing blood loss than ordinary surgery, patients are encouraged to get out of bed on the day of surgery after adequate pain relief and no indwelling of the catheter. Chewing gum and eating from the mouth as soon as possible after surgery are suggested to stimulate gastrointestinal motility, promote early exhaust, and prevent intestinal obstruction. The use of elastic stockings effectively prevents the occurrence of deep vein thrombosis in elderly patients. The unconventional use of urinary catheters and the removal of urinary catheters 24 h after surgery effectively prevented infections. The application of pain assessment ruler effectively relieved the patient's pain. The implementation of standardized work processes and individualized nursing programs has effectively promoted the rehabilitation of elderly patients after laparoscopic radical resection of colorectal cancer patients and has also significantly improved the quality of care, reduced the length of hospitalization, and saved medical costs.

As accelerated rehabilitation surgery nursing involves three nursing links before, during, and after the operation, the patient needs comprehensive nursing such as physical, psychological, and rehabilitation, combined with the characteristics of laparoscopic surgery and the unique features of the elderly. Physiological and psychological changes require nurses to have good professional qualities and abilities in accelerated rehabilitation surgery.

The management team is well constructed, united, and cooperative, so the professional training of nurses and teams needs to be further strengthened. With time, it is necessary to stimulate the enthusiasm of the patients and their family to improve their cooperation in order to achieve the best treatment and care effectiveness.

CONCLUSION

The accelerated rehabilitation surgery nursing measures have high-value application in laparoscopic colorectal cancer

radical surgery for elderly patients and are beneficial of clinical application.

Ethics approval and consent to participate

The study was approved by the Qinghai University Affiliated Hospital Science Research Ethics Committee (P-SL-2018074). Informed consent was obtained.

AUTHORS' CONTRIBUTIONS

CXS: Conceptualization, Data curation, Formal Analysis, Writing – original draft, Writing – review & editing. **BJC:** Conceptualization, Formal Analysis, Writing – review & editing. **XH:** Conceptualization, Formal Analysis, Writing – original draft. **JFH:** Conceptualization, Data curation, Formal Analysis, Writing – original draft, Writing – review & editing.

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REVIEW ARTICLE

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Cross talk mechanisms of aerobic exercise training on obesity, type 2 diabetes, and Alzheimer's disease: the role of insulin resistance

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INTRODUCTION

Obesity is characterized by the presence of excessive white adipose tissue, inflammation, and insulin resistance[1]. It is known that a sedentary lifestyle, commonly seen in subjects with type 2 diabetes (T2D) and obesity, is associated with many deleterious health outcomes. The overexpression of white adipose tissue is associated with higher levels of insulin resistance, which, in turn, is crucial for cognitive impairment and mental health[1,2]. T2D main feature is insulin resistance, which occurs mainly due to molecular impairments in the phosphatidylinositol 3-kinase (PI3K) pathway[3,4]. Disruption of normal functioning of insulin receptor substrates 1 (IRS-1) and 2 (IRS-2) in PI3K pathway can lead to T2D[5]. The changes in IRS-1 and IRS-2 in the brain mediate the alterations in glucose metabolism[6]. However, failure of activating any protein of PI3K pathway can lead to insulin resistance, obesity, and T2D[7]. Insulin resistance is also a common feature present in Alzheimer's disease (AD). Thus, T2D and obese individuals are at increased risk for dementia, particularly AD[7,8].

AD is the most common type of dementia worldwide[9]. The impairment of the insulin signaling increases the amyloidogenic processing of the amyloid precursor protein, leading to the increased generation of the neurotoxic protein amyloid beta (Aβ). Cognitive impairment and memory deficits have been attributed to the aggregation of these insoluble amyloid fibrils and brain insulin resistance[10]. Another important hallmark of AD is the overexpression of Tau protein, which also favors the development of insulin resistance[11]. Inflammation is also present concomitantly to insulin resistance and hyperphosphorylation of Tau protein during the development and establishment of AD[6]. Thus, insulin resistance, hyperphosphorylation of Tau protein, and inflammation contribute to the development of AD. The development and progression of obesity, T2D, and AD can lead to cognitive decline and mental health impairment, which can be overcome by performing aerobic exercise training (AET), which is characterized by performing exercises where the utilization and transport of oxygen are predominant and occur concomitantly to the recruitment of red fibers, also known as type I fibers, or fibers of slow contraction. In this study, we aimed to review some of the most important molecular mechanisms that can be changed by the practice of AET in obesity, T2D, and AD.

ROLE OF AEROBIC EXERCISE TRAINING ON OBESITY

AET can contribute to fight and avoid the development of obesity. AET activates the beta-oxidative pathway, which is a multienzymatic pathway that degrades fat to produce energy in skeletal muscle12. Gene expression is modulated by peroxisome proliferator-activated receptor alpha (PPAR-α), and a co-activator (PGC-1α)13. PGC-1α is a member of a family of transcription co-activators that plays an important role in the regulation of cellular energy metabolism14. It has been reported that PGC-1α would play a role in the occurrence of white tissue browning by exercise in mice, but this is still a controversial topic regarding humans15. PGC-1α induces the expression of fibronectin type III domain-containing 5 (FNDC5), which is cleaved at the C-terminal to produce Irisin16. Irisin is a myokine which was identified for its ability to induce browning of the white adipose tissue, increasing energy expenditure, and protecting against insulin resistance17. AET can induce positive changes in the mental health of overweight and obese individuals18.

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ROLE OF AEROBIC EXERCISE TRAINING ON TYPE 2 DIABETES

Physical exercise, specially AET, has a crucial role on the glucose metabolism because it leads AKT to signalize to cytoplasmic vesicles that carry GLUT4, a glucose transporter found inside these vesicles, to be translocated to the cell membrane by these vesicles to catch and take glucose to the adipose and muscle tissues[4]. This glucose will be stocked and used as energy fuel to perform daily activities. AET reduces and manages blood glucose in T2D, controlling hyperglycemia and hyperinsulinemia through insulin-dependent and insulin-independent pathways[19,20]. The insulin-independent pathway that activates translocation of GLUT4 to the muscle membrane is not impaired in T2D, hence the surprising value of exercise. These physiological changes contribute to a higher VO_{2max}, and this higher oxidative contributes to energy generation at a particular exercise workload, improves the blood pressure, and lowers the risk of developing cardiovascular diseases in T2D individuals[4,21].

ROLE OF AEROBIC EXERCISE TRAINING ON ALZHEIMER'S DISEASE: FOCUS ON COGNITIVE DECLINE AND MEMORY LOSS

Cognitive decline and memory loss are not a direct natural consequence of aging, and instead are related to heritability, illness, or damage in the brain tissue[22]. A recent meta-analysis evaluated if physical exercise programs had a significant impact in improving cognition and the ability to perform activities of daily living in people with all types of dementia, with a strong focus on AD[23]. The 16 included trials (n=937 participants) were extremely heterogeneous in terms of classifying the participants' dementia and the duration, intensity, and frequency of exercise. Only two trials included participants who were living at home. The meta-analysis suggested that all types of physical exercise programs may have a significant impact on improving cognitive function and the ability of people facing cognitive decline or memory loss to perform daily activities normally.

AEROBIC EXERCISE TRAINING REGULATES THE MOLECULAR MECHANISMS IN ALZHEIMER'S DISEASE, TYPE 2 DIABETES, AND OBESITY

AET induces changes in the expression of several genes, by altering epigenetic patterns of DNA methylation and histone acetylation, modulating signal transduction pathways and metabolic pathways, and especially promoting a more efficient stimulation of the PI3K pathway[24] and also insulin-independent pathways, such as interleukins (ILs) pathway[25]. PGC-1α/FNDC5/Irisin pathway is only activated by skeletal muscle during physical exercise and has been positively correlated with biceps circumference and insulin-like growth factor-1 (IGF-1) levels in humans[26] and growth-related genes in mice[27]. Irisin has unidentified receptors and plays a role in metabolism, synaptic plasticity, neurogenesis, cognitive function, and memory through different pathways, such as PI3K[21]. On the other hand, excessive adiposity is associated with poor mental health[28,29].

AET increases lipid oxidation via upregulating genes involved in regulating fatty acid uptake across the plasma and mitochondrial membranes[30]. AET increases carnitine palmitoyltransferase (CPT) complex activity and malonyl-CoA production is inhibited[13], which is the precursor of all fatty acids. This contributes to reduced body fat mass, thus contributing to a reduced risk of obesity and cardiovascular disease. A recent study showed that obese individuals who did bicycle training for 3 months did not lose visceral adipose tissue when a selective inhibitor of the IL-6 receptor was used, compared to the exercise group who received a placebo[31]. This study showed that loss of visceral adipose tissue mass with exercise training is dependent on IL-6, but it remains unclear whether inhibition of IL-6 also inhibited PGC-1α and/or CPT complex or how it would interfere with Irisin production and related pathways.

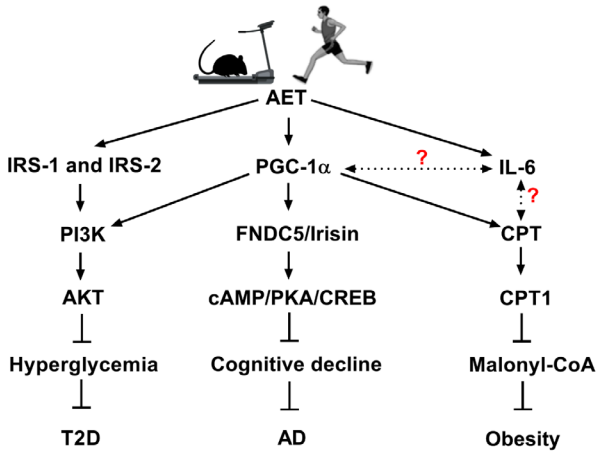
In addition, it is now clear that AET can increase the levels of brain-derived neurotrophic factor (BDNF)[32], stimulate neurogenesis[33], and improve learning and mental performance[34]. Irisin levels are diminished in the hippocampus of AD experimental models. When boosting brain or peripheral levels of Irisin through AET or injecting recombinant Irisin, in animal models and human cells, respectively, BDNF levels are enhanced, and memory and synaptic plasticity are rescued[35]. Recombinant Irisin also had neuroprotective actions in human cells stimulating cyclic AMP (cAMP), protein kinase A (PKA), and CREB, which together form a very important pathway (i.e., cAMP/PKA/CREB) that plays several roles in memory formation (Figure 1).

AEROBIC EXERCISE TRAINING STIMULATES GLUCOSE METABOLISM AND MITOCHONDRIA FUNCTION IN THE BRAIN

We have demonstrated a connection between obesity, T2D, and AD, and the role of AET in stimulating glucose metabolism and mitochondria function in the brain. These changes

will also fight the development and progression of these diseases[36-38]. The brain is also important for managing compensatory mechanisms to hypoglycemia in addition to its regulation of energy metabolism[39]. It is known that glucose is the most important circulating energy substrate for the brain and is actively oxidized to produce ATP, generating a synergistic effect with mitochondria in several metabolic pathways[40].

There is a growing body of evidence showing a crucial role of impaired mitochondrial function in pathogenesis of several neurodegenerative diseases and thus biochemical factors in mitochondria are considered promising targets for pharmacological-based therapies[41]. It is known that the activation of PGC-1α is essential for mitochondrial dynamics and function, and AET triggers the enhancement of its expression together with greater expression of BDNF and FNDC5[42,43]. Acute or chronic AET can favor greater expression of PGC-1α, mitochondria biogenesis and elongation, and autophagy, which together will also favor the enhancement of glucose uptake and utilization[44,45].



AET: aerobic exercise training; IRS: insulin receptor substrates; PGC: Peroxisome proliferator-activated receptor gamma coactivator; IL: interleukins PI3K: phosphatidylinositol 3-kinase; FNDC: fibronectin; CPT: carnitine palmitoyltransferase; AKT: Protein kinase B; COA: Coenzyme A; T2D: type 2 diabetes; AD: Alzheimer's disease.

Figure 1. Representative scheme of the influence of aerobic exercise training on different molecular pathways. Aerobic exercise training can contribute to a better functioning of the phosphatidylinositol 3-kinase pathway, thus inhibiting the development of hyperglycemia and, consequently, obesity and type 2 diabetes. Aerobic exercise training needs to activate Interleukins-6 to induce weight loss. It is not known if IL-6 plays a role in elevating the activity of the carnitine palmitoyltransferase complex and the production of PGC-1α and/or vice versa. Aerobic exercise training also favors the activation of PGC-1α/fibronectin type III domain-containing 5/Irisin and cyclic Adenosine monophosphate/protein kinase A/ Cyclic adenosine monophosphate response element-binding protein pathways, thus inhibiting, in this way, cognitive decline and development of Alzheimer's disease.

Many governments and their health research funding agencies include scientific research into the determinants of exercise behavior and its role in healthy aging as an important item on their agenda. Many studies of the practice of exercise in T2D or AD lack appropriate sample power, randomization and allocation concealment, and standardized protocols. There is also a lack of information provided in many studies about how to implement the AET (especially for long-term exercise regimens). It is essential to describe the frequency, intensity, volume, duration, rate of progression, and type of the AET performed in sufficient detail to allow replication. In addition to the physiological adaptations related to the AET, it is also necessary to describe factors such as age, gender, ethnicity, heritability, geographic location, climate temperature, nutritional habits, and emotional and psychological parameters. All these variables will influence the physiological effect of AET; however, many of the studies target just one or two of these variables, which may not be the ones mainly responsible for the physiological changes captured in the study.

Finally, AET leads to peripheral and central protective effects. Thus, AET can be seen not only as a therapeutic tool but also as a preventive strategy in order to avoid the development and/or progression of obesity, T2D, and AD. However, an accurate and individualized approach following the standards of prescribing the training based in the frequency, intensity, volume, duration, rate of progression, and type of the AET should be followed.

CONCLUSION

AET is a very useful non-pharmacological tool that can bring positive physiological adaptations to AD, T2D, and obesity. AET stimulates a better efficiency of the PI3K pathway and also insulin-independent pathways. Finally, AET can induce the enhancement of PGC-1α/FNDC5/Irisin and cAMP/PKA/CREB pathways, thus inhibiting, in this way, cognitive decline, development or progression of hyperglycemia, and weight gain.

AUTHORS' CONTRIBUTIONS

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

Visualization, Writing – original draft, Writing – review & editing. **IRD:** Conceptualization, Data curation, Formal Analysis, Funding acquisition, Methodology, Supervision, Validation, Visualization, Writing – original draft, Writing – review & editing. **LRSO:** Conceptualization, Data curation, Formal Analysis, Funding acquisition, Methodology, Supervision, Validation, Visualization, Writing – original draft, Writing – review & editing. **ACIC:** Conceptualization; data curation; formal analysis; funding acquisition; methodology; supervision; validation; visualization; roles/writing – original draft; writing – review & editing. **RCC:** Supervision, Validation, Visualization, Writing – original draft, Writing – review & editing.

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REVIEW ARTICLE

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Evaluation of the cardioprotective and antihypertensive effect of AVE 0991 in normotensive and hypertensive rats

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INTRODUCTION

Arterial pressure, or blood pressure (BP), consisting of the pressure that is generated by blood flow over the blood vessel wall, is determined by the volume that is ejected from the heart into the arteries during cardiac systole and arterial elastance and the rate in which blood flows out of the arteries. This generated pressure, in ideal values, guarantees the supply of oxygen and nutrients to the tissues[1]. BP control occurs through the synergistic interaction between various systems, through hemodynamic, neural, humoral, and renal processes[2]. Changes in these regulatory systems can lead to the development of systemic arterial hypertension (SAH)[3].

Systemic arterial hypertension (SAH) is one of the leading chronic diseases that affect individuals worldwide. When uncontrolled, it can dramatically increase the risk of complications such as stroke, coronary artery disease, and kidney and heart failure[4], in addition to representing the primary risk factor for death worldwide[5].

In the pathophysiology of SAH, several mechanisms may be related to its development and progression, such as oxidative stress, increased activity of matrix metalloproteinases[6], inflammation, expression and activation of nicotinamide adenine dinucleotide phosphate (NADPH) oxidase subunits[7], increased baroreflex sensitivity[8], and increased activity of the sympathetic nervous system and the renin-angiotensin-aldosterone system (RAAS)[3].

Renin-angiotensin-aldosterone system (RAAS) is one of the main components of fluid and electrolyte volume control and BP. The cascade of reactions leads to angiotensin II (Ang-II), an octapeptide that promotes vasoconstriction, stimulates the release of aldosterone, and promotes an increase in sodium and water reabsorption, generating an increase in BP[8,9]. Overactivation of this system, mainly through type I angiotensin receptors (AT1), can result in deleterious effects on the cardiovascular and renal systems[9].

Recent evidence has shown that in addition to the pathways related to the classical RAAS pathway, there are other components with opposite activities. These include angiotensin 1-9, alamandine, and angiotensin 1-7 [Ang-(1-7)], the latter being a product of the conversion of Ang-II by the converting enzyme-type II angiotensin (ACE-2) (Figure 1), related to an axis of beneficial activities and opposite to the classic RAAS pathway, and mediated by the action of its binding on MAS receptors[9,10]. MAS receptor agonists have been used in studies as a possible alternative for SAH treatment due to their vasodilatory activities, among them AVE 0991, a synthetic non-peptide agonist of this receptor, which showed cardiorenal protective effects in diabetic rats[11,12]. Hence, the objective of this study was to evaluate the effect of the agonist AVE 0991 on the cardiovascular system of hypertensive and normotensive rats, specifically if it promotes cardioprotective and antihypertensive effects and by what mechanisms these effects are generated.

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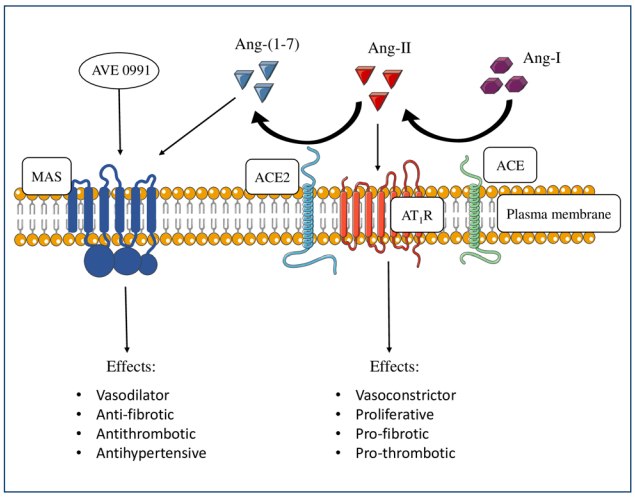

Figure 1. Actions generated by the ligation of AVE 0991 on the MAS receiver. Ang-II is converted to Ang-(1-7) by ACE2. Binding of Ang-(1-7) or other agonists, such as AVE 0991, on MAS receptors, generates effects contrary to those of binding of Ang-II on AT1 receptor.

METHODOLOGY

This is an integrative literature review study with a qualitative and descriptive character. The research brought together international studies to assess the effects of binding a non-peptide MAS receptor agonist and its effects on the cardiovascular system. The elaboration of this integrative review, as recommended, followed six steps[13]:

- Identification of the theme and selection of the guiding question
- Establishment of inclusion and exclusion criteria for studies
- Extraction of information to be extracted and categorization of selected studies
- Evaluation of included studies
- Interpretation of results
- Presentation of the review/synthesis of knowledge

Formulation of the review question

The following questions generated led to the review: Does the binding of the non-peptide agonist AVE 0991 to the MAS receptor promote cardioprotection and BP reduction in rats? And what are the actions related to the cardioprotective and antihypertensive effect of the interaction between AVE 0991 and the MAS receptor?

Literature search strategy

The bibliographic survey was developed through the electronic databases National Library of Medicine (PubMed), Medical Literature Analysis and Retrieval System Online (MEDLINE), and Elsevier Database (Scopus). The search terms used during the survey were as follows: "Hypertension," "Renin-Angiotensin System," "Angiotensin 1-7," and "AVE0991." The combination of terms was performed using the Boolean connector "AND."

Inclusion and exclusion criteria

The inclusion criteria were as follows: studies that addressed the effects generated by AVE 0991 on the cardiovascular system of hypertensive or normotensive rats; studies published in full, in English; and titles published in the period it comprises (2002–2022). Duplicate studies, clinical studies, and gray literature materials, such as theses, dissertations, course conclusion works, and studies published in event proceedings, were excluded.

Search and selection process

The literature search was performed in December 2021. To assist in identifying and selecting studies, the Statement for Reporting Systematic Reviews and Meta-Analyses of Studies (PRISMA) flowchart was used (Figure 1).

Data extraction and analysis

From the selection of the studies, a thorough analysis of the studies was carried out. The studies were characterized in author/year of publication, title, experimental model, and cardioprotective and antihypertensive actions generated by the treatment with AVE 0991 through a standardized data form as shown in Figure 2.

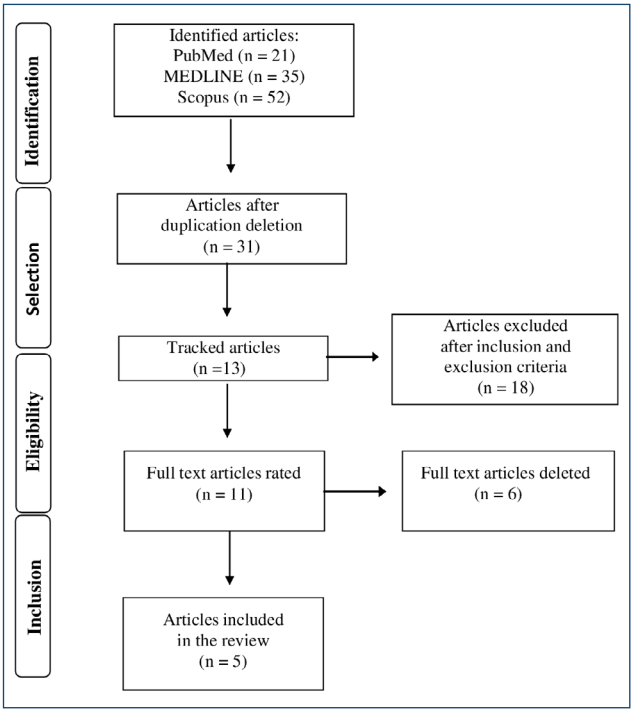

Figure 2. Flowchart of the article selection process.

RESULTS

The titles identified by searching the PubMed, MEDLINE, and Scopus databases corresponded to 108 articles. After excluding duplicates, 31 articles returned, of which, after reading the texts and abstracts applying the inclusion criteria, 5 articles remained for reading the entire text in full, as shown in Figure 1.

The results of this integrative review summarize the cardioprotective and antihypertensive effects generated by treatment with a non-peptide agonist of the MAS receptor, i.e., AVE 0991, in rats with and without hypertension. The summary of the studies included in this review is shown in Table 1, which is characterized and described according to the author, year of publication, article title, experimental model, and cardioprotective and antihypertensive actions induced by AVE 0991.

This brief review had numerous limitations. A limited number of studies were identified that addressed the use of AVE 0991 and its effects on the cardiovascular system. Given the limited number of studies found, the time interval used was 20 years to enhance the search for studies and provide as much evidence as possible. However, the results obtained were enough to show that using AVE 0991 plays beneficial actions on the cardiovascular system, such as those already described related to Ang-(1-7).

DISCUSSION

The RAAS cascade consists of converting angiotensinogen into Ang-I by an enzyme released by the juxtaglomerular cells of the kidney, renin. Ang-I, in turn, is enzymatically converted by the ACE into Ang-II. When Ang-II binds to the AT1 receptor, it promotes various activities, including vasoconstrictor, proliferative, pro-inflammatory, pro-fibrotic, and pro-thrombotic effects[8,14]. On the other hand, Ang-II can be converted to Ang-(1-7) through ACE-2. Through its binding to MAS receptors, Ang-(1-7) promotes effects contrary to Ang-II, such as vasodilator, anti-thrombotic, antihypertensive, and anti-fibrotic (Figure 2)[14].

Although Ang-(1-7) supplementation seems promising for the treatment of cardiovascular diseases, including SAH, by reducing the contractile response of Ang-II and in the long term attenuating vascular remodeling and BP[15], there are limitations; the peptide has a short biological half-life and is not helpful for oral ingestion[16]. With a longer half-life and stability, these peptide analogs, such as AVE 0991, have drawn research attention[11]. AVE 0991 is a selective non-peptide agonist of the MAS receptor. MAS is a G-protein-coupled receptor discovered in the 1980s, but its binding relationship with Ang-(1-7) was only discovered in the 2000s[17]. The MAS receptor, Ang-(1-7), and ACE-2 form the so-called ACE2-Ang-(1-7)-Mas

Table 1. Distribution of articles included in the review, according to author, year, experimental model, and AVE 0991 action.

Author/year	Title	Experimental model	Cardioprotective and antihypertensive action induced by AVE 0991
Cunha et al., 2013[12]	The non-peptide Ang-(1-7) mimic AVE 0991 attenuates cardiac remodeling and improves baroreflex sensitivity in renovascular hypertensive rats	Fischer rats with renovascular hypertension 2 kidneys 1 clip	Treatment with AVE 0991 reduced fibrosis, inflammation, and increased cardiac weight, in addition to improving baroreflex sensitivity and blood pressure.
Ferreira et al., 2007[21]	Isoproterenol-induced impairment of heart function and remodeling are attenuated by the non-peptide Ang-(1-7) analog AVE 0991	Normotensive Wistar rats treated with isoproterenol	Treatment with AVE 0991 in rats undergoing chronic isoproterenol treatment prevented muscle hypertrophy and collagen fiber deposition in the heart, in addition to improving cardiac function.
Raffai and Lombard, 2016[23]	Ang-(1-7) selectively induces relaxation and modulates endothelium-dependent dilation in mesenteric arteries of salt-fed rats	Sprague-Dawley rats fed a high-salt diet	Oral treatment with AVE 0991 promotes vascular relaxation and improves relaxation of other vasodilators such as bradykinin and acetylcholine and promotes vasoprotective effect.
Zeng et al., 2010[22]	Impairment of cardiac function and remodeling induced by myocardial Infarction in rats are attenuated by the non-peptide Ang-(1-7) analog AVE 0991	Normotensive Sprague-Dawley rats with coronary artery ligation	Treatment with AVE 0991 was able to attenuate hypertrophy and increase in cardiac weight, in addition to improving cardiac function after myocardial infarction.
Carvalho et al., 2007[24]	Evidence for MAS-mediated bradykinin potentiation by the Ang-(1-7) non-peptide mimic AVE 0991 in normotensive rats	Normotensive Wistar rats	Treatment with AVE 0991 improved the action of bradykinin through a mechanism related to the activity mediated by the MAS receptor and potentiated the release of nitric oxide.

axis, with actions supporting and regulating the traditional ACE-Ang II-AT1 axis[18,19].

A study carried out in hypertensive animals with two kidneys one clip treated for 28 days with AVE 0991 showed that the treatment was able to reduce collagen deposition and thickening of the heart induced by hypertension and reduce cardiac and renal inflammation, thus improving baroreflex sensitivity and BP[12]. This is in agreement with a study carried out in China, where treatment with AVE 0991 for 4 weeks was able to attenuate the thickening and hypertrophy of cardiomyocytes induced by pressure overload, in addition to improving cardiac function, evidenced by the increase in ejection fraction and increase in the ventricular shortening fraction[20].

Ferreira et al. evaluated the treatment with AVE 0991 on the remodeling of the heart in a model of cardiac dysfunction induced by treatment with isoproterenol, a non-selective agonist of beta-adrenergic receptors. Treatment with AVE 0991 reduced myocardial hypertrophy and the deposition of collagen fibers in the heart, in addition to improving cardiac function[21]. Similarly, in a study carried out with an experimental model of myocardial infarction, it was observed that treatment with AVE 0991 generated anti-hypertrophic and anti-fibrotic actions on the heart, preserving systolic function and reducing the synthesis and deposition of collagen type I and type III in the heart[22].

A previous study showed that oral treatment with the non-peptide agonist AVE 0991 in Sprague-Dawley rats fed with a high-sodium diet effectively improved vascular function and promoted vasodilatory and vasoprotective effects[23]. In addition, treatment with AVE 0991 improved the action of an endogenous vasodilator, bradykinin[24]. This shows that AVE 0991 has beneficial actions similar to Ang-(1-7) in the cardiovascular system, including reduced cell proliferation, inflammation, oxidative stress, vascular remodeling, and fibrosis[25].

CONCLUSION

The results showed that the use of AVE 0991 generates cardioprotective actions in hypertensive and normotensive rats, in addition to promising antihypertensive activity. AVE 0991 reduced inflammation, cardiac remodeling and fibrosis, and oxidative stress. In addition to improving baroreflex sensitivity, it reduces BP and vascular changes resulting from SAH.

AUTHORS' CONTRIBUTIONS

MVBS: Conceptualization, Writing, Formal Analysis, Methodology. **CPSJ**: Data curation. **FIMF**: Data curation. **AOB**: Supervision. **HVCS**: Visualization, Supervision, Edition. **VMS**: Visualization, Supervision, Edition. **JACRTM**: Visualization, Supervision, Edition.

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COMMENTARY

https://doi.org/10.1590/1806-9282.20220383

Comment on: "Evaluating treatment options in managing thyroid nodules with indeterminate cytology of TBSRTC in thyroidology: *addendum aut non?*"

Ilker Sengul[1,2], Demet Sengul[3*]

Management of thyroid nodules with indeterminate cytology remains a major challenge for thyroidology. We read with a great deal and respect the article by Kuta and colleagues[1] entitled, "Treatment choices in managing Bethesda III and IV thyroid nodules: a Canadian multi-institutional study." The authors reported their objective as identifying the factors associated with decision-making in that population and concluded that the larger nodules, younger age, and higher category of The Bethesda System for Reporting Thyroid Cytopathology (TBSRTC)[2] were associated with decision for surgery. However, they stated that they considered 3 cm as the cutoff point for the determination of nodule size[1]. Nevertheless, the 8th edition of The American Joint Committee on Cancer/Tumor, Node, and Metastasis (AJCC/TNM) Staging System reported the size cutoff points of 2 and 4 cm for T2 and T3 tumors, respectively. The size cutoff point of 20 mm, *per se*, is widely considered by the authorities and also stated as a stage by AJCC/TNM, 8th ed., again, after its 7th ed.[3] In addition, the 2017 American College of Radiology (ACR) guidelines emphasized the size cutoff point of 25 mm[4]. Of note, the 2015 American Thyroid Association (ATA) Management Guidelines for Adult Patients with Thyroid Nodules and Differentiated Thyroid Cancer[5] recommended prophylactic central compartment neck dissection, ipsilateral or bilateral, for cases with papillary thyroid carcinoma with over T3 tumor, by remarking significantly to the size cutoff point of 40 mm [Recommendation 36(B); Weak recommendation, Low-quality evidence], like in the 2009 ATA Management Guidelines. In this sense, why did the authors opt for a size cutoff point of 3 cm instead of 2 or 4 cm? Would the outcomes of their valued work be affected in the case of utilizing 2 or 4 cm as the size cutoff point of the nodules? In addition, the age cutoff used for staging was increased from 45 to 55 years at diagnosis in AJCC/TNM, 8th ed. compared with AJCC/TNM, 7th ed.[3] Furthermore, the authors declared that they handled indeterminate cytology as Categories III and IV, TBSRTC. Nevertheless, many authorities in thyroidology, even the 2015 ATA Management Guidelines for Adult Patients with Thyroid Nodules and Differentiated Thyroid Cancer[4], expressed and described indeterminate cytology as thyroid nodules, possessing cytology adjusted to Categories III, IV, and V, TBSRTC, 2nd ed.[6], which possess the higher risk of malignancies (ROMs) that compared with its 1st ed. Herewith, would the relevant outcomes be affected in the case of incorporating the possible nodules with Category V, TBSRTC, which possess a higher ROM, into the study design of their respectable study? As such, would it differ in case incorporating both the size cutoff points of 2 and 4 cm with Category V, TBSRTC into the study? As a matter of fact that this issue merits further investigation. *Ubi dubium ibi libertas.* We thank Kuta et al.[1] for their valued study.

AUTHORS' CONTRIBUTIONS

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

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COMMENTARY

https://doi.org/10.1590/1806-9282.20220386

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

Tufan Çınar[1*], Mert İlker Hayıroğlu[2], Vedat Çiçek[1], Murat Selçuk[1]

Dear Editor,

We read with interest the article entitled "Comparison of C-reactive protein and C-reactive protein-to-albumin ratio in predicting mortality among geriatric coronavirus disease 2019 patients."[1]. A previous study explored the clinical relevance of the C-reactive protein-to-albumin (CRP/CAR) ratio for in-hospital mortality in patients with coronavirus disease 2019 (COVID-19)[2]. In this study, the findings revealed that both CRP and CRP/CAR ratio were effective in predicting mortality in elderly COVID-19 patients[1]. However, from our point of view, there are several issues that need to be addressed further in this investigation.

The authors solely gathered data on baseline characteristics and divided the study population depending on survival status. However, tables did not include certain key laboratory values, such as D-dimer and cardiac troponin. Previous investigations in COVID-19 patients indicated that D-dimer at admission, mean D-dimer of 5 days during index hospitalization, and D-dimer assessed on the third day of hospitalization were independently related to in-hospital mortality[3,4]. However, the authors of this study did not include data on D-dimer levels in these individuals. Higher cardiac troponin levels, in addition to elevated D-dimer levels, were found to be an independent predictor of in-hospital mortality in COVID-19 patients with and without coronary artery disease[5].We suggest the authors should provide the cardiac troponin levels of the analyzed patients.

The authors only compared the area under the curve values of CRP and CAR in predicting in-hospital mortality among geriatric COVID-19 patients in this study, and they discovered no statistically significant difference in the pairwise comparison of the receiver operating characteristic (ROC) curves among these patients. Both CRP and CRP/CAR ratio were shown to be effective in predicting death in elderly COVID-19 patients, as indicated in "Conclusion" section. However, the authors did not conduct any appropriate statistical analysis in order to draw such a conclusion. Both univariate and multivariate logistic regression analyses should be performed to evaluate if CRP and CRP/CAR were independent predictors of in-hospital mortality in geriatric COVID-19 patients. The authors may thus conclude that both CRP and CRP/CAR can be used to predict in-hospital mortality in elderly COVID-19 patients.

The authors of this study reported that they also investigated the association between patients' comorbidities and mortality. It is commonly recognized that comorbidities tend to accumulate as people age. To determine whether comorbidities have an effect on in-hospital mortality in geriatric COVID-19 patients, the authors should estimate the Charlson Comorbidity Index, which is routinely used to predict mortality in elderly patients with a variety of comorbid diseases.

Despite the study's main limitations, we would like to congratulate the authors for demonstrating that both CRP and CRP/CAR ratio were effective in predicting mortality in geriatric COVID-19 patients.

AUTHORS' CONTRIBUTIONS

TÇ: Conceptualization, Formal Analysis, Writing – original draft, Writing – review & editing. **MİH**: Writing – review & editing. **VÇ**: Writing – review & editing. **MS**: Writing – review & editing.

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