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XIV Congresso Paulista de NEUROLOGIA

31 de maio a 3 de junho

Santos - SP • • • 2023

INSCRIÇÕES ABERTAS!

O Congresso Paulista de Neurologia desembarca em Santos para a sua **14ª. edição. Há mais de 25 anos** no mercado médico, o Congresso tem como objetivo reunir diversos especialistas na área da Neurologia para discussões de novas abordagens e tratamentos, além de conteúdos inovadores em um ambiente de total imersão e troca de experiências e confraternização entre os congressistas.

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- Semiologia
- Distúrbios do Movimento
- Doença Cerebrovascular
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São Paulo Medical Journal
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Challenges in Managing a Medical School

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We recently had the honor and enormous challenge of taking over as co-directors of the School of Medicine of the University of São Paulo (FMUSP).

FMUSP has been nationally and internationally recognized for its pioneering spirit and excellence, both in terms of teaching and research and university extension. It has been training professionals for 110 years in the fields of medicine, physiotherapy, speech therapy, and occupational therapy, and the most recent Medical Physics Program establishes a partnership between the School of Medicine and the Physics Institute of the University of São Paulo.

Our numbers speak for themselves: we have approximately 1,400 undergraduate students; more than 1,000 employees, including 368 professors; 2,000 graduate students; and 1,600 residents. We publish more than 2,500 scientific articles annually.

Our Clinical Hospital (CH) is the largest hospital in Latin America, a state institution linked to the Secretary of Health of the State of São Paulo for administrative coordination purposes and associated with FMUSP for teaching, research, health initiatives, and community services. The CH comprises eight institutes (Central Institute, Psychiatry Institute, Heart Institute, Radiology Institute, Cancer Institute, Institute for Children and Adolescents, Orthopedics and Traumatology Institute, and Physical Medicine and Rehabilitation Institute) and two auxiliary hospitals (Suzano Auxiliary Hospital and Cotoxó Hospital Complex). Annually, we provide more than one million outpatient appointments, 180,000 urgent and emergency care appointments, and approximately 50,000 surgeries.

We are one of the largest medical-scientific research centers in Brazil, with 66 medical investigation laboratories, 230 research groups, and extensive intellectual output.

Our faculty and healthcare professionals represent a huge competitive advantage for obtaining resources in the areas of clinical research, innovation, education, and assistance. Many of our professors are among the most influential researchers in the world, according to an assessment by the British consultancy Clarivate Analytics.[1]

In the search for community-based planning that reflects the best strategies to meet the institution's needs and define its future directions, the FMUSP 2030 strategic plan was prepared in December 2021 to outline new goals, processes, and guidelines for the new cycle that has just begun. Several CH leaders and representatives from the Zerbini Foundation (ZF) and the School of Medicine Foundation (SMF) participated in it.

Planning is integrated between the FMUSP and the CH, with a focus on care, technical, and administrative teaching processes, research and innovation actions, and human resources.

The actions are developed according to strategic axes, which deal with current themes of high social relevance, such as Excellence in Teaching, Culture, and Extension; Excellence in Care; Integration; Humanization-Participatory Management; Internationalization; Sustainability; and Research, Innovation, and Entrepreneurship.

Faced with this challenge, we chose "talent retention" as our management motto. This motto represents our institution's conviction that guaranteeing the future of our school as a place of transformation and excellence depends on our greatest immaterial wealth: the employees working at the FMUSP complex.

However, "talent retention" requires economic sustainability; thus, we need to improve our capacity to retain qualified human resources, which involves competitive compensation and greater investments in infrastructure, innovation, and internationalization.

The SMF and the ZF are private, non-profit institutions that provide FMUSP with support and institutional assistance for the viable management of our hospitals, also strengthening teaching and research. We have the challenge of increasing fundraising so that we can continue investing and financing extension courses, research projects, conferences, clinical studies, technological innovation, and entrepreneurship programs, among many other initiatives.

It is with this focus on sustainability and welcoming that we intend to guarantee the excellence of our school, which today has three very solid pillars, teaching, research, and care, in addition to another pillar present in each of these axes, innovation.

We envision the need for investment in the School of Permanent Education (SPE), a unit that promotes technical, graduate, medical, and multidisciplinary training programs for the community, in addition to being a fundraising source. We intend to renew this unit so that it becomes even better recognized and more attractive to the community and to provide our employees with the possibility of improvement, with a remuneration compatible with market rates, giving them even more of a stake in our institution.

Our health complex offers one of the largest fields of professional practice in Latin America, with potential for training human resources in other areas of knowledge that remain underused. We understand that the challenges of today's world are complex and that responding to them requires dialogue between different areas of knowledge, transcending the limits of each individual profession and going beyond teamwork.

Research and innovation must be integrated as a central objective of professional training. Our students must be provided with this qualification in their training to advance science and technological development.

We need to enhance interprofessional and intersectoral training and expand the support network for undergraduate students, residents, and graduate students (pedagogical, financial, and mental health needs), while also assuring an institutional environment that respects human rights and diversity. We are also convinced that internationalization within a globalized world must be one of the missions of higher education so that we can reap the benefits of global interconnection and avoid having a limited view of our scientific role. We need more programmatic and organizational strategies to help us in this process of cooperation and international academic mobility.

We need to clearly define which health professionals we want to train, considering the enormous social investment in this school, its high qualifications, and its ability to create knowledge, not just transmit it.

Our challenges are enormous. The COVID-19 health crisis we are facing is one of them. There was an unprecedented mobilization in the face of so much adversity. FMUSP has adapted to a new reality, incorporating tools for distance learning and conferences, regrouping teams and lines of research around a single goal, adjusting and adapting all the care offered in our health units, training and qualifying collaborators, developing innovative solutions to meet care needs, in addition to many other initiatives, all of them emergencies. It was necessary to leave the comfort zone, integrate new knowledge, spread initiatives, in short, unite the "house," to offer the population quality care and to receive more than 10,000 critically ill patients.[2]

We count on the commitment of our very talented team to working tirelessly so that "Casa de Arnaldo" continues its trajectory of excellence and pioneering spirit, training and transforming people and welcoming human beings.

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Computer-aided diagnosis system versus conventional reading system in low-dose (< 2 mSv) computed tomography: comparative study for patients at risk of lung cancer

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Radiation dose.

ABSTRACT

BACKGROUND: Computer-aided diagnosis in low-dose (≤ 3 mSv) computed tomography (CT) is a potential screening tool for lung nodules, with quality interpretation and less inter-observer variability among readers. Therefore, we aimed to determine the screening potential of CT using a radiation dose that does not exceed 2 mSv.

OBJECTIVE: We aimed to compare the diagnostic parameters of low-dose (< 2 mSv) CT interpretation results using a computer-aided diagnosis system for lung cancer screening with those of a conventional reading system used by radiologists.

DESIGN AND SETTING: We conducted a comparative study of chest CT images for lung cancer screening at three private institutions.

METHODS: A database of low-dose (< 2 mSv) chest CT images of patients at risk of lung cancer was viewed with the conventional reading system (301 patients and 226 nodules) or computer-aided diagnosis system without any subsequent radiologist review (944 patients and 1,048 nodules).

RESULTS: The numbers of detected and solid nodules per patient (both $P < 0.0001$) were higher using the computer-aided diagnosis system than those using the conventional reading system. The nodule size was reported as the maximum size in any plane in the computer-aided diagnosis system. Higher numbers of patients (102 [11%] versus 20 [7%], $P = 0.0345$) and nodules (154 [15%] versus 17 [8%], $P = 0.0035$) were diagnosed with cancer using the computer-aided diagnosis system.

CONCLUSIONS: The computer-aided diagnosis system facilitates the diagnosis of cancerous nodules, especially solid nodules, in low-dose (< 2 mSv) CT among patients at risk for lung cancer.

INTRODUCTION

Low-dose computed tomography is an effective imaging modality to reduce mortality in patients at high risk of lung cancer.[1-4] In China, the computed tomography interpretation systems for the management of lung cancer vary among institutions. Moreover, the experiences of radiologists have an impact on computed tomography interpretation.[5] Therefore, standardized computed tomography interpretation and management of nodule screening is crucial.[6-9]

Computer-aided diagnosis is reportedly a potential measurement tool for screening lung nodules, with quality interpretation and fewer variabilities among readers.[10-13] The European Society of Radiology and European Respiratory Society recommend computer-aided diagnosis of lung cancer nodules.[14] The investigated computed tomography scans were considered low dose at 3 mSv or less; however, the requirement for low-dose computed tomography is actually < 2 mSv.[5,15] However, computer-aided diagnosis in computed tomography can miss lung cancer nodules that are detected by radiologists.[11] A computer-aided diagnosis system has less sensitivity for ground-glass nodules than the conventional reading system.[16] Computer-aided diagnosis systems often miss lesions that are large, endobronchial, and inseparable from the mediastinum or perihilar. In addition, computer-aided diagnosis is typically used to aid radiologists in screening trials; therefore, both methods are used in clinical practice. Hence, the feasibility and efficacy of computer-aided diagnosis in computed tomography for lung cancer nodules should be investigated in detail.

OBJECTIVE

In this retrospective study, we aimed to compare the diagnostic parameters of low-dose (< 2 mSv) computed tomography interpretation results using a computer-aided diagnosis system for lung cancer screening with those of a conventional reading system by radiologists.

METHODS

Ethics approval and consent to participate

The present study involved chart reviews from a database (of lung cancer diagnosis) of chest computed tomography images of patients at risk for lung cancer. Therefore, the requirements for ethics approval from The First Affiliated Hospital of Nanchang Medical College Review Board, consent to participate, consent to publish, and registration in the Chinese Clinical Trial Registry were waived by Xianyang Cai-Hong Hospital (China), Hospital of Shaanxi University of Chinese Medicine (China), and Jiangxi Provincial People's Hospital Affiliated with The First Affiliated Hospital of Nanchang Medical College (China).

Study population

Low-dose (< 2 mSv) chest computed tomography images of patients at risk of lung cancer according to the risk prediction model, including demographics and metabolic markers for lung cancer,[17] from the radiology departments of Xianyang Cai-Hong Hospital, Hospital of Shaanxi University of Chinese Medicine, and The First Affiliated Hospital of Nanchang Medical College from December 8, 2019, to January 1, 2021 were included in the analyses. Patients without nodules were excluded from this study. A flowchart of the patient selection is shown in **Figure 1**.

Imaging protocols of chest computed tomography

The detailed protocols for chest computed tomography were based on individual institutional guidelines; there were no differences between the image acquisition protocols and basic characteristics of each center. The basic configuration comprised a computed tomography scanner with at least 16 detector rows. A whole thoracic scan was performed with a one-breath hold at full inspiration. The slice thickness was 1.5 mm, and the image acquisition settings were 80–120 kVp, 22 mA, and the lowest possible collimation on the scanner; the radiation dose was less than 2 mSv.

Computed tomography image analyses

Computer-aided diagnosis system

The AVIEW LCS Lung Cancer Screening SW system (Coreline Europe GmbH, Eschborn, Germany) was available at the three institutions. All chest computed tomography scans were uploaded to the cloud included with the software. All participating radiologists interpreted the chest computed tomography scans irrespective of the availability of the software. Interpretations of the chest computed tomography scans were based on a computer-aided diagnosis system for lung nodules (Visia™, MeVis Medical

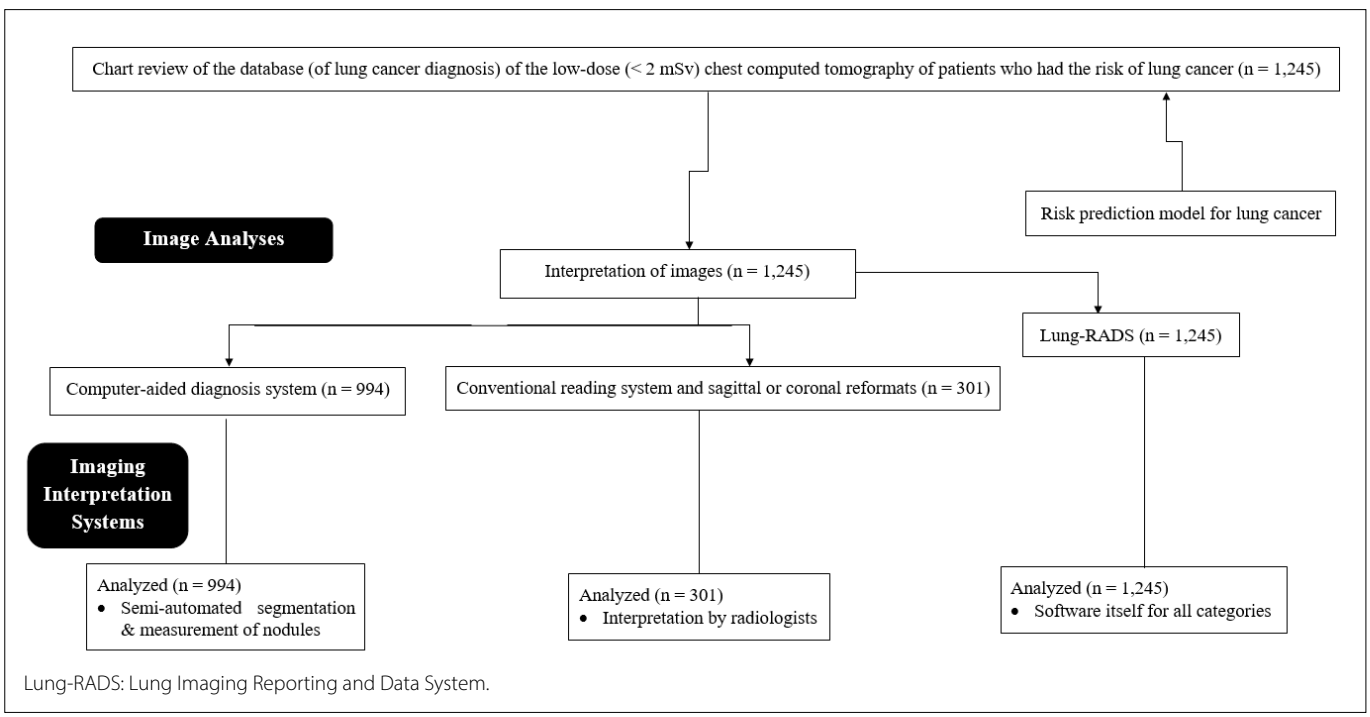

Figure 1. Flowchart of patient selection.

Solutions AG, Bremen, Germany), including semi-automated segmentation and measurement of the nodules (the diameter of the nodules was automatically measured by automatic segmentation).

Conventional reading system

The computed tomography images were initially screened for interpretations using the institutional conventional system, and other reformats (sagittal or coronal) were accessible to the radiologists, who had a minimum of three years of experience in thoracic imaging, at each hospital. The nodule diameters were measured manually using an electronic caliper (DIGITAL CALIPER, Model No. DT-300/D-300W, Niigata seiki Co., Ltd., Sanjo, Niigata, Japan).

Lung Imaging Reporting and Data System

The chest computed tomography scan interpretations were based on the Lung Imaging Reporting and Data System (Lung-RADS) Version 1.1.[18] The software displays the Lung-RADS category results. The predictions of the different Lung-RADS categories are presented in **Table 1**.

Statistical analysis

InStat 3.01 (GraphPad Software, San Diego, California, United States) was used for statistical analysis. Continuous data were compared using the Mann-Whitney *U* test, unpaired *t*-test with Kolmogorov-Smirnov test, or one-way analysis of variance. Categorical data were compared using the chi-square test for independence (for comparisons of more than two classes) or Fisher's exact test (for comparisons of two classes).[5] Tukey-Kramer multiple comparisons tests (considering a critical value [q] > 3.314 as significant) were performed for *post hoc* analysis. McNemar's tests were used to compare diagnostic parameters between the two systems.[5] P values less than 0.05 were considered statistically significant.

RESULTS

Characteristics of participants and nodules

A database of 1,245 patients was retrospectively reviewed. Among them, a database of 301 patients was viewed using the conventional reading system with the radiologists unaware of the computer-aided diagnosis system data. In addition, the data of 944 patients were viewed using a computer-aided diagnosis system without any subsequent review by a radiologist. Details of the participants' characteristics are presented in **Table 2**. A total of 226 nodules among the database of 301 patients were detected by radiologists using the conventional reading system, and 1,048 nodules in the database among 944 patients were detected using the computer-aided diagnosis system. The numbers of detected nodules per patient (P < 0.0001, Fisher's test) and solid nodules (P < 0.0001, Fisher's test) were higher in the database of patients evaluated with the computer-aided diagnosis systems compared with those with the conventional reading system. The number of pure-ground nodules was fewer in the database of patients evaluated with the computer-aided diagnosis system compared with patients evaluated with the conventional reading system (P = 0.0003, Fisher's test). The nodule size in the transverse plane detected by the conventional reading and computer-aided diagnosis systems was 4.41 ± 1.22 mm and 4.32 ± 1.85 mm, respectively, and 4.61 ± 2.05 mm and 4.92 ± 1.81 mm in the maximum orthogonal plane, respectively. The size of the nodules was reported as the maximum in any plane for the computer-aided diagnosis system. The nodule characteristics are presented in **Table 3**.

Lung-RADS category distribution and positivity rates

A total of 20 (7%) and 102 (11%) patients were diagnosed with cancer using the conventional reading and computer-aided diagnosis systems, respectively. The computer-aided diagnosis system detected a higher number of patients with cancer than the conventional reading system (P = 0.0345, Fisher's test). If nodules were measured in a transverse plane, there were no significant differences between the two systems in the number of patients diagnosed with cancer (P = 0.6150, Fisher's test). However, if nodules were measured in any maximum plane with the computer-aided diagnosis system, a higher number of patients with cancers were detected than with the transverse plane measurement using the conventional reading or computer-aided diagnosis systems.

Table 1. Lung Imaging Reporting and Data System category distribution

Parameters	Predicted categories
No computed tomography images available	0 (Incomplete)
No appearances of nodules in computed tomography images	1 (Absent)
< 6 mm ϕ for solid nodules and part-solid nodules	2 (Benign)
≥ 6 to < 8 mm ϕ for solid nodules and ≥ 6 ϕ with solid component < 6 mm for part-solid nodules	3 (Probably benign)
≥ 8 to < 15 mm ϕ for solid nodules and ≥ 6 ϕ with solid components ≥ 6 mm to < 8 mm for part-solid nodules	4A (Suspicious)
≥ 15 mm ϕ for solid nodules and > 8 ϕ with solid components ≥ 8 mm for part-solid nodules	4B (Very suspicious)
Suspicious nodules with additional features in imaging analysis	4X (Very suspicious)
Significant clinical and imaging parameters	4S (Clinically significant)

ϕ: diameter (mean diameter of both the long and short axis) according to the 2019 American College of Radiology guidelines.

The details of the per-patient Lung-RADS category distribution screening results for lung cancers are presented in **Table 4**.

A total of 17 (8%) and 154 (15%) nodules were diagnosed using the conventional reading and computer-aided diagnosis systems, respectively (P = 0.0035, Fisher's test). If nodules were measured in a transverse plane, there were no significant differences between the two systems in the number of nodules diagnosed with cancer (P = 0.6921, Fisher's test). However, if nodules were measured in any maximum

Table 2. Participants characteristics

Characteristics		Conventional reading system by radiologists	Computer-aided diagnosis system	Comparisons			
Numbers of patients included in the analysis		**301**	**944**	**P value**	**95% CI**	**Df**	**F value**
Sex	Male	281 (93)	873 (92)	0.7032 (Fisher's test)	0.7424–1.6529	N/A	N/A
	Female	20 (7)	71 (8)				
Age (years)		61.15 ± 8.14	62.15 ± 8.55	0.0741 (*t*-test)	N/A	1243	1.1030
Smoking status	Current	15 (5)	55 (6)	0.8054 (χ^2-test)	N/A	2	N/A
	Previous	126 (42)	381 (40)				
	None	160 (53)	508 (54)				
Participants with available prior computed tomography		51 (17)	141 (15)	0.4099 (Fisher's test)	0.8636–1.4499	N/A	N/A

Continuous data are presented as the mean ± standard deviation and constant data are presented as the frequency (percentage).
Continuous data were compared using a ***t***-test, and categorical data were compared using the chi-square test for independence or Fisher's exact test for statistical analysis.
Results were considered significant if the P value was less than 0.05.
CI = confidence interval; Df = degree of freedom; N/A = not applicable; χ^2-test = chi-square test.

Table 3. Nodule characteristics

Characteristics		Conventional reading system by radiologists	Computer-aided diagnosis system	Comparisons		
Total numbers of nodules included in the analysis		**226**	**1,048**	**P value**	**95% CI**	**F value**
Nodule(s)/Patient		0.75	1.11*	< 0.0001 (Fisher's test)	0.6108 – 0.8256	N/A
Characters of nodules						
Solid		180 (80)	943 (90)*	< 0.0001 (Fisher's test)	0.3994 – 0.6932	N/A
Part-solid		18 (8)	50 (5)	0.0707 (Fisher's test)	1.0130 – 2.3240	N/A
Pure-ground glass		2 8 (12)*	55 (5)	0.0003 (Fisher's test)	1.4630 – 2.8150	N/A
Size (mm)						
Transverse plane		4.41 ± 1.22	4.32 ± 1.85	0.4846 (*t*-test)	-0.3425 – 0.1625	2.2990
Maximum orthogonal plane		N/A	4.61 ± 2.05	N/A	N/A	N/A
Any maximum plane		N/A	4.92 ± 1.81*	N/A	N/A	N/A
Comparison for size						
P value		N/A	< 0.0001 (ANOVA; F value: 25.9670)	N/A	N/A	N/A
***q* value**	Transverse plane versus maximum orthogonal plane	N/A	4.9250 (95% CI: -0.4851 – -0.0949)	N/A	N/A	N/A
	Transverse plane versus any maximum plane	N/A	10.1900 (95% CI: -0.7951 – -0.4049)	N/A	N/A	N/A
	Maximum orthogonal plane versus any maximum plane	N/A	5.2650 (95% CI: -0.5051 – -0.1149)	N/A	N/A	N/A

Continuous data are presented as the mean ± standard deviation and categorical data are presented as the frequency (percentage).
Continuous data were compared using an unpaired ***t***-test or one-way analysis of variance and categorical data were compared using Fisher's exact test for statistical analysis.
Tukey-Kramer multiple comparisons test was used for *post hoc* analysis.
Results were considered significant if the P value was less than 0.05 and *q*-value was greater than 3.314.
*Significant difference.
ANOVA = analysis of variance; CI = confidence interval; N/A = not applicable.
Size = to calculate the nodule mean diameter, we measured both the long and short axes to two decimal points and reported the mean nodule diameter to two decimal points.

plane with the computer-aided diagnosis system, then higher numbers of cancerous nodules were detected compared with the transverse plane measurement using the conventional reading or computer-aided diagnosis systems. The details of the per-nodule Lung-RADS category distribution screening results and lung cancers are presented in **Table 5**.

Diagnostic parameters

Sensitivity and positive predictive values were higher if nodules were measured in any maximum plane of the computer-aided diagnosis system compared with that measured in any plane of any system. The sensitivity, specificity, and positive predictive values did not differ between the transverse plane in the conventional reading and computer-aided diagnosis systems, transverse plane in the conventional reading system, and maximum orthogonal plane in the computer-aided diagnosis system. The details of the diagnostic parameters for the imaging interpretation systems for lung cancer are presented in **Table 6**.

DISCUSSION

This study revealed that the sensitivity and positive predictive values were higher if nodules were measured with the computer-aided diagnosis system than those measured with the conventional reading system. The diagnostic parameter results of the current study are consistent with those of previous retrospective studies.[5,15] Small nodules missed using a conventional reading system can be detected by the computer-aided diagnosis system.[15,19] The computer-aided diagnosis system facilitates the diagnosis of cancerous nodules in patients at risk of lung cancer.

Table 4. Per patient Lung-RADS category distribution, screening results, and lung cancers

Lung-RADS category		Conventional reading system by radiologists	Computer-aided diagnosis system		
		Transverse plane	Transverse plane	Maximum orthogonal plane	Any maximum plane
Number of patients included in analysis		301	944	944	944
1	Numbers of patients	181 (60)	47 8 (51)	461 (49)	472 (50)
	Number of patients with cancer	0 (0)	0 (0)	0 (0)	0 (0)
2	Number of patients	91 (30)	352 (37)	363 (38)	368 (39)
	Number of patients with cancer	7 (2)	18 (2)	25 (3)	42 (4)
3	Number of patients	17 (6)	55 (6)	69 (7)	56 (6)
	Number of patients with cancer	4 (1)	12 (1)	14 (1)	19 (2)
4A	Number of patients	7 (2)	31 (3)	35 (4)	31 (3)
	Number of patients with cancer	5 (2)	21 (2)	23 (2)	28 (3)
4B	Number of patients	3 (1)	11 (1)	12 (1)	13 (1)
	Number of patients with cancer	2 (1)	8 (1)	9 (1)	10 (1)
4X	Number of patients	2 (1)	17 (2)	4 (1)	4 (1)
	Number of patients with cancer	2 (1)	11 (1)	2 (1)	3 (1)
Total number of patients with cancers		20 (7)	70 (7)	73 (8)	102 (11)
Comparison of total number of patients with cancer			P value		95% CI
Transverse plane in the conventional reading system versus transverse plane in the computer-aided diagnosis system			0.7032		0.6124–1.3620
Transverse plane in the conventional reading system versus maximum orthogonal plane in the computer-aided diagnosis system			0.6150		0.5901–1.3170
Transverse plane in the conventional reading system versus any maximum plane in the computer-aided diagnosis system			0.0345		0.4333–0.9906
Transverse plane in the computer-aided diagnosis system versus maximum orthogonal plane in the computer-aided diagnosis system			0.8620		0.8214–1.1630
Transverse plane in the computer-aided diagnosis system versus any maximum plane in the computer-aided diagnosis system			0.0130		0.6632–0.9627
Maximum orthogonal plane in the computer-aided diagnosis system versus any maximum plane in the computer-aided diagnosis system			0.0260		0.6844–0.9834

Data are presented as the frequency (percentage).
Fisher's exact test was used for statistical analysis.
Results were considered significant if the P value was less than 0.05.
CI = confidence interval; Lung-RADS = Lung Imaging Reporting and Data System; N/A = not applicable.
Bold values represent statistical significance.

We found that the specificity and negative predictive values were the same when nodules were measured with the computer-aided diagnosis or conventional reading systems. There was a difference in nodule sizes measured by the two systems. The radiologists did not measure oversized nodules, and the computer-aided diagnosis system did not measure undersized nodules. Nodule size and the risk of lung cancer are separate issues that require investigation.

In this study, we found that the Lung-RADS screening rate per patient was higher with the computer-aided diagnosis system than that of the conventional reading system. In addition, the Lung-RADS screening rates per nodule differed between imaging interpretation systems for lung cancer. The per patient and per nodule Lung-RADS screening rates in the current study were inconsistent with those of retrospective studies.[5,15] The increased diagnosis of small nodules with cancer resulted in a higher per patient Lung-RADS screening rate. Moreover, the increased diagnosis rate of small nodules significantly changed the per-nodule Lung-RADS screening rate. The use of data from more than one institution, heterogeneity of the patients,[20] and higher numbers of involved radiologists[21] may explain the contradictory results between imaging interpretation systems for lung cancer in the current study and those of other retrospective studies.[5,15] A computer-aided diagnosis system is a more accurate tool for lung cancer screening among at-risk patients.

We found that the diagnostic parameters did not differ between the transverse plane in the conventional reading and

Table 5. Per nodule Lung-RADS category distribution, screening results, and lung cancers

Lung-RADS category		Conventional reading system by radiologists	Computer-aided diagnosis system		
		Transverse plane	Transverse plane	Maximum orthogonal plane	Any maximum plane
Number of nodules included in analysis		226	1,048	1,048	1,048
2	Number of nodules	189 (84)	905 (86)	864 (82)	785 (75)
	Number of nodules with cancer	5 (2)	65 (6)	57 (5)	65 (6)
3	Number of nodules	20 (9)	71 (7)	105 (10)	161 (15)
	Number of nodules with cancer	1 (1)	12 (1)	24 (2)	31 (3)
4A	Number of nodules	8 (4)	45 (4)	32 (3)	52 (5)
	Number of nodules with cancer	5 (2)	9 (1)	22 (2)	29 (3)
4B	Number of nodules	7 (3)	18 (2)	36 (3)	35 (3)
	Number of nodules with cancer	5 (2)	2 (0.5)	18 (2)	22 (2)
4X	Number of nodules	2 (1)	9 (1)	11 (1)	15 (1)
	Number of nodules with cancer	1 (1)	2 (0.5)	5 (1)	7 (1)
Total number of nodules with cancer		17 (8)	90 (9)	126 (12)	154 (15)
Comparison of total number of nodules with cancer		P value		95% CI	
Transverse plane in the conventional reading system versus transverse plane in the computer-aided diagnosis system		0.6921		0.5639–1.396	
Transverse plane in the conventional reading system versus maximum orthogonal plane in the computer-aided diagnosis system		0.0622		0.4050–1.022	
Transverse plane in the conventional reading system versus any maximum plane in the computer-aided diagnosis system		0.0035		0.3288–0.8373	
Transverse plane in the computer-aided diagnosis system versus maximum orthogonal plane in the computer-aided diagnosis system		0.0119		0.6940–0.9633	
Transverse plane in the computer-aided diagnosis system versus any maximum plane in the computer-aided diagnosis system		< 0.0001		0.6016–0.8452	
Maximum orthogonal plane in the computer-aided diagnosis system versus any maximum plane in the computer-aided diagnosis system		0.0830		0.7727–1.0170	

Data are demonstrated as the frequency (percentage).
Fisher's exact test was used for statistical analysis.
Results were considered significant if the P value was less than 0.05.
CI = confidence interval; Lung-RADS = Lung Imaging Reporting and Data System; N/A = not applicable.
Bold values represent statistical significance.

Table 6. Diagnostic parameters for imaging interpretation systems for lung cancer

Parameters	CRS by radiologists	CAD			Comparisons					
					P value					
	TP (%)	TP	MOP	AMP	TP of CRS vs. TP of CAD	TP of CRS vs. MOP of CAD	TP of CRS vs. AMP of CAD	TP of CAD vs. MOP of CAD	TP of CAD vs. AMP of CAD	MOP of CAD vs. AMP of CAD
Sensitivity	92.69% (68.21–99.81%)	92.61% (67.89–99.11%)	95.87% (70.12–99.15%)	96.15% (71.12–99.85%)	0.8541	0.0612	0.0431	0.0581	0.0411	0.0981
Specificity	89.91% (88.12–92.15%)	88.11% (86.15–91.11%)	87.12% (84.11–89.99%)	82.98% (80.11–88.15%)	0.9121	0.0852	0.0421	0.0651	0.0391	0.0382
PPV	7.52% (5.15–9.15%)	8.59% (7.11–10.12%)	12.02% (10.15–14.11%)	14.69% (11.12–16.52%)	0.6891	0.0611	0.0041	0.0131	< 0.0001	0.0891
NPV	99.81% (98.12–100%)	99.82% (98.08–99.89%)	99.81% (98.15–99.81%)	99.89% (98.86–99.89%)	0.5831	0.6211	0.5541	0.6541	0.6321	0.6641

Parameters are presented as the mean (range).

McNemar's tests were used to compare parameters.

Results were considered significant if the P value was less than 0.05.

CRS = conventional reading system; CAD = computer-aided diagnosis system; TP = transverse plane; MOP = maximum orthogonal plane; AMP = maximum plane; PPV = positive predictive value; NPV = negative predictive value.

computer-aided diagnosis systems, transverse plane of the conventional reading system, and maximum orthogonal plane of the computer-aided diagnosis system. The results of the different planes using the computer-aided diagnosis system in the current study were consistent with those of a previous retrospective study.[5,22] Lung cancer can be missed by radiologists using computer-aided diagnosis systems.[11] Lung-RADS does not recommend any specific plane in computed tomography imaging for the measurement of nodules,[5] although Lung-RADS Version 1.1[18] is validated in the transverse plane. However, nodules measured in the transverse plane cannot reflect the actual nodule size.[23] Low-dose noncontrast computed tomography images are also responsible for insignificant results.[19] Further research is required to overcome missed lung cancer nodules, and clear instructions are required for the specific planes in computed tomography imaging for the measurement of nodules in lung cancer screening.

The current study revealed significantly fewer pure ground nodules and significantly more solid nodules among patients evaluated by the computer-aided diagnosis system compared with patients evaluated by the conventional reading system. The pure-ground and solid nodule results observed in the current study were consistent with those of other retrospective studies.[5,15] A computer-aided diagnosis system has less sensitivity for ground-glass nodules than that of the conventional reading system.[16] Solid nodules that can be detected by a computer-aided diagnosis system are sometimes missed by radiologists.[15,19] The conventional reading system is recommended for pure-ground nodules, whereas computer-aided diagnosis systems are recommended for solid nodules in lung cancer screening among at-risk patients.

We also found insignificant differences in part-solid nodules between patients evaluated with the computer-aided diagnosis and conventional reading systems. The performance results of the imaging systems for the detection of part-solid nodules in the current study were consistent with those of a prospective multicenter study.[24] The conventional reading system showed comparable performance to the computer-aided diagnosis system for part-solid nodules.

This was an interesting study on a highly relevant topic that included a large database with follow-up data on malignancy diagnoses. This study had some limitations, mainly its retrospective design (the datasets of the conventional reading and computer-aided diagnosis systems were different) and lack of cross-sectional analysis. It may be more valuable to compare the performance of both systems using the same dataset. However, the gold standard (biopsy, surgical pathology, or position emission tomography) has not yet been described. This study noted that the data were organized according to a local "risk prediction model" established for a single institution. This is problematic as it did not translate to other universally standardized classifications (United States Preventive Services Task criteria). There was an apparent difference between the small number of cases (n = 301) read by radiologists and an entirely different large (n = 944) set of cases read by the computer. Consequently, this study included the two separate, albeit overlapping, issues of diagnosis and measurement. This might be responsible for the overall differences between the radiologists' and computer's results. A possible justification for this is that the study included clinical features, which showed broad similarities between the patients diagnosed by radiologists and patients diagnosed by computer (P > 0.05). This study used size in maximum

length rather than volume, which is not conventionally used when screening populations in the United Kingdom. The possible justification for this is that nodule diameter or volume can be used for lung cancer screening.[25] When comparing radiologist interpretations and computer-aided diagnoses it is critical to use the same images. Given that there were two different image sets in this study, it was not possible to validate their performance because there were many different variables between the two groups. Therefore, the increased diagnosis of lung cancer using a computer-aided system may also reflect differences in underlying risks among patients.

CONCLUSIONS

This study validates a commercial computer-aided diagnosis system (Lung-RADS) in a clinical setting, tackling an important question on the utility of computer-aided diagnosis of nodules in the evaluation of computed tomography scans. Use of a computer-aided diagnosis system in low-dose computed tomography (< 2 mSv) for lung cancer screening resulted in higher per-patient and per-nodule Lung-RADS screening rates among patients at risk of lung cancer. Therefore, we recommend a computer-aided diagnosis system for lung cancer screening with low-dose (< 2 mSv) computed tomography, especially for solid nodules. In addition, clear instructions are required regarding the specific plane measured in computed tomography imaging for lung cancer nodule screening. Further investigation of diagnosis rates and measurement accuracy in ultra-low-dose computed tomography (< 1 mSv and < 0.5 mSv) may be of interest.

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Clustering of cardiovascular disease risk factors among first-year students at the University of Ibadan, Nigeria: a cross-sectional study

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ABSTRACT

BACKGROUND: Cardiovascular disease (CVD) is the second leading cause of death in sub-Saharan Africa. Globally, there is substantial evidence that modifiable risk factors for CVD are increasing in adolescents. Unfortunately, there is a paucity of information on the prevalence and clustering of these risk factors in adolescents.

OBJECTIVES: This study explores the modifiable risk factors for CVD among first-year students at the University of Ibadan, Nigeria.

DESIGN AND SETTING: This cross-sectional study was conducted at the University of Ibadan, Nigeria.

METHODS: A total of 546 newly admitted students at the University of Ibadan, Nigeria, were recruited using stratified random sampling. An interviewer-administered questionnaire was used to obtain information from study participants between January and February 2016.

RESULTS: The mean age of respondents was 19 ± 2.2 years with a male-to-female ratio of 1:1. The reported risk factors for CVD were smoking (1.6%), abdominal obesity (3.3%), alcohol consumption (3.7%), overweight/obesity (20.7%), unhealthy diet (85.3%), and physical inactivity (94.5%). Clustering of ≥ 2 risk factors was reported in 23.4% of students. Female students were twice as probably overweight/obese as male students (adjusted odds ratio [AOR] = 2.2; confidence interval [CI] = 1.41–3.43). Students whose fathers were skilled workers were 3.5 times more likely to be physically inactive (AOR = 1.7; CI = 0.97–2.96). The clustering of ≥ 2 risk factors was significantly higher among women and Muslims in bivariate analysis, whereas no significant association was found in multivariate analysis.

CONCLUSIONS: Public health strategies to prevent CVD risk factors should begin in schools and extend to the entire community.

INTRODUCTION

Cardiovascular disease (CVD) is a global public health problem and a leading cause of disability-adjusted life years in 2019.[1] Most of these risk factors are caused by unhealthy lifestyles and habits; therefore, they are sometimes referred to as lifestyle risk factors and include smoking, tobacco, and excessive alcohol use, poor dietary patterns, and physical inactivity. Adolescents and young adults are particularly susceptible to these CVD risk factors in both developing and developed countries.[2,3] Nearly all deaths from CVD occur among young people in Africa than in Europe and North America.[4]

Modifiable behaviors like physical inactivity, tobacco use, unhealthy diet and harmful alcohol consumption increase the risk of CVDs.[5] About 38% of men and 40% of women aged at 18 years or older were overweight in 2014, and this figure is more than double the rate between 1980 and 2015.[4] In Nigeria, the prevalence of overweight and obesity is 26.8% and 6.5%, respectively according to WHO.[6] In southwestern Nigeria, a study revealed that only 60% of university undergraduates consumed the minimum recommended number of servings of grain (cereal) foods, while 60%, 85%, and 40% of students did not meet the recommended daily allowance for protein, calcium, and iron respectively.[7]

Globally, 23% of men and 32% of women over the age of 18 years were insufficiently physically active in 2016.[8] Not having sufficient physical activity is one of the ten leading risk factors for global mortality. These people have at 20%–30% increased risk in all-cause mortality compared with those who engage in at least 150 minutes in moderate-intensity physical activity per week,

or equivalent, as recommended by the World Health Organization.[9] Physical inactivity causes 6% in the burden of disease from coronary heart disease, 30% of ischemic heart disease, 7% of type 2 diabetes, 10% of breast cancer, and 10% of colon cancer.[9]

Excessive fat accumulation produces an accumulation of lipids around the visceral adipose tissue, which is another risk factor for developing CVDs.[10] A study also shows that the prevalence of abdominal obesity was low among young adults in a tertiary institution.[11] A study among Nigerian university students found a higher proportion of abdominal obesity (5.9%) among female undergraduate students compared with their male counterparts (0.8%)[12]

The clustering of CVD risk factors has an amplifying effect that induces increased CVD risk.[13,14] These risk factors can be observed in early adolescence and continue into adulthood.[15] Multiple clustering of these risk factors in adolescents and young adults leads to an initial stage of CVD such as atherosclerosis.[13] The accumulation of cholesterol, lipids and fibrous plagues begins in arterial walls at the age of 10 years and increases over time until it manifests overtime and manifests as an atherosclerotic lesion in adulthood.[13,14] Therefore, tracking of the clustering of multiple CVD risk factors is highly essential and is a sine qua non for mitigating the threat of CVD in adolescents and young adults.

Clustering of CVD risk factors among young people has been well explored in the literature, with interesting findings in low-, middle-, and high-income countries.[16-19] However, there is a paucity of information on this subject matter among university students in Nigeria, particularly newly admitted students who will most likely experience a significant change in their lifestyle. Therefore, this study examined the risk factors for CVD and their clustering in first-year undergraduate students at the University of Ibadan.

OBJECTIVE

Against this background, this study investigated CVD risk factors and their clustering in first-year undergraduate students at the University of Ibadan.

METHODS

Study site

The University of Ibadan has 13 faculties and enrolls at least 3,000 students annually. The University of Ibadan maintains a well-rounded program of sport and athletic activities on campus under the supervision of the Director of Sports. Aside from maintaining a sound body, which is beneficial for progressive thinking and rigorous academic pursuits, students have the added benefit of being exposed to modern facilities and techniques through active participation in various sports.

Study design and population

This was a cross-sectional study among the first-year students of the 2014/2015 academic year at the University of Ibadan, Oyo State, Nigeria. All consenting first-year students at the University of Ibadan aged 15–35 years were eligible to participate in the study while those with physical deformities were excluded.

Sample size and sampling procedure

The sample size was calculated using the Leslie-Kish formula, representing 23.7% of adolescents with a cluster of three CVD risk factors,[3] and a sampling error of 5%. A stratified random sampling technique was used to recruit eligible respondents. The University of Ibadan has academic programs in 13 faculties. Out of the nine faculties, six faculties were randomly selected while all faculties in the College of Medicine, University of Ibadan were selected for the study. In each randomly selected faculty, 50% of the departments were considered except in the Faculty of Dentistry and Public Health, where only one department was chosen while in Clinical Sciences, 100% of the departments were admitted for the 2014/2015 academic session were used. The total number of first-year students (study population) in the randomly selected departments was determined. Then, a proportional allocation of the sample was carried out to determine the number of first-year students in each department. Then, systematic random sampling was used to select the study participants (students) from each department based on the sampling interval. Each person (student) in each department was then assigned a number, and each Kth person was taken from the total number of first-year undergraduate students in each randomly selected department, and the starting point was randomly selected.

The data collection instrument

A semi-structured questionnaire was used to obtain information on the socio-demographic, anthropometric, and lifestyle characteristics of the respondents. Data were collected from January 2016 to February 2016. The questionnaire was validated by experts and then tested among 20 first-year students at another faculty that was not selected for the study. A Cronbach's alpha of 0.8 was obtained. These students had a similar age range to the study participants.

Scale and meter rules, respectively, measured weight and height. The waist circumference (WC) of each participant was measured with a nonelastic tape measure. WC was measured midway between the lowest rib and the superior border of the iliac crest at the end of normal exhalation to the nearest 0.1 cm.[6]

The validated International Physical Activity Questionnaire Short Form (IPAQ-SF) was used to measure students' level of physical activity. Respondents with less than 600 metabolic equivalent

minutes of work/week were classified as not physically active.[20] Respondents with body mass index ≥ 29.9 kg/m^2 were classified as overweight/obese.[21]

Respondents with waist circumference greater than or equal to 88 cm (women) and greater than or equal to 102 cm (male) were classified as abdominally obese.[21]

Dietary patterns were assessed using eating habit questionnaires. Respondents who consumed fewer than five servings of fruits and vegetables per day on at least five days per week were classified as having an unhealthy diet.[22]

Alcohol consumption of more than three standard units/day for men or more than two standard units/day for womenwas classified as excessive alcohol consumption.[23] Current Smoking status was measured as use of tobacco (smoke and/or smokeless) within the past month.[24]

Data analysis

Data were entered and analyzed using SPSS version 24 (IBM Corp. Released 2016. IBM SPSS Statistics for Windows, version 24.0. Armonk, New York: IBM Corp). The general characteristics of the respondents are presented using descriptive statistics. Factors associated with CVD risk factors and their clusters (≥ 2) were assessed using the chi-square test. Binary logistic regression was used to analyze CVD predictors considering a CI of 95%. The significance level was set at $P < 0.05$.

Ethical considerations

This study was approved by the Ethics Committee of the of Ibadan on October 23, 2015 under the approval number: NHREC/05/01/2008a. The chairman of this committee can be contacted at the Biode Building, Room 210, 2nd Floor, Institute for Advanced Medical Research and Training, College of Medicine, University of Ibadan. e-mail: uiuchirc@yahoo.com and, uiuchec@gmail.com.

RESULTS

A total of 546 first-year students (first-year students) participated in the survey. **Table 1** shows that most respondents (81.7%) were between 20 years old and younger, while the mean age of the respondents was 19 ± 2.2 years. **Table 1** shows the socio-demographic characteristics of the study participants. More than half of the respondents were female (55.1%) and the majority (99.3%) were single. Christianity (86.1%) was the predominant faith. Most students (93.0%) lived in university dormitories. The majority (49.6%) of the participants had fathers who held skilled occupations, others (38.3%) had fathers who held semi-skilled occupations, and a few (12.1%) of the respondents' fathers had unskilled occupations. About (62.5%) of the respondents received monthly allowances between N10,001 and N20,000, while (31.3%) received monthly allowances between N10,000 and below.

The various CVD risk factors and their clustering are shown in **Table 1**. These included current smoking (1.6%), abdominal obesity (3.3%), alcohol consumption (3.7%), overweight/obesity (20.7%), unhealthy diet (85.3%), and physical inactivity (94.5%), whereas 23.4% had at least two of these CVD risk factors. **Figure 1** shows the number of CVD risk factors and their clustering by sex. Most respondents had one CVD risk factor (70.1%), followed by two risk factors (20.7%), three risk factors (2.4%), and four risk factors (0.4%); 6.4% had none of the risk factors studied.

Table 2 shows the bivariate analysis of the factors associated with CVD risk factors and their clusters. The clustering of CVD risk

Table 1. Socio-demographic characteristics and cardiovascular disease risk factor clustering among newly admitted undergraduate students of the University of Ibadan, Nigeria (n = 546)

Variables	Frequency	Percent (%)
Gender		
Male	245	44.9
Female	301	55.1
Age group (years)		
≤ 20	446	81.7
≥ 21	100	18.3
Marital status		
Single	542	99.3
Married	4	0.7
Religion		
Christianity	470	86.1
Islam	76	13.9
Residence		
University hostel	508	93.0
Off campus	38	7.0
Fathers' occupation		
Skilled	271	49.6
Semi-skilled	209	38.3
Unskilled	66	12.1
Mothers' occupation		
Skilled	277	50.7
Semi-skilled	236	43.2
Unskilled	33	6.0
Monthly allowance (N)		
≤ 10,000	171	31.3
10,001-20,000	341	62.5
≥ 20,001	34	6.2
Cardiovascular disease risk factors		
Overweight/obese	113	20.7
Unhealthy diet	466	85.3
Currently smoking	9	1.6
Physical inactivity	516	94.5
Abdominal obesity	18	3.3
Alcohol use	20	3.7
Clustering risk factors (≥ 2)	128	23.4

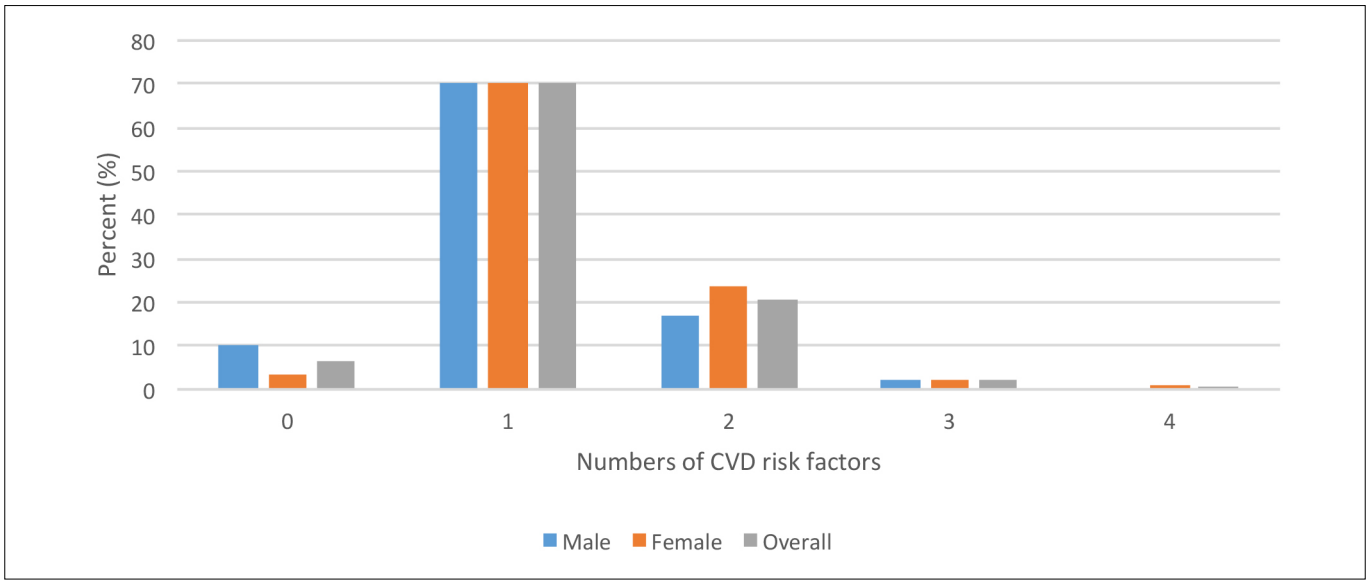

Figure 1. Clustering of cardiovascular diseases (CVD) risk factors among newly admitted undergraduate students at the University of Ibadan, Nigeria.

Table 2. Bivariate analysis of the risk factors of cardiovascular diseases and its clustering among newly admitted undergraduate students at the University of Ibadan, Nigeria

	Overweight/ obesity % (95% CI)	Unhealthy diet % (95% CI)	Smoking % (95% CI)	Physical inactivity % (95% CI)	Abdominal obesity % (95% CI)	Alcoholic consumption % (95% CI)	Clustering of risk factors (≥ 2) % (95% CI)
Gender							
Male	13.9 (0.21–0.74)	86.1 (0.67–1.79)	0.8 (0.08–2.51)	6.5 (0.92–5.64)	0.3 (0.01–0.05)	4.5 (0.77–5.52)	19.6 (0.01–0.03)
female	26.2 (1.35–4.75)	84.7 (0.56–1.48)	2.3 (0.04–0.19)	4.7 (0.04–0.16)	6.0 (0.12–0.36)	3.0 (0.04–1.16)	26.6 (0.01–0.06)
P for trend	< 0.001*	0.644	0.168	0.338	< 0.001*	0.353	< 0.001*
Age (in years)							
≤ 20	20.9 (0.62–2.93)	86.8 (0.95–2.99)	1.6 (0.15–5.38)	5.6 (0.49–4.17)	2.9 (0.09–0.89)	3.1 (0.21–1.72)	22.9 (0.46–1.50)
≥ 21	20.0 (0.34–1.61)	79.0 (0.33–0.54)	2.0 (0.05-1.04)	5.0 (0.08–1.66)	5.0 (1.16–1.61)	6.0 (0.18–1.33)	26.0 (0.66–2.16)
P for trend	0.849	0.047*	0.760	0.810	0.220	0.169	0.504
Religion							
Christianity	19.8 (0.42–2.29)	86.2 (0.77–2.79)	1.1 (0.06–1.47)	5.1 (0.25–2.10)	3.2 (0.33–3.89)	3.0 (0.06–0.12)	19.0 (0.04–0.19)
Islam	26.3 (0.44–2.37)	80.3 (0.36–1.29)	5.3 (0.14–1.50)	7.9 (0.17–1.19)	3.9 (0.07–1.82)	7.9 (1.23–1.69)	4.4 (0.03–0.30)
P for trend	0.192	0.177	0.008*	0.322	0.732	0.034*	0.020*
Residence							
University hostel	18.9 (0.11–1.11)	85.8 (0.60–3.26)	1.8 (0.01–2.08)	5.9 (0.45–10.86)	3.3 (0.18–5.51)	3.7 (0.19–4.45)	22.0 (0.01–1.04)
Off campus	1.8 (0.90–8.57)	78.9 (0.30–1.65)	0.4 (0.01–1.23)	1.2 (0.01–0.45)	2.6 (0.02–1.87)	2.6 (0.02–1.88)	1.5 (0.10–1.49)
P for trend	0.375	0.247	0.408	0.123	0.812	0.726	0.366
Father's occupation							
Skilled job	23.2 (0.56–4.34)	87.5 (0.49–2.59)	1.5 (0.03–5.98)	3.3 (0.03–0.45)	3.0 (0.43–12.73)	3.7 (0.12–1.48)	12.5 (0.14–0.42)
Semi-skilled	18.2 (0.43–3.49)	82.3 (0.31–1.61)	2.4 (0.03–8.58)	6.7 (0.13–1.38)	4.3 (0.14–5.64)	2.4 (0.06–1.99)	8.1 (0.01–0.16)
Unskilled	18.2 (0.40–1.52)	86.4 (0.27–2.23)	0.4 (0.08–1.59)	10.6 (0.21–0.83)	1.5 (0.14–2.67)	7.6 (0.05–0.38)	2.9 (0.57–2.23)
P for Trend	0.344	0.276	0.393	0.041*	0.490	0.148	0.237
Mother's occupation							
Skilled job	22.7 (0.37–5.40)	84.5 (0.26–2.23)	1.4 (0.03–1.34)	4.7 (0.06–1.55)	4.3 (0.12–5.64)	3.2 (0.15–4.31)	11.9 (0.01–1.15)
Semi-skilled	17.8 (0.23–3.44)	86.4 (0.37–3.13)	1.7 (0.03–0.30)	5.9 (0.06–1.68)	2.1 (0.04–2.34)	3.8 (0.21–5.23)	9.7 (0.06–1.49)
Unskilled	24.2 (0.33–1.20)	84.8 (0.82–2.38)	3.0 (0.028–0.30)	9.1 (0.10–1.49)	0.2 (0.02–1.40)	6.1 (0.08–1.39)	1.8 (0.83–3.31)
P for trend	0.338	0.819	0.793	0.535	0.374	0.709	0.609

*Statistically significant at P < 0.05.

factors was significantly higher in women than in men (P < 0.05) and higher in Christians than in Muslims (P < 0.05). **Table 3** shows the multivariate analysis of the predictors of CVDs and their clusters. Women were twice as likely as male respondents to be overweight/obese (adjusted odds ratio, AOR = 2.2; 95% CI = 1.41–3.43; P value = 0.001). Muslims were 5.1 times more likely to smoke than Christians (AOR = 5.1; 95% CI = 1.32–19.37; P value = 0.018). Respondents whose parents were skilled workers were 3.5 times more likely to be physically inactive than respondents whose parents were unskilled workers (AOR = 3.5; 95% CI = 1.24–9.85; P value = 0.018).

Table 3. Multivariate analysis of the risk factors of cardiovascular diseases and its clustering among newly admitted undergraduate students at the University of Ibadan, Nigeria

Variables	AOR	95% CI (AOR)		P value
		Lower	Upper	
Overweight/Obese				
Gender				
Male (ref)	1.0			
Female	2.2	1.41	3.43	0.001*
Religion				
Christianity (ref)	1.0			
Islamic	1.4	0.80	2.51	0.220
Dietary pattern				
Age (years)				
≤ 20 (Ref)	1.0			
≥ 21	1.7	0.97	2.96	0.061
Religion				
Christianity (ref)	1.0			
Islamic	1.5	0.78	2.75	0.229
Smoking				
Gender				
Male (ref)	1.0			
Female	2.8	0.57	13.75	0.202
Religion				
Christianity (ref)	1.0			
Islamic	5.1	1.32	19.37	0.018*
Physically inactive				
Residence				
University hostel (ref)	1.0			
Off campus	2.3	0.48	10.88	0.298
Fathers' occupation				
Unskilled (ref)	1.0			
Semi-skilled	2.1	0.88	4.96	0.090
Skilled	3.5	1.24	9.85	0.018*
Clustering of CVD risk factor (≥ 2)				
Gender				
Male (ref)	1.0			
Female	1.5	0.98	2.22	0.061
Religion				
Christianity (ref)	1.0			
Islamic	1.6	0.95	2.74	0.080

*Statistically significant at P < 0.05; AOR = adjusted odds ratio, ref = reference.

DISCUSSION

To our knowledge, our study is one of the first to explore the clustering of CVD risk factors in newly admitted students in this part of the continent. We found that clustering of two CVD risk factors was observed in one-fifth of the students. The most common of these risk factors were physical inactivity, unhealthy diet, and overweight/obesity, whereas alcohol consumption, smoking, and abdominal obesity were rare in our study population.

The high response rate (98.0%) observed in this study is consistent with similar studies in Nigeria., [25] and Ghana.[12] The proportion of women who participated in this study was higher than that of male respondents. The female predilection in our study corresponds with the reports of Ekerand colleagues among high school students in Turkey.[26] and a national survey of students in various tertiary institutions between 2010 and 2015 in Nigeria.[27]

An unhealthy dietary pattern was evident among undergraduate students in this study, which corresponds to previous studies in Nigeria[28,29] A higher rate of unhealthy dietary lifestyle among women supports the report by Omage and Omuemu.[29]

In line with the report on students in Bangladesh,[30] we found that students who lived off campus had poorer dietary patterns than students who lived in a university dormitory. One plausible reason for this is that students who live off campus prepare their own food, which is better than what is available in school cafeterias. Others live with family members or relatives who prepare the food for them.

The prevalence of current smoking was low in our study (1.6%), compared with previous studies among adolescents and young adults that found 6.8% in Ethiopia,[31] We found that students who lived off campus had lower dietary behaviors than students who lived in a university dormitory. One plausible reason is that students living off campus prepare their own food, which is better than what is available in school cafeterias. Others live with family members or relatives who prepare the food for them.

The prevalence of current smoking in our study was low (1.6%), compared with previous studies among adolescents and young adults that found 6.8% in Ethiopia,[32] 9.0% in Oman,[33] 11.1% in New Zealand[34] and 27.9% in Turkey.[35] The low prevalence of smoking observed in our study is likely due to risky behaviors such as smoking are reportedly more common among students in higher grades students than newly admitted students.[7] Muslims were more likely to smoke than Christians in our study, which contradicts the report by Hussain and colleagues.[36] Nonetheless, the teachings of both religions have been reported to influence the behavior of their believers and to condemn smoking and alcohol consumption.[37,38] Some authors have argued that people tend not to disclose their correct smoking status despite assurances of confidentiality of data collected.[39] Hence, the reported smoking status should be interpreted with this in mind.

This study also show that a small proportion of the study population was highly engaged in physical activity. This is very similar to the findings in the study by Eleojo et al., who proved that only a small proportion of the study population was physically active.[40] A previous multicentre study revealed that a proportion of male respondents were physically inactive compared with female respondents,[40] which corresponds to our findings. Our study found an association between physical inactivity and father's occupation. This supports the assertion that parental factor influences the level of physical activity of their children. Parents' occupation and type of living environment have been seriously implicated.[41,42] The low prevalence of obesity in our study is in contrast to the report of Sabageh and Ojofeitimi with higher prevalence.[43] A study also showed that the prevalence of abdominal obesity was high in the study population.[11] A study showed that the prevalence of abdominal obesity as determined by the waist circumference, was higher in male respondents than in female respondents.[44] This present study also revealed that abdominal obesity is significantly related to gender of which male respondents have a higher proportion of central obesity than female respondents.

This study revealed a low prevalence of alcohol intake among the study population. Another study was done by Alex-Hart and colleagues showed that the prevalence of alcohol consumption was 28.6% significantly higher prevalence from this study.[45] Another study reported a higher proportion of alcohol consumption among males students compared to their female colleagues.[46] Several studies revealed that excessive alcohol consumption is much more common among undergraduate students who reside in the university hostels away from their permanent domicile. This is very similar to the findings reported in this study which shows that students who live on campus had a higher proportion of alcohol intake compared to those who live off campus.[47] This study revealed that most of the respondents had at least two risk factors. This study also corresponds to another study done by Olawuyi and Adeoye, which revealed that a higher proportion of the population had at least two non-communicable disease risk factors.[48] The clustering risk factors have been associated with a higher risk of developing CVDs.[49] A study conducted among young adults in southwest Nigeria reported that there is no significant difference in clustering risk factors for CVDs between the males and females who participated in the study, which is in contrast with the finding of this study. Another study conducted among university students in Libya revealed that there was a significant relationship between clustering risk factors and socio-demographic characteristics of university students.[50] A study conducted among young adults in Yaoundé, Cameroon revealed that the prevalence of some major CVD risk factors increase due to a lack of a appropriate behavioral approach towards healthy living.[51] A previous study also showed a higher proportion of obesity among the females' respondents compare to the male respondents.[52] It is vital to know the relationship between socio-demographic characteristics such as age, gender, and clustering risk factors for CVDs explicitly because it will help to control and prevent CVDs especially among undergraduate students.[53] A previous study revealed that male undergraduate students had lower awareness of the clustering risk factors to CVD compared to their female counterparts.[54] A study conducted among Nigeria undergraduate students revealed that there was no significant difference between the risk factors for CVD among the gender stratification.[55] The findings of our study suggest there is urgent need for public health strategies that will improve physical activity and consumption of healthy diets. This should be done in corroboration with the university management.

Implications of the findings of the study

Note that most young adults do not take care of their health before coming to university. The missed opportunities that result from poor health facilities for young people could be addressed at the university where health facilities exist, through the approach prevention strategy developed by Leavell:

(i) Primary prevention: adding physical activity to the academic calendar will improve physical fitness.
(ii) Primary prevention: every restaurant in the university community offers fruit for consumption by students after meals. This will also encourage students to consume less high cholesterol foods.
(iii) Secondary prevention: screening and treatment (i.e., Dietary changes, exercise, behavior modification, and prescription of weight loss medications).
(iv) Tertiary prevention: this stage is important for the management and control of obesity in obese/overweight students by attending school-based sports facilities specialized in exercise, such as the gymnasium.

Strengths and limitations

The strength of our study was that it was interviewer-administered, which explains the high response rate and limited missing data. Nevertheless, like any other cross-sectional study, our study shows an association and not a causal relationship. Additionally, our study investigated the level of clustering in a selected university in Ibadan, Nigeria. Additionally, this study focused on first-year students from the selected departments. Therefore, these results may not be generalizable to other universities in Ibadan or Nigeria.

CONCLUSION

Our study's clustering of cardiovascular risk factors was unexpectedly high, with high levels of physical inactivity and an

unhealthy diet. The results of this study underscore several issues that need to be considered in reducing the risk of CVD in first-year students at the University of Ibadan.

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One-year mortality of hematopoietic stem cell recipients admitted to an intensive care unit in a dedicated Brazilian cancer center: a retrospective cohort study

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ABSTRACT

BACKGROUND: Hematopoietic stem cell transplantation (HSCT) recipients requiring intensive care unit (ICU) admission early after transplantation have a poor prognosis. However, many studies have only focused on allogeneic HSCT recipients.

OBJECTIVES: To describe the characteristics of HSCT recipients admitted to the ICU shortly after transplantation and assess differences in 1-year mortality between autologous and allogeneic HSCT recipients.

DESIGN AND SETTING: A single-center retrospective cohort study in a cancer center in Brazil.

METHODS: We included all consecutive patients who underwent HSCT less than a year before ICU admission between 2009 and 2018. We collected clinical and demographic data and assessed the 1-year mortality of all patients. The effect of allogeneic HSCT compared with autologous HSCT on 1-year mortality risk was evaluated in an unadjusted model and an adjusted Cox proportional hazard model for age and Sequential Organ Failure Assessment (SOFA) at admission.

RESULTS: Of the 942 patients who underwent HSCT during the study period, 83 (8.8%) were included in the study (autologous HSCT = 57 [68.7%], allogeneic HSCT = 26 [31.3%]). At 1 year after ICU admission, 21 (36.8%) and 18 (69.2%) patients who underwent autologous and allogeneic HSCT, respectively, had died. Allogeneic HSCT was associated with increased 1-year mortality (unadjusted hazard ratio, HR = 2.79 [confidence interval, CI, 95%, 1.48–5.26]; adjusted HR = 2.62 [CI 95%, 1.29–5.31]).

CONCLUSION: Allogeneic HSCT recipients admitted to the ICU had higher short- and long-term mortality rates than autologous HSCT recipients, even after adjusting for age and severity at ICU admission.

INTRODUCTION

Hematopoietic stem cell transplantation (HSCT) is a potentially curative therapy for many hematological malignancies. HSCT is mainly classified as either autologous or allogeneic. Stem cells are obtained from the patients in autologous HSCT and related or unrelated donors in allogeneic HSCT. The most common indications for autologous HSCT are multiple myeloma and lymphomas. Allogeneic HSCT is commonly indicated for leukemia and myelodysplastic syndromes.[1]

HSCT may also cause life-threatening complications secondary to the conditioning regimen, engraftment, and posterior immunosuppression in the case of allogeneic HSCT, which may ultimately lead to intensive care unit (ICU) admission.[2,3] Historically, HSCT recipients admitted to the ICU had grim prognoses. Nevertheless, outcomes have significantly improved during the past decades.[4,5] However, outcomes in allogeneic HSCT recipients with ICU admission may have plateaued in the last 10 years.[6]

Previous studies have focused mainly on allogeneic HSCT recipients,[7] been carried out in specific centers in high-income countries,[4,5] and focused on short-term outcomes.[4,7] Few studies have addressed the characteristics and outcomes of autologous HSCT recipients admitted to the ICU,[8-10] in middle- or low-income countries,[11] or focused on long-term outcomes.[12,13]

OBJECTIVE

The present study aimed to describe a cohort of HSCT recipients admitted to the ICU in a dedicated Brazilian cancer center from 2009 to 2018 and assess differences in long-term mortality between autologous and allogeneic HSCT recipients admitted to the ICU shortly after HSCT.

METHODS

Design and setting

This retrospective cohort study was conducted at a dedicated reference center for HSCT in São Paulo, Brazil. The current database included all patients admitted between September 2009 and December 2018. The local institutional review board approved the study (CAAE 86761718.0.0000.5432; dated June 6, 2018) and waived the need for informed consent. We followed the recommendations of the STROBE statement, which guides the reporting of observational studies.[14]

Participants

We included all consecutive patients who underwent HSCT less than a year before ICU admission during the study period. We only considered the first admission in patients admitted to the ICU more than once. We excluded patients younger than 18 years of age. We retrieved patient data from a local database and electronic medical records. We collected baseline data on age, sex, Eastern Cooperative Oncology Group (ECOG) performance status before ICU admission (registered by the intensivist in charge at the ICU admission, based on reports by family members or emergency department/rapid response team physician), comorbidities, Charlson Comorbidity Index (CCI) from the ICU admission chart, hematological malignancy ultimately leading to HSCT, type of HSCT (autologous or allogeneic), conditioning regimen, and graft-versus-host disease (GVHD) from the HSCT multidisciplinary chart. We also collected data on ICU admission: type of admission (medical or surgical), the reason for admission, and patient severity at admission (measured by the Simplified Acute Physiology Score [SAPS] 3).[15,16] We calculated the Sequential Organ Failure Assessment (SOFA) score from days 1 to 7 after ICU admission, retrieving the vital signs and laboratory results from the medical chart. When laboratory results (i.e., bilirubin and creatinine) were considered normal.[17] Additionally, we collected data on the use of organ support (vasopressor therapy, non-invasive and invasive mechanical ventilation, and renal replacement therapy), ICU and hospital outcomes (length of stay [LOS] and mortality), and 1-year mortality. We checked the medical records to identify patients' last appointments. All patients were censored at this time point. We compared the characteristics; of ICU, hospital, and 1-year outcomes; and overall survival of autologous and allogeneic HSCT recipients.

Statistical analysis

This study was mainly descriptive. We did not perform sample size or power calculations; instead, we presented all available data of the included patients. All data are presented as frequencies (percentages) for categorical variables and medians (interquartile range [IQR]) for continuous variables. We used the Chi-square test of independence or Fisher's exact test for categorical variables and the Mann–Whitney test for continuous variables to compare the two groups.

We used Kaplan–Meier plots and log-rank tests to analyze the differences in overall survival time between autologous and allogeneic HSCT recipients. We used the Cox proportional hazard regression model to assess the effect of allogeneic HSCT compared with autologous HSCT on 1-year mortality risk in an unadjusted model and an adjusted model for age and SOFA score at admission. The proportional hazard assumption for the models was verified using the Schoenfeld residuals method. We calculated this model's hazard ratio (HR) and 95% confidence interval (CI 95%). We used R version 4.1.1 (R Core Team, Vienna, Austria, 2021) for all analyses with the following packages: survival, survminer, and ggplot2.

RESULTS

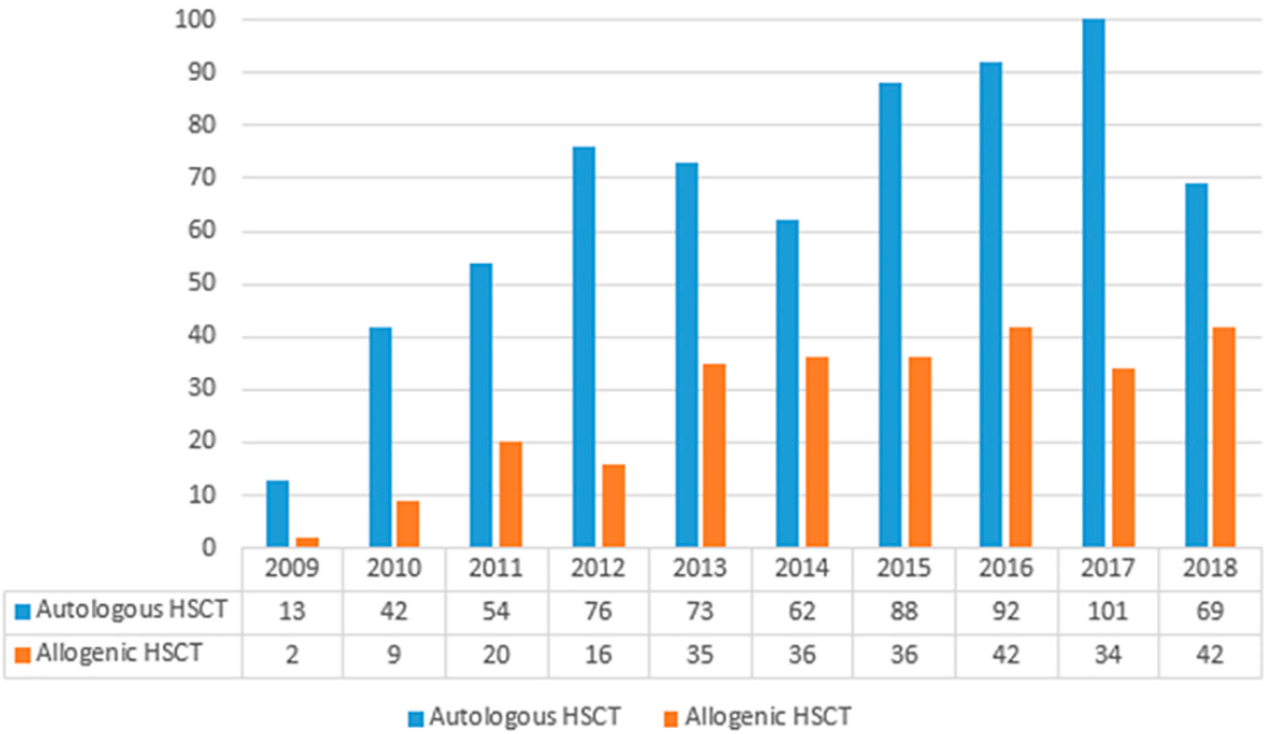
During the study period, 942 patients underwent HSCT (autologous, n = 670 [71.1%]; allogeneic, n = 272 [28.9%]) (**Figure 1**). There were 178 admissions of patients to the ICU up to 1 year after HSCT. Of these, 83 patients were included in the study (**Figure 2**). The median time from HSCT to ICU admission was 12 (IQR, 7–94) days.

Acute leukemia was the most common malignancy necessitating allogeneic HSCT. Multiple myeloma and lymphoma were the most common malignancies leading to autologous HSCT. Allogeneic HSCT recipients were younger, more commonly admitted due to acute respiratory failure, and more frequently required mechanical ventilation than autologous HSCT recipients. Sepsis was the most common reason for admission for autologous HSCT. The SAPS 3 and SOFA scores at admission were not different between autologous and allogeneic HSCT recipients. However, allogeneic HSCT recipients had higher ICU and hospital mortality rates (**Table 1**).

Among allogeneic HSCT recipients, 19 patients (73.1%) received a myeloablative conditioning regimen, and seven (26.9%) received a non-myeloablative conditioning regimen. Only six (23.1%) patients received stem cells from an unrelated donor. A total of 16 patients had GVHD (61.5%): 13 (81.2%) had skin involvement; eight (50%), gastrointestinal; three (18.7%), lung; and two (12.5%), liver.

Although not different at admission, HSCT recipients who ultimately died at hospital discharge had increased SOFA scores 2 to 7 days after ICU admission (**Figure 3**).

After ICU admission, we followed up the patients for a median of 279 (IQR, 29–1670) days. Median survival after ICU admission was 50.5 (CI 95%, 20–430) days for allogeneic HSCT recipients and 1115 (CI 95%, 337–NA) days for autologous HSCT recipients. At 1



HSCT = hematopoietic stem cell transplant.

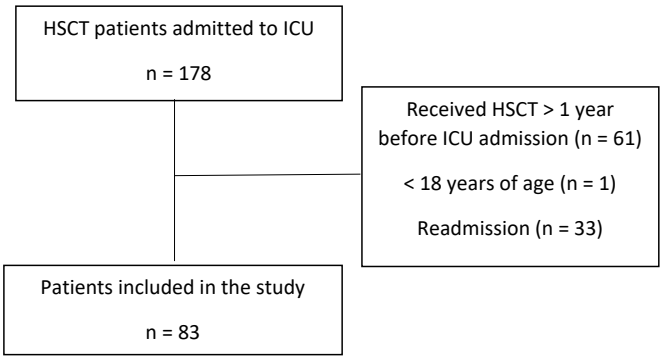
Figure 1. Total number of patients who underwent hematopoietic stem cell transplantation between September 2009 and December 2018.

year after ICU admission, 21 (36.8%) autologous HSCT recipients and 18 (69.2%) allogeneic HSCT recipients had died (**Figure 4**). Allogeneic HSCT was associated with an increased 1-year mortality (unadjusted HR = 2.79 [CI 95%, 1.48–5.26]; adjusted HR = 2.62 [CI 95%, 1.29–5.31]).

DISCUSSION

Almost 9% of the HSCT recipients were admitted to the ICU during the study period. As expected, allogeneic HSCT recipients were younger and had acute leukemia as the primary hematological cancer. Autologous HSCT recipients were older and had mainly multiple myeloma and lymphoma as baseline malignancies. Although not more severely ill at ICU admission, allogeneic HSCT recipients had higher short-term mortality rates than autologous HSCT recipients. Allogeneic HSCT was also associated with 1-year mortality, even after adjusting for age and severity of organ dysfunction at admission.

Previous studies have found that approximately 3%–10% of autologous HSCT recipients[8,10,18] and 15%–25% of allogeneic HSCT recipients require ICU admission after the first few months of transplantation. ICU and hospital mortality in allogeneic HSCT recipients admitted to the ICU ranges from 40% to 90%.[4,12,19,20] Small



HSCT = hematopoietic stem cell transplant; ICU = intensive care unit.

Figure 2. Study flowchart.

cohorts of autologous HSCT recipients had ICU mortality rates from 20 to 60%.[8,10] We found similar mortality rates in both autologous and allogeneic HSCT recipients to those reported in studies carried out in high-income countries. In contrast, a Mexican study of 17 autologous and 51 allogeneic HSCT recipients who required

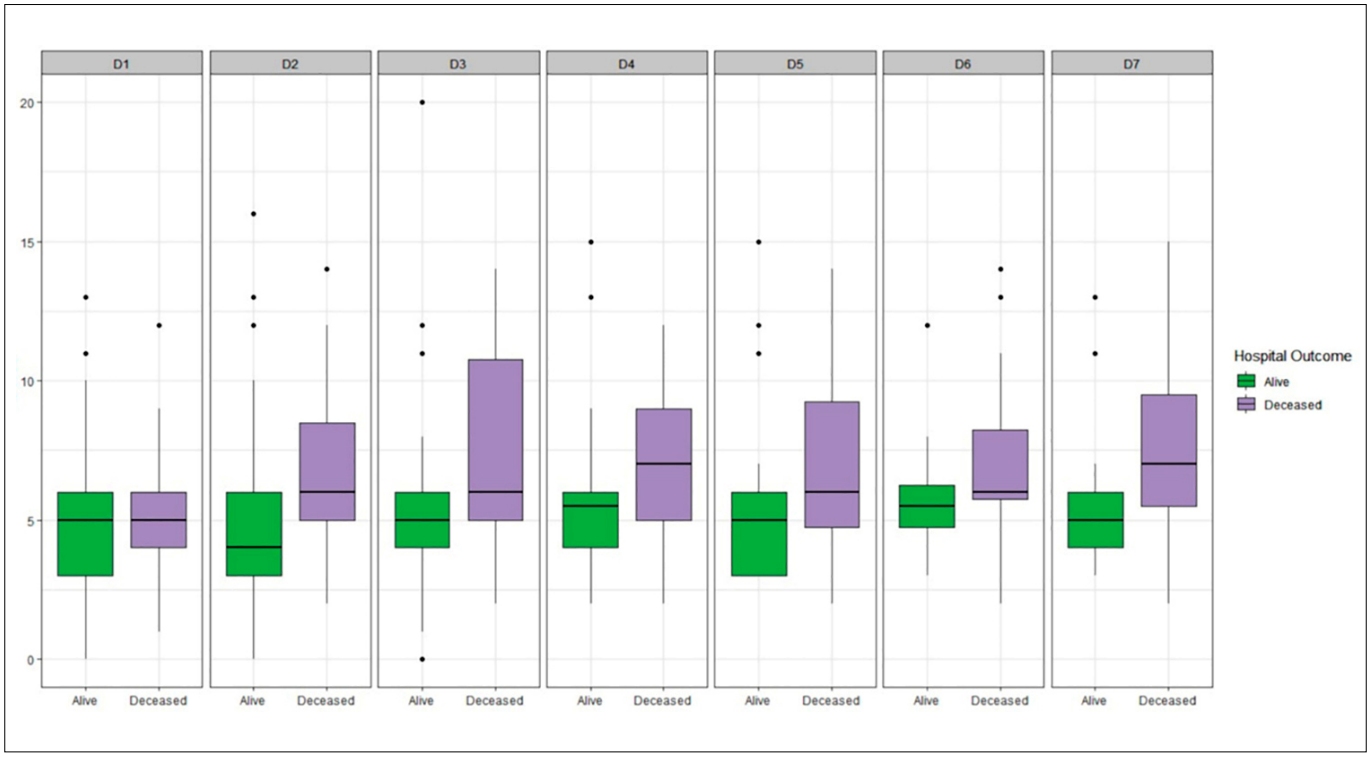


Figure 3. Sequential Organ Failure Assessment (SOFA) from days 1 to 7 in alive and deceased patients at hospital discharge.

ICU admission during a 20-year period found that 88% and 90% of the patients died at ICU discharge, respectively,.[21]

The severity of organ dysfunction has consistently been associated with worse outcomes in critically ill HSCT recipients.[20] Our data suggested that patients who did not survive to hospital discharge had worsening organ dysfunction during the first days after ICU admission. The requirement for mechanical ventilation is an important predictor of mortality in allogeneic HSCT recipients. Studies that included allogeneic and autologous HSCT recipients have also suggested high mortality rates for patients requiring mechanical ventilation.[18,22,23] In our study, although the initial severity measured by SAPS 3 and SOFA scores did not differ between autologous and allogeneic HSCT recipients, 50% of allogeneic HSCT recipients required invasive mechanical ventilation during their ICU stay. In comparison, it only occurred in 21% of autologous HSCT recipients. The severity of respiratory failure after ICU admission may be responsible for our study's higher ICU and hospital mortality rates found in allogeneic HSCT recipients.

Few studies have addressed the long-term outcomes of HSCT recipients admitted to the ICU. Approximately 70% to 80% of all allogeneic HSCT recipients admitted to the ICU shortly after the transplant die within 1 year.[5,12,19] The median overall survival may be as poor as 41 days.[24] Our findings of a 1-year mortality rate of 69% and median survival of 50 days are similar to those of previous studies. A French study of 27 autologous HSCT recipients admitted to the ICU showed a 6-month mortality rate of 27%.[8] On the other hand, a study with data from 1992 to 2002 in Ontario, Canada, showed a 1-year mortality rate of 70% for autologous HSCT recipients admitted to ICU.[18] Another Canadian study of 34 autologous HSCT recipients showed a mean survival of almost 29 months.[10] In our study, we found a mortality rate of 36.8% at 1 year and a median survival of more than 3 years.

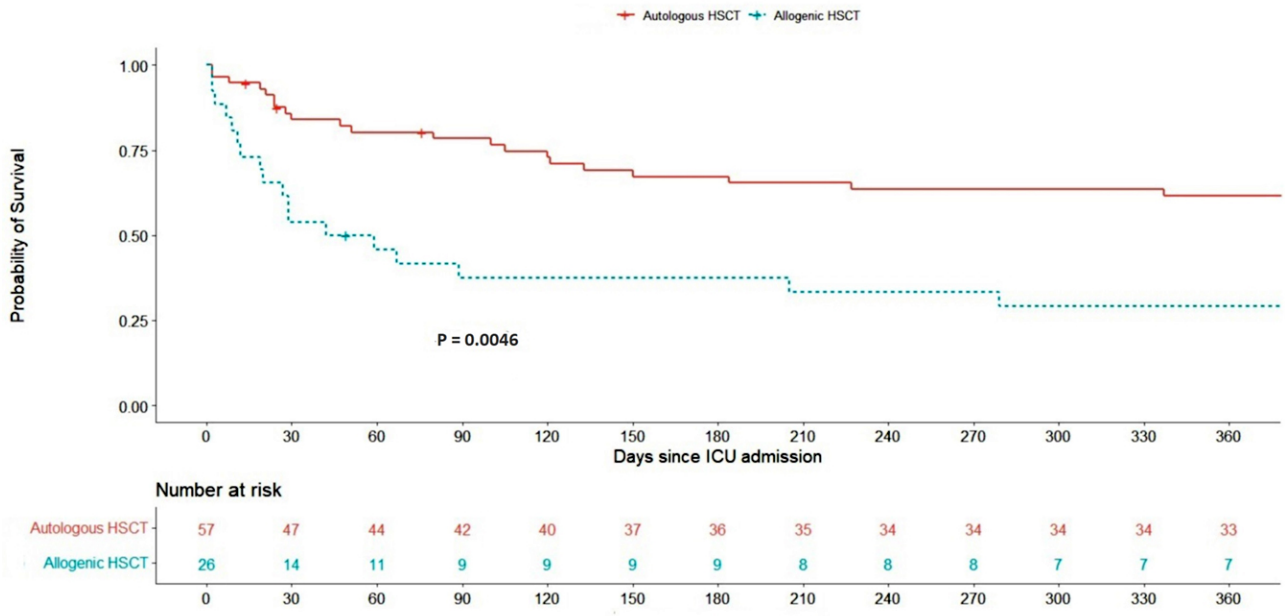
Allogeneic HSCT was associated with higher 1-year mortality, even when adjusted for age and severity of organ dysfunction at ICU admission. In addition, a previous study had shown that allogeneic HSCT was associated with an increased risk of mortality 6 months after ICU admission in an adjusted Cox proportional hazards model, which also included the requirement for mechanical ventilation and vasopressor during ICU stay.[22] Probably, the severity of the hematological baseline condition that led to the transplant and specific characteristics of the allogeneic HSCT, such as the requirement for immunosuppression and GVHD occurrence, may have a negative impact on the survival of allogeneic HSCT recipients admitted to the ICU.

Our study had some limitations. First, it was a single-center study. Therefore, our findings may not be generalizable to other settings. However, this has been a common limitation in most studies addressing critically ill HSCT recipients, as only a few were multicenter studies. Second, the small sample size precluded further

Table 1. Characteristics and outcomes of hematopoietic stem cell transplant (HSCT) recipients admitted to the intensive care unit

	Autologous HSCT (n = 57)	Allogeneic HSCT (n = 26)	P
Gender			0.47
Female	28 (49.1)	15 (57.7)	
Male	29 (50.9)	11 (42.3)	
Age	57.8 (45.6–62.4)	43.2 (24.7–58.2)	< 0.01
Comorbidities			
Arterial hypertension	36 (63.2)	7 (26.9)	0.38
Diabetes mellitus	8 (14.0)	4 (15.4)	0.87
Heart failure	7 (12.3)	1 (3.8)	0.31
Coronary artery disease	5 (8.8)	0	0.12
Peripheral vascular disease	4 (7.0)	0	0.17
Chronic obstructive pulmonary disease	6 (10.5)	1 (3.8)	0.31
Chronic kidney disease	5 (8.8)	2 (7.7)	0.87
CCI	2 (2–3)	2 (2–3)	0.38
Hematological malignancy			< 0.01
Multiple myeloma	27 (47.4)	1 (3.8)	
Non-Hodgkin Lymphoma	13 (22.8)	5 (19.2)	
Hodgkin Lymphoma	16 (28.1)	2 (7.7)	
Acute lymphocytic leukemia	0	7 (26.9)	
Acute myeloid leukemia	0	7 (26.9)	
Chronic myeloid leukemia	0	2 (7.7)	
Other hematological malignancies	1 (1.8)	2 (7.7)	
ECOG			0.44
0	19 (33.3)	4 (15.4)	
1	14 (24.6)	10 (38.5)	
2	12 (21.1)	5 (19.2)	
3	4 (7.0)	3 (11.5)	
4	8 (14.0)	4 (15.4)	
Source of admission			0.59
Wards	47 (82.5)	19 (73.1)	
Emergency room	9 (15.8)	6 (23.1)	
Surgical room	1 (1.8)	1 (3.8)	
Type of admission			0.67
Medical	55 (96.5)	25 (96.1)	
Surgical	2 (3.5)	1 (3.9)	
Reason for admission			< 0.01
Sepsis	27 (47.4)	7 (26.9)	
Acute respiratory failure	16 (28.1)	12 (46.2)	
Cardiovascular	12 (21.1)	1 (3.8)	
Neurological	5 (8.8)	5 (19.2)	
Acute kidney injury	3 (5.3)	1 (3.8)	
SAPS 3	82 (68–86)	75 (64.5–82.5)	0.16
SOFA	5 (3.5–6)	5 (3–6)	0.68
ICU Organ support			
Vasopressors	22 (38.6)	13 (50.0)	0.68
Non-invasive mechanical ventilation	16 (28.1)	11 (42.3)	0.32
Invasive mechanical ventilation	12 (21.1)	13 (50.0)	0.01
Renal replacement therapy	7 (12.3)	5 (19.2)	0.60
ICU mortality	7 (12.3)	10 (38.5)	< 0.01
ICU LOS	3 (2–7)	4.5 (1–11.25)	0.62
Hospital mortality	12 (21.1)	15 (57.7)	< 0.01
Hospital LOS	19 (13–26)	20.5 (11–42.5)	0.51

CCI = Charlson Comorbidity Index; ECOG = Eastern Cooperative Oncology Group; ICU = intensive care unit; LOS = length of stay; SAPS 3 = Simplified Acute Physiology Score 3.



HSCT = hematopoietic stem cell transplant; ICU = intensive care unit.

Figure 4. Survival of autologous and allogeneic hematopoietic stem cell recipients admitted to the intensive care unit.

analysis of the impact of other variables, such as GVHD or conditioning regimens, on long-term mortality. Therefore, our study should be considered descriptive. Third, retrospective studies are prone to information bias, and some useful information may have been inadequately described in medical charts.

CONCLUSION

In conclusion, almost 9% of all patients who underwent HSCT were admitted to the ICU within 1 year of the transplantation. Allogeneic HSCT recipients had higher short- and long-term mortality rates than autologous HSCT recipients, even after adjusting for age and severity at ICU admission. Worsening organ dysfunction in the first days after ICU admission in HSCT recipients should be considered to establish realistic goals of care for these patients.

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Validation of the Brazilian version of the Hip Sports Activity Scale (HSAS) for patients with femoroacetabular impingement: a cross-sectional study

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ABSTRACT

BACKGROUND: The Hip Sports Activity Scale (HSAS) is a hip-specific instrument for assessing the present levels of physical activity among patients with femoroacetabular impingement (FAI) syndrome. When evaluating treatment outcomes in patients with FAI syndrome, it is necessary to use joint-specific instruments and ones that can evaluate the levels of physical activity in these patients, such as the HSAS-Brazil.

OBJECTIVE: To validate the HSAS-Brazil among a group of physically active patients after arthroscopic treatment of FAI syndrome.

DESIGN AND SETTING: Cross-sectional research of quantitative and qualitative types using data obtained from July 2018 to October 2019.

METHODS: A total of 58 patients of both genders diagnosed with FAI syndrome and who had undergone hip arthroscopy participated in this research. To establish reliability and validity, patients first answered the Brazilian versions of the 12-Item Short-Form Health Survey (SF-12), Nonarthritic Hip Score (NAHS), and HSAS; after a 48-hour interval, they answered the HSAS-Brazil again.

RESULTS: For test-retest reliability, the interclass correlation was 0.908 ($P < 0.001$). The HSAS-Brazil correlated to the NAHS-Brazil ($r = 0.63$, $P < 0.001$), as well as the SF-12 (Physical Health) ($r = 0.42$, $P = 0.001$).

CONCLUSION: The HSAS-Brazil was validated and proved to be a reliable and valid scale to assess sports activity levels in physically active patients with FAI syndrome after arthroscopic treatment.

INTRODUCTION

Over the past decade, femoroacetabular impingement (FAI) syndrome has become a frequent source of hip pain in physically active patients with no radiological evidence of osteoarthritis. Initially reported by Ganz et al.,[1] this event may result from two main configurations of an anatomical abnormality. The cam type of impingement, usually detected in young men, is triggered by an aberrant femoral head-neck junction such that the peripheral radius of the head moving into the acetabulum increases along with the range of motion of the hip. The pincer type of impingement, often seen in aged women, results from contact of the femoral head-neck junction on the acetabular rim as a consequence of acetabular over coverage. Most patients present associated forms of these two arrangements, categorized as mixed impingement.[2-4]

Sports and physical exercises that demand energetic and repeated flexion and internal hip rotation are often associated with symptomatic FAI syndrome. Throughout internal rotation in flexion, the anterior portion of the head-neck juncture approaches the anterosuperior portion of the acetabular rim. These trigger recurrent tension of the labrum and contiguous cartilage. FAI syndrome may also injure the cartilage in the hip joint and can be a subjacent reason for osteoarthritis (OA).[5-7]

Hip arthroscopy is an increasingly performed surgical procedure for youth and mature adults with hip-related pain or dysfunction. Indications for hip arthroscopy mainly consist of frequent pain and abnormal bony morphology related to FAI syndrome, labral tears, chondral imperfections, and ligamentum teres injuries.[8,9]

Youth and mature adults undergoing hip arthroscopy greatly desire to return to sports and physical activities.[8] In 2013, Naal et al.[10] published a hip joint-specific sports activity scale, the Hip Sports Activity Scale (HSAS), to define the present physical activity levels among patients with FAI syndrome. Since then, this scale has been extensively adopted in English-speaking

countries. A translation and cultural adaptation of the HSAS into the Brazilian Portuguese language has already been produced.[11]

OBJECTIVE

This study aimed to validate the Brazilian version of the HSAS (HSAS-Brazil) among a group of physically active patients after arthroscopic treatment of FAI syndrome.

METHODS

Type of study

This was a cross-sectional study of quantitative and qualitative nature using data obtained from July 2018 to October 2019.

Ethical issues

The ethics committee of our institution approved the study (no. 998.832 – March 15, 2015), and all patients signed a free and informed consent statement. Dr. Florian D. Naal (first author of HSAS) was permitted to translate, cross-culturally adapt, and validate the HSAS for use in the Brazilian Portuguese language.

Participants

A total of 58 patients of both genders participated in the study. They had received a medical diagnosis of FAI syndrome and had undergone hip arthroscopy. These patients were selected consecutively at a private healthcare clinic in Rio de Janeiro. Patients with proficient literacy (complete high school education) were included, regardless of gender or ethnicity. They all complained of hip pain and had either received a medical diagnosis of FAI syndrome or undergone hip arthroscopy. Patients presenting with visual or cognitive disorders that hindered reading and interpretation of the questionnaires or those who did not completely answer the questionnaires, either at the time of the first application or at the time of the second application, were excluded.

Description of the Hip Sports Activity Scale (HSAS)

The HSAS determines the levels of physical activity among patients with FAI syndrome. The HSAS consists of nine distinct degrees of physical activity. It has nine topics graded from 0 to 8, with 0 for sedentary persons and 8 for high-performance athletes, without subscales.[10]

Study protocol

The study protocol consisted of the following steps: requiring participants to fill out an identification and clinical assessment file with each patient's demographic and clinical characteristics and application of three self-administered questionnaires: the validated Brazilian version of the 12-Item Short-Form Health Survey (SF-12);[12] validated Brazilian version of the Nonarthritic Hip Score (NAHS-Brazil);[13] and HSAS-Brazil.[11] The patients were asked to answer all three questionnaires (first application). Then, after a 48-hour interval, they were asked to answer only the HSAS-Brazil (second application). Finally, the second application of HSAS-Brazil was responded to using e-mail.

Reliability

The reliability of the HSAS-Brazil was evaluated through intra-evaluator test-retest reliability. For this, it was necessary to apply the questionnaires to the same patient at two different times. These two applications were evaluated using the intraclass correlation coefficient (ICC), ascertaining whether the same effects were reproduced. ICC values less than 0.5 suggest poor reliability; values between 0.5 and 0.75, moderate reliability; values between 0.75 and 0.9, good reliability; and values greater than 0.90, excellent reliability.[14,15] No inter-evaluator assessment was made due to the self-applicable scale characteristic, which does not demand any intermediation from the evaluator.

Validity

The validity of the Brazilian version of HSAS was investigated through construct and content validity.[14,15]

Construct and content validity

The validity of the HSAS-Brazil was evaluated by analyzing the strength of the correlation of its scores with those of the NAHS-Brazil and SF-12. The aim was to estimate whether the construct and content validity of the Brazilian version of HSAS was convergent with or divergent from those of the other two questionnaires. To assess construct convergence, correlations between scores were examined among the three questionnaires: the HSAS-Brazil, NAHS-Brazil (total score), and SF-12 (physical health subscale). To assess the divergence of construct, the correlation between the HSAS-Brazil score and SF-12 (mental health subscale) was examined. Spearman correlation coefficient was adopted to assess both the convergent and the divergent construct validity. This generates an indicator that can vary from –1 (perfect negative correlation) to +1 (perfect positive correlation), in which zero represents the lack of correlation between the studied variables.[14-16]

Statistical analysis

Descriptive statistical analysis was used to delineate the survey population. The psychometric properties of reliability and validity needed for validating the Brazilian version of the HSAS questionnaire were evaluated statistically using the statistical package for the social sciences, SPSS (version 26, 2019; SPSS Inc, Chicago, Illinois, United States).

RESULTS

Patient characteristics

The participants selected were literate, but their level of schooling was only up to high school. Thirteen patients (22.4%) were female. The mean age of the patients was 39.4 years (range, 13 to 61 years) (**Table 1**).

Questionnaire results

Score values of each outcome measurement of the HSAS-Brazil, NAHS, and SF-12 questionnaires in the final testing are presented in **Table 1**.

Intra-evaluator test-retest reliability

The ICC was 0.908 ($P < 0.001$), and the confidence interval (95% CI) ranged from 0.849 to 0.944.

Construct and content validity

The HSAS-Brazil was moderately correlated with the NAHS-Brazil and weakly correlated with SF-12 physical and mental health subscales (**Table 2**). The HSAS-Brazil presented good content validity in patients with FAI syndrome.

DISCUSSION

The HSAS was initially created and validated for German-speaking patients with FAI syndrome and then cross-culturally adapted and validated for a North American English-speaking population.[10] The HSAS was also translated and cross-culturally adapted into Swedish and Brazilian Portuguese languages.[11,17] The Swedish version has already been validated. The current study showed that the Brazilian version of the HSAS is a reliable and valid scale to estimate sports activity levels in patients with FAI syndrome, comprising characteristics equivalent to those in the original version.[10,17]

For the validation of the HSAS-Brazil, a total of 58 patients (average age of 39.4 years) with FAI syndrome who had undergone hip arthroscopy were evaluated. In the English and the Swedish version, the numbers of patients studied were 29 and 30 (average age of 32.5 and 30.6 years, respectively). The mean age of the patients in the original study was similar to that of the patients in the present study.[10]

Intra-evaluator reliability is assessed when an evaluator applies the same assessment instrument on two different occasions to the same patient or when a patient responds to the same questionnaire alone at two different times. Intra-evaluator test-retest reliability estimates the fraction of the total variability of measurements. For example, the selected patients initially answered the Brazilian versions of three questionnaires: the SF-12,[12] NAHS, and HSAS;[11,13] after a 48-hour interval, they answered the HSAS-Brazil again. During this time, no new medication, therapy, or procedures that might have rapidly changed the patient's clinical state were introduced. The ICC in this study was 0.91, indicating excellent test-retest reliability, similar to the original research (0.94) and the Swedish version (0.93).[10,17] The higher the test-retest reliability, the higher the instrument's internal reliability. Thus, the HSAS-Brazil has strong reliability for the complete questionnaire.

Construct validity represents the degree to which an instrument's scores are consistent with the hypothesis about expected internal relationships. Content validity represents the degree to which a measuring instrument can be considered a reasonable reflection of the construct to be measured. In this study, the convergent and divergent construct validities were assessed under the hypothesis that the physical health subscale score of the SF-12 and the total score of the NAHS-Brazil should show a moderate to high correlation between the instruments since the NAHS-Brazil has a domain on activity levels. A greater correlation between HSAS-Brazil and NAHS-Brazil would be expected because both are specific for hip evaluation. A low correlation would be expected between the HSAS-Brazil and SF-12 mental health subscale scores.[14,16]

For content validity (hip specificity), we analyzed the strength of the correlation between HSAS-Brazil and SF-12. We presumed moderate correlations ($r = 0.50$) with SF-12 (physical health subscale) (convergent validity). To support divergent validity, we presumed low or no correlations ($r > 0.30$) between the HSAS-Brazil and SF-12 (mental health subscale).[14,16] Our results showed that

Table 1. Patients' characteristics and score values of the instruments used in this study

Parameter/Score	Patients sample
Age (years)	39.4 ± 12.3
Female	22.4%
HSAS-Brazil	2.4 ± 1.8
NAHS-Brazil	80.9 ± 21.4
SF-12 (physical health subscale)	46.2 ± 10.3
SF-12 (mental health subscale)	52.4 ± 9.3

HSAS-Brazil = Brazilian version of the Hip Sports Activity Scale; NAHS-Brazil = Brazilian version of the Nonarthritic Hip Score; SF-12 (physical health subscale) = Short-Form Physical Component Scale; SF-12 (mental health subscale) = Short-Form Mental Component Scale.

Table 2. Correlations between the HSAS-Brazil and other instruments used in this study

Instruments	HSAS-Brazil	P value
NAHS-Brazil	0.63	< 0.001
SF-12 (physical health subscale)	0.42	0.001
SF-12 (mental health subscale)	0.30	0.021

HSAS-Brazil = Brazilian version of the Hip Sports Activity Scale; NAHS-Brazil = Brazilian version of the Nonarthritic Hip Score; SF-12 (physical health subscale) = Short-Form Physical Component Scale; SF-12 (mental health subscale) = Short-Form Mental Component Scale.

there was no significant correlation between the HSAS-Brazil and SF-12 (mental health subscale) (r = 0.30), a low and statistically significant correlation between the HSAS-Brazil and SF-12 (physical health subscale) (r = 0.42), and a moderate and statistically significant correlation between the HSAS-Brazil and NAHS-Brazil (r = 0.63). Thus, HSAS-Brazil has good construct and content validity.

For the HSAS Swedish version, there was a high and statistically significant correlation between the HSAS and Tegner scores (r = 0.794), revealing good construct validity. No significant correlation was found between the HSAS and iHOT-12 or any of the Hip and Inguinal Outcome Score (HAGOS) subscales, unsurprisingly, aside from HAGOS "physical activity", suggesting low content validity. The original study found a moderate to high and statistically significant correlation between HSAS and HOS.[10,17]

Patient-reported outcomes are appraised in epidemiological and clinical surveys using data reported by survey participants.[10,13,17,18] There are two ways to obtain these patient-reported outcomes: the instruments can be completed by the survey participants (self-administered) or applied by an interviewer. Self-administered questionnaires benefit from not demanding a research team, as participants can complete the questionnaires in their own time at the survey site or at home by mail or web-based applications. Interviewer-administered questionnaires consume additional resources but provide extra control over measurement quality. Interviewers can apply the questionnaires in person or via telephone.[19,20]

Some recent studies investigated whether self-administered and interview-based questionnaires provided different results.[19,20] Lozano et al.[19] demonstrated that the format of administration has no significant repercussion on the measurements for assessing patients with intermittent claudication using the WIQ and EQ-5D instruments, provided that the patient can complete a self-applicable questionnaire. Puhan et al.[20] administered the Medical Outcome Study – human immunodeficiency virus (HIV) questionnaire, European Quality of Life Scale (EuroQol), Feeling Thermometer, and Visual Function Questionnaire 25 every 6 months to volunteers engaged in the Longitudinal Study of Ocular Complications in acquired immunodeficiency syndrome (AIDS) using self- or interviewer-administration. A large print questionnaire was accessible for volunteers with visual deficiency. They concluded that administration templates did not significantly impact repeated measurements of patient-reported outcomes. For this reason, the present study used the self-administered format for the application of the SF-12,[12] NAHS-Brazil,[13] and HSAS-Brazil questionnaires.[11]

This study also has some limitations. First, the NAHS we used as a reference measure has been construct validated. Hence, the association between the HSAS and NAHS has to be considered supporting content validity (measuring the same content, i.e., hip) but not real construct validity. Another limitation is the absence of responsiveness data for the NAHS-Brazil, which was not evaluated.

When assessing treatment outcomes in patients with FAI syndrome, it is necessary to use not only joint-specific instruments, including the NAHS-Brazil or HOS-Brazil,[13,18] but also instruments that can evaluate the levels of physical activity in these patients, especially the HSAS-Brazil.

The HSAS-Brazil scale is available in **Annex 1**.

CONCLUSION

The Brazilian version of the HSAS was validated and proved reliable for assessing sports activity levels in physically active patients after arthroscopic treatment of FAI syndrome. Therefore, the HSAS-Brazil can be a beneficial instrument for clinicians and researchers for detailed assessment of patients with FAI syndrome who practice sports and better compare distinct therapies or patient cohorts in terms of sports levels as a prognostic factor.

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Annex 1. The Brazilian version of the Hip Sports Activity Scale, HSAS-Brazil (Escala de Atividade Esportiva do Quadril, HSAS-Brasil).

Escala de Atividade Esportiva do Quadril (HSAS-Brasil)
Por favor, marque na lista a seguir o mais alto nível de atividade esportiva ou recreacional atual que você consegue realizar.
8. Esportes de Competição *(nível elite)* Futebol, Hóquei, Futebol americano/Rugby, Artes marciais, Tênis, Atletismo, Esportes de quadra*, Vôlei de praia, Beisebol/Softbol.
7. Esportes de Competição *(nível elite)* Surfe, Wakeboard. **Esportes de Competição** *(ligas menores/estudantil)* Futebol, Hóquei, Futebol americano/Rugby, Artes marciais, Tênis, Atletismo, Esportes de quadra*, Vôlei de praia, Beisebol/Softbol.
6. Esportes de Competição *(nível elite)* Golfe, Ciclismo, Mountain bike, Natação, Remo, Hipismo. **Esportes de Competição** *(ligas menores/estudantil)* Surfe, Wakeboard.
5. Esportes de Competição *(ligas menores/estudantil)* Golfe, Ciclismo, Mountain bike, Natação, Remo, Hipismo. **Esportes Recreativos** Futebol, Hóquei, Futebol americano/Rugby, Artes marciais, Tênis, Atletismo, Vôlei de praia.
4. Esportes Recreativos Tênis, Surfe, Wakeboard, Esportes de quadra*, Beisebol/Softbol.
3. Esportes Recreativos Ginástica aeróbica, Corrida, Musculação para membros inferiores, Hipismo.
2. Esportes Recreativos Golfe, Ciclismo, Mountain bike, Natação, Remo, Dança, Patinação.
1. Esportes Recreativos Natação, Andar de bicicleta, Caminhada em trilhas, Caminhada em alta velocidade.
0. Nenhum Esporte Recreativo ou de Competição
***Esportes de Quadra:** Basquete, Squash, Handebol, Vôlei.
Por favor, indique seu esporte preferido: _____.

https://doi.org/10.1590/1516-3180.2021.0952.R2.11052022

The impact of bariatric and metabolic surgery on the morbidity and mortality of patients infected during the COVID-19 pandemic: a retrospective cohort study

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Obesity.
COVID-19.
Body mass index.

AUTHOR'S KEYWORDS:
Comorbidities.
Protective factor.
Hospitalization rate.
Infection rate.

ABSTRACT

BACKGROUND: Since the impact of the coronavirus disease 2019 (COVID-19) pandemic in March 2020, several studies have shown a strong relationship between obesity and severe cases of COVID-19. It is imperative to assess whether bariatric surgery exerts a protective effect in such cases.

OBJECTIVE: This study aimed to assess the impact of bariatric surgery on the morbidity and mortality in obese patients during the COVID-19 pandemic. A comprehensive search was performed using the PubMed and Cochrane Library databases.

DESIGN AND SETTING: Retrospective cohort studies conducted in the Faculdade de Medicina da Universidade Cidade de São Paulo, São Paulo (SP), Brazil.

METHODS: The search comprised the following descriptors: "bariatric, surgery, COVID-19". Current retrospective cohort studies that examined the influence of bariatric surgery on the morbidity and mortality of obese patients during the COVID-19 pandemic were considered eligible.

RESULTS: After removing duplicates, 184 studies were obtained from the databases. Of these, 181 were excluded from the analysis as they did not meet the eligibility criteria. Patients undergoing postoperative follow-up of bariatric surgery had a similar probability of SARS-CoV-2 infection compared to the general population, and persistent comorbidities were associated with an increased risk and severity of infection.

CONCLUSION: Bariatric surgery has a protective effect against severe COVID-19 in the obese population, bringing the prevalence of severe disease cases to levels equivalent to those of the nonobese general population, with a positive impact on morbidity and mortality.

INTRODUCTION

In March 2020, the World Health Organization (WHO) declared the coronavirus disease 2019 (COVID-19) a pandemic. Since then, the impact of this infection on the public and private health systems of many countries has become evident.[1] The overcrowding of intensive care beds has led to the cancellation of elective surgeries, as there has been an increasing demand for professionals and and resources to treat infected patients.[2,3] In this context, Hussain et al.[4] presented a flowchart scaling priority among candidates for elective and revision procedures during the pandemic. Patients with severe obesity, comorbidities, or surgical complications should be prioritized when performing procedures. Outpatient activities began to be performed through telemedicine, and only urgent procedures such as early and late surgical complications remained in the usual routine.

Studies indicate obesity as an isolated risk factor for severe cases of COVID-19.[4-6] In addition, biochemical and endocrine factors related to obesity, such as type 2 diabetes and insulin resistance, are worse prognostic factors in infected patients.[7,8] Therefore, it has become imperative to evaluate whether bariatric surgery exerts a protective effect against severe covid-19 conditions. Retrospective studies have evaluated outcomes in patients with previous bariatric surgery infected with severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) regarding the severity of the disease, need for intensive care and impact on mortality.[6,9,10] However, there remains a lack of controlled clinical trials or other prospective studies evaluating such parameters.

OBJECTIVE

The present study aimed to evaluate, through a literature review, the impact of bariatric surgery on the morbidity and mortality of obese patients during the COVID-19 pandemic in reference centers inside and outside Brazil.

METHODS

Data sources and surveys

A comprehensive search was conducted using the PubMed and Cochrane Library databases. The search strategies comprised the following descriptors: "bariatric, surgery, COVID-19". These have been adapted for use in various databases. The access routes to the descriptions of the studies used in this article are presented in **Table 1**.

Current retrospective cohort studies that examined the influence of bariatric surgery on the morbidity and mortality of obese patients during the COVID-19 pandemic were eligible for this review without restrictions on dates and languages.

Further inclusion criteria included studies that evaluated adult patients over 18 and under 65 years of age, obese patients who underwent bariatric surgery, and those infected by SARS-CoV-2, in reference centers inside and outside Brazil.

Studies with patients outside the age group of 18 to 65 years, those that did not deal with bariatric surgery, and those performed outside the pandemic period were excluded.

Data extraction

Data extraction was performed using a standardized data extraction form. The data extracted from all studies included study details, demographic data of participants, and available information on the interventions used.

RESULTS

Search results

A total of 186 studies were obtained from the surveyed databases. After removing duplicates, 184 studies were retained for the analysis. Of these, 181 were excluded after analyzing titles, abstracts, and full texts because they did not meet the eligibility criteria. Only three studies were included in this review (**Figure 1**).

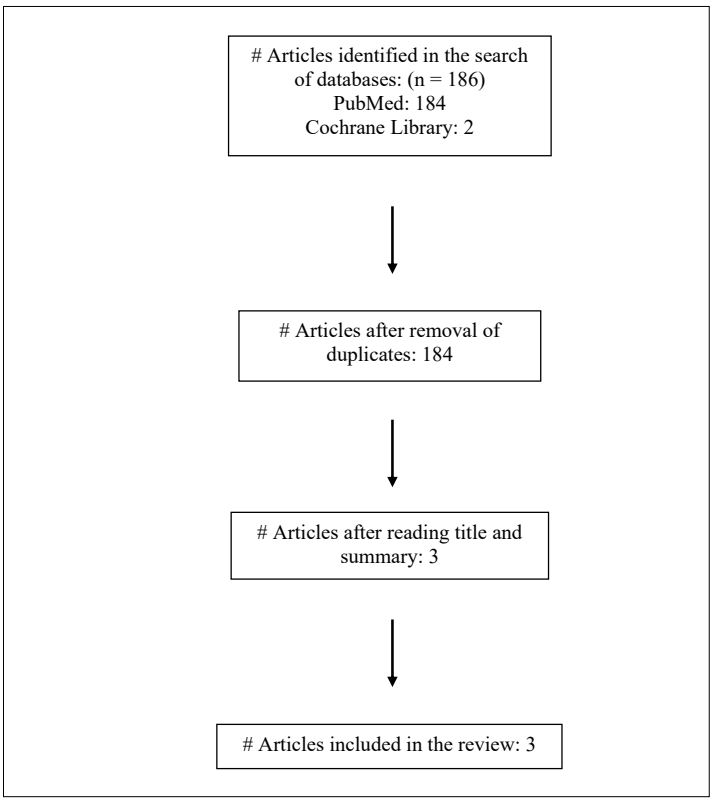

Figure 1. Flow diagram of the results.

Table 1. Comprehensive search strategy for research on bariatric and metabolic surgery during the coronavirus-2019 pandemic using harvesting information retrieval framework

Author (year)	Date searched	Article title	Journal	Search terms	Databases
Aminian et al.[9] (2020)	September 15, 2021	Association of prior metabolic and bariatric surgery with severity of coronavirus disease 2019 (COVID-19) in patients with obesity	Official Journal of the American Society for Bariatric Surgery	Bariatric surgery; Obesity; COVID-19; Body mass index	PubMed
Bel Lassen et al.[10] (2021)	September 15, 2021	COVID-19 and its Severity in Bariatric Surgery-Operated Patients	Obesity (Silver Spring)	Bariatric surgery; Obesity; COVID-19; Body mass index	PubMed
Uccelli et al.[6] (2020)	September 15, 2021	COVID-19 and Obesity: Is Bariatric Surgery Protective? Retrospective Analysis on 2,145 Patients Undergone Bariatric-Metabolic Surgery from High Volume Center in Italy (Lombardy)	Obesity Surgery	Bariatric surgery; Obesity; COVID-19; Body mass index;	PubMed

The characterization of the participants included in the studies is shown in **Table 2**.

A description of studies evaluating the impact of bariatric surgery on the morbidity and mortality of obese patients during the COVID-19 pandemic is shown in **Table 3**.

Table 2. Characterization of the participants included in the study

Study	n	Average age (years)	Sex	Diagnosis
Aminian et al.[9]	4,365	46	Male and female	Obesity
Bel Lassen et al.[10]	738	50	Male and female	Obesity
Uccelli et al.[6]	2,145	44	Male and female	Obesity

DISCUSSION

Studies indicate obesity as an isolated risk factor for severe cases of COVID-19.[4-6] In addition, biochemical and endocrine factors related to obesity, such as type 2 diabetes and insulin resistance, are associated with a worse prognosis in infected patients.[7,8,11] In this context, the publications evaluated in this study explore bariatric surgery as an intervention capable of serving as a protective factor against severe cases of COVID-19.[6,9,10] There is great heterogeneity between the methodology of the studies since the situation of social isolation itself made it impossible to conduct controlled clinical trials.

The publication by Uccelli et al.,[6] whose data collection was carried out from March to May 2020, presented many participants

Table 3. Description of studies evaluating the impact of bariatric surgery on morbidity and mortality of obese patients during the coronavirus disease 2019 (COVID-19) pandemic

Study	Aminian et al.[9]	Bel Lassen et al.[10]	Uccelli et al.[6]
Participants	n = 363 tested positive for COVID-19 Group with previous surgery: 33; Group of non-operated: 330	n = 738; All underwent bariatric surgery Group "probably infected": 62; Group "probably not infected": 676	n = 2,145; All underwent bariatric surgery
Goals	Investigate the relationship between previous metabolic surgery and the severity of COVID-19 in patients with severe obesity.	Estimate the prevalence of COVID-19 and evaluate factors associated with the incidence and severity of the disease in patients who underwent bariatric surgery.	Investigate the incidence of SARS-CoV-2 infection and its severity in patients who underwent bariatric surgery.
Collection procedures	A search was performed in medical records of the institution that conducted the study for patients who tested positive in RT-PCR for COVID-19, evaluating the rate and time of hospitalization, need for ICU, mechanical ventilation, dialysis, and mortality in patients who tested positive in RT-PCR for COVID-19, evaluating the rate and time of hospitalization, need for ICU, mechanical ventilation, dialysis and mortality.	A standardized questionnaire was conducted through telephone calls in which probable symptoms of COVID-19 were questioned, such as anosmia, fever, rhinorrhea, odynophagia, or patients who tested positive for the disease. In addition, a medical record search was performed for anthropometric and laboratory data before and after the patients.	A questionnaire was sent to patients previously submitted to bariatric surgery in which age, gender, BMI, origin, comorbidities, and type of surgery were questioned, and they were asked about the main symptoms of COVID-19, and occurrence of hospitalization and ICU admission.
Main findings	The mean preoperative BMI in the group with previous surgery was 49.1 ± 8.8kg/m^2, decreasing to 37.2 ± 7.1 kg/m^2 at the time of testing for COVID-19. The mean BMI of the non-operated group was 46.7 ± 6.4 kg/m^2. Six patients (18.2%) from the group submitted to surgery, and 139 patients (42.1%) from the non-operated group were admitted to the hospital (P = 0.013). 43 patients (13%) from the non-operated group required ICU admission (P = 0.021). 22 patients (6.7%) required mechanical ventilation. Five patients (1.5%) underwent dialysis. Eight patients (2.4%) died. In the group with previous surgery, none of these four outcomes were identified.	Patients had a mean age of 50 ± 12.3 years, with most being female (78.3%) and 44% having type 2 diabetes before surgery. The most used surgical technique was gastric bypass (54.4%), followed by sleeve gastrectomy (45.0%). The mean postoperative time at collection was 3.7 ± 2.7 years. There was no difference in the surgical technique outcomes between the groups. The mean postoperative time was significantly longer in the "probably infected" group, with a considerably higher proportion of persistently diabetic patients than in the "probably not infected" group.	All patients underwent elective bariatric surgery. The mean preoperative BMI was 44 ± 6.8 kg/m^2 with a reduction to 29.3 ± 5.5 kg/m^2 in the postoperative period. The main technique used was laparoscopic sleeve gastrectomy (82.4%). The reduction in the number of comorbidities was almost entirely statistically significant. A total of 181 patients (8.4%) reported at least one symptom related to COVID-19. Nevertheless, only 26 cases (1.2%) were tested, and only 13 individuals (0.6%) tested positive. Six patients (0.3%) were admitted to hospital units; two patients (0.1%) required ICU with mechanical ventilation. The mean length of hospital stay was 23 ± 13 days.
Conclusions	The study identified that previous bariatric surgery is associated with lower hospitalization rates and the need for ICU for patients infected with SARS-CoV-2.	Patients under postoperative follow-up of bariatric surgery presented a probability of SARS-CoV-2infection similar to that of the general population. The persistence of type 2 diabetes and the presence of lower BMI are associated with increased risk and severity of SARS-CoV-2 infection.	Because the rate of hospitalization and need for ICU of the patients evaluated was equivalent to those of the general nonobese population, the study concludes that bariatric surgery can be considered a protective factor for severe acute respiratory syndrome caused by SARS-CoV-2 infection

RT-PCR = reverse transcription polymerase chain reaction; ICU = intensive care unit; BMI = body mass index; SARS-CoV-2 = severe acute respiratory syndrome-coronavirus 2.

from several different areas of Italy, which allowed a global analysis of the involved population. However, there was a population bias as only patients who had already undergone surgery answered the questionnaire, and there was no control group of non-surgical patients. There was also a low testing rate with reverse transcription polymerase chain reaction (RT-PCR) (1.2%), which may have underestimated the number of infected patients. Moreover, as the questionnaire was self-applicable online, seeking the most common symptoms of COVID-19, there was bias in the collection not being performed by an examiner trained to perform the necessary anamnesis.

The study conducted by Aminian et al.,[9] whose data collection was carried out between March and July 2020, analyzed patients who tested positive for COVID-19 through RT-PCR and anthropometric data extracted from the institution's medical records confirmed the reliability of the research. However, the major limitation of this study was the small number of patients with a history of previous bariatric surgery, which resulted in a longer confidence interval and may have influenced the statistical analysis of the results. Moreover, as only six operated patients were hospitalized for COVID-19, laboratory, radiological, and oxygenation data were unavailable for most patients in this group; therefore, they were not included in the statistical analysis.

Bel Lassen et al.[10] performed data collection between March and May 2020. Similar to the study by Aminian et al.,[9] this study used anthropometric data collected from medical records with good reliability. Additionally, a large number of participants were included in the study. However, the postoperative time among the patients was extremely heterogeneous, with an interval of up to 16 years. This introduced a population bias that may have interfered with the results. Similar to the study by Uccelli et al.,[6] a self-administered questionnaire was made available, which may have been subject to different interpretations by individuals regarding the symptoms of COVID-19.

Despite the heterogeneity in the methodology employed by the different authors and the complicating factors between data collection and statistical analysis of results, the three publications concluded that the prevalence of severe COVID-19 conditions in patients in the postoperative period of bariatric and metabolic surgery does not differ from the prevalence in the general nonobese population. From the perspective of countries' health systems that have managed COVID-19 in the long term, it is necessary to develop controlled clinical trials with a good methodology to assess whether such results are reproducible and whether there are other clinical implications in carrying out such procedures.

CONCLUSION

Based on the results of the analyzed studies, even with the reservations described regarding the methodological limitations employed, it can be concluded that bariatric surgery exerts a protective effect against severe cases of COVID-19 in the obese population, with a positive impact on morbidity and mortality.

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Spiritual needs among hospitalized patients at a public hospital in Brazil: a cross-sectional study

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Religion.
Brazil.

AUTHORS' KEY WORDS:
SNAP.
Sao Paulo.
Spiritual distress.
Observational study.
Spiritual needs.

ABSTRACT

BACKGROUND: The relationship between spirituality and health has been the object of growing discussion. There is a lack of data on spiritual needs assessments in Brazil.

OBJECTIVE: This study aimed to assess the spiritual needs of patients admitted to a public tertiary hospital and perform a comparative analysis between patients with and without indications for palliative care.

DESIGN AND SETTING: A cross-sectional observational study included patients hospitalized between August and December 2020 in Hospital do Servidor Publico Municipal, Sao Paulo, Brazil.

METHODS: The included patients answered a questionnaire consisting of sociodemographic data, the Duke religiosity scale, and the Spiritual Needs Assessment for Patients (SNAP) tool for a spiritual needs assessment. The World Health Organization Palliative Needs tool (NECPAL) was used to evaluate the indications for palliative care. The level of significance adopted was 5%.

RESULTS: A total of 66 patients were included in this study. Most participants (97%) declared themselves as belonging to a religion. The group without indication for palliative care by the NECPAL showed greater spiritual (P = 0.043) and psychosocial needs (P = 0.004). No statistically significant difference was observed in the religious needs domain (P = 0.176). There were no statistically significant differences in the Duke scale scores between the two groups.

CONCLUSION: Spiritual, psychosocial, and religious needs are prevalent among hospitalized patients, and multidisciplinary teams must consider these needs in their management approach. In addition, this study suggests that psychosocial and spiritual needs can be even higher in patients who do not receive palliative care.

INTRODUCTION

The relationship between spirituality and health has been the subject of growing discussion and study. Spirituality has long been related only to religion; however, its definition has expanded to include what is sacred and gives the final purpose to life.[1,2]

Spirituality can also be understood as a human propensity to seek meaning in life through concepts that transcend the tangible. Its association with health has become a paradigm to be established in daily medical practice since disease remains an entity with a broad impact on clinical approaches.[3]

Religious and spiritual beliefs have proven to aid in coping with the most diverse situations of imbalance and the health of individuals as a preparation for death.[4]

Diagnosis of life-threatening conditions can lead to spiritual suffering. Most patients with life-threatening health conditions have reported the importance of spirituality.[5] This demonstrates that patients' beliefs are increasingly related as a protective factor against the development of high emotional stress throughout the diagnosis.[6] The benefits of spirituality, including treatment adherence and resilience of patients living with HIV,[7] chronic kidney disease,[8] heart failure,[9] and cancer, have been studied in several populations.[10]

Conversely, patients with unmet spiritual demands may experience compromised care.[11] This condition is also a predictive factor for worse quality of life in patients with advanced chronic diseases.[12] Despite the evidence regarding the influence of spiritual well-being in the disease process, published data on this subject remain scarce.

Several tools have been developed to identify patients experiencing spiritual distress. A review showed at least eight validated questionnaires assessing spiritual needs.[13] Cultural diversity

may influence the results obtained from different populations. Therefore, the Spiritual Needs Assessment for Patients (SNAP) scale, culturally adjusted and translated into Portuguese, is the primary tool validated for assessing spiritual needs in Brazil.[14,15]

Interest in spiritual care is growing worldwide, including in Brazil. However, there is a lack of data on spiritual needs in hospitalized patients.[16] In this context, this study proposes identifying spiritual needs in different domains using the adapted SNAP scale.

OBJECTIVE

This study aimed to assess the spiritual needs of patients admitted to a public tertiary hospital and to conduct a comparative analysis between patients with and without indications for palliative care.

METHODS

Study design

This observational cross-sectional study aimed to assess the spiritual needs of hospitalized patients at the Hospital do Servidor Publico Municipal (HSPM) in Sao Paulo, Brazil.

The patients hospitalized between August and December 2020 were included. The inclusion criteria consisted of patients who were at least 18 years old, voluntarily provided written informed consent, and were capable of understanding, interpreting, and answering the questionnaires. Patients who could not complete the questionnaires or had impaired consciousness were excluded.

Data collection

The data were obtained through questionnaires administered during face-to-face interviews conducted by the author, co-authors, and the research volunteers. Patients were randomly selected through a draw, and questionnaires were administered from August to December 2020. The questionnaire consisted of three main parts. The first part included clinical and sociodemographic data evaluating variables such as age, sex, marital status, and aspects of the patient's primary diagnosis. Next, patients were assessed for religiosity using a version of the Duke religiosity scale (DUREL) validated in Brazil, consisting of organizational, non-organizational, and intrinsic religiosity domains.[17] The third part was the assessment of spiritual needs using the SNAP scale, using a version adapted for a Brazilian population.[15] This questionnaire evaluates the patient through three subscales: psychosocial (5 items), spiritual (13 items), and religious (5 items), with objective questions to quantify the patient's needs in each respective domain. Patients were divided into two groups according to whether palliative care was indicated by the World Health Organization Palliative Needs tools (NECPAL) in its adapted form for Brazilian culture.[18,19] The palliative performance score (PPS) was evaluated for every patient in this study.

Statistical analysis

For sample size calculation, an effect size of 0.66 was considered. In addition, the probabilities of type I and type II errors were set to 0.05 and 0.20, respectively. Thus, a sample of 31 cases per group was calculated, with a total of 62 cases. The Wilcoxon–Mann–Whitney test was used to compare means.

Descriptive analyses of the data were carried out using tables containing absolute values and proportions (in the case of qualitative variables), mean, median, standard deviation (SD), and quartiles (in the case of quantitative variables). The Chi-square and Fisher's exact tests were used for categorical variables comparisons. For comparisons between categorical and numerical variables, the T-test and analysis of variance (ANOVA) (in the case of data showing normality) or Mann–Whitney and Kruskal–Wallis tests (in the non-parametric context) were used. The level of significance adopted was 5%. Statistical analyses were performed using the IBM SPSS Inc. (version 18.0) package for Windows (IBM, Chicago, United States, 2009).

Ethical considerations

This study was approved by the Research Ethics Committee of HSPM (protocol number 29728920.0.0000.5442) on August 13, 2020. This project complies with the Declaration of Helsinki (1964 and later versions of 1975, 1983, 1989, 1996, 2000, and 2008) and Resolution No. 466 of 2012 of the National Health Council. The study details were adequately explained, and informed consent was obtained from each participant.

RESULTS

A total of 66 patients were included in the study, with a mean hospital stay of 11.3 days (standard deviation [SD] = 15.5). Among the participants, 65.2% were female, and 34.8% were male. The mean age was 60.1 years, ranging from 21 to 84 years (SD = 15.3). The predominant marital status in the study population was married (39.4%), while 28.8% of the participants were widowed, 16.7% single, and 10.6% divorced. The majority (97%) declared themselves as belonging to one or more religions, the most prevalent being Catholic and Evangelical (33.3%), and spiritism was also prevalent (13.6%). Most patients were hospitalized for clinical conditions (81.8%), surgical causes accounted for 18.2% of the sample, and the mean length of stay was 11.3 days (SD = 15.1). The most frequent diagnoses of the studied population were neoplasms (37.9%), cardiovascular and cerebrovascular diseases (25.8%), and gastrointestinal and liver disorders (13.7%). Participants were classified as with or without an indication for palliative care according to the NECPAL tool. There were 33 (50%) participants in each group. The mean PPS was 69.8 (SD = 25). The demographic data are detailed in **Table 1**.

Table 1. Clinical and demographic data of patients included in the study's analysis. Sao Paulo, Brazil, 2020

		n	%
Sex	Female	43	65.2%
	Male	23	34.8%
Marital status	Married	26	39.4%
	Widowed	19	28.8%
	Single	11	16.7%
	Divorced	7	10.6%
	Stable union	3	4.5%
Work	Yes	27	40.9%
	No	39	59.1%
Retired	Yes	39	59.1%
	No	27	40.9%
Public Server	Yes	48	72.7%
	No	18	27.3%
Type of hospitalization	Clinical	54	81.8%
	Surgical	12	18.2%
Main diagnosis	Neoplasm	25	37.9%
	Cardiovascular and cerebrovascular diseases	17	25.8%
	Gastrointestinal tract diseases	9	13.7%
	Pulmonary diseases	4	6.0%
	Infectious conditions	4	6.0%
	Other	4	6.0%
	Kidney diseases	3	4.6%
PC indication	Yes	33	50.0%
	No	33	50.0%
Religion	Yes	64	97.0%
	No	2	3.0%
Religious practice	Catholic	22	33.3%
	Evangelical	22	33.3%
	Spiritist	9	13.6%
	Believes in God without a religion	6	9.2%
	Buddhist	3	4.6%
	Umbanda	2	3.0%
	Catholic and Spiritist	2	3.0%

PC = palliative care.

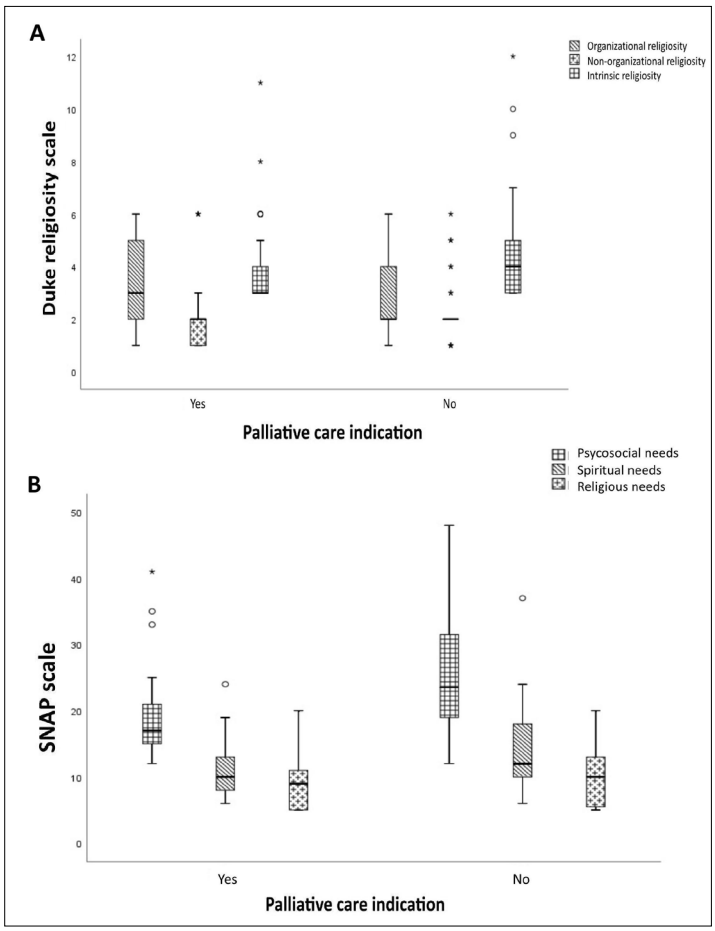

Figure 1. Domain scores from the Duke scale (**A**) and Spiritual Needs Assessment for Patients (SNAP) questionnaire (**B**), according to the indication of palliative care follow-up. Sao Paulo, Brazil, 2020.

The Duke and SNAP scores for each group are represented graphically in **Figures 1A** and **1B**, respectively. When comparing patients between groups with and without indications for palliative care, a statistically significant difference was observed, indicating greater spiritual (P = 0.043) and psychosocial (P = 0.004) needs in the groups that had no indication for follow-up palliative care. The religious need variable was not statistically significant between the groups (P = 0.176). We did not observe any statistical differences in the Duke scale scores between the two groups (**Table 2**).

DISCUSSION

This study used the SNAP tool to assess spiritual needs in a sample of hospitalized patients in the public health system in Brazil. The results showed a greater need for psychosocial and spiritual domains in patients who did not meet the NECPAL criteria for palliative care follow-up.

To fulfill the spiritual needs using a medical approach, it is necessary to recognize the importance of this topic. People experience deep and wide-ranging demands in life according to different personal contexts. In particular, psychosocial and spiritual needs become more evident in the illness process. Data suggest that patients in Brazil are often not assessed for religiosity and spirituality. In most cases, physicians are unaware of the patient's religion and spiritual values, which could lead to spiritual distress and inadequate assistance.[20]

Studies have shown that spiritual needs can be related to variables such as the time of diagnosis and stage of the disease, showing the need for an individualized approach to spiritual care.[21] This care is often directed at patients with chronic illnesses in end-of-life care. However, patients with acute conditions that are potentially life-threatening bring spiritual needs that require validation and a professional approach.[22]

Table 2. Comparative analysis of religiosity and spiritual needs between groups with and without indications for palliative care follow-up. Sao Paulo, Brazil, 2020

		PC indication		P value
		Yes	No	
Organizational religiosity (Duke)	Mean	3.25	2.82	0.427
	SD	1.83	1.42	
	Median	3.00	2.00	
	Minimum	1.00	1.00	
	Maximum	6.00	6.00	
Non-organizational religiosity (Duke)	Mean	2.25	2.45	0.169
	SD	1.55	1.25	
	Median	2.00	2.00	
	Minimum	1.00	1.00	
	Maximum	6.00	6.00	
Intrinsic religiosity (Duke)	Mean	4.03	4.52	0.242
	SD	1.77	2.17	
	Median	3.00	4.00	
	Minimum	3.00	3.00	
	Maximum	11.00	12.00	
Psychosocial needs (SNAP)	Mean	19.00	25.00	0.004
	SD	6.74	9.15	
	Median	17.00	23.50	
	Minimum	12.00	12.00	
	Maximum	41.00	48.00	
Spiritual needs (SNAP)	Mean	11.12	14.28	0.043
	SD	4.27	6.59	
	Median	10.00	12.00	
	Minimum	6.00	6.00	
	Maximum	24.00	37.00	
Religious needs (SNAP)	Mean	9.03	10.59	0.176
	SD	4.29	4.87	
	Median	9.00	10.00	
	Minimum	5.00	5.00	
	Maximum	20.00	20.00	

PC = palliative care; SD = standard deviation; SNAP = Spiritual Needs Assessment for Patients.

In this context, palliative care professionals should be able to approach the spiritual suffering of hospitalized patients. A model of spiritual care by trained professionals that seeks to obtain a focused spiritual history and screen for possible unmet demands, involving cultural limits and individual values of family members and patients is suggested.[23] Training healthcare professionals in spiritual care is a promising strategy for a holistic approach, as suggested by a Brazilian study.[24] The inclusion of spiritual care in the continuing education of these professionals can benefit a greater number of patients who do not have access to specialized palliative care staff to meet their spiritual needs.

Vilalta et al. suggested that awareness of the reality of the disease may be a beneficial factor for spiritual needs to be met.[25] A reason for the findings in our study is that patients who have an indication for palliative care are approached more frequently about their health condition and, therefore, have greater knowledge about the disease, thus finding the resilience to face the illness process.

Finally, it is important to note that this study has some limitations. As an observational analytical study, it was impossible to evaluate the impact of the differences in the spiritual needs of the patients analyzed. Regarding the small sample with a heterogeneous population, factors such as the time of diagnosis and severity of the current disease may be confounding factors in the data analysis.

As most published studies on spiritual care focus only on patients with advanced chronic illnesses and considering the lack of studies addressing this topic in Brazil, further research is suggested. This should involve larger samples and focus on the hospitalized population, using spiritual assessment tools to evaluate the need for spiritual intervention regardless of health conditions.

CONCLUSION

Spiritual, psychosocial, and religious needs are prevalent among hospitalized patients, and a multidisciplinary team must consider these needs in their management approaches. This study suggests that according to the SNAP scale, psychosocial and spiritual needs can be even higher in patients who are not under palliative care.

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25-Hydroxyvitamin D as a biomarker of vitamin D status in plaque psoriasis and other dermatological diseases: a cross-sectional study

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Fitzpatrick phototypes.
Retrospective cross-sectional study.

ABSTRACT

BACKGROUND: Hypovitaminosis D is a public health problem associated with several chronic inflammatory and immunological diseases, including psoriasis.

OBJECTIVES: This study aimed to determine the prevalence of hypovitaminosis D in patients with plaque psoriasis. A comparison was made between vitamin D levels in patients with psoriasis and those with other non-inflammatory dermatoses without photosensitivity. In addition, it evaluated the effects of the patients' Fitzpatrick skin phototype and the season of the year on the serum levels of vitamin D.

DESIGN AND SETTINGS: A retrospective cross-sectional study was conducted at an outpatient clinic in a university center in Juiz de Fora (MG), Brazil.

METHODS: A review of dermatology patients' demographic data, including skin phototype and serum levels of 25-hydroxyvitamin D [25(OH)D], over 12 months in 2016.

RESULTS: This study included 554 patients: 300 patients allocated to the plaque psoriasis group and 254 control patients with other dermatological diseases. Regarding the season of the year, 229, 132, 62, and 131 participants were evaluated in summer, autumn, winter, and spring, respectively. As for the skin phototype, 397, 139, and 18 patients had phototypes III, IV, and V, respectively. The serum levels of 25(OH)D were significantly lower in the psoriasis group (24.91 ± 7.16 ng/mL) than in the control group (30.37 ± 8.14 ng/mL).

CONCLUSIONS: Hypovitaminosis D (< 30 ng/mL) was present in 76.66% of patients with psoriasis versus 53.94% of control patients. Vitamin D deficiency (< 20 ng/mL) was observed in 25% of the patients with psoriasis versus 8.66% in the control group (P < 0.001). The season and patient's skin phototype were independent predictors of serum vitamin D levels.

INTRODUCTION

Psoriasis is a chronic inflammatory disease with a genetic predisposition involving the skin, joints, and immunological effector mechanisms, affecting approximately 2–5% of the world population. The pathogenesis is multifactorial, involving innate and adaptive immunity, and potentially associated with several comorbidities.[1,2]

Vitamin D is a steroid hormone that acts genomically and non-genomically in different metabolic processes in most tissues. In the skin it plays several important biological functions in the physiology of keratinocytes and cells of innate and adaptive immunity. Several studies have demonstrated a high prevalence of vitamin D deficiency in the general population and its various associations with bone, autoimmune, inflammatory, hormonal, cardiac, and neoplastic diseases.[3-8] Scientific literature suggests an association between psoriasis and inadequate levels of vitamin D.[9,10] Therefore, it is believed that the prevalence of hypovitaminosis D is higher in patients with psoriasis. Although vitamin D analogs treat psoriasis, its exact mechanism of action and relationship with the disease is unclear.[11]

OBJECTIVES

The present study aimed to evaluate the serum levels of 25-hydroxyvitamin D [25(OH)D] in patients with plaque psoriasis. In addition, a comparison was made with levels in dermatology patients with other non-inflammatory dermatoses without photosensitivity. This study also aimed

to explore the factors associated with vitamin D synthesis. It evaluated the effect of the patient's Fitzpatrick skin phototype[12] and season of the year on the serum levels of 25(OH)D.

METHODS

Study design and ethics statement

A cross-sectional, retrospective, and comparative study was conducted from January to December 2016 at the Dermatology Service of the University Hospital of the Faculty of Medicine of Universidade Federal de Juiz de Fora (UFJF). The study included 554 patients: 300 patients with plaque psoriasis and 254 control patients with other dermatological diseases. The study reviewed 650 medical records: 350 patients treated at the psoriasis outpatient clinic with a standardized medical record, including serum levels of 25(OH)D, and 300 patients treated at the general dermatology outpatient clinic. Exclusion of patients in both groups was based on the lack of accordance with the inclusion and exclusion criteria, missing data in the medical records, and the patient belonging to a different geographic region. Fifty patients were excluded from the psoriasis group and 46 from the general dermatology group. As the medical records for this study were obtained from the Dermatology Service of a university hospital, the data were collected by postgraduate doctors and supervised by doctors, and standardized medical records were used. To minimize geographic effects on vitamin D levels, all included patients were from Minas Gerais State, Zona da Mata region, southeastern Brazil. The inclusion criteria were patients of both sexes, aged between 18 and 60 years, with a clinical or histopathological diagnosis of plaque psoriasis. The exclusion criteria were patients with other clinical forms of psoriasis; severe and decompensated systemic diseases (hepatic, renal, metabolic, and cardiac); thyroid and parathyroid diseases; malignant neoplasms, AIDS, and pregnancy; oral supplementation of vitamin D, bisphosphonates, systemic corticosteroids, and calcium; treatment with phototherapy or use of sunscreens; use of topical vitamin D analogs such as calcipotriol; and diseases with altered intestinal absorption or other autoimmune and photosensitivity diseases.

This retrospective study was performed after the research was approved by our institution's ethics committee (protocol 3.142.153; approved on November 2, 2019, by the Research Ethics Committee of the University Hospital, UFJF). All the procedures involved in this study were in accordance with the Declaration of Helsinki of 1975, updated in 2013.

Clinical predictors and laboratory screening

The standardized medical records of each patient were reviewed, and the following variables were evaluated: sex, age, Fitzpatrick skin phototype, and season of the year in which serum levels of 25(OH) vitamin D were measured. All serum sample vitamin D levels were analyzed at the Biochemistry Laboratory of the University Hospital using the chemiluminescence technique (ARCHITECT 25-OH Vitamin D, Abbott Diagnostics, Lake Forest, Illinois, United States). According to the American Association of Endocrinology,[13] the following parameters were adopted: values lower than 20 ng/mL were considered deficient, values from 20 ng/mL to lower than 30 ng/mL were considered insufficient, and values equal to or above 30 ng/mL were considered sufficient.

Statistical analysis

A descriptive data analysis was performed, and the normality of distribution was assessed using the Shapiro–Wilk test. Levene's test was used to test for homogeneity of variance. When the distribution and homogeneity of variance were met, Student's t-test was used to test the differences in quantitative variables between the two groups. The Chi-square test ($\chi 2$) or Fisher's exact test for less than five data points was used to test possible differences in the proportions of qualitative variables. Multivariate linear regression analysis was used to determine independent predictors of serum vitamin D. vitamin D was used continuously in multivariate regression. Season, skin phototype, sex, and age were used as determining variables. The significance level was set for all statistical analyses at 5% ($P < 0.05$). Analyses were performed using the R software package for Windows [R Core Team (2019); version 3.4.4 (R Foundation for Statistical Computing, Vienna, Austria) and URL HTTPS://WWW.R-PROJECT.ORG/].

RESULTS

The demographic characteristics and parameters of the two groups are shown in **Table 1.** Our sample consisted of 554 patients, 300 with plaque psoriasis (54.15%) and 254 patients (45.85%) with other dermatoses.

The mean age in the case group was significantly higher (47.23 ± 12.82 versus 41.59 ± 12.09 years; $P < 0.001$). Regarding sex distribution, 338 were women, and 216 were men. The distribution by sex showed statistically significant differences between the two groups ($P < 0.001$). The case group had more men (53.6%), and the control group had more women (78.4%). Serum 25(OH)D levels were significantly lower in the psoriasis group (24.91 ± 7.16 ng/mL) than in controls (30.37 ± 8.14 ng/mL), with $P < 0.001$ **(Figure 1).**

Regarding the skin phototype, there was a predominance of phototype III (397 patients, 71.66%), followed by phototype IV (139 patients, 25.09%), and 18 patients with phototype V (3.25%). Serum levels of 25(OH)D were assessed more frequently during the summer (229 patients, 41.34%) and to a lesser extent during the winter (62 patients, 11.19%). Patients with psoriasis had vitamin D deficiency levels (< 20 ng/mL) in 25% of cases versus 8.66% in controls

Table 1. Demographic characteristics and serum 25(OH)D concentration in patients with plaque psoriasis and controls

Variables	Psoriasis n (%) 300 (54.15)	Controls n (%) 254 (45.85)	P value
Age in years (mean ± SD)	47.23 ± 12.82	41.59 ± 12.09	0.000*
Male/Female (n)	161/139	55/199	0.000*
Prevalence in men (%)	53.6	21.6	0.000*
Fitzpatrick skin phototype, [n (%)]			NA
III	178 (59.33)	219 (73.0)	
IV	105 (35.0)	34 (11.33)	
V	17 (5.66)	1 (0.33)	
Season of the year during test, [n (%)]			NA
Autumn	56 (42.9)	76 (57.6)	
Winter	23 (37.1)	39 (62.9)	
Spring	57 (43.5)	74 (56.5)	
Summer	164 (71.6)	65 (28.4)	
25(OH)D			
[(Mean ± SD), (ng/mL)]	24.91 ± 7.16	30.37 ± 8.14	0.000*
Minimum	9.17	13.20	
Maximum	48.0	57.0	
< 20 ng/mL, [n (%)]	75 (25.00)	22 (8.66)	0.000*
Between 20 and 30 ng/mL, [n (%)]	155 (51.66)	11 5(45.28)	0.132
≥ 30 ng/mL, [n (%)]	70 (23.34)	117 (46.06)	0.000*

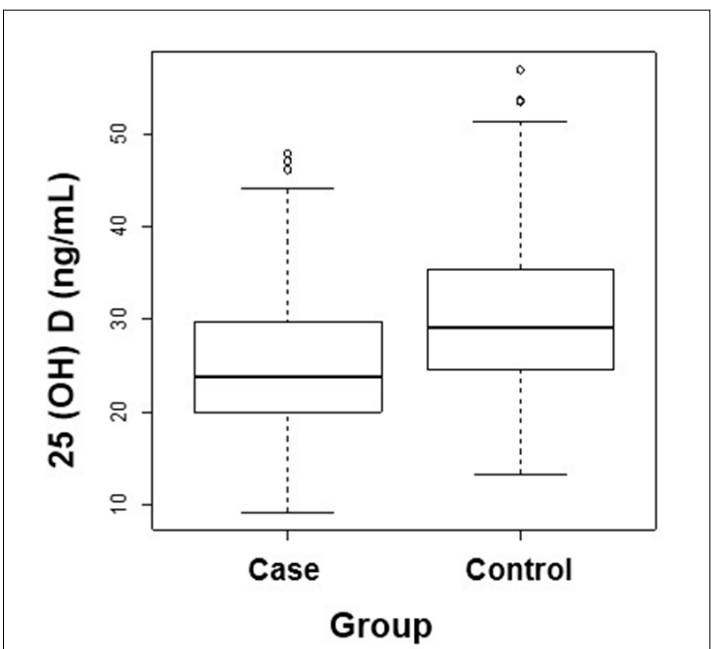
25(OH)D = 25-hydroxyvitamin D; NA = not applicable; SD = standard deviation; *P < 0.0001.

(P < 0.001). The levels of insufficiency (between 20 and 30 ng/mL) were 51.66% in patients with psoriasis versus 45.28% in controls. In contrast, levels ≥ 30 ng/mL were present in 46.06% of the control group and 23.34% of the case group (P < 0.001). Therefore, hypovitaminosis D (< 30 ng/mL) was observed in 76.66% of patients with psoriasis versus 53.94% of control patients (**Figure 2**).

The results of the multivariate linear regression, in which the determinant variables of serum vitamin D levels were studied, are shown in **Table 2** (adjusted model $R^2 = 0.21$, P < 0.001). There was a positive association between the summer season and vitamin D serum levels (β coefficient: 6.64, confidence interval [CI]: 4.56 to 8.72). Regarding skin phototypes, there was an inverse association between vitamin D levels and the highest phototype classifications, such as phototype V (β coefficient: -5.06 CI: -8.54 to -1.59). There were no significant effects of age or sex.

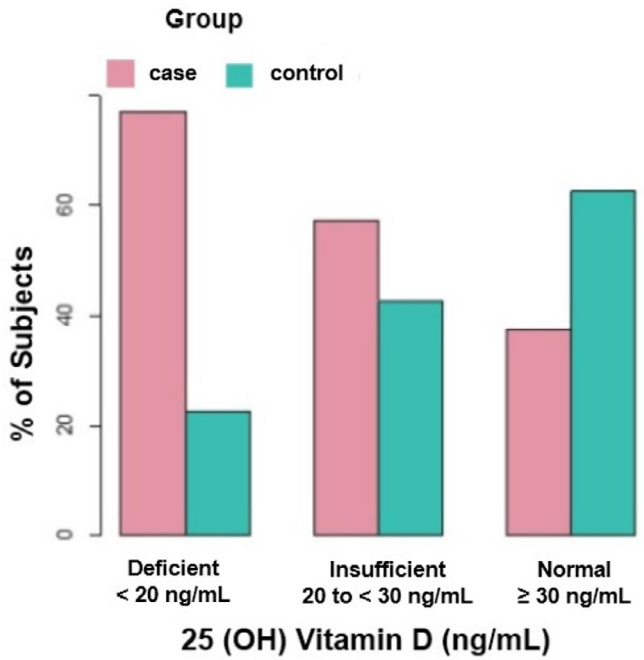
DISCUSSION

This study involved 554 patients, with 300 patients allocated to the plaque psoriasis group and 254 control patients with other dermatological diseases. Regarding the season of the year, 229, 132, 62, and 131 participants were evaluated in summer, autumn, winter, and spring, respectively. For the skin phototype, 397, 139,



The serum 25(OH)D concentration was significantly lower in patients with psoriasis than in control subjects (P < 0.001).

Figure 1. Comparison of serum 25-hydroxyvitamin D [25(OH)D] concentration between the psoriasis and control groups.



Deficient (< 20 ng/mL), insufficient (between 20 and 30 ng/mL), or normal (≥ 30 ng/mL).

Figure 2. Percentage of patients according to the serum level of 25-hydroxyvitamin D [25(OH)D].

Table 2. Multivariate linear regression model - analysis of independent predictors of serum 25(OH)D levels in the cohort

Predictors	β coefficient	P value	95% CI
Group			
Psoriasis*			
Control	6.94	0.000€	5.53 – 8.34
Sex			
Female*			
Male	1.24	0.06	−0.08 – 2.58
Age	−0.02	0.22	−0.07 – 0.01
Season			
Winter*			
Autumn	2.98	0.007	0.81 – 5.15
Spring	1.66	0.13	−0.50 – 3.83
Summer	6.64	0.000€	4.56 – 8.72
Skin phototype			
III*			
IV	0.45	0.54	−1.00 – 1.95
V	-5.06	0.000€	−8.54 – −1.59

*Reference Category €P < 0.001 Adjusted model R^2 = 0.21 P < 0.001; CI = confidence interval.

and 18 patients had phototypes III, IV, and V, respectively. The serum levels of 25(OH)D were significantly lower in the psoriasis group (24.91 ± 7.16 ng/mL) than in the control group (30.37 ± 8.14 ng/mL). A negative association was found among 25(OH)D, psoriasis, and phototypes IV and V, and a positive association between 25(OH)D and summer.

The importance of vitamin D in systemic homeostasis has attracted great interest in the scientific community, with numerous studies on its physiology and impact on global health. However, several issues remain controversial, such as the reasons for a substantial portion of the world population having low levels of vitamin D, the best laboratory test for vitamin D dosage, and the parameters to be used to properly define the cut-off (point) to express vitamin D sufficiency, insufficiency, or deficiency.[13,14]

According to the Central and Eastern European Expert Consensus Statement,[15] recently published serum creatinine measurements have been advised in individuals with a 25(OH)D concentration of < 10 ng/mL or > 100 ng/mL. As only one patient in the study presented with levels of vitamin D < 10 ng/mL, the creatinine levels in the patients were not evaluated, and the creatinine level of this single patient was normal.

According to the American Academy of Endocrinology guidelines,[13] a 66.24% prevalence of hypovitaminosis D (< 30 ng/mL) was found in the cohort. In Brazil, studies have shown a prevalence of hypovitaminosis D in adults of approximately 33 to 71.2%.[14,16-19] Moreover, the mean was significantly lower in the psoriasis group (24.91 ± 7.16 versus 30.37 ± 8.14 ng/mL; P < 0.001). Approximately 25% of the patients with psoriasis were deficient (< 20 ng/mL). The prevalence of hypovitaminosis was 76.66% in patients with psoriasis versus 53.94% in the control group. Levels considered adequate (≥ 30 ng/mL) were present in 46.06% of the control group and 23.34% of the case group.

Our data coincided with those of Orgaz-molina et al.,[9] who found that 25.6% of patients with psoriasis were deficient, and Ricceri et al.,[10] who found a 68% rate of deficiency and 97% rate of insufficiency in patients with psoriasis versus 10% and 53% in the control group, respectively. The prevalence levels of hypovitaminosis were similar to those in the Brazilian study by Zuchi et al.,[20] who analyzed 40 patients: 20 with psoriasis (15 with mild plaque form and 5 palmoplantar) and 20 control patients. This study was conducted from July to September 2013 in Curitiba City, South Brazil, and the most frequent skin phototypes were I and II. In the analysis of 25(OH)D, a prevalence of 85% for hypovitaminosis D (< 30 ng/mL) was found in the studied sample. When analyzing the levels of deficiency in patients with psoriasis, the results were 25% versus 20% in the controls. However, no statistically significant differences were observed between the studied populations.

Furthermore, several factors can influence the prevalence of deficiency and insufficiency, such as race, ultraviolet radiation index,

dietary intake, and year's season.[21] In the multivariate analysis, phototype and season of the year were the independent variables statistically significantly associated with 25(OH)D serum concentrations.

Juiz de Fora is a city in the Zona da Mata region of Minas Gerais, located in the intertropical zone. Therefore, it receives a large amount of sunlight throughout the year, and this study was conducted in a city with a high ultraviolet index, ranging from moderate to high. Although more than 40% of the tests were performed during summer and to a lesser extent in winter (11%), a high insufficiency rate of 25(OH)D was detected.

In a review carried out by Corrêa[22] in Brazil, he concluded that the ultraviolet index (UVI) values observed usually reach the highest UVI scales recommended by the World Health Organization (WHO), with very high (UVI between 8 and 10) or extreme (UVI greater than 11) damage to human health. In the North and Northeast regions of the country, similar values can be observed before 9 am throughout the year. In the south and southeast, at solar noon, UVI values are characterized by marked seasonality, with extreme UVI values in summer and between medium and high in winter. However, it is during the summer in the southeast region of the country where Brazilian records of UVI episodes above 15 are observed. This new knowledge about the distribution of UVI in Brazil is important to consider with respect to the problem of hypovitaminosis D, which may be associated with other factors, such as genetic and nutrigenomic polymorphisms and little sun exposure.[22]

Another factor involved in the serum concentration of vitamin D is the amount of melanin in the skin. A reduction in serum 25(OH) D concentrations in people with higher skin phototype classifications is expected because they synthesize less vitamin D when exposed to the same amount of radiation compared to a person with a lower skin phototype classification. This is explained by the fact that melanin competes for the photon of ultraviolet B radiation (UVB), which promotes the photolysis of 7-dehydrocholesterol and triggers the synthesis of vitamin D in the skin. Consequently, radiation exposure should be longer in higher skin phototype classifications.[23] More than 70% of the patients in our sample had skin phototype III, and the prevalence of hypovitaminosis D was still high. The literature data indicates disagreement about the phototype variable, such as those by Glass et al.,[24] who studied the relationship between vitamin D, skin pigmentation, and exposure to UV rays in the United Kingdom. The study analyzed 1400 white women. It was observed that individuals with the highest phototype classifications (III and IV) had higher serum levels of 25(OH)D (mean 32.9 ng/mL) when compared to those with low phototype classifications (types I and II) (mean 28.5 ng/ml, $P < 0.0001$). The data showed an inclination towards sun-seeking behavior in darker-skinned patients, which correlated positively with vitamin D status. Malvy et al.[25] conducted a similar study in France involving 1191 individuals and found that serum 25(OH)D levels were lower in fair-skinned individuals ($P < 0.024$).

The exacerbation of psoriasis in winter may be partly due to low sun exposure and the subsequent low vitamin D production in the skin. Therefore, the therapeutic effect of UVB therapy in treating psoriasis may be, at least in part, mediated by UVB causing the synthesis of vitamin D in the skin. In addition, UVB therapy increased serum 25(OH)D levels in patients with psoriasis in parallel with disease improvement.[26] The exposure of the skin to sunlight is the major source of vitamin D. Moreover, the epidermis and hair follicle keratinocytes express the hydroxylases needed to produce the active hormone 1,25-Dihydroxyvitamin D [1,25(OH)2D], and vitamin D receptor has been shown on keratinocytes.

Vitamin D appears to influence the innate and acquired immune systems with complex effects, which are still not completely elucidated. It has been shown that 1 α-hydroxylation produces active hormones within different immune system cells, where it exerts autocrine and paracrine effects. In contrast, vitamin D mainly inhibits the acquired immune system by reducing the expression of MHC class II and co-signaling molecules on antigen-presenting cells, decreasing the activity of TH1 and TH17 cells, and upregulating regulatory T cells. The final result is the promotion of regulatory and protective phenotypes of T-cells.[27]

The benefits of vitamin D analogs for psoriasis treatment are well established. A topical vitamin D analog is the first-line choice for managing psoriasis, either alone or in combination with topical corticosteroids. Unlike corticosteroids, which can be associated with tachyphylaxis, topically administered vitamin D analog treatment is long-term and effective without side effects in patients of all ages.[28]

Stanescu et al.,[29] in their review of the systemic use of vitamin D in psoriasis, examined the pros and cons of this treatment to determine whether systemic vitamin D would be a feasible therapeutic option for these patients and whether more large-scale studies are needed to determine the efficacy, optimal dosing, and adverse effects of vitamin D administration in patients with psoriasis. Genetic variation in vitamin D metabolism can lead to a personalized vitamin D response. Moreover, biomarkers of vitamin D status different from 25(OH)D status have been identified in new metabolic pathways of vitamin D.[30]

Although sunlight was the primary source of vitamin D during more than 99% of human evolution, it is clear that mainly owing to increased longevity, people need to try to accomplish a delicate balance between limiting sunlight exposure, avoiding skin damage, and optimizing vitamin D status. In many cases, this balance implies that vitamin D supplementation is necessary.

A Brazilian study conducted by Coutinho et al.[31] in 174 fishermen analyzed the relationship between sun exposure index, vitamin D levels, and clinical changes in the skin caused by the sun. Vitamin D deficiency was verified in only 11.46% of the patients due to chronic sun exposure in Brazil's northeast region, with high levels of UVI

throughout the year. The lack of association between our study and that conducted by Coutinho et al. can be explained by the fact that our study showed a higher prevalence of vitamin D deficiency, as it was performed in a geographic region with a variation in sun exposure according to the season of the year, as well as the presence of atmospheric pollution in the Southeast region. On the other hand, our findings are similar to those of Cabral et al.,[32] found in another Brazilian study in the Northeast region.

To the best of our knowledge, this is the first Brazilian study to assess the prevalence of hypovitaminosis D in dermatological patients for 12 months in an expressive cohort. Therefore, the data from this study can be considered representative of a considerable proportion of dermatological patients, including patients with psoriasis in Brazil.

The limitations of our study include the absence of a dietary and sun-exposure survey (with time and duration of exposure). In addition, 25(OH)D production and degradation is a continuous process. Therefore, establishing an ideal period to study the effects of UV radiation on vitamin D production and its action on immunosuppression is a challenge in clinical research. Consequently, it needs to be better evaluated in prospective studies. In addition, as this study was cross-sectional, the patients were not followed up over a long period of restrictive selection criteria.

CONCLUSION

Considering the geographic location in which the study was carried out, with moderate to high levels of ultraviolet radiation throughout the year and the predominance of skin phototype III, it can be concluded that daily solar radiation was insufficient to promote the adequate synthesis of 25(OH)D. Furthermore, vitamin D deficiency was greater in the psoriasis group. A negative association was found among 25(OH)D, psoriasis, and phototypes IV and V, and a positive association between 25(OH)D and summer. Future randomized, blinded, long-term studies investigating the role of vitamin D supplementation in psoriasis are necessary.

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Cross-sectional evaluation of socioeconomic and clinical factors and the impact of fibromyalgia on the quality of life of patients during the COVID-19 pandemic

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AUTHORS' KEY WORDS:
Pharmacological treatment.
Fibromyalgia impact questionnaire.
Self-reported quality of life.

ABSTRACT

BACKGROUND: The fibromyalgia impact questionnaire (FIQ) relates to the functional capacity, professional situation, psychological disorders, and physical symptoms, and can identify the factors that determine the impact of the syndrome and characteristics of its carriers; the higher the score, the greater the impact of fibromyalgia on the quality of life.

OBJECTIVE: To evaluate the impact of fibromyalgia on the quality of life of individuals with fibromyalgia, who were categorized according to the FIQ during the coronavirus disease pandemic.

DESIGN AND SETTING: A cross-sectional study was conducted at an institution of higher education in Taquara, RS, Brazil.

METHODS: A quantitative study was carried out, with the application of a sociodemographic and clinical questionnaire, and the FIQ in 163 Brazilian individuals with a medical diagnosis of fibromyalgia. Data were collected using SurveyMonkey software.

RESULTS: Of the female carriers, 98.2% were living in urban areas, working, and under pharmacological and complementary treatment. The FIQ results showed that seven of the 10 items had the maximum score. The items "physical function" and "feel good" had intermediate scores, and the item "missed work" had a low score. The average total score was 79.9 points, indicating that fibromyalgia had a severe impact on the participants' lives. A severe impact of fibromyalgia was observed in 61.3% of the participants, a moderate impact in 30.7%, and a low impact in 8%.

CONCLUSION: The survey findings suggest a severe impact in the majority of the Brazilian fibromyalgic population.

INTRODUCTION

Fibromyalgia is a complex systemic disorder characterized by diffuse pain, fatigue, anxiety and depression, among other symptoms.[1] Approximately 2.1% of the population is a carrier of fibromyalgia worldwide; however, it should be noted that regional differences can be observed.[2,3] A prevalence of 6.1% was observed in the United States,[4] while similar proportions to those worldwide were observed in Spain and Brazil (2.6% and 2%, respectively).[5,6]Moreover,this syndrome is more prevalent in women.[2]

Diffuse pain is the symptom that prevails in patients with fibromyalgia; additionally, it is difficult to accurately assess its intensity, since pain is perceived subjectively and individually.[7] The symptoms can increase according to modulating factors, such as climate change,[8] degree of physical activity, and high stress levels,[9] such as those experienced throughout the year 2020 with the confrontation of the global pandemic of coronavirus disease (COVID-19)[10] by the reduction of social contact, leisure activities, financial concern, and with the health of friends and family members.[11,12] Regarding the consequences of the syndrome, fibromyalgia has a direct influence on the mental health of the carrier, since the fewer symptoms the patient presents, the closer to a positive mental health model the patient will be.[13]

A concept linked to mental health is the quality of life, defined by the World Health Organization as an individual's perception of their position in life, in their own context and in relation to their goals and expectations.[14] To assess the quality of life of patients with fibromyalgia, several instruments can be used, including the fibromyalgia impact questionnaire (FIQ), which relates to the functional capacity, work situation, psychological disorders, and physical symptoms. It is a very

useful tool that can identify the factors that determine the impact and collaborate to define the best treatment.[15] However, it is often used incompletely and does not explore the categorization of the scores obtained individually by the participants. As fibromyalgia negatively impacts different aspects of the lives of individuals affected by the syndrome, it is of utmost importance to understand the profile and characteristics of its carriers and how often different impacts occur in the populations studied.

OBJECTIVE

This study aimed to assess the impact of fibromyalgia on the lives of individuals with the syndrome during the COVID-19 pandemic as well as to map the socioeconomic and clinical factors associated with this diagnosis. It is the first study to present the Brazilian frequencies in a categorized way according to the FIQ.

METHODS

Study design

A cross-sectional, quantitative study was conducted, with the application of a sociodemographic and clinical questionnaire and the fibromyalgia impact questionnaire (FIQ). This study was approved as per the certificate of presentation of ethical appreciation (CAAE) (number 35691120.2.0000.8135) on August 28, 2020. The study was conducted according to the Strengthening the Reporting of Observational Studies in Epidemiology (STROBE) reporting guidelines.[16]

Population and sample

We included Brazilian individuals (living in Brazil or not) with a medical diagnosis of fibromyalgia and older than 18 years of age. Participants who agreed to participate in the study but did not answer the questionnaire were excluded.

To calculate the sample size, the effect of fibromyalgia on the lives of patients with the syndrome was the primary outcome. As no studies were found that evaluated the ratio of severe impact on the lives of the study population, an estimated 50% of individuals suffering from a severe impact on their lives were included for the sample size calculation. A confidence level of 95% was adopted with a maximum error of 8%; additionally, the calculated sample size was 151 individuals. An additional 15% was included in the sample to minimize the possible sample losses for a total intended sample size of 173 subjects.

The participants completed digital questionnaires generated on the SurveyMonkey platform (Momentive, San Mateo, California, United States; https://pt.surveymonkey.com), from August to October 2020, during the third quarter of the COVID-19 pandemic in Brazil. The sample was selected, and access to the questionnaires was provided through social media.

The FIQ version that was validated in Brazil was applied. This questionnaire aimed to evaluate the quality of life of patients with fibromyalgia and was composed of 19 questions organized into 10 items. All the items were measured by a visual scale corresponding to values from 0 to 10 (0 = the best possible and 10 = the worst possible).[17] To obtain the total score, the individual scores of the first three items were properly recoded by a rule of three to ten points per item; subsequently, they were added to the next seven items. If any question was left blank, the scores obtained were summed and divided by the number of questions answered.[18] The total FIQ scores ranged from 0 to 100, where higher values indicated a greater negative impact of the syndrome, and were be classified into the following categories: low impact (< 50 points), moderate impact (50–75 points), and severe impact (> 75 points).[19]

Statistical analysis

The Statistical Package for Social Science Professional software (version 25.0; IBM Corp., Armonk, New York, United States) was used for data analysis. The mean and standard deviation were used to describe parametric continuous variables; additionally, the median and interquartile range were used for nonparametric variables, while absolute and relative frequencies were used for categorical variables. The Shapiro–Wilk test was used to test the normality of the data; furthermore, the chi-square test was used to assess the difference in proportions between the FIQ categories.

RESULTS

A total of 173 acceptances were obtained for participation in the survey; however, only 163 participants completed the questionnaires. The general characteristics of the participants are presented in **Table 1**. The questionnaires were answered by 160 women and three men, aged between 19 and 63 years.

Considering the impact of fibromyalgia, 13 subjects, who were evaluated as having low impact, that is, 100% of this group, lived in urban areas. Similarly, 49 subjects with moderate impact and 96 subjects with severe impact, equal to 98% and 96% of the total in each group, respectively, also lived in urban areas.

Clinical data of the participants are presented in **Table 2**. The participants had a symptom onset between 7 and 50 years of age and between 13 and 52 years of age at diagnosis. The time of illness, current age, age at diagnosis, and age at symptom onset did not seem to be related to the category of impact according to the FIQ of the participants. The age of the participants with low impact, moderate impact, and severe impact was 37.08 ± 8.30 years, 39.22 ± 9.28 years, and 38.93 ± 9.09 years (P = 0.798), respectively; the age of symptom onset of participants with low impact, moderate impact, and severe impact was 29.69 ± 12.23 years, 29.14 ± 9.23 years, 28.02 ± 9.59 years (P = 0.306), respectively; the age at diagnosis of participants with low impact, moderate impact,

and severe impact was 32.91 ± 8.62 years, 34.40 ± 8.48 years, and 34.14 ± 8.73 years (P = 0.895), respectively; the length of illness since diagnosis for participants with low impact, moderate impact, and severe impact was 4 (0–5) years, 3 (1–6) years, and severe 3 (1–6) years (P = 0.214), respectively; and the length of illness from the onset of symptoms for participants with low impact, moderate impact, and severe impact was 5 (3–9) years, 8 (4–16) years and 9 (4–15) years (P = 0.352), respectively.

Regarding the symptoms of fibromyalgia, it is important to note that the impact of fibromyalgia does not seem to be related to symptoms, namely localized pain (low - 13, 100%; moderate - 45, 90%; and severe - 93, 93%; P = 0.458), memory loss (low - 11, 84.6%; moderate 38, 76.0%; and severe - 87, 87.0%; P = 0.231), tingling (low - 7, 53.8%; moderate - 37, 74.0%; and severe - 79, 79.0%;

Table 1. General characteristics of the study population

General characteristics	Mean/ Absolute frequency	Standard deviation/Relative frequency	n
Age (years)	38.87	±9.05	163
Sex			
Male	3	(1.8)	163
Female	160	(98.2)	
Marital status			
Married	102	(62.6)	
Single	43	(26.4)	163
Stable union	7	(4.3)	
Divorced	11	(6.7)	
Residence			
Urban area	158	(96.9)	163
Rural area	5	(3.1)	
Brazil region			
South	19	(11.7)	
Southeast	75	(46.0)	
Midwest	11	(6.7)	163
North	8	(4.9)	
Northeast	47	(28.8)	
Outside Brazil	3	(1.8)	
Education			
Up to the 4th grade	5	(3.1)	
Elementary school	7	(4.3)	
High school	58	(35.6)	163
Higher education	42	(25.8)	
Graduate school	51	(31.3)	
Working			
Yes	106	(65.0)	163
No	57	(35.0)	
Work (hours/day)			
4	41	(25.2)	
6	36	(22.1)	163
8	60	(36.8)	
12	26	(16.0)	

Continuous variables are expressed as the mean ± standard deviation. Categorical variables are expressed as numbers (%).

Table 2. Clinical data of the study population

Clinical characteristics	Mean/ Absolute frequency	Standard deviation/ Relative frequency	n
Age at symptom onset (years)	28.5	±9.7	163
Age at diagnosis (years)	34.1	±8.6	160
Time of diagnosis (years)	3	(0-6)	160
Time of illness (years)	8	(4-15)	163
Physicians who made the diagnosis			
Rheumatologists	103	(63.2)	
General Practitioner	12	(7.4)	
Neurologist	14	(8.6)	163
Orthopedist	27	(16.6)	
Others	7	(4.3)	
Physicians who performed the treatment			
Rheumatologists	55	(33.7)	
General Practitioner	8	(4.9)	
Neurologist	4	(2.5)	
Orthopedist	12	(7.4)	163
Psychologist or Psychiatrist	11	(6.7)	
Others	6	(3.7)	
More than one	57	(35.0)	
None	10	(6.1)	
Event that triggered the FM symptoms			
Depression	27	(16.6)	
Occupational disease	7	(4.3)	
Emotional trauma	35	(21.5)	
Genetic inheritance	7	(4.3)	
Physical trauma (accident/fall)	9	(5.5)	163
Change in lifestyle	6	(3.7)	
Medication use	2	(1.2)	
Surgery	5	(3.1)	
did not know	65	(39.9)	
FM symptoms			
Tiredness/Fatigue	156	(95.7)	163
Localized pain	151	(92.6)	163
Sleep disturbances	144	(88.3)	163
Memory loss	136	(83.4)	163
Joint stiffness	124	(76.1)	163
Anxiety	143	(87.7)	163
Difficulty concentrating	138	(84.7)	163
Tingling	123	(75.5)	163
Others	47	(28.8)	163
Increasing symptoms aspects			
Exaggerated physical exertion	114	(69.9)	163
Stress	146	(89.6)	163
Nighttime	45	(27.6)	163
Emotional state	144	(88.3)	163
Others	28	(17.2)	163
Period of de day with major pain			
Morning	72	(44.2)	
Evening	17	(10.4)	163
Night	74	(45.4)	

Continue...

Table 2. Continuation

Clinical characteristics	Mean/ Absolute frequency	Standard deviation/ Relative frequency	n
FM impact self-reported			
Low	1	(0.6)	
Moderate	52	(31.9)	163
Severe	110	(67.5)	
Associated disorders			
RSI	47	(28.8)	163
Musculoskeletal disorder	17	(10.4)	163
Lupus	7	(4.3)	163
Chronic fatigue syndrome	47	(28.8)	163
None	76	(46.6)	163

FM = fibromyalgia; RSI = repetitive strain injury. The time of illness refers to the age at symptom onset. Continuous variables are expressed as mean ± standard deviation or median [interquartile range (p25–75)]. Categorical variables are expressed as numbers.

Table 3. Fibromyalgia treatment of the study participants

Treatment characteristics	Absolute frequency	Relative frequency	n
Non-pharmacological treatment			
Physiotherapy/Massage	21	(12.9)	
Psychologist/Psychiatrist	17	(10.4)	
Acupuncture/Auriculo therapy	5	(3.1)	163
Other alternative treatments	42	(25.8)	
None	78	(47.9)	
Pharmacological treatment			
Antidepressants	64	(39.3)	
Antidepressants and analgesics	24	(14.7)	
Antidepressants and muscle relaxants	27	(16.6)	
Antidepressants and anti-inflammatory drugs	3	(1.8)	163
Muscle relaxants	8	(4.9)	
Other drug combinations	7	(4.2)	
None	30	(18.4)	
Physical exercise			
Walking/Running/Cycling	30	(18.4)	
Pilates/Yoga	16	(9.8)	
Weightlifting	18	(11.0)	
Other modalities	21	(12.9)	163
More than one	16	(9.8)	
None	62	(38.0)	
Exercise frequency			
Up to 2 times a week	40	(24.5)	
Up to 4 times a week	41	(25.2)	
Up to 6 times a week	24	(14.7)	163
None	58	(35.6)	

Categorical variables are expressed as numbers.

P = 0.134) and tiredness or fatigue (low - 11, 84.6%; moderate - 47, 94.0%; and severe - 98, 98.0%; P = 0.063), while there was a higher frequency of individuals with sleep disturbances (low - 9, 69.2%; moderate - 41, 82.0%; and severe - 94, 94.0%; P = 0.008), difficulty concentrating (low - 10, 76.9%; moderate - 35, 75.0%; and severe 93, 93%; P = 0.001), joint stiffness (low - 11, 84.6%; moderate - 29, 58.0%; and severe - 84, 84.0%; P = 0.002), and anxiety (low - 9, 69.2%; moderate - 40, 80.0%; and severe - 94, 94.0%; P = 0.005) in those most impacted by fibromyalgia.

Notably, when the results of the impact self-reported by the participants and the one obtained by the FIQ questionnaire were cross-checked, there was better agreement on the greatest impact, where 83 subjects in the severe group (83%) declared themselves to be in the same group (the other 17 considered themselves to have moderate impact), 26 subjects classified by the FIQ as moderate considered moderate impact (52%), the remaining 23 subjects (46%) considered their impact as severe, and 1 (2%) subject considered their impact as low, while the participants evaluated as having low impact indicated moderate (9, 69.2%) or severe impact (4, 30.8%).

Regarding other associated disorders, repetitive strain injury (28.8%), chronic fatigue syndrome (28.8%), musculoskeletal disorder (10.4%), and lupus (4.3%) were observed, with 46.6% of the participants having only fibromyalgia; additionally, among these participants, 30.8% had a low impact by fibromyalgia, 54.0% had a moderate impact, and 45.0% had a severe impact, according to the FIQ.

Data related to the treatments used by the participants are presented in **Table 3**. Regarding non-pharmacological treatments, most participants used some non-pharmacological support treatment, while 47.9% did not use any treatment (among them, 67.9% had a severe impact).

The pharmacological treatments used by the participants included only antidepressants (39.3%, of whom 6.3% belonged to the low-impact group of fibromyalgia, 32.8% belonged to moderate-impact group, and 60.9% belonged to the severe-impact group), antidepressants and muscle relaxants (16.6%, low 4.2%, moderate 25.0%,and 70.8% severe), antidepressants and analgesics (14.7%, 0.0% low, 37.0% moderate, and 63.0% severe), muscle relaxants only (4.9%, 25% low, 25% moderate, and 50% severe), other drug combinations (4%, 3% low, 14.3% moderate, and 85.7% severe), antidepressants and anti-inflammatory drugs (1.8%, 33.3% in each category), and no medication (18.4%, 16.7% low, 30.0% moderate, and 53.3% severe).

Regarding the performance of physical exercise, analyzing the categories of impact of fibromyalgia on the lives of the participants, 45.0% of the members of the severe impact group did not perform any kind of physical exercise, while the others were divided into walking, running, or cycling (21.0%), other modalities (14.0%), pilates or yoga (8.0%), weight training (8.0%), and more than one modality (4.0%).

Table 4 presents the results of the FIQ. The results show that of the 10 items, 7 items (do work, pain, fatigue, rested, stiffness, anxiety, and depression) had the maximum score of 10 points,

Table 4. Scores in the fibromyalgia impact questionnaire (FIQ)

FIQ items	Median/Absolute frequency	Interquartile range/ Relative frequency	n
Physical function	5.33	(3.83–6.67)	
Feel good	7.14	(5.71–8.57)	
Missed work	2.86	(0–7.14)	
Do job	10	(7–10)	
Pain	10	(8–10)	
Fatigue	10	(10–10)	
Rested	10	(8–10)	
Stiffness	10	(8–10)	
Anxiety	10	(7.5–10)	
Depression	10	(6.5–10)	
FIQ scores	**79.9**	**(66.7–85.9)**	**163**
FIQ categories			
Low	13	(8.0)	
Moderate	50	(30.7)	163
Severe	100	(61.3)	

Continuous variables are expressed as the mean ± standard deviation or median [interquartile range (p25–75)]. Categorical variables are expressed as numbers.

demonstrative of a worse condition relative to each item. The items of physical function and feeling good were scored with intermediate scores (5.33 and 7.14, respectively), while in the item missed work, we could consider the low score obtained (2.86). The median total score was 79.9 points, with an interquartile range of 66.7–85.9, indicating that fibromyalgia has a severe impact on the lives of the participants. A severe impact of fibromyalgia was observed in 61.3% of the participants, moderate impact in 30.7%, and low impact in 8% of the participants.

DISCUSSION

The present study evaluated the impact of fibromyalgia on the lives of its carriers and investigated the socioeconomic and clinical factors present. This is the first study with a sample of the Brazilian population to measure the ratio among the categories of the FIQ. The results indicate a severe impact on the lives of the individuals with fibromyalgia, not only by the high result obtained in the FIQ score, but also by a large number of individuals in the severe impact category.

This research pointed to a total score of 79.9 for the FIQ, a value similar to that found in the literature by Martinez et al., who obtained a score of 70.3.[20] Even higher scores can be found; of the 10 items evaluated, nine had high scores.[21] This fact suggests that most carriers suffer from a severe impact of the syndrome. It is important to emphasize that the more pain the patient reports, the higher the FIQ score and consequently, the worse the quality of life of that individual will be.[22] Contrastingly, patients who have low impact due to fibromyalgia have better acceptance of their pain than those with severe impact.[23] An important observation to be made is that when the participant was asked about the impact of fibromyalgia on their life, 67.5% indicated having a severe impact, which was not far from the results found by the FIQ, which showed that 61.3% of participants have severe impact. This demonstrated an accurate self-perception of the participant with respect to their condition. In addition, notably, there seems to be a link between self-awareness related to the syndrome and management of the crises generated by it with the FIQ scores, which are lower in carriers who have this control.[6]

High frequencies of depressive and anxiety symptoms are also found in carriers of fibromyalgia,[24] noting that these symptoms occur in greater intensity in those in whom fibromyalgia causes a severe impact.[25] In the present study, no analysis was performed with specific questionnaires for depression and anxiety; however, in the clinical questionnaire, more than 70% of the participants reported having memory loss, even though no relationship was observed with the fibromyalgia impact group. In addition, a higher frequency of anxiety, difficulty in concentrating, and sleep disturbances was observed among those with the highest impact. Regarding the emotional aspects of the syndrome, we observed a high proportion of individuals participating in this study who reported not knowing the origin of the onset of their symptoms. However, of those who did know, 65 participants (39.4% of the total) reported an emotional relationship, either depression or emotional trauma, and most of them were individuals categorized by the FIQ as being severely impacted by fibromyalgia.

The data collection period corresponded to the third quarter of the COVID-19 pandemic in Brazil. This could be related to the high severity of fibromyalgia found in the study subjects. Therefore, besides the fact that the presence of the viral infection itself (a parameter not evaluated in the clinical questionnaire applied) seems to worsen all domains of the FIQ in fibromyalgia patients,[26] the potential aggravation of stress and fear caused by the pandemic on the symptoms faced by fibromyalgia sufferers is discussed.[27] Hausmann et al. observed substantial changes in the employment status in their study sample and linked this to decreased access to fibromyalgia health care and treatment during the pandemic.[28]

With respect to work, a study conducted in 2020 in Saudi Arabia found a high prevalence of fibromyalgia sufferers among healthcare workers.[29] The frontline healthcare workers for COVID-19 had to deal directly with an overload of work, being drastically affected by emotional stress, causing depression and anxiety.[30] These factors are related to the management of fibromyalgia and, as previously mentioned, with a high frequency in the group severely impacted by the syndrome. Although the present study did not access the participants' areas of expertise, this could be a factor that may have influenced the results obtained. In addition to those who worked directly with healthcare in the pandemic, the confinement situation adopted by several countries forced many patients

to discontinue their treatments[31] and exacerbated the main symptoms of fibromyalgia.[32] Moreover, some authors found no influence of the pandemic on the clinical manifestations of fibromyalgia,[33] keeping this question open.

The fact that more than 90% of the participants reside in an urban area is in agreement with a previous study that showed that a greater number of individuals with fibromyalgia live in urban areas, with a prevalence ranging between 0.69% and 11.4%, higher than in a rural area that showed a prevalence between 0.6% and 5.2% of the population.[3] Corroborating the findings of the present study, Martinez et al., in a Brazilian study, selected patients with fibromyalgia according to the degree of severity obtained by the FIQ, and showed that there seems to be no relationship between the degree of severity and the patient's age, age at onset of symptoms, family income, education, or other diseases associated with fibromyalgia.[34]

In this research, the number of female participants was the majority, which corroborates with other studies that also demonstrate a higher number of women with the syndrome for example, the study conducted by Tangenet al., in which 97% of the sample were women.[23] Additionally, Cabo-Meseguer et al. also observed a higher number of women (4.3%) than men (0.49%) with fibromyalgia.[2] Our findings showed that most of the participants resorted to non-pharmacological interventions, mainly physiotherapy or therapeutic manipulation. A systematic review involving different musculoskeletal diseases of chronic pain, including fibromyalgia, demonstrated a positive effect of myofascial release when compared to placebo treatment on pain frequency and intensity, as well as the level of functionality and quality of life.[35] However, a more recent systematic review focused on patients with fibromyalgia showed that the technique showed no improvement in the outcomes of pain, FIQ, and quality of life.[36] Additionally, although a high adherence to acupuncture has not been found in the present results, this therapy proves to be very efficient for pain reduction[37] and pain threshold increase[38] among the non-pharmacological treatment modalities.

Another category of non-pharmacological supportive treatment used by some of the participants was physical exercise, which demonstrates an improvement of fibromyalgia symptoms and mainly imparts a willingness to perform daily activities.[39] It has been shown that training with stretching exercises, strength training, and aerobic training for at least 60 min, 3 times a week, can improve the patient's condition[40] and that walking brings benefits in the quality of sleep.[41] Even an umbrella systematic review confirmed an improvement in pain, quality of life, physiological function, and psychological function of fibromyalgia patients by the practice of physical exercise.[42]

Among the medications used today are those that can modulate some specific neurotransmitters, such as noradrenaline, serotonin, gamma-aminobutyric acid, opioid receptors, and calcium channel blockers, among others.[43] Moreover, although we did not assess which medications are part of the treatment of the interviewed individuals, we obtained results that show that most of the interviewed individuals use at least one drug combination.

A limitation of this study is the lack of use of a comparative tool for general quality of life measurements. In addition, although the study is quite comprehensive from a regional point of view, it may have a search bias, since, possibly, patients impacted by their condition will be concerned about participating in research. Likewise, the fact that the subjects filled out the questionnaires themselves may have generated differences in the interpretation of the questions and collection of the answers. Moreover, as previously discussed, the period chosen for data collection may have increased the scores obtained because of the COVID-19 pandemic, and future studies are essential to visualize the consequent effects.

CONCLUSION

In the evaluated sample, we observed a higher frequency of the severe impact category, as well as a higher FIQ score during the observation during the COVID-19 pandemic, which demonstrates a poor quality of life in these individuals. In addition, the majority of fibromyalgia patients are women who live in urban areas, work, and use pharmacological and complementary treatments. A higher frequency of anxiety, difficulty concentrating, and sleep disturbances were related to a severe impact. Moreover, even if individuals practice some physical activity, fibromyalgia is observed to severely affect their lives.

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Examining the correlation between sexual and reproductive health stigmatization level and gender perception: a case of a university in Turkey - a descriptive cross-sectional study

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ABSTRACT

BACKGROUND: Stigmatization, which emerges depending on the sexual behavior of young individuals, leads to negative health and social outcomes, such as shame, social marginalization, violence, and mental health morbidity.

OBJECTIVE: This study aimed to examine the correlation between the level of sexual and reproductive health stigma and gender perception in female university students.

DESIGN AND SETTING: This descriptive cross-sectional study was conducted at the Faculty of Health Sciences of a university in Turkey.

METHODS: The data of this study were collected from digital media between July and October 2020 from a study population of 385 students. The data were collected using the Personal Information Form, including the socio-demographic characteristics of students, the Sexual and Reproductive Health Stigmatization Scale in Young Women and the Perception of Gender Scale. Descriptive statistics, independent samples t-test, analysis of variance, and Pearson's correlation test were used to assess the data.

RESULTS: It was determined that there was a negative correlation between the Sexual and Reproductive Health Stigmatization Scale in Young Women and the Perception of Gender Scale ($r = -0.173$, $P = 0.001$).

CONCLUSION: It was determined that as the gender perception in the young women who participated in the study increased, the sexual and reproductive health stigmatization level decreased. The sexual and reproductive health stigmatization levels of the participants were at an above average level, and gender perception was at a medium level.

INTRODUCTION

Social norms determine the sexual behavior, marriage traditions, punishments for unapproved sexual behavior, prevention of pregnancy, sex education, homosexuality, and attitudes concerning sexual taboos.[1] According to these norms, the sexual behavior of young individuals and pregnancy, abortion, premature birth, and sexually transmitted infections, which occur as a result of such behavior, are defined as immoral according to the social, cultural, and religious norms in some societies and cause the individual to be stigmatized.[2,3]

Stigmatization is a condition preventing young women from using birth control methods and services.[4] Stigmatization that emerges depending on the sexual behavior of young individuals leads to negative health and social outcomes, such as shame, social marginalization, violence, and mental health morbidity worldwide.[5] The inability of young people to benefit from reproductive health and counseling services due to stigmatization increases unsafe miscarriages and maternal mortality.[6]

Gender role, which is defined as the individual's perception of himself/herself as a woman or a man and the exhibition of behaviors required by his/her sex, is taught to the individual according to the moral principles of his/her society. He/she is expected to behave in line with this role.[1] The role of protecting the "family's honor," which is attributed to women, causes women to be accused in all kinds of sexual relations. In addition, a reason for honor killings is when single women experience their sexuality against the roles that are expected from them. Moreover, pre-marital sexual intercourse experienced by single women in Turkey is one of the reasons for honor killings.[7]

Under the influence of gender inequality, sexuality in societies such as that of Turkey is associated with marriage for women, whereas for men it becomes an expected and acclaimed activity.[7] While women are completely forbidden to have sexual intercourse before marriage, men in the same societies are encouraged to have it.[8] Therefore, women, who experience their sexual life within the boundaries allowed by society, are under the inspection of society.[9] Morever, the pressure created by society leads to hymen control, adolescent or unintended pregnancies, miscarriages under unhealthy conditions, and an inability of benefiting from healthcare services.[7] Virginity control, which is another application containing gender discrimination, is observed in most traditional societies. Virginity examination, which has been created as a means of controlling the sexuality of women, leads to mental and physical problems in women, besides honor killings and suicides because it removes the voice of women over their own body.[8]

The knowledge and behaviors of young people going to university in Turkey concerning sexuality are different from married young people. A significant part of university students is single, and most are men and minors; however, a significant part of women experience the first contact and sexual intercourse with the opposite sex.[10] In the literature, we have not encountered studies examining the correlation between sexual and reproductive health stigmatization and perception of gender in young women.

OBJECTIVE

Therefore, in this study, we aimed to examine the correlation between the sexual and reproductive health stigmatization level and perception of gender in female university students. In line with this purpose, we believe that the present study would contribute to the literature.

Research questions

- Is there a difference between the socio-demographic characteristics of the participants and their sexual and reproductive health stigma levels?
- Is there a difference between the socio-demographic characteristics of the participants and their gender perceptions?
- Is there a relationship between the stigma of sexual and reproductive health and perception of gender?

METHODS

The population of the descriptive cross-sectional study comprised 615 female students receiving education in the Faculty of Health Sciences of a university in Turkey. The simple random sampling method, one of the non-probability sampling methods, was used in the study. While calculating the sample size of the study, the sampling method with a known universe was used. The sample of the study is; it was calculated as 237 individuals according to 5% margin of error and 95% confidence interval. However, since it was planned to reach the entire universe, the study was conducted with a total of 385 female students who volunteered to participate. The data were collected via a web-based survey form in digital media between July and October 2020. The digital survey form was shared with students in social media platforms, such as Whatsapp, Instagram, and Twitter. The online form allowed students to give only one answer. It took nearly 10 minutes to complete the survey form.

Inclusion criteria

- Being of the female sex and aged between 18 to 24 years,
- Receiving education in the Faculty of Health Sciences in the university where the study was conducted, and
- Being able to use social networks.

Exclusion criteria

- Individuals who were not students in the Faculty of Health Sciences of the university where the research was conducted, who were not women between the ages of 18–24 years, and who could not use social networks were not included in the study.

Data collection form

The "Personal Information Form," the "Sexual and Reproductive Health Stigmatization Scale in Young Women," and the "Perception of Gender Scale" were used as the data collection forms.

Personal information form

Prepared by the researchers in line with the literature,[1,7,10] this form comprised a total of 13 questions containing the socio-demographic characteristics of students, such as age, grade, parental education, number of siblings, and the region they lived in. There were no open-ended questions in the "Personal Information Form".

Sexual and Reproductive Health Stigmatization Scale in Young Women (SRHSSYW)

A scale developed by Hall et al.[5] in 2017 to determine the stigmatization associated with the sexual and reproductive health in women aged 15 to 24 years. The Turkish validity study of the scale was conducted by Bayrakçeken in 2018.[11] The original version of the scale has three subscales and 20 items. The subscales of the scale are; "Accepted Stigmatization," "Internalized Stigmatization," and "Stigma-based Attitudes." The three-point likert scale is rated as 0 = disagree, 0 = neutral, and 1 = agree. The lowest and highest scores to be obtained from the overall scale are 0 and 20, respectively. Higher scores indicate an increase of stigmatization. The Cronbach's alpha value of the scale is 0.74.[11] In this study, the Cronbach's alpha reliability coefficient of the scale was found to be 0.758.

Perception of Gender Scale (PGS)

A five-point likert scale [strongly agree (5), agree (4), undecided (3), disagree (2), and strongly disagree (1)] with 25 items was developed to evaluate gender perception of individuals. Of the items, 10 were written positively, whereas 15 were written negatively.[12] The lowest and highest scores to be obtained from the scale were 25 and 125, respectively. Higher scores indicated a "positive" gender perception, while lower scores indicated a "negative" gender perception. The Cronbach's alpha reliability coefficient of the scale was 0.872.[13] In this study, the Cronbach's alpha reliability coefficient of the scale was found to be 0.792.

Statistical analysis

The data were evaluated using the IBM SPSS statistics software, version 22 (IBM SPSS, Osmaniye, Turkey). First, the convenience of the data for normal distribution was evaluated using a Skewness and Kurtosis (±1) distribution test. All of the data were found to be normally distributed. An independent samples t-test and analysis of variance test, alongside descriptive statistics (percentage, frequency, mean, standard deviation, minimum, and maximum) were applied to assess the data. A Pearson correlation analysis was used to measure the relationship between the Stigma of Young Women's Sexual and Reproductive Health Stigma Scale and Gender Perception Scale total and sub-dimension scores.

Ethical considerations

To conduct the study, ethics committee approval (Date of approval: June 22, 2020/ Ethics committee no: E.454), institutional permission, and permissions for use of the scales were received. There was information about the purpose and content of the study and voluntary basis of the study in the survey, which was submitted to the participants. The survey did not record the the identity-related information of the participants. This study was conducted in accordance with the Declaration of the Principles of Helsinki.

RESULTS

Of the students who participated in the study, 87% were aged 19 years and above, 37.9% were the 2nd-year students, mothers of 80% of the students were primary school graduates, mothers of 89.9% were housewives, fathers of 56.4% were primary school graduates, fathers of 32.5% were self-employed, and 53% of the students had 4 or more siblings. It was determined that 77.7% of the students had an income equal to the expense, 81.3% had a monthly allowance under 1000 Turkish lira, 47.8% lived in the Mediterranean Region, 56.4% lived in a province, and 88.6% lived with their parents (**Table 1**).

It was determined that the difference between the PGS total and SRHSSYW total and subscale mean scores of the students who took part in the study was not statistically significant according to their age, mother's profession, father's education, income status, region lived, and place of residence ($P > 0.05$). There was a statistically significant difference between the Accepted Stigmatization subscale scores of the participants according to their grade; between the Stigma-based Attitudes subscale scores according to their mother's education; between the PGS total mean scores according to their father's profession and number of siblings; and between the SRHSSYW total mean scores according to their monthly allowance ($P < 0.05$) (**Table 2**).

Table 1. Distribution of the socio-demographic characteristics of the individuals (n = 385)

		n	%
Age	Under 19 years	50	13
	19 years and above	335	87
Year	1st year	106	27.5
	2nd year	146	37.9
	3rd year	74	19.2
	4th year	59	15.3
Mother's education	≤ Primary education	308	80
	High school	58	13.1
	≥ University	19	4.9
Mother's profession	Housewife	346	89.9
	Civil servant	10	2.6
	Worker	23	6
	Self-employed	6	1.6
Father's education	≤ Primary education	217	56.4
	High school	111	28.8
	≥ University	57	14.8
Father's profession	Civil servant	111	28.8
	Worker	114	29.6
	Self-employed	125	32.5
	Unemployed	35	9.1
Number of siblings	Not applicable	8	2.1
	1 sibling	87	22.6
	2-3 siblings	86	22.3
	≥ 4 siblings	204	53.0
Income status	Income less than expense	49	12.7
	Income equal to expense	299	77.7
	Income more than expense	37	9.6
Monthly allowance	Under 1000 ₺	313	81.3
	1000-2000 ₺	52	13.5
	Above 2000 ₺	20	5.2
Region lived	Mediterranean Region	184	47.8
	Aegean Region	30	7.8
	Central Anatolia Region	76	19.7
	Black Sea Region	9	2.3
	Eastern/Southeastern Anatolia Region	86	22.3
Place of residence	Province	217	56.4
	District	110	28.6
	Rural	58	15
People they lived with	Parents	341	88.6
	Mother	19	4.9
	Father	8	2.1
	Family elders	17	4.4
	Total	**385**	**100.0**

₺ = Turkish lira.

Table 2. Distribution of the socio-demographic characteristics and the Sexual and Reproductive Health Stigmatization Scale in Young Women (SRHSSYW) and Perception of Gender Scale (PGS) total and subscale mean scores of the individuals

		Accepted stigmatization	Internalized stigmatization	Stigma-based attitudes	Total SRHSSYW	PGS
		$\bar{X} \pm SD$	$\bar{X} \pm SD$	$\bar{X} \pm SD$	$\bar{X} \pm SD$	$\bar{X} \pm SD$
Age	≤ 19 years	4.58 ± 1.55	3.54 ± 1.4	6.18 ± 2.33	14.3 ± 4.02	66.76 ± 4.81
	≥ 19 years	4.73 ± 1.36	3.67 ± 1.3	6.08 ± 2.37	14.4 ± 3.67	66.85 ± 4.88
	Significance[a]	P = 0.456	P = 0.511	P = 0.788	P = 0.733	P = 0.902
Year	1st year	4.64 ± 1.40	3.86 ± 1.25	5.85 ± 2.29	14.36 ± 3.64	67.12 ± 5.17
	2nd year	4.73 ± 1.40	3.67 ± 1.29	6.21 ± 2.36	14.61 ± 3.65	66.85 ± 5.08
	3rd year	4.83 ± 1.27	3.29 ± 1.46	5.97 ± 2.38	14.10 ± 3.75	65.71 ± 4.11
	4th year	4.66 ± 1.48	3.67 ± 1.23	6.38 ± 2.45	14.72 ± 3.99	67.69 ± 4.45
	Significance[b]	P = 0.805	**P = 0.041**	P = 0.471	P = 0.732	P = 0.105
Mother's education	≤ Primary education	4.69 ± 1.39	3.63 ± 1.30	5.94 ± 2.36	14.27 ± 3.37	67.02 ± 4.59
	High school	4.89 ± 1.29	3.79 ± 1.28	6.62 ± 2.36	15.31 ± 3.45	65.58 ± 5.93
	≥ University	4.47 ± 1.57	3.52 ± 1.64	7.0 ± 1.94	15.0 ± 3.29	67.63 ± 5.16
	Significance[b]	P = 0.448	P = 0.448	**P = 0.031**	P = 0.123	P = 0.090
Mother's profession	Housewife	4.71 ± 1.40	3.63 ± 1.31	6.02 ± 2.38	14.36 ± 3.76	66.90 ± 4.85
	Civil servant	4.80 ± 0.91	4.00 ± 1.33	6.30 ± 2.31	15.10 ± 3.87	66.20 ± 4.84
	Worker	5.00 ± 1.16	4.00 ± 1.41	6.78 ± 2.19	15.78 ± 2.95	66.39 ± 5.50
	Self-employed	3.83 ± 1.60	3.00 ± 1.41	7.16 ± 1.47	14.0 ± 2.82	65.83 ± 3.65
	Significance[b]	P = 0.331	P = 0.281	P = 0.316	P = 0.322	P = 0.877
Father's education	≤ Primary education	4.76 ± 1.33	3.64 ± 1.27	5.98 ± 2.35	14.39 ± 3.19	67.0 ± 4.95
	High school	4.56 ± 1.49	3.61 ± 1.42	6.27 ± 2.17	14.45 ± 3.59	66.5 ± 4.42
	≥ University	4.82 ± 1.37	3.78 ± 1.30	6.15 ± 2.73	14.77 ± 3.97	66.8 ± 5.36
	Significance[b]	P = 0.390	P = 0.695	P = 0.557	P = 0.790	P = 0.679
Father's profession	Civil servant	4.82 ± 1.24	3.68 ± 1.29	6.24 ± 2.51	14.75 ± 3.61	65.72 ± 4.51
	Worker	4.63 ± 1.39	3.57 ± 1.40	6.00 ± 2.43	14.21 ± 3.81	66.94 ± 4.89
	Self-employed	4.72 ± 1.45	3.64 ± 1.31	5.94 ± 2.26	14.31 ± 3.80	67.43 ± 4.78
	Unemployed	4.62 ± 1.59	3.82 ± 1.17	6.48 ± 1.96	14.94 ± 3.44	67.88 ± 5.65
	Significance[b]	P = 0.732	P = 0.792	P = 0.557	P = 0.573	**P = 0.025**
Number of siblings	N/A	4.87 ± 1.35	3.12 ± 1.64	7.12 ± 1.45	15.12 ± 4.05	67.12 ± 4.79
	1 sibling	4.67 ± 1.36	3.74 ± 1.17	6.49 ± 2.29	14.91 ± 3.41	65.31 ± 5.47
	2-3 siblings	4.95 ± 1.21	3.76 ± 1.36	6.06 ± 2.56	14.79 ± 3.77	67.37 ± 5.07
	≥ 4 siblings	4.62 ± 1.46	3.58 ± 1.34	5.89 ± 2.31	14.11 ± 3.79	67.25 ± 4.38
	Significance[b]	P = 0.320	P = 0.415	P = 0.142	P = 0.257	**P = 0.011**
Income status	Income less than expense	5.08 ± 1.11	3.64 ± 1.18	6.05 ± 2.43	14.78 ± 3.51	66.27 ± 4.35
	Income equal to expense	4.70 ± 1.37	3.60 ± 1.38	6.08 ± 2.39	14.39 ± 3.76	66.89 ± 5.04
	Income more than expense	4.51 ± 1.63	3.97 ± 0.96	6.20 ± 2.17	14.69 ± 3.62	66.93 ± 4.13
	Significance[b]	P = 0.161	P = 0.179	P = 0.941	P = 0.751	P = 0.756
Monthly allowance	Under 1000 ₺	4.65 ± 1.39	3.66 ± 1.33	6.05 ± 2.34	14.38 ± 3.71	67.01 ± 4.56
	1000-2000 ₺	5.09 ± 1.08	3.76 ± 1.13	6.61 ± 2.26	115.48 ± 3.30	65.98 ± 6.40
	Above 2000 ₺	4.65 ± 1.84	3.20 ± 1.43	5.35 ± 2.70	13.20 ± 4.40	66.30 ± 4.85
	Significance[b]	P = 0.109.	P = 0.249	P = 0.101	**P = 0.041**	P = 0.321
Region lived	Mediterranean Region	4.65 ± 1.44	3.67 ± 1.23	6.26 ± 2.16	14.59 ± 3.56	66.70 ± 4.95
	Aegean Region	4.90 ± 1.24	3.60 ± 1.27	6.36 ± 2.23	14.86 ± 2.86	64.66 ± 3.67
	Central Anatolia Region	4.73 ± 1.34	3.69 ± 1.36	5.77 ± 2.69	14.21 ± 3.92	67.27 ± 4.73
	Black Sea Region	5.88 ± 0.33	3.88 ± 1.16	7.77 ± 1.09	17.55 ± 1.66	66.44 ± 5.61
	Eastern/Southeastern Anatolia Region	4.65 ± 1.38	3.55 ± 1.49	5.75 ± 2.51	13.96 ± 4.13	67.53 ± 4.94
	Significance[b]	P = 0.109	P = 0.920	P = 0.060	P = 0.068	P = 0.073
Place of residence	Province	4.67 ± 1.31	3.58 ± 1.32	6.11 ± 2.29	14.38 ± 3.61	66.53 ± 4.83
	District	4.85 ± 1.43	3.73 ± 1.33	6.10 ± 2.52	14.70 ± 3.84	67.02 ± 4.86
	Rural	4.60 ± 1.56	3.74 ± 1.27	5.98 ± 2.35	14.32 ± 3.88	67.63 ± 4.95
	Significance[b]	P = 0.441	P = 0.551	p = 0.924	P = 0.737	P = 0.273
Home residents	Parents	4.74 ± 1.33	3.64 ± 1.31	6.08 ± 2.34	14.47 ± 3.67	66.86 ± 4.88
	Mother	4.42 ± 1.62	4.00 ± 1.10	7.00 ± 1.59	15.42 ± 2.93	66.36 ± 3.78
	Father	4.50 ± 2.07	4.12 ± 1.12	7.12 ± 1.55	15.75 ± 4.13	65.75 ± 3.15
	Family elders	4.64 ± 1.76	3.17 ± 1.59	4.76 ± 3.23	12.58 ± 4.70	67.35 ± 6.37
	Significance[b]	P = 0.752	P = 0.208	**P = 0.021**	P = 0.087	P = 0.856

SD = Standard deviation, P < 0.05 ([a]independent samples t-test, [b]analysis of variance); ₺ = Turkish lira.
Bold values indicate statistical signifcance.

It was determined that the SRHSSYW total mean score was 14.46 ± 3.71 and the Accepted Stigmatization subscale mean score was 4.71 ± 1.38; the Internalized Stigmatization subscale mean score was 3.65 ± 1.31; additionally, the Stigma-based Attitudes subscale mean score was 6.09 ± 2.36 and the PGS mean score was 66.83 ± 4.86 (**Table 3**).

It was determined that there was a negative weak correlation between the SRHSSYW and the PGS (r = -0.173, P = 0.001). In other words, as the gender perception in young women increases, the sexual and reproductive health stigmatization level decreases. It was determined that there was a negative correlation between the subscales of the SRHSSYW and the PGS (**Table 4**).

DISCUSSION

Stigmatization is defined as a key social determinant of health and a driving force of health inequalities.[14] Stigmatization is conceptualized as a quality which turns humans from whole and ordinary individuals into imperfect and despised individuals and disgraces them.[4] In sexual health and reproductive health (SHRH), social, cultural, and religious norms, which enframe the sexual behaviors of adolescents and their consequences (pregnancy, early childbirth, abortion, and sexually transmitted infections) to be immoral and problematical, lead to stigmatization.[2,15]

In this study, it was seen that factors, such as age, mother's profession, father's education, income status, and region lived did not affect the gender perception and reproductive health stigmatization perception level in young women. Another study suggested that factors, such as age, city, religious belief, educational background, relationship status, unemployment, health and sexual relationship histories graded by oneself, receiving family planning services, use of modern contraceptives, number of pregnancies, and sexual intercourse, affected the SHRH stigmatization perception.[5] Additionally, in studies, it is stressed that age, marital status, income, place of residence of individuals, and socio-demographic and cultural factors especially when it comes to those who are unmarried, pose a great obstacle to benefiting from reproductive health services due to the fear of stigmatization.[16,17] A previous study conducted in Iran demonstrated that the fear of stigmatization was the greatest obstacle to benefiting from reproductive health services.[18] The basis of stigmatization is formed by prejudices and beliefs. The social, cultural, and religious norms define sexual behaviors of adolescents and their consequences (such as pregnancy, early childbirth, abortion, and sexually transmitted infections) to be immoral, and this causes the individual to be stigmatized.[2]

In the study, the sexual health stigmatization perception of the young people was higher according to the mother's education, number of siblings, and monthly allowance. It was observed that the socioeconomic level of the family affected this perception. No matter from what standpoint it is viewed, physical and psychosocial welfare has a profoundly negative impact on reproductive health stigmatization perception.[19,20] This may restrain the health and development of young people.[21] The occurrence of stigmatization is closely associated with the context and structure of society.[22] Stigmatization is experienced when an individual or a group is defined differently from a perceived norm and is subjected to labeling, shame, disapproval, and discrimination.[14] When social circumstances restrain the welfare and access to opportunities and resources, the access to healthcare services and quality care is also restrained, while the social, cultural, and gender norms hardly affect stigmatization. Notably, community-based or belief-based organizations or politicians play a key role in sustaining or struggling with stigmatization.[23]

Upon examining the literature, it has been shown that stigmatization, which is attributed to unmarried women benefiting from reproductive health services, contains situations, such as stereotypes, fear of being labeled, discrimination, and shame of receiving reproductive health services. In South Asian countries, where premarital sexual relationships are forbidden[24] and a woman's premarital virginity status is valued very much, the procurement of reproductive health services to unmarried women causes significant

Table 3. Distribution of the PGS and SRHSSYW total and subscale mean scores and minimum-maximum values

	$\bar{X}$	SD	Min-Max received
Total SRHSSYW	14.46	3.71	0-20
Accepted Stigmatization	4.71	1.38	0-6
Internalized Stigmatization	3.65	1.31	0-5
Stigma-based Attitudes	6.09	2.36	0-9
Total PGS	66.83	4.86	25-125

PGS = Perception of Gender Scale; SRHSSYW = Sexual and Reproductive Health Stigmatization Scale in Young Women; SD = standard deviation; Min-Max = minimum-maximum.

Table 4. Correlation distribution of the Perception of Gender Scale (PGS) scores and Sexual and Reproductive Health Stigmatization Scale in Young Women (SRHSSYW) total and subscale scores (n = 385)

		1	2	3	4
1 SRHSSYW Total	r				
	P				
2 Accepted Stigma	r	0.620**			
	P	**0.001**			
3 Internal Stigma	r	0.848**	0.261**		
	P	**0.001**	**0.001**		
4 Stigma-based Attitudes	r	0.646**	0.228**	0.324**	
	P	**0.001**	**0.001**	**0.001**	
5 PGS Total	r	-0.173**	-0.135**	-0.181**	-0.021
	P	**0.001**	**0.008**	**0.001**	0.678

P < 0.01 (**Correlation test); **Correlation is significant at the level of 0.01 (2-tailed). Bold values indicate statistical signifcance.

exposure from these cultures.[25] The belief that a reproductive health problem experienced by a young woman may be associated with sexual relationships causes the woman to be stigmatized and rejected by the society.[26] Stereotypical thoughts and assumptions concerning this issue lead to stigmatization and make it difficult for unmarried individuals to access reproductive health services.

There is an increasing interest in promoting gender equality and Women's and Girls' Empowerment as a way of accelerating the progress and enhancing women's health and welfare by accepting the restrictions of unequal gender power dynamics in a woman's life.[27] According to the results of the study, negative gender perception had a negative effect on sexual and reproductive health stigmatization level. Examining similar studies, it is indicated that the society associates reproductive health matters with sexual relationships, and this shapes stigmatization.[28] In their study, Rehnström Loi et al. indicated that more than 50% of Kenyan secondary school students have stigmatizing attitudes toward abortion and the use of contraceptive methods. Students of age 13–15 years and male students have a higher potential of having stigmatizing views.[29] Another study conducted in Nepal stated that cultural and gender norms were factors increasing stigmatization and discrimination.[30] This can be associated with the fact that the views of young people are influenced by social norms and cultural traditions.

The studies have stated that the SHRH understanding and perception of young women coincide with a variety of stigmatization areas. These areas are sex, pregnancy, childbirth and abortion, stigmatization of adolescent girls as "immoral," "disrespectful," and "disobedient" by society, description of adolescent girls as "mean girls" by community, stigmatization or gossip applied to young women, and negative attitudes arising from marginalization and maltreatment are shame and guilt felt by young women as a result of legalized stigmatization. Due to the stigmatization, these situations also prevent young women from using contraceptive methods and services.[15]

Limitations

This study was limited to female students, who were of age between 18 and 24 years and were enrolled at the Faculty of Health Sciences of a Turkish university, used social networks, and agreed to participate in the study. The other limitations of our research are the facts that the data collection process coincided with the pandemic period and the study was carried out within a certain time period.

CONCLUSION

According to the results of this study, factors, such as age, mother's profession, father's education, income status, region lived, and place of residence, do not affect the sexual and reproductive health stigmatization and gender perception of young women. However, socioeconomic factors, such as the mother's level of education, father's profession, number of siblings, and monthly allowance affect the stigmatization perception. The increase of gender perception in young women decreases the sexual and reproductive health stigmatization level.

In line with the results, it is important that women and girls be empowered for SHRH and global development goals, especially concerning the increasing gender equality. It is also important that universal access to SHRH services be included within the scope of healthcare services. Society, families, and unmarried women themselves should understand that sexual and reproductive health is an important part of the whole life cycle of a woman. It is necessary to overcome the prejudice that conditions related to reproductive health are certainly associated with the conclusion that a person is having sexual intercourse, to provide reproductive health service as part of health in every period of life and provide an equality of opportunity to young women to benefit from this service. It is recommended to carry out similar studies in different regions of Turkey, to plan training programs in line with the results obtained, and to establish research programs to combat the stigma.

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Ultrasound techniques for the detection of developmental dysplasia of the hip: a systematic review and meta-analysis

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ABSTRACT

BACKGROUND: Developmental dysplasia of the hip (DDH) encompasses a broad spectrum of hip pathologies, including femoral or acetabular dysplasia, hip instability, or both. According to the medical literature, ultrasonography is the most reliable diagnostic method for DDH. Several techniques for the assessment of hips in newborns and infants, using ultrasonography, have been described.

OBJECTIVE: To compare the accuracy of the Graf technique and other diagnostic techniques for DDH.

DESIGN AND SETTING: A systematic review of studies that analyzed ultrasound techniques for the diagnosis of DDH within an evidence-based health program of a federal university in São Paulo (SP), Brazil.

METHODS: A systematic search of relevant literature was conducted in the PubMed, EMBASE, Cochrane Library, CINAHL, and LILACS databases for articles published up to May 5, 2020, relating to studies evaluating the diagnostic accuracy of different ultrasound techniques for diagnosing DDH. The QUADAS 2 tool was used for methodological quality evaluation.

RESULTS: All hips were analyzed using the Graf method as a reference standard. The Morin technique had the highest rate of sensitivity, at 81.12–89.47%. The Suzuki and Stress tests showed 100% specificity. The Harcke technique showed a sensibility of 18.21% and specificity of 99.32%.

CONCLUSION: All the techniques demonstrated at least one rate (sensibility and specificity) lower than 90.00% when compared to the Graf method. The Morin technique, as evaluated in this systematic review, is recommended after the Graf method because it has the highest sensitivity, especially with the three-pattern classification of 89.47%.

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INTRODUCTION

Developmental dysplasia of the hip (DDH) encompasses a broad spectrum of hip pathologies, including femoral dysplasia, acetabular dysplasia, hip instability, and any combination of these, as well as the subluxation or dislocation of the femoral head.[1-5] Although the exact cause of DDH remains unknown,[5] it is the most common congenital abnormality of the musculoskeletal system,[4,6] with an incidence of 1.6–28.5 cases per 1,000 live births and a prevalence of 0.15–4.0%.[5,7-11] Of individuals in whom congenital dislocation of the hip is not treated, up to 94% of individuals will develop moderate or severe osteoarthritis in the second decade of life.[8]

Although DDH was first described more than two millennia ago, there is still some controversy regarding the etiology, diagnosis, and methods of treatment.[12,13] Early diagnoses became more meaningful after it was discovered that hip dysplasia was not only genetic, but also developmental.[8] Studies on the diagnosis, monitoring, and treatment of DDH have produced results that are controversial or contradictory.[12] Those discrepancies could be attributable to a variation in the physiological development of the hip being misinterpreted as a pathological process, to differences in the terminology employed by radiologists and clinicians, or to differences in the physical examination and hip ultrasound standards.[12]

An early diagnosis of DDH aids in the prognosis and success of treatment, especially nonsurgical treatment.[7,14–16] Approximately 10% of all hip arthroplasty procedures in adults are performed to correct disorders that arise in childhood, primarily DDH.[15] A diagnostic delay of three months or more increases the probability of surgery being needed to correct the problem.[4] A diagnosis of DDH is the indication for hip arthroplasty in up to 9% of patients under 65 years

of age and in 25% in those under 40 years of age who develop premature arthrosis.[4,8,11,17,18]

In cases in which DDH is treated inappropriately, the main complication is avascular necrosis of the femoral head.[5,11,19] In such cases, the diagnostic method of choice is magnetic resonance imaging.[20] The risk factors for DDH include the following:[1,19]

- Family history
- Female sex (4–6 times higher risk)
- First-born status
- Low birth weight (< 2,500 g)
- Oligohydramnios
- Breech position *in utero*
- Prematurity (< 37 weeks of gestation)
- Twinning
- The practice of swaddling (wrapping the newborn tightly in cloth), which keeps the hips in an extended, adducted position that can create an abnormal relationship between the head of the femur and acetabulum

Despite being operator-dependent, ultrasonography is considered as the most reliable method for the diagnosis of DDH in the neonatal period.[12,17,21,22] It is a noninvasive method that does not involve the use of radiation, and is portable and easy to use. However, a physician must perform more than 100 ultrasound examinations to be considered as qualified.[13,15,23-26] Ultrasonography of the hip detects 52% more pathological hips than the Ortolani and Barlow tests.[14] In addition, ultrasonography makes it possible to perform a dynamic study and the Ortolani and Barlow maneuvers simultaneously.[14,15] Various techniques have been described for the ultrasound assessment of hips in newborns and infants, although there is no consensus as to which technique is the best.[27,28]

OBJECTIVE

The objective of this study was to determine the detection rates and accuracy of different two-dimensional ultrasound techniques for the diagnosis of DDH using the Graf method as a reference. To this end, we conducted a systematic review of the literature on this topic.

METHODS

Study model

The study design followed the model outlined in the Cochrane Handbook for Systematic Reviews of Diagnostic Test Accuracy, version 5.1.[29] The review was registered with the International Prospective Register of Systematic Reviews (identifier: CRD42020189686).

Inclusion criteria

This review was performed in accordance with the Preferred Reporting Items for Systematic Reviews and Meta-Analyses statement.[30] We included comparative studies on the diagnostic accuracy of the Graf technique and at least one other technique for diagnosing DDH in the first year of life, among patients with or without risk factors for the condition. The other techniques included the Finnbogason, Harcke, Morin, Rosendahl, stress test, Suzuki, Terjesen, and Tréguier techniques. We did not impose any restrictions with respect to the patient origin, article language, sample size, or publication status of the studies.

Patients

Among the selected studies, all patients were of age ≤ 12 months. The study sample included infants who underwent ultrasound for routine screening or were considered to be at a high risk for DDH.

Study selection and data extraction

The selected studies were those potentially eligible for inclusion in terms of the relevance of the abstracts or full texts. Two authors, working independently, determined their eligibility. Disagreements were resolved through a consensus. Data extraction was performed using a standardized form. The selection process was carried out on the Rayyan platform.[31] In case of missing data, we contacted the authors of the study by e-mail.

Evaluation of the methodological quality

For all the eligible studies, we employed the Quality Assessment of Diagnostic Accuracy Studies 2 tool,[32] which focuses on the evaluation of bias and accuracy. All analyses were performed and all diagrams were created using the Review Manager program (version 5.3, RevMan; Cochrane Collaboration, Oxford, United Kingdom). The Review Manager program was used to calculate the sensitivity and specificity, as well as the corresponding 95% confidence intervals (CIs), for the previously mentioned criteria.

Search strategies

We performed a thorough systematic search for original articles in the following databases (from inception to May 5, 2020): PubMed, Excerpta Medica, Cochrane Library, Cumulative Index to Nursing and Allied Health Literature, and Latin-American and Caribbean Health Sciences Literature. We used the National Library of Medicine Medical Subject Headings "Hip Dislocation, Congenital" and "Ultrasonography," together with the term "Graf." Additionally, we performed manual searches of the reference lists of the included studies and evaluated the main reviews of the subject. **Appendix 1** provides the full search strategy.

Evaluated techniques of ultrasonography

Graf

The Graf method consists of the evaluation of a conventional coronal view with the patient in the lateral position, providing

qualitative and quantitative assessments of the hip.[17,33-35] The Graf method classifies the degree of coverage of the bony acetabular roof (alpha angle) and cartilaginous acetabular roof (beta angle). For the meta-analysis, we considered that following the guidance provided by Graf,[36] a type IIA–hip was an indication for treatment.

Morin

In the Morin technique,[37] a coronal image of the flexed hip was evaluated to estimate the percentage of the femoral head that was medial to the lateral iliac margin (the "iliac line," resembling the Graf "baseline") and consequently covered by the bony acetabulum. The studies analyzed used different classifications of normal test results. Therefore, each study was evaluated individually.

Suzuki

In the Suzuki technique,[14,38] the hips of the patient were maintained in abduction (in flexion or extension) and a long linear probe was positioned transversely over the lower pelvis in the region of the pubic bones. The purpose was to delineate the location of the femoral head. In the meta-analysis, we considered that a slight dislocation should not be classified as a normal test result and was an indication for treatment.

Terjesen

In the Terjesen technique,[27,28,39] a coronal profile image was evaluated with the hip lightly flexed, and a line was traced parallel to the long axis of the ultrasound probe. The iliac bone should always be examined as a straight line parallel to the edge of the coronal mid-acetabular image. The analyzed studies used different classifications of normal test results. Therefore, we individually evaluated each classification.

Tréguier

Tréguier et al.[40] defined the pubofemoral distance (PFD) as the distance between the most medial aspect of the femoral head and the most lateral aspect of the pubis. The Tréguier technique involved the measurement of the pubofemoral distance (PFD) in the coronal plane, which includes the largest circumference of the femoral head and the most lateral aspect of the pubis.

Harcke

In the Harcke technique,[13,14,17] the patient was placed in the supine position, the hip was maneuvered through the neutral and flexed positions with and without the aid of stress (Barlow maneuver), and the lateral transverse and coronal aspects were evaluated. The main target was the femoral head at rest and during the stress examination.

Finnbogason

In the Finnbogason technique,[41,42] the patient was placed in the supine position and the ultrasound probe was positioned anterior and parallel to the longitudinal axis of the femoral neck. This produced an oblique sagittal image of the hip, including the anterior acetabular rim as well as the femoral head and neck. The probe was placed in a holder, which allowed the physician to have both hands free. The physician employed downward pressure, with the target hip in the flexion and mid-abduction positions (Barlow maneuver) with one hand while using the other hand to keep the patient in the correct position. In the meta-analysis, an unstable hip was classified as abnormal.

Stress test

For the ultrasound stress test,[43] the patient was placed in the lateral position, and a dynamic stress test was performed in the coronal plane, with the hip in flexion. For the meta-analysis, a lax hip was classified as abnormal.

Rosendahl

In the Rosendahl technique,[44] the patient was placed in the lateral position, the ultrasound probe was positioned laterally, and the physician performed a stress test (adjusted Barlow maneuver) with one hand while using the other hand to maintain the ultrasound probe in the correct position. In this meta-analysis, an elastic hip was classified as abnormal.

RESULTS

Selected studies

We conducted a systematic review of 494 studies. At the end of the selection process, 15 studies were deemed to meet the inclusion criteria and present acceptable quality, as determined using the Quality Assessment of Diagnostic Accuracy Studies 2 tool. Therefore, all 15 studies were included in the systematic review (**Figure 1**), as well as in the meta-analysis.

Analysis on the studies

In one study, there was a concern of bias in patient selection because the study sample included only male patients. Two other studies did not describe the patient-selection process. In two studies, the comparative technique was performed after the results of the Graf method were known, and in five studies, the order of application of the methodologies was not noted. In three studies, there were concerns regarding the application of the Graf method because only the alpha angle was evaluated. All the patients were younger than 12 months of age. In most studies, the Graf method and comparative technique were performed on the same day (**Figures 2** and **3**). Overall, 15 studies evaluated 16,736 hips. The Graf method was

compared with the Morin technique in two studies,[37,45] with the Suzuki technique in two studies,[14,38] with the Terjesen technique in three studies,[27,28,39] with the Tréguier technique in two studies,[46,47] with the Harcke technique in two studies,[14,48] with the Finnbogason technique in two studies,[41,42] with the stress test in one study,[43] and with the Rosendahl technique in one study.[44]

As shown in **Table 1A**, Gunay et al.[45] used the Morin technique to evaluate 2,074 hips, dividing the findings into two categories by the proportion of acetabular coverage of the femoral head: ≥ 51% (mature hip) and < 51% (immature hip). The authors found that the Morin technique had a sensitivity of 81.12% and specificity of 82.70% ($P < 0.05$), with an overall accuracy of 82.59%. In a study of 100 hips, Irha et al.[37] also evaluated the Morin technique, dividing the findings into three categories according to the proportion of acetabular coverage of the femoral head: ≥ 58% (normal hip), 33–58% (borderline pathological hip), and < 33% (pathological hip). We considered hips with a coverage ≥ 58% as normal when the three-category Morin technique was used because borderline cases could evolve to a pathological status. Irha et al.[37] found a technique with a sensitivity of 89.47% and a specificity of 83.95% ($P < 0.05$), with an overall accuracy of 85.00% (**Table 1B**).

Table 2 shows the detection rates for the Suzuki technique, which was analyzed in two studies.[14,38] The technique was found to have a sensitivity of 39.36% and a specificity of 100.00% ($P < 0.05$), with an overall accuracy of 69.21%. The two studies evaluated a total of 1,166 hips.

Falliner et al.[28] and Peterlein et al.[39] compared the Graf method with the Terjesen technique (**Table 3A**), evaluating a collective total of 878 hips and dividing the findings into two categories according to the proportion of acetabular coverage of the femoral head, each

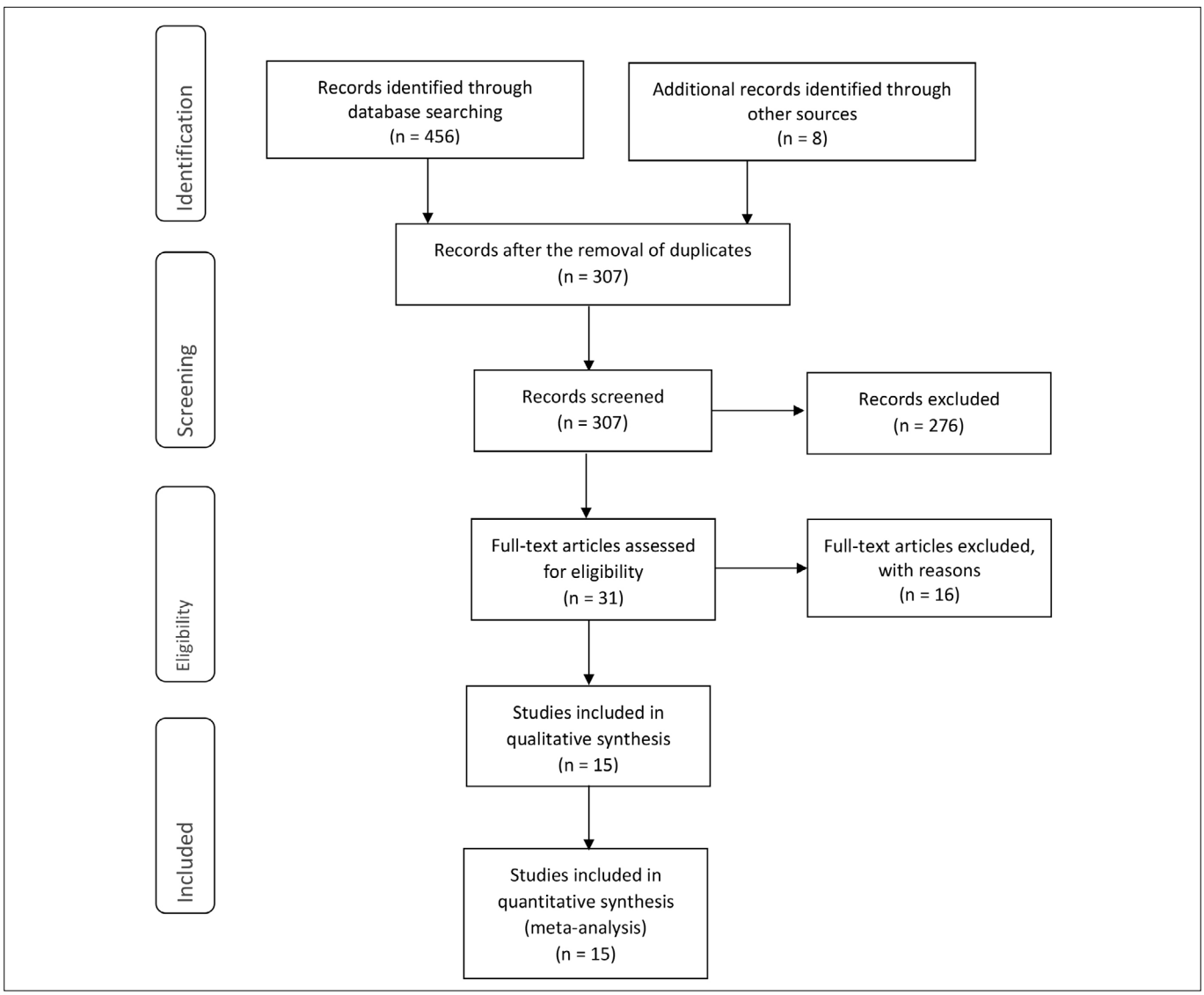


Figure 1. Preferred Reporting Items for Systematic Reviews and Meta-Analyses flow diagram.

with separate cutoff values for male and female patients: ≥ 47% and ≥ 44%, respectively (normal hip), and < 47% and < 44%, respectively (pathological hip). Collectively, the two studies showed that the technique had a sensitivity of 14.41% and a specificity of 99.74% (P < 0.05), with an overall accuracy of 88.30%. In a study involving 1,312 hips, Czubak et al.[27] also evaluated the Terjesen technique (**Table 3B**), dividing the hips into four categories according to the proportion of femoral head coverage: ≥ 50% (normal hip), 49–40% (possible hip dysplasia), 39–10% (hip subluxation), and < 10% (hip dislocation). In this systematic review, findings of possible dysplasia, subluxation, and dislocation were considered to be indicative of an abnormal hip. In the Czubak et al.[27] study, the technique was found to have a sensitivity of 39.39% and specificity of 93.47% (P < 0.05), with an overall accuracy of 75.99%.

Teixeira et al.[46] used the Tréguier technique to evaluate 232 hips under four different conditions (**Table 4A**):

- A hip in flexion with a PFD of 3.3 millimeters (mm)—sensitivity of 76.19% and a specificity of 64.21% (P < 0.05), with an overall accuracy of 66.38%.
- A hip in flexion with a PFD of 4.9 mm—sensitivity of 59.52% and a specificity of 88.95% (P < 0.05), with an overall accuracy of 83.62%.
- A hip in the neutral position with a PFD of 4.0 mm—sensitivity of 50.00%, specificity of 93.68% (P < 0.05), and an overall accuracy of 85.78%.
- A hip in the neutral position with a PFD of 4.6 mm—sensitivity of 50.00%, specificity of 93.68% (P < 0.05), and an overall accuracy of 85.78%.

In a similar study, Motta et al.[47] applied the Tréguier technique to 1,980 hips, all of which were evaluated with the hip in flexion and with a PFD of 3.0 mm (**Table 4B**). The authors found that the technique had a sensitivity of 63.55% and a specificity of 62.22% (P < 0.05), with an overall accuracy of 62.42%.

Diaz et al.[14] and Koşar et al.[48] both evaluated the Harcke technique (**Table 5**). Collectively, the two studies showed that the technique had a sensitivity of 18.21% and specificity of 99.32% (P < 0.05), with an overall accuracy of 84.47%. The two studies evaluated a collective total of 3,058 hips.

As detailed in **Table 6**, the Finnbogason technique was evaluated in two separate studies.[41,42] Collectively, the two studies showed that the technique had a sensitivity of 39.48% and specificity of 96.83% (P < 0.05), with an overall accuracy of 83.73%. Two studies evaluated a collective total of 1,186 hips.

Poul et al.[43] applied the stress test technique to the evaluation of 1,744 hips (**Table 7**). The authors found that the technique had a sensitivity and specificity of 39.48% and 96.83%, respectively (P < 0.05), with an overall accuracy of 97.94%.

Figure 3. Summary risk of bias and applicability concerns, as determined with the Quality Assessment of Diagnostic Accuracy Studies 2 tool.

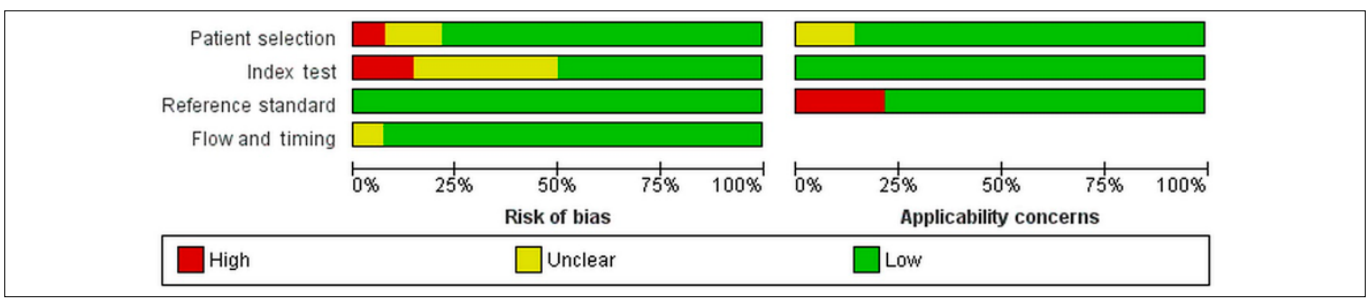


Figure 2. Risk of bias and applicability concerns, as determined with the Quality Assessment of Diagnostic Accuracy Studies 2 tool.

Table 8 shows the results of a study analyzing the accuracy of the Rosendahl technique in a sample of 3,006 hips.[44] This technique was found to have a sensitivity of 50.78% and specificity of 97.51% ($P < 0.05$), with an overall accuracy of 89.49%.

The accuracy and DDH prevalence data for all 15 studies have been summarized in **Table 9**. The sensitivity and specificity data were also analyzed in forest plots (**Figure 4**), along with summary receiver operating characteristic curves (**Figure 5**).

DISCUSSION

In the studies selected for review, the Graf method was used as a reference for the diagnosis of DDH. Among the other analyzed techniques, the Morin technique had the highest sensitivity (81.12%) when the proportion of acetabular coverage of the femoral head was divided into two categories and 89.47% when it was divided into three categories, whereas the specificity was 83.95% and 82.70%, respectively. In terms of the

Table 1A. Summary of detection rates using the Morin technique with two categories

	Graf method		Morin technique	
	DDH/Hips evaluated	Detection rate	DDH/Hips evaluated	Detection rate
Gunay et al.,[45] 2009	143/2074	6.89%	450/2074	21.69%

DDH = developmental dysplasia of the hip.

Table 1B. Summary of detection rates using the Morin technique with three categories

	Graf method		Morin technique	
	DDH/Hips evaluated	Detection rate	DDH/Hips evaluated	Detection rate
Irha et al.,[37] 2004	19/100	19.00%	30/100	30.00%

DDH = developmental dysplasia of the hip.

Table 2. Summary of detection rates using the Suzuki technique

	Graf method		Suzuki technique	
	DDH/Hips evaluated	Detection rate	DDH/Hips evaluated	Detection rate
Diaz et al.,[14] 1993	206/416	49.51%	79/416	18.99%
Diaz et al.,[38] 1995	386/750	51.46%	154/750	20.53%
Total	**592/1,166**	**50.77%**	**233/1,166**	**19.98%**

DDH = developmental dysplasia of the hip.

Table 3A. Summary of detection rates using the Terjesen technique with two categories

	Graf method		Terjesen technique	
	DDH/Hips evaluated	Detection rate	DDH/Hips evaluated	Detection rate
Falliner et al.,[28] 2006	86/464	18.53%	19/464	4.09%
Peterlein et al.,[39] 2010	32/414	7.72%	00/414	00.00%
Total	**118/878**	**13.43%**	**19 / 878**	**2.16%**

DDH = developmental dysplasia of the hip.

Table 3B. Summary of detection rates using the Terjesen technique with four categories

	Graf method		Terjesen technique	
	DDH/Hips evaluated	Detection rate	DDH/Hips evaluated	Detection rate
Czubak et al.,[27] 1998	424/1,312	32.31%	225/1,312	17.14%

DDH = developmental dysplasia of the hip.

Table 4A. Summary of detection rates using the Tréguier technique according to Teixeira et al.,[46] 2015

	Graf method		Tréguier technique	
	DDH/Hips evaluated	Detection rate	DDH/Hips evaluated	Detection rate
Flexion 3.3 mm	42/232	18.10%	100/232	43.10%
Flexion 4.9 mm	42/232	18.10%	46/232	19.82%
Neutral 4.0 mm	42/232	18.10%	33/232	14.22%
Neutral 4.6 mm	42/232	18.10%	33/232	14.22%

DDH = developmental dysplasia of the hip.

Table 4B. Summary of detection rates using the Tréguier technique according to Motta et al.,[47] 2021

	Graf method		Tréguier technique	
	DDH/Hips evaluated	Detection rate	DDH/Hips evaluated	Detection rate
Flexion 3.0 mm	310/1,980	15.65%	828/1,980	41.81%

DDH = developmental dysplasia of the hip.

Table 5. Summary of detection rates using the Harcke technique

	Graf method		Harcke technique	
	DDH/Hips evaluated	Detection rate	DDH/Hips evaluated	Detection rate
Diaz et al., [14] 1993	206/416	49.51%	79/416	18.99%
Koşar et al., [48] 2011	354/2,642	13.39%	40/2,642	1.51%
Total	**560/3,058**	**18.31%**	**119/3,058**	**3.89%**

DDH = developmental dysplasia of the hip.

Table 6. Summary of detection rates using the Finnbogason technique

	Graf method		Finnbogason technique	
	DDH/Hips evaluated	Detection rate	DDH/Hips evaluated	Detection rate
Finnbogason et al.,[42] 1997	20/114	17.54%	05/114	4.38%
Finnbogason et al.,[41] 2008	251/1,072	23.41%	131/1,072	12.22%
Total	**271/1,186**	**22.84%**	**136/1,186**	**11.46%**

DDH = developmental dysplasia of the hip.

Table 7. Summary of detection rates using the Stress test technique

	Graf method		Stress test technique	
	DDH/Hips evaluated	Detection rate	DDH/Hips evaluated	Detection rate
Poul et al.,[43] 1998	39/1,744	2.23%	03/1,744	0.17%

DDH = developmental dysplasia of the hip.

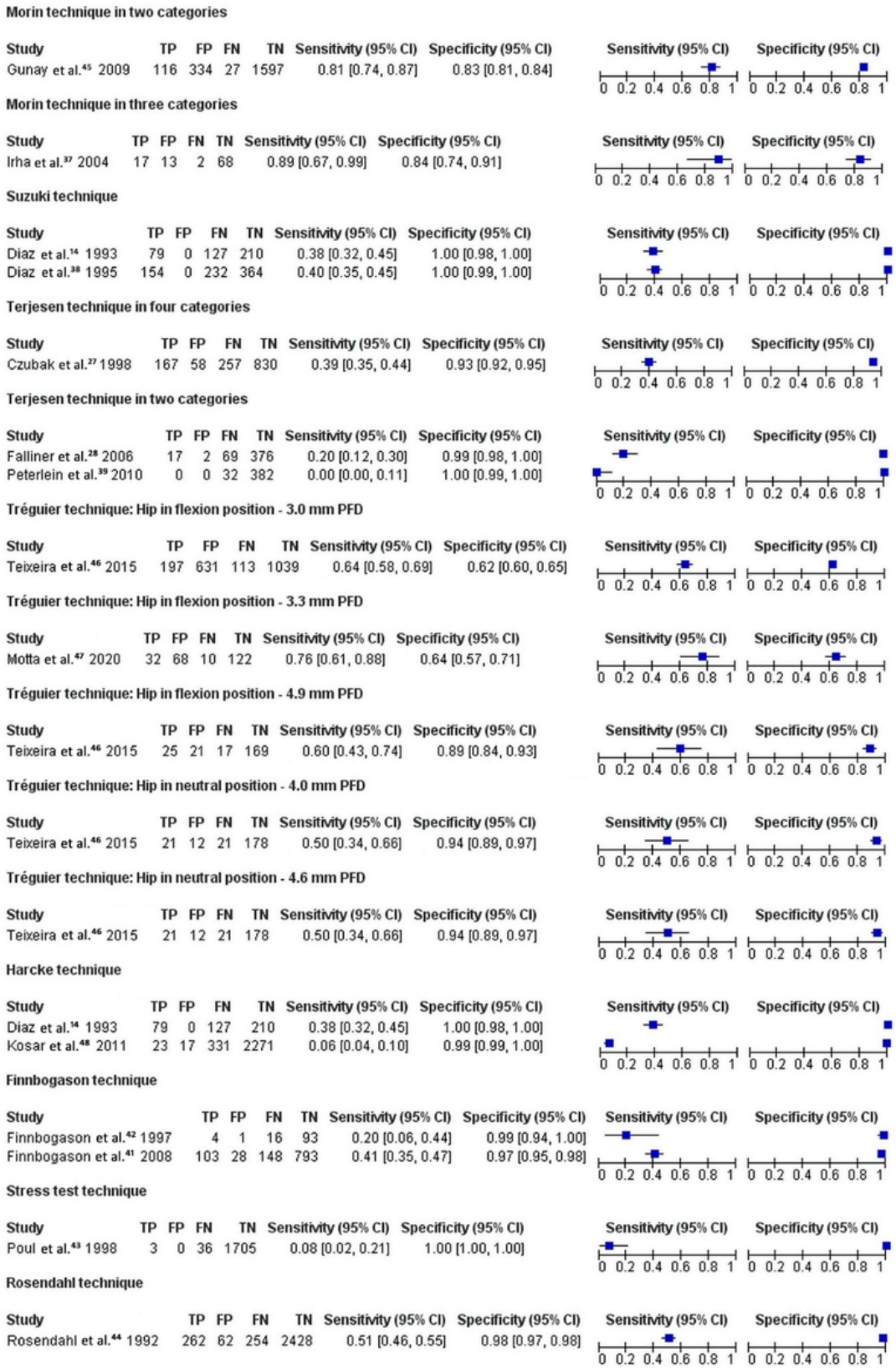
Table 8. Summary of detection rates using the Rosendahl technique

	Graf method		Rosendahl technique	
	DDH/Hips evaluated	Detection rate	DDH/Hips evaluated	Detection rate
Rosendahl et al.,[44] 1992	416/3,006	13.83%	324/3,006	10.77%

DDH = developmental dysplasia of the hip.

Table 9. Summary of sensitivity, specificity, prevalence, and hips evaluated by all techniques

	Sensitivity	Specificity	Prevalence	Accuracy	Hips evaluated
Morin with two patterns	81.12%	82.70%	6.89%	82.59%	2,074
Morin with three patterns	89.47%	83.95%	19.00%	85.00%	100
Suzuki	39.36%	100.00%	50.77%	62.21%	1,166
Terjesen with two patterns	14.41%	99.74%	13.41%	88.30%	878
Terjesen with four patterns	39.39%	93.47%	32.32%	75.99%	1,312
Tréguier flexion 3.0 mm	63.55%	62.22%	15.66%	62.42%	1,980
Tréguier flexion 3.3 mm	76.19%	64.21%	18.10%	66.38%	232
Tréguier flexion 4.9 mm	59.52%	88.95%	18.10%	83.62%	232
Tréguier neutral 4.0 mm	50.00%	93.68%	18.10%	85.78%	232
Tréguier neutral 4.6 mm	50.00%	93.68%	18.10%	85.78%	232
Harcke	18.21%	99.32%	18.31%	84.47%	3,058
Finnbogason	39.48%	96.83%	22.85%	83.73%	1,186
Stress test	7.69%	100.00%	2.24%	97.94%	1,744
Rosendahl	50.78%	97.51%	17.17%	89.49%	3,006

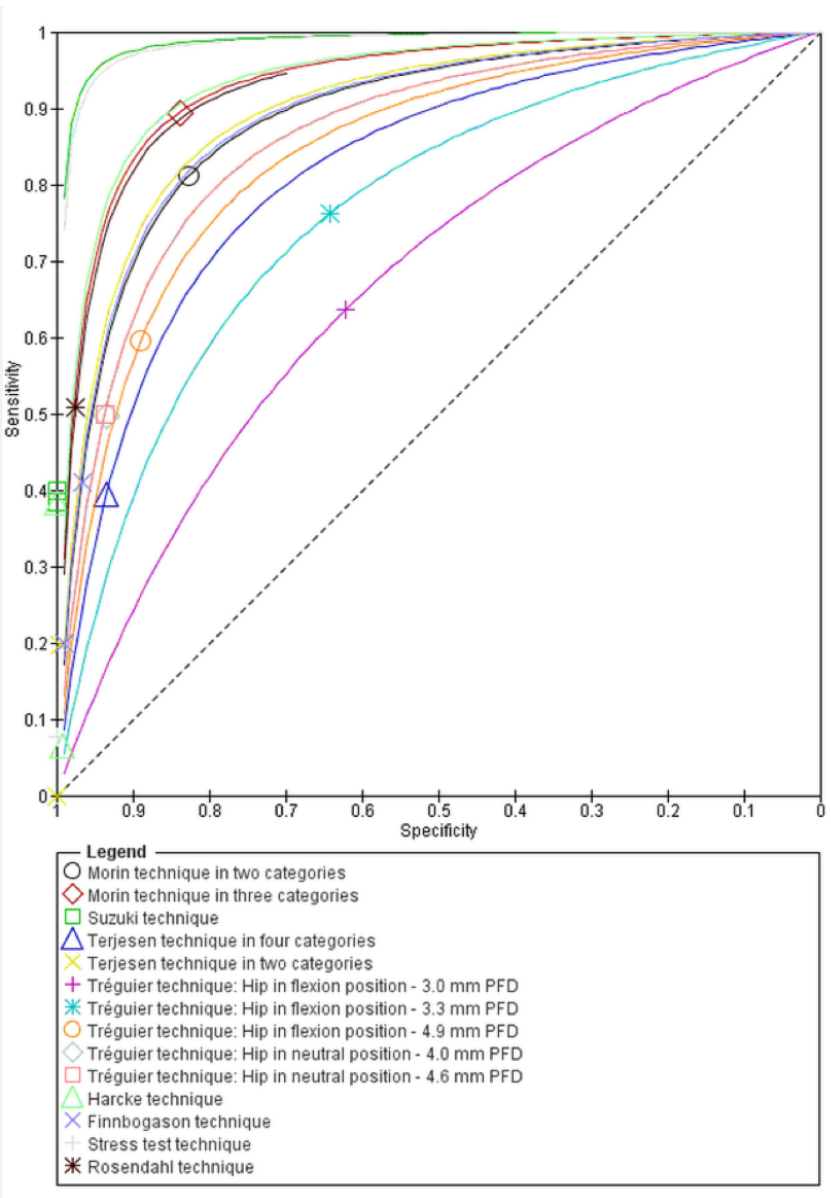


TP = true positive; FP = false positive; FN = false negative; TN = true negative; PFD = pubofemoral distance; CI = confidence interval.

Figure 4. Forest plots of the sensitivity and specificity of the ultrasound techniques evaluated.

specificity, the techniques that showed the best performance were the Suzuki technique and stress test, both of which showed a specificity of 100.00%, compared with 99.74% for the two-category Terjesen technique, 99.32% for the Harcke technique, 96.83% for the Finnbogason technique, and 97.51% for the Rosendahl technique.

The technique that showed the stress test had the highest overall accuracy, which was found to be 97.94%, compared with that of the Graf method, although its sensitivity was low (7.69%). The Rosendahl technique provided the second-highest overall accuracy, which was 89.49%, compared with 88.30% for the two-category Terjesen technique, 85.00% for the three-category Morin technique, 83.73% for the Finnbogason technique, and 83.73% for the Harcke technique. The high accuracy of some of these techniques could be attributed to the low prevalence of DDH in the hips that were studied. The sensitivity of the Tréguier technique was highest (76.19%) when the hip was in flexion and the PFD was 3.3 mm, whereas the specificity and accuracy of the technique were highest (93.68% and 85.78%, respectively) when the hip was in the neutral position, regardless of the PFD. Techniques with the highest specificity were also those with the lowest sensitivity.



PFD = pubofemoral distance.

Figure 5. Summary receiver operating characteristic curves for the sensitivity and specificity of the ultrasound techniques evaluated.

The most common methods of screening for DDH in newborns are serial physical examinations of the hip, using the Ortolani and Barlow maneuvers, and ultrasonography.[12,23] The American Academy of Pediatrics recommends routine screening for DDH through clinical examination by qualified personnel.[49] However, the physical examination does not safely diagnose dysplastic hips and may also fail to identify unstable or even dislocated hips.[12] Regarding newborns who undergo universal ultrasound screening, 5–7% are treated for hip dysplasia, compared with only 2% of those who undergo clinical screening alone.[2]

The Graf method is the ultrasound technique preferred by most physicians and is most widely employed.[35] Although relatively simple and reproducible, the Graf method requires that the image of the hip be acquired in a specific spatial plane and that anatomical landmarks are properly identified.[17] Those requirements can be challenging, especially for less experienced examiners,[17] and some studies have shown poor intraobserver and interobserver agreement.[50] The main complaint related to the Graf method is that it requires considerable training. Nevertheless, the image recommended by the Graf method is the same as that recommended by other techniques. To perform a satisfactory examination, it is crucial to recognize eight anatomical markers of the hip, namely:[17] acetabular bony rim, acetabular bony roof, acetabular hyaline cartilage, acetabular labrum, chondro-osseous junction, femoral head, hip joint capsule and synovial fold.

After the Graf method, which is considered to be the gold standard, the Morin technique is the second most recommended because it has the highest sensitivity, particularly when the three-category version of the technique is employed. Because the Morin technique is more easily performed and has a relatively high sensitivity and specificity, it could be used as a screening method in locations where there is no specialist with sufficient experience to perform the Graf method. If the Morin technique indicated a pathological hip, the patient was transferred to a referral center for evaluation using the Graf method. Owing to its low sensitivity, the Harcke technique is not recommended as a screening method. The Suzuki technique and the stress test both show high specificity and could therefore serve as complements to other techniques with high sensitivity, such as the Morin technique.

CONCLUSION

The importance of this systematic review is to demonstrate the detection rates and accuracy of different techniques of ultrasound diagnosis of DDH using the Graf method as a reference. None of the techniques displayed a sensitivity greater than 90.00% compared to the Graf method; the most comparable is the Morin technique divided into three patterns of bony rim percentage coverage over the femoral head (89.47%). With respect to the specificity, only the Morin technique (82.00–84.00%) and three different measures with the flexioned hip in the Tréguier technique (62.00–89.00%) demonstrated a rate inferior to 90.00%. Regarding the accuracy, the stress test proposed by Poul showed a rate superior to 90.00% (97.94%), followed by the Rosendahl technique (89.49%) and the Terjesen technique, which was divided into two groups of femoral head cover (88.30%).

However, all techniques demonstrated at least one rate lower than 90.00% when compared to the Graf method. The Morin technique, as evaluated in this systematic review, is recommended after the Graf method because it has the highest sensitivity, especially with the three-pattern classification of 89.47%. The Morin technique is simpler than the Graf technique. With this advantage, the Morin technique can be used for screening in areas that do not have a professional with satisfactory expertise to perform the Graf method. In circumstances where the Morin technique defines an unhealthy hip, the patient is forwarded to a reference location for a specific test using the Graf method.

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Appendix 1. Search strategy by database

Database	Search strategy
Cochrane Library	1: MeSH descriptor: [Hip Dislocation, Congenital] explode all trees #2: MeSH descriptor: [Ultrasonography] explode all trees #3: "Graf" #4: #1 AND #2 AND #3
MEDLINE	#1: "Hip Dislocation, Congenital"[MeSH] OR (Congenital Hip Dislocations) OR (Dislocations, Congenital Hip) OR (Hip Dislocations, Congenital) OR (Congenital Hip Dislocation) OR (Congenital Hip Displacement) OR (Congenital Hip Dysplasia) OR (Congenital Hip Dysplasias) OR (Dysplasias, Congenital Hip) OR (Hip Dysplasias, Congenital) OR (Hip, Dislocation Of, Congenital) OR (Dislocation, Congenital Hip) OR (Displacement, Congenital Hip) OR (Dysplasia, Congenital Hip) OR (Hip Displacement, Congenital) OR (Congenital Hip Displacements) OR (Displacements, Congenital Hip) OR (Hip Displacements, Congenital) OR (Hip Dysplasia, Congenital) OR (Congenital Dysplasia Of The Hip) OR (Dislocation Of Hip, Congenital) OR (Hip Dysplasia, Congenital, Nonsyndromic) #2: "Ultrasonography"[MeSH] OR (Echotomography) OR (Diagnostic Ultrasound) OR (Diagnostic Ultrasounds) OR (Ultrasound, Diagnostic) OR (Ultrasounds, Diagnostic) OR (Sonography, Medical) OR (Medical Sonography) OR (Ultrasound Imaging) OR (Imaging, Ultrasound) OR (Imagings, Ultrasound) OR (Ultrasound Imagings) OR (Echography) OR (Ultrasonic Imaging) OR (Imaging, Ultrasonic) OR (Echotomography, Computer) OR (Computer Echotomography) OR (Tomography, Ultrasonic) OR (Ultrasonic Tomography) OR (Diagnosis, Ultrasonic) OR (Diagnoses, Ultrasonic) OR (Ultrasonic Diagnoses) OR (Ultrasonic Diagnosis) #3: "Graf" #4: #1 AND #2 AND #3
EMBASE (OvidSP)	#1: congenital hip dislocation/exp #2: "echography"/exp #3: "Graf" #4: #1 AND #2 AND #3
LILACS	#1: mh: "Luxação Congênita de Quadril" OR (Luxación Congénita de la Cadera) OR (Hip Dislocation, Congenital) OR (Congenital Dysplasia Of The Hip) OR (Congenital Hip Dislocation) OR (Congenital Hip Dislocations) OR (Congenital Hip Displacement) OR (Congenital Hip Displacements) OR (Congenital Hip Dysplasia) OR (Congenital Hip Dysplasias) OR (Dislocation Of Hip, Congenital) OR (Dislocation, Congenital Hip) OR (Dislocations, Congenital Hip) OR (Displacement, Congenital Hip) OR (Displacements, Congenital Hip) OR (Dysplasia, Congenital Hip) OR (Dysplasias, Congenital Hip) OR (Hip Dislocations, Congenital) OR (Hip Displacement, Congenital) OR (Hip Displacements, Congenital) OR (Hip Dysplasia, Congenital) OR (Hip Dysplasia, Congenital, Nonsyndromic) OR (Hip Dysplasias, Congenital) OR (Hip, Dislocation Of, Congenital) OR mh:C05.660.449 OR mh:C16.131.621.449 #2: mh: "Ultrassonografia" OR (Ultrasonografía) OR (Ultrasonography) OR (Ecografia) OR (Ecotomografia Computador) OR (Sonografia Médica) OR (Ecografia Médica) OR (Tomografia Ultrassônica) OR (Diagnóstico Ultrassom) OR (Imagem Ultrassônica) OR (Imagem Ultrassonográfica) OR (Imagem Ultrassom) OR (Imagem Ultrassom) OR (Ecotomografia) OR mh:E01.370.350.850$ #3: "Graf" #4: #1 AND #2 AND #3
CINAHL	#1: Hip Dislocation, Congenital #2: Ultrasonography or ultrasound or sonography or echography #3: Graf #4: #1 and #2 and #3

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Effectiveness and safety of tocilizumab for COVID-19: a systematic review and meta-analysis of randomized clinical trials

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KEY WORDS (MeSH terms):
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SARS-CoV-2.
Tocilizumab [supplementary concept].

AUTHORS' KEY WORDS:
COVID-19 treatment.
Respiratory failure.
COVID-19 pneumonia.

ABSTRACT

BACKGROUND: Tocilizumab is an anti-human interleukin 6 receptor monoclonal antibody that has been used to treat coronavirus disease 2019 (COVID-19). However, there is no consensus on its efficacy for the treatment of COVID-19.

OBJECTIVE: To evaluate the effectiveness and safety of tocilizumab for treating COVID-19.

DESIGN AND SETTING: Systematic Review of randomized controlled trials (RCTs), Universidade Federal de São Paulo (UNIFESP), São Paulo (SP), Brazil.

METHODS: We searched MEDLINE via PubMed, EMBASE, CENTRAL, and IBECS for RCTs published up to March 2021. Two authors selected studies and assessed the risk of bias and the certainty of the evidence following Cochrane Recommendations.

RESULTS: Eight RCTs with 6,139 participants were included. We were not able to find differences between using tocilizumab compared to standard care on mortality in hospitalized patients with COVID-19 (risk ratio (RR) 0.97, 95% confidence interval (CI) 0.84 to 1.13; 8 trials; 5,950 participants; low-certainty evidence). However, hospitalized patients under tocilizumab plus standard care treatment seemed to present a significantly lower risk of needing mechanical ventilation (risk ratio = 0.78; 95% CI 0.64–0.94 moderate-certainty of evidence).

CONCLUSIONS: To date, the best evidence available shows no difference between using tocilizumab plus standard care compared to standard care alone for reducing mortality in patients with COVID-19. However, as a finding with a practical implication, the use of tocilizumab in association to standard care probably reduces the risk of progressing to mechanical ventilation in those patients.

REGISTRATION: osf.io/qe4fs.

INTRODUCTION

Description of the condition

Over 160 million cases of coronavirus disease 2019 (COVID-19) have been reported around the world, with more than 3.3 million deaths.[1] The COVID-19 pandemic, initiated in 2020, encouraged extraordinary efforts on research regarding pharmacological interventions and vaccines. Despite that, few pharmacological interventions have shown to be effective in the treatment of COVID-19.

COVID-19 infection is similar to Middle East respiratory syndrome and severe acute respiratory syndrome (SARS-COV-1),[2] with two phases of development: the intense viral replication followed by the immune system response, flooding the host with proinflammatory cytokines. The uncontrolled inflammatory response leads to severe acute respiratory syndrome, which represents the worst prognostic factor in patients with COVID-19.[3] Interleukin-6 (IL-6) is released as part of the acute-phase response. When higher levels are achieved, the probability of severe coronavirus disease and risk of mechanical ventilation are elevated.[4-6]

Description of the intervention

Tocilizumab (TCZ) is an anti-human IL-6 receptor monoclonal antibody that inhibits IL-6 signaling by blinding soluble and membrane IL-6 receptors. The drug has long been used for rheumatoid arthritis, juvenile inflammatory arthritis, and refractory giant cell arteritis.[7]

How the intervention might work

COVID-19 creates a hyperinflammatory condition, activated by a cytokine cascade. Of all cytokines identified so far, IL-6 is most closely connected to disease severity.[7] TCZ inhibits IL-6 action and might be a way to reduce COVID-19 severe cases.

Why it is important to do this review

Several observational studies have been conducted on treating COVID-19 and they suggest that TCZ is beneficial for moderate, severe, or critical cases of COVID-19.[8-10] However, non-randomized studies may report spurious associations mainly arising from the introduction of confounding factors into the comparative groups, and relying on such results may lead to the introduction of potentially hazardous interventions into clinical practice. Randomized clinical trials (RCTs) became available only by the end of 2020 and they have, so far, shown mixed results for mortality. Therefore, systematic reviews evaluating the effects of tocilizumab considering only RCTs are urgently needed.

OBJECTIVES

The aim of this review was to evaluate the effectiveness and safety of tocilizumab for treating COVID-19.

METHODS

Criteria for considering studies for this review

We undertook a systematic review including only RCTs. Participants must have been diagnosed with COVID-19 by one of the following methods: real time reverse-transcriptase polymerase chain reaction, serum immunoglobulin M antibody assay, or clinical evaluation (typical computed tomographic scan with signs of pneumonia). We included trials evaluating the effect of tocilizumab used alone or in combination with standard care or other interventions.

Outcomes

Our primary outcome was mortality. Secondary outcomes included the need for mechanical ventilation, days until discharge from hospital, and adverse events.

Search methods for identification of studies

The search was for all relevant published and unpublished trials without restrictions on language, year, or publication status. Electronic search included PubMed (1966-2021), EMBASE (1974-2021), CENTRAL – 2021 (Cochrane Library) and BVS portal. All RCTs published up to 03/24/2021 were considered for inclusion. Search strategies for each database are provided in **Appendix 1**. References of included trials were checked to identify additional, relevant trials. When necessary, authors were contacted.

Study selection and data extraction

All abstracts and reports identified by the search were retrieved and independently evaluated by two authors. If the reference appeared relevant to the review topic, the full text was obtained. The same two authors assessed and selected any relevant trials according to the review's eligibility criteria. In the presence of any disagreements, a third author was consulted.

Assessment of risk of bias and certainty of evidence

The risk of bias in each trial was assessed by two independent authors. We assessed the methodological quality of each included study using the risk of bias (RoB 2.0) tool as per the Cochrane recommendations. We evaluated the following domains: risk of bias arising from the randomization process, risk of bias due to deviations from the intended interventions (effect of assignment to intervention), missing outcome data, risk of bias in measurement of the outcome, risk of bias in selection of the reported result, and overall risk of bias. Each study was evaluated on all six domains and for each domain the evaluations were scored by assigning the classifications "low risk of bias", "some concerns of risk of bias", or "high risk of bias".[11] We used the GRADE (Grading of Recommendations Assessment, Development and Evaluations) approach to classify the strength of evidence as very low, low, moderate, or high.[12] We evaluated the following criteria: risk of bias, inconsistency, imprecision, and indirectness. We summarized the findings, considering the primary outcomes from comparisons, using the GRADE pro platform.

Measures of treatment effect

We estimated the effects of tocilizumab treatments for our predefined outcomes. Relative risks with their 95% confidence intervals (CI) were estimated using Review Manager 5.4.1 software (London, United Kingdom). We pooled data from the included studies using the generic inverse variance method with a random-effects model. We assessed heterogeneity using the I^2 statistic.[13] The interpretation of I^2 depends on the magnitude and direction of the effect as well as the strength of evidence for heterogeneity. We used the following thresholds to assess I^2: 0% to 40%: likely not important; 30% to 60%: moderate heterogeneity; 50% to 90%: substantial heterogeneity; 75% to 100%: considerable heterogeneity.

RESULTS

Results of the search

Our database search strategies yielded 413 records. After excluding duplicated reports and reports that were clearly irrelevant or not directly related to the review question, we assessed eleven full-text studies for further scrutiny. Eight multi-center RCTs[7,14-20]

with 6,139 participants were finally included in our systematic review (**Figure 1**). Details of each trial are described in **Table 1**.

Characteristics of included studies

Participants over 18 years from Europe and South and North America were randomized in each included trial into two groups: standard care alone or associated with tocilizumab 8 mg/kg (maximum dose of 800 mg/day). Tocilizumab was administered to participants as soon as they were randomized.

Standard care was not specified in the majority of the trials. All trials used tocilizumab (8 mg/kg) as soon as the participants were randomized. A second dose was given in most trials if the participant did not improve their clinical status within 24 hours after the first dose. BAAC[14] and TOCIBRAS[15] used only one dose. Important baseline characteristics of the participants and interventions are described in **Table 1**. All trials included hospitalized patients with moderate to severe COVID-19.

Risk of bias in included studies

The RCTs were assessed by RoB 2.0 (**Figure 2**). Three of them were judged as being of some concern regarding the risk of bias, four of them were judged as having low risk of bias and only one was graded as having high risk of bias. The most penalized domain was deviation from intended interventions, which occurred mainly because of lack of blinding and/or inappropriate analyses (intention-to-treat).

Effect of intervention

Certainty of evidence

We rated the certainty of the evidence using the GRADE approach. We found low certainty of evidence for the all-cause mortality outcome (**Table 2**). For that outcome, we downgraded one level due to methodological limitation (risk of bias) and one level due to imprecision (the 95% CI included both a benefit and harm, showing imprecision of the estimated effect). We found

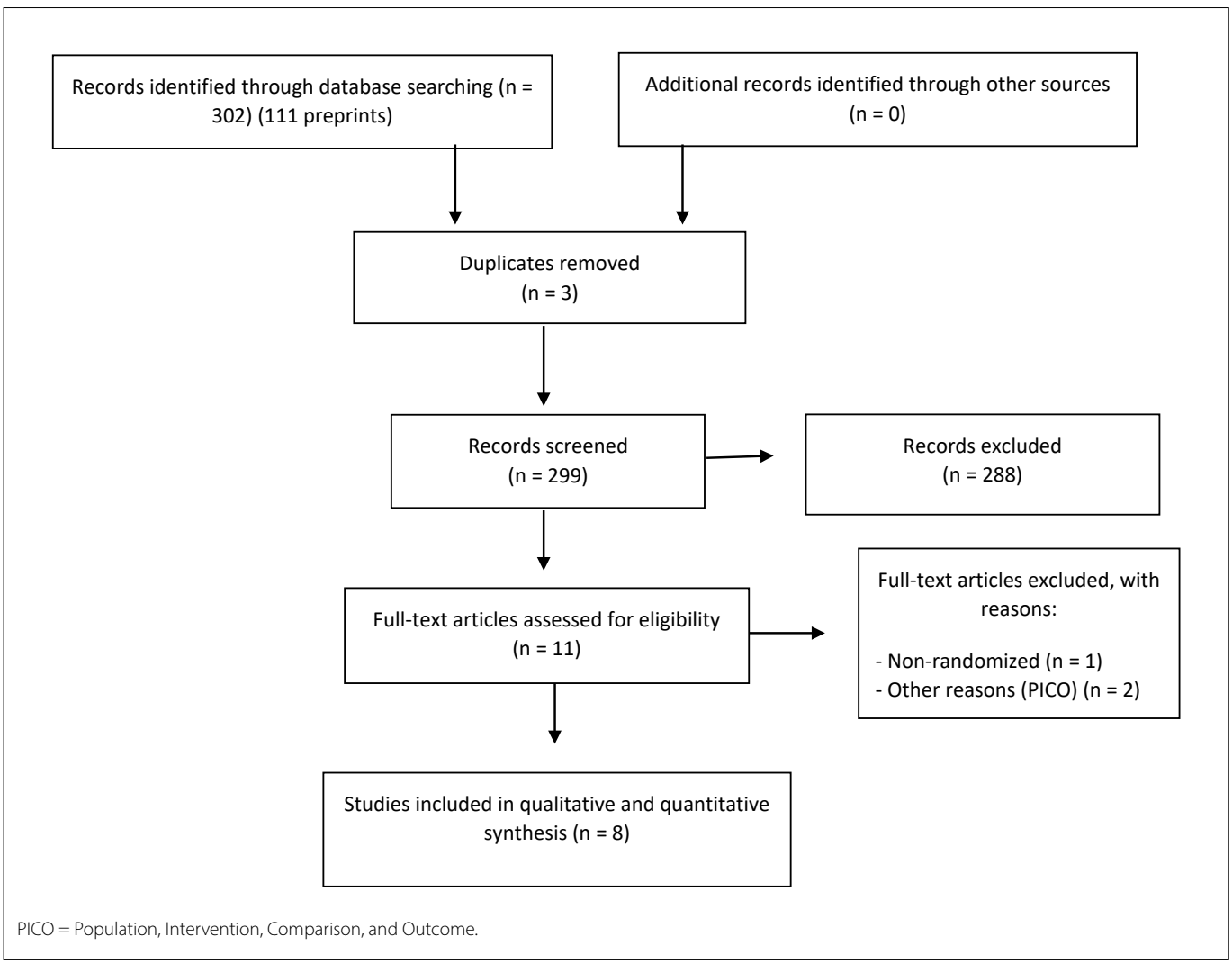

Figure 1. Study flow diagram.

Table 1. Characteristics of the included studies

Study/Country	Participants	Interventions	Outcome
REMAP-CAP Investigators et al.[17]/United Kingdom	350 adults' participants (age 61.4) hospitalized with moderate, severe, or critical pneumonia (O_2 > 3 L/minutes, WHO Clinical Progression Scale [WHO-CPS] score ≥ 5 due to COVID-19	Standard care (glucocorticoids) plus single dose TCZ (8 mg/kg – up to 800 mg) versus Standard Care alone	All-cause mortality Time point: 21 days
Hermine et al.[7]/France	131 adults' patients (age 64.0) hospitalized with moderate-to-severe COVID-19 pneumonia	Standard care (no information) plus single dose TCZ (8 mg/kg – up to 800 mg) versus Standard Care alone	All-cause mortality Need of mechanical ventilation Time point: 4 and 14 days
Tone et al.[14]/ United States	243 adults' patients (age 59.8) with severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) infection, hyperinflammatory states, and at least two of the following signs: fever (body temperature > 38 °C), pulmonary infiltrates, or the need for supplemental oxygen in order to maintain an oxygen saturation greater than 92%	Standard Care (no information) plus single dose TCZ (8 mg/kg – up to 800 mg) versus- Standard care alone	All-cause mortality Need of mechanical ventilation Time point: 28 days
Salama et al.[18]/ United States	389 adults' participants (age 55.9) hospitalized with COVID-19 with blood oxygen saturation below 94% while breathing ambient air	Standard care (antivirals; glucocorticoids - methylprednisolone, supportive care) plus one or two doses of TCZ (8 mg/kg – up to 800 mg) versus Standard Care plus placebo	All-cause mortality Need of mechanical ventilation Time point: 28 and 60 days
Veiga et al.[15]/ Brazil	129 adults' participants (age 60) with confirmed covid-19 who were receiving supplemental oxygen or mechanical ventilation and had abnormal levels of at least two serum biomarkers (C reactive protein, D dimer, lactate dehydrogenase, or ferritin)	Standard Care (no information) plus single dose TCZ (8 mg/kg – up to 800 mg) versus Standard care alone	All-cause mortality Need of mechanical ventilation Time point: 14 and 30 days
Rosas et al.[19]/ United States	438 adult participants (age 60.9) hospitalized with Severe COVID-19	Standard Care (antivirals; low-dose glucocorticoids, convalescent plasma) plus single dose TCZ (8mg/kg – up to 800 mg versus Standard care alone	All-cause mortality Need of mechanical ventilation Time point: 28 and 60 days
RECOVERY Collaborative Group[16]/ United Kingdom	Patients hospitalized (age 63.3) with COVID-19 with hypoxia (oxygen saturation < 92% on air or requiring oxygen therapy) and evidence of systemic inflammation (C-reactive protein [CRP] ≥ 75 mg/L)	Standard care (no information) plus single dose TCZ (8 mg/kg – up to 800 mg) versus Standard Care alone	Need of mechanical ventilation Time point: 28 and 180 days
Salvarani et al.[22]/Italy	123 adult participants (age 60) hospitalized with COVID-19 Pneumonia, with a partial pressure of arterial oxygen to fraction of inspired oxygen (PaO2/FIO2) ratio between 200 and 300 mm/Hg, an inflammatory phenotype defined by a temperature greater than 38 °C during the last 2 days, and/or serum CRP levels of 10 mg/dL or greater and/or CRP level increased to at least twice	Standard Care (no information) plus single dose TCZ (8 mg/kg – up to 800 mg) versus Standard care alone	Need of mechanical ventilation Time point:14 days

moderate certainty of evidence for need of mechanical ventilation. For that outcome, we downgraded one level due to methodological limitation (risk of bias).

All-cause mortality

We were not able to find any difference in mortality of patients with COVID-19 between tocilizumab plus standard care compared to standard care alone (risk ratio [RR] 0.97, 95% CI 0.84 to 1.13; 8 trials; 5,950 participants; low-certainty evidence) (**Figure 3**).

Need for mechanical ventilation

Patients with COVID-19 treated with tocilizumab plus standard care presented significantly lower risk of progressing to mechanical ventilation when compared to those receiving standard care alone (RR 0.78, 95% CI 0.64 to 0.94; 6 trials; 4,705 participants; moderate certainty of evidence) (**Figure 4**).

A few trials, including EMPACTA,[18] COVACTA,[19] TOCIBRAS,[15] and RECOVERY[16], described the number of days from the beginning of the trial to participants' discharge. The average number of days to discharge in the Tocilizumab group was 13.5 days (standard deviation [SD] = 7.5) and in the standard care group was 17.9 (SD = 11.6).

Adverse events were reported in all trials. No difference was found between groups in any trial. Minor events (non-fatal) included variations on hepatic enzymes, neutropenia, thrombosis, hypersensitivity, and anemia.

DISCUSSION

In this systematic review, including only RCTs assessing the effects of tocilizumab in patients with COVID-19, we found moderate-certainty evidence from six RCTs demonstrating that the use of tocilizumab in combination with standard care was effective for the reduction of need for mechanical ventilation in hospitalized patients with COVID-19. Additionally, we were not able to find any difference between using tocilizumab in association with standard care or standard care alone on mortality in hospitalized patients with COVID-19.

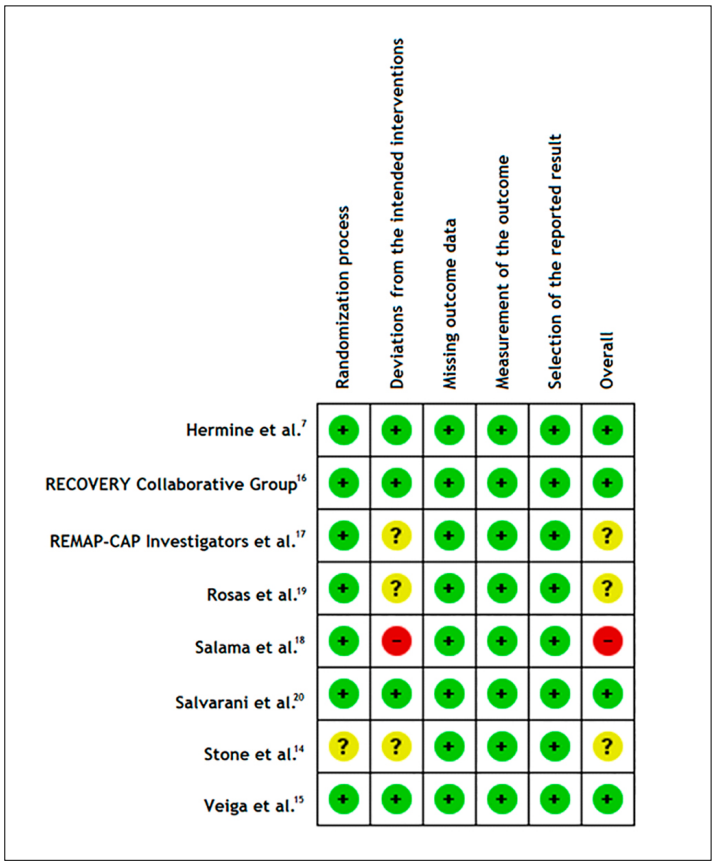

Figure 2. Risk of bias.

A previous review found no positive effect of using tocilizumab in COVID-19. However, this review included non-randomized trials.[21] Of note, non-randomized trials may have confounding factors in the comparative groups which often leads to spurious associations.[22] Relying on such results may lead to the introduction of potentially hazardous interventions into clinical practice.

Tocilizumab, a drug capable of controlling massive inflammation caused by IL-6, has begun to be studied globally. Many observational studies were completed up to the end of 2020, when the first randomized trials were published. These trials were important because the first studies could not come to a conclusion on tocilizumab effectiveness.

Effects on mortality were not observed in participants receiving tocilizumab. It is possible that this intervention is not capable of dealing with the inflammatory discharge of the disease that includes multiple types of interleukins and tumor necrosis factors.[23] Another possible explanation is that the elevation of interleukins is only part of the normal body reaction to the infection, and its suppression achieves no benefit. Finally, it is possible that the presence of a highly heterogeneous comparison group, using different pharmacological treatments, notably the concomitant administration of corticosteroid therapy, could have influenced our final results for this outcome. Further RCTs should report cointerventions and should minimize bias by stratification of those patients

Table 2. GRADE analysis.[24]

Certainty assessment							Summary of findings				
							Study event rates (%)			Anticipated absolute effects	
Participants (studies) Follow-up	Risk of bias	Inconsistency	Indirectness	Imprecision	Publication bias	Overall certainty of evidence	With standard care	With Tocilizumab	Relative effect (95% CI)	Risk with standard care	Risk difference with Tocilizumab
All-cause mortality											
5,950 (8 RCTs)	serious[a]	not serious	not serious	serious[b]	none	⨁⨁◯◯ Low	761/2686 (28.3%)	810/3264 (24.8%)	**RR 0.97** (0.84 to 1.13)	28 per 100	**1 fewer per 100** (from 5 fewer to 4 more)
Need of mechanical ventilation											
4,705 (6 RCTs)	serious[c]	not serious	not serious	not serious	none	⨁⨁⨁◯ Moderate	365/2230 (16.4%)	329/2475 (13.3%)	**RR 0.78** (0.64 to 0.94)	16 per 100	**4 fewer per 100** (from 6 fewer to 1 fewer)

CI = confidence interval; RR = risk ratio; RCTs = randomized clinical trials.

Explanations

a. We downgraded one level because three studies (n = 1,075) had some concerns on the risk of bias and one study (n = 377) had a high risk of bias.

b. We downgraded one level because the 95% CI includes both no effect and a possible benefit.

c. We downgraded one level because two studies (n = 515) had some concerns on the risk of bias and one study (n = 377) had a high risk of bias.

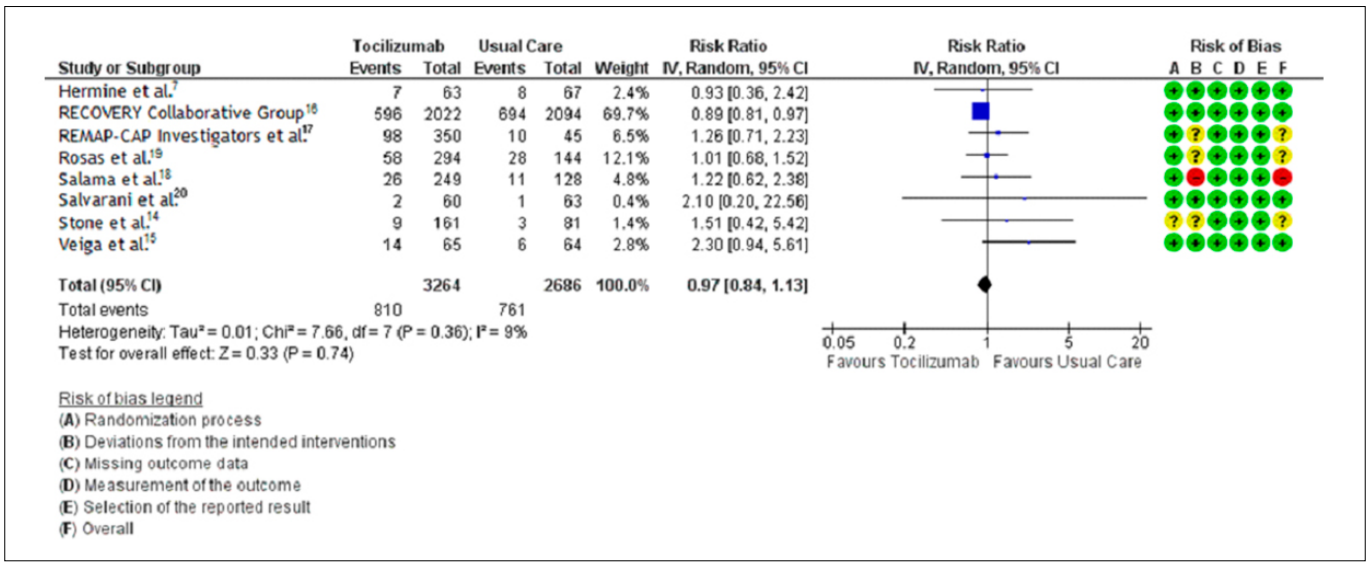

Figure 3. Mortality in COVID-19 patients under tocilizumab plus standard care vs. standard care alone

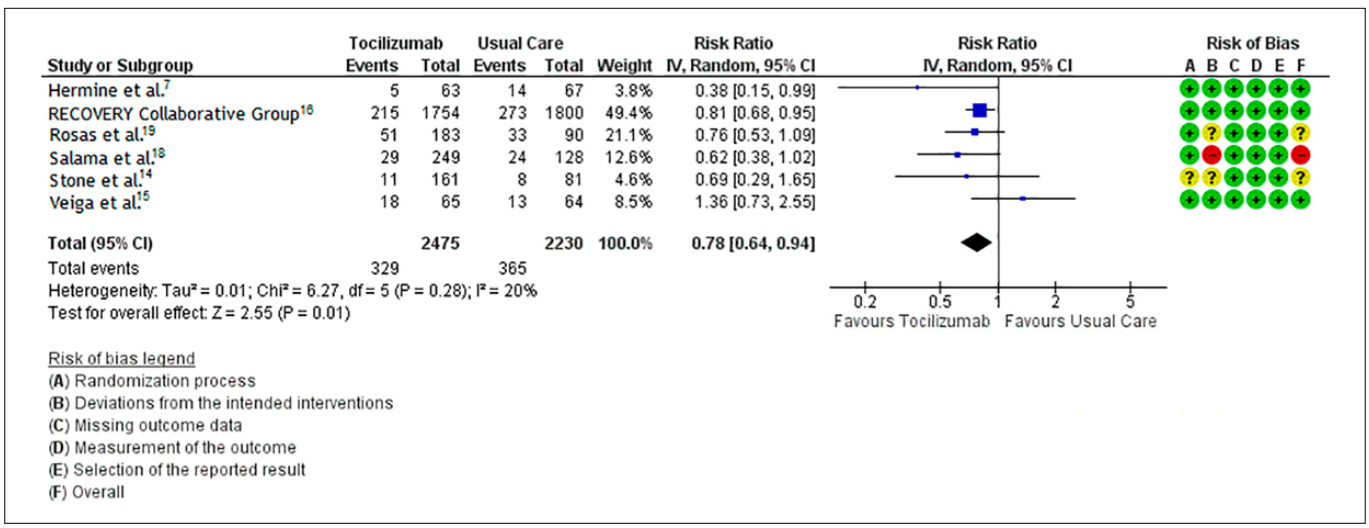

Figure 4. Need of mechanical ventilation in COVID-19 patients under tocilizumab plus standard care versus standard care alone

at randomization. As a consequence, a balanced use of comedications could be guaranteed after randomization in future analyses.

It should also be emphasized that most of the included studies recruited moderate to severe COVID-19 patients. Therefore, these results should not be generalized to mild COVID-19 patients. Furthermore, even among patients with moderate to severe COVID-19, more trials are needed to determine the best dosage and timing for initiating tocilizumab. Of note, we did not find a significant effect of tocilizumab on the risk of adverse events. Although no safety concerns associated with tocilizumab were observed in our analysis, it should be noted that the best dosage and timing for initiating tocilizumab still need to be further investigated. All included studies used the tocilizumab standard dose: 8 mg per kilogram of body weight (one or two doses, up to 800 mg). Another problem that we saw was the heterogeneity of the basic treatment in the comparative groups. There were variations in medications and doses that did not allow us to rule out interference in the final results found for the treatment.

Some observational studies of tocilizumab treatment have described reduction in the need for invasive mechanical ventilation, or death. Many trials claimed that using tocilizumab in early stages may alter the results. In our subgroup analysis this evidence was not confirmed. Time from beginning of the disease ends just when the inflammatory stage begins and the latter is the bigger problem.

All included studies had limitations related to blinding and treatment allocation. This is another concern of ours and, combined

with the degree of moderate certainty that we found, suggests the need for new RCTs.

We suggest carrying out new quality RCTs, with a balanced use of comedications in both groups, so that the question can be answered more robustly. These studies should be standardized as to the basic parameters for describing clinical trial results, such as using the CONSORT Statement (Consolidated Standards of Reporting Trials).

CONCLUSIONS

The best evidence available showed no difference between tocilizumab plus standard care compared to standard care alone for reducing mortality in patients with COVID-19. However, as a further result with a practical implication, the use of tocilizumab in association to standard care seemed to reduce the risk of progressing to mechanical ventilation in those patients. There is a need for further high-quality randomized double-blind studies using rigorous methodology.

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Appendix 1. Search strategy.

MEDLINE via PubMed
#1 "COVID-19" [Supplementary Concept] OR (COVID 19) OR (COVID-19) OR (2019-nCoV) OR (nCoV) OR (Covid19) OR (SARS-CoV) OR (SARSCov2 or ncov*) OR (SARSCov2) OR (2019 coronavirus*) OR (2019 corona virus*) OR (Coronavirus (COVID-19)) OR (2019 novel coronavirus disease) OR (COVID-19 pandemic) OR (COVID-19 virus infection) OR (coronavirus disease-19) OR (2019 novel coronavirus infection) OR (2019-nCoV infection) OR (coronavirus disease 2019) OR (2019-nCoV disease) OR (COVID-19 virus disease)
#2 "tocilizumab" [Supplementary Concept] OR (RHPM-1) OR (RG-1569) OR (R-1569) OR (MSB11456) OR (MSB-11456) OR (atlizumab) OR (monoclonal antibody, MRA) OR (RO-4877533) OR (Actemra) OR (Roactemra)
#3 #1 AND #2 = 62
Filters applied: Clinical Trial, Meta-Analysis, Randomized Controlled Trial, Systematic Review. Clear all
COCHRANE LIBRARY
#1 (COVID-19) OR (COVID 19) OR (COVID-19) OR (2019-nCoV) OR (nCoV) OR (Covid19) OR (SARS-CoV) OR (SARSCov2 or ncov*) OR (SARSCov2) OR (2019 coronavirus*) OR (2019 corona virus*) OR (Coronavirus (COVID-19)) OR (2019 novel coronavirus disease) OR (COVID-19 pandemic) OR (COVID-19 virus infection) OR (coronavirus disease-19) OR (2019 novel coronavirus infection) OR (2019-nCoV infection) OR (coronavirus disease 2019) OR (2019-nCoV disease) OR (COVID-19 virus disease)
#2 tocilizumab OR (RHPM-1) OR (RG-1569) OR (R-1569) OR (MSB11456) OR (MSB-11456) OR (atlizumab) OR (monoclonal antibody, MRA) OR (RO-4877533) OR (Actemra) OR (Roactemra)
#3 #1 AND #2 = 144
EMBASE
#1 'covid 19'/exp OR (COVID 19) OR (COVID-19) OR (2019-nCoV) OR (nCoV) OR (Covid19) OR (SARS-CoV) OR (SARSCov2 or ncov*) OR (SARSCov2) OR (2019 coronavirus*) OR (2019 corona virus*) OR (Coronavirus (COVID-19)) OR (2019 novel coronavirus disease) OR (COVID-19 pandemic) OR (COVID-19 virus infection) OR (coronavirus disease-19) OR (2019 novel coronavirus infection) OR (2019-nCoV infection) OR (coronavirus disease 2019) OR (2019-nCoV disease) OR (COVID-19 virus disease)
#2 'tocilizumab'/exp OR Actemra OR (actemra 200) OR atlizumab OR lusinex OR (r 1569) OR (r1569) OR roactemra
#3 #1 AND #2 = 86
#1 AND #2 AND ([cochrane review]/lim OR [systematic review]/lim OR [meta analysis]/lim OR [controlled clinical trial]/lim OR [randomized controlled trial]/lim)
#4 AND [embase]/lim NOT ([embase]/lim AND [medline]/lim)
BVS PORTAL
#1 MH:"Infecções por Coronavirus";OR (Infecções por Coronavirus) OR (Infecciones por Coronavirus) OR (Coronavirus Infections) OR (COVID-19) OR (COVID 19) OR (Doença pelo Novo Coronavírus (2019-nCoV)) OR (Doença por Coronavírus 2019-nCoV) OR (Doença por Novo Coronavírus (2019-nCoV)) OR (Epidemia de Pneumonia por Coronavirus de Wuhan) OR (Epidemia de Pneumonia por Coronavírus de Wuhan) OR (Epidemia de Pneumonia por Coronavírus de Wuhan de 2019-2020) OR (Epidemia de Pneumonia por Coronavírus em Wuhan) OR (Epidemia de Pneumonia por Coronavírus em Wuhan de 2019-2020) OR (Epidemia de Pneumonia por Novo Coronavírus de 2019-2020) OR (Epidemia pelo Coronavírus de Wuhan) OR (Epidemia pelo Coronavírus em Wuhan) OR (Epidemia pelo Novo Coronavírus (2019-nCoV)) OR (Epidemia pelo Novo Coronavírus 2019) OR (Epidemia por 2019-nCoV) OR (Epidemia por Coronavírus de Wuhan) OR (Epidemia por Coronavírus em Wuhan) OR (Epidemia por Novo Coronavírus (2019-nCoV)) OR (Epidemia por Novo Coronavírus 2019) OR (Febre de Pneumonia por Coronavírus de Wuhan) OR (Infecção pelo Coronavírus 2019-nCoV) OR (Infecção pelo Coronavírus de Wuhan) OR (Infecção por Coronavirus 2019-nCoV) OR (Infecção por Coronavírus 2019-nCoV) OR (Infecção por Coronavírus de Wuhan) OR (Infecções por Coronavírus) OR (Pneumonia do Mercado de Frutos do Mar de Wuhan) OR (Pneumonia no Mercado de Frutos do Mar de Wuhan) OR (Pneumonia por Coronavírus de Wuhan) OR (Pneumonia por Novo Coronavírus de 2019-2020) OR (Surto de Coronavírus de Wuhan) OR (Surto de Pneumonia da China 2019-2020) OR (Surto de Pneumonia na China 2019-2020) OR (Surto pelo Coronavírus 2019-nCoV) OR (Surto pelo Coronavírus de Wuhan) OR (Surto pelo Coronavírus de Wuhan de 2019-2020) OR (Surto pelo Novo Coronavírus (2019-nCoV)) OR (Surto pelo Novo Coronavírus 2019) OR (Surto por 2019-nCoV) OR (Surto por Coronavírus 2019-nCoV) OR (Surto por Coronavírus de Wuhan) OR (Surto por Coronavírus de Wuhan de 2019-2020) OR (Surto por Novo Coronavírus (2019-nCoV)) OR (Surto por Novo Coronavírus 2019) OR (Síndrome Respiratória do Oriente Médio) OR (Síndrome Respiratória do Oriente Médio (MERS)) OR (Síndrome Respiratória do Oriente Médio (MERS-CoV)) OR (Síndrome Respiratória do Oriente Médio por Coronavírus); OR MH:C01.925.782.600.550.200$
#2 TOCILIZUMAB OR (atlizumab) OR (monoclonal antibody, MRA) OR (RO-4877533) OR (Actemra) OR (Roactemra)
#3 #1 AND #2 = 121

In the manuscript titled "Clinical and laboratory differences between chromosomal and undefined causes of non-obstructive azoospermia: A retrospective study", DOI number 10.1590/1516-3180.2022.0281.R1.30082022, published in the Sao Paulo Medical Journal - Epub ahead of print:

Where it read:
"Grupo Interdisciplinar de Estudos da Determinação e Diferenciação do Sexo (GIEDDS), Hospital das Clínicas da Universidade Estadual de São Paulo (UNICAMP), Campinas (SP), Brazil."

It should read:
"Grupo Interdisciplinar de Estudos da Determinação e Diferenciação do Sexo (GIEDDS), Hospital das Clínicas da Universidade Estadual de Campinas (UNICAMP), Campinas (SP), Brazil."

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Typical main headings in the text include Introduction, Methods, Results, Discussion and Conclusion. The authors can and should use short subheadings too, especially those concerning the reporting guideline items.

Trial and systematic review registration policy

São Paulo Medical Journal supports the clinical trial registration policies of the World Health Organization (WHO) and the International Committee of Medical Journal Editors (ICMJE) and recognizes the importance of these initiatives for registration and international dissemination of information on randomized clinical trials, with open access. Thus, since 2008, manuscripts on clinical trials are accepted for publication if they have received an identification number from one of the public clinical trial registration database (such as ClinicalTrials.gov and/or REBEC and/or the World Health Organization; the options are stated at http://www.icmje.org). The identification number should be declared at the end of the abstract. Articles describing systematic reviews must provide the protocol registration number from a reliable database, such as PROSPERO, Open Science Framework, Cochrane, Joanna Briggs and others. Articles presenting clinical trials or systematic reviews without registration protocols will be promptly rejected without peer review.

Results from cases with DNA sequences must be deposited in appropriate public databases. The protocol number or URL can be requested at any time during the editorial review. Publication of other research data in public repositories is also recommended, since it contributes towards replicability of research, increases article visibility and possibly improves access to health information.

Sample size

All studies published in SPMJ must present a description of how the sample size was arrived at. If it was a convenience or purposive sample, the authors must declare so and explain the characteristics of this sample and recruitment method. For clinical trials, for instance, it is mandatory to inform each of the three main values used to calculate sample size:

- power (usually 80% or more);
- level of significance (usually 0.05 or lower);
- clinically meaningful difference (effect size targeted), according to the main outcome measurement.

Regardless of study results (if "positive" or "negative"), the journal will probably reject articles of trials using underpowered samples, when sample size has not been properly calculated or the calculation has not been fully described as indicated above.

Abbreviations, acronyms and products

Abbreviations and acronyms must not be used, even those in everyday use, unless they are defined when first used in the text. However, authors should avoid them for clarity whenever possible. Drugs or medications must be referred to using their generic names (without capital letters), with avoidance of casual mention of commercial or brand names.

Interventions

All drugs, including anesthetics, should be followed by the dosage and posology used.

Any product cited in the Methods section, such as diagnostic or therapeutic equipment, tests, reagents, instruments, utensils, prostheses, orthoses and intraoperative devices, must be described together with the manufacturer's name and place (city and country) of manufacture in parentheses. The version of the software used should be mentioned.

Any other interventions, such as exercises, psychological assessments or educational sessions, should be described in enough details to allow reproducibility. The Journal recommends that the TIDieR reporting guidelines should be used to describe interventions, both in clinical trials and in observational studies.[13]

Supplementary material

Because supplementary material comprises documents that do not form part of the text of the manuscript, São Paulo Medical Journal will not publish it. The authors should cite an access link that allows readers to view the supplementary material.

Short communications

Short communications are reports on the results from ongoing studies or studies that have recently been concluded for which urgent publication is important. They should be structured in the same way as original articles. The authors of this kind of communication should explain, in the covering letter, why they believe that publication is urgent. Short communications and case reports must be limited to 1,000 words (from the introduction to the end of the conclusion).

Case reports, case series, narrative reviews and letters to the editor

Starting in June 2018, only individual case reports dealing with situations of public health emergencies will be accepted by *São Paulo Medical Journal*. Case reports that had already been accepted for publication up to May 2018 will still be published in a timely manner.

After initial evaluation of scope by the editor-in-chief, case reports, case series and narrative reviews will be considered for peer-review evaluation only when accompanied by a systematic search of the literature, in which relevant studies found (based on their level of evidence) are presented and discussed.[12] The search strategy for each database and the number of articles obtained from each database should be shown in a table. This is mandatory for all case reports, case series and narrative reviews submitted for publication. Failure to provide the search description will lead to rejection before peer review.

The access route to the electronic databases used should be stated (for example, PubMed, OVID, Elsevier or Bireme). For the search strategies, MeSH terms must be used for Medline, LILACS, and Cochrane Library. DeCS terms must be used for LILACS. EMTREE terms must be used for Embase. Also, for LILACS, the search strategy must be conducted using English (MeSH), Spanish (DeCS) and Portuguese (DeCS) terms concomitantly. The search strategies must be presented exactly as they were used during the search, including parentheses, quotation marks and Boolean operators (AND, OR, and NOT). The search dates should be indicated in the text or in the table.

Patients have the right to privacy. Submission of case reports and case series must contain a declaration that all patients gave their consent to have their cases reported (even for patients cared for in public institutions), in text and images (photographs or imaging examination reproductions). The Journal will take care to cover any anatomical part or examination section that might allow patient identification. For deceased patients whose relatives cannot be contacted, the authors should consult the Editor-in-Chief. All case reports and case series must be evaluated and approved by an ethics committee.

Case reports should be reported in accordance with the CARE Statement,[7] including a timeline of interventions. They should be structured in the same way as original articles.

Case reports must not be submitted as letters. Letters to the editor address articles that have been published in the *São Paulo Medical Journal* or may deal with health issues of interest. In the category of letters to the editor, the text has a free format, but must not exceed 500 words and five references.

FORMAT: FOR ALL TYPES OF ARTICLES

Title page

The title page must contain the following items:

1. Type of paper (original article, review or updating article, short communication or letter to the editor);
2. Title of the paper in English, which should be brief but informative, and should mention the study design.[14] Clinical trial, cohort, cross-sectional or case-control study, and systematic review are the most common study designs. Note: the study design declared in the title should be the same in the methods and in the abstract;
3. Full name of each author. The editorial policy of the *São Paulo Medical Journal* is that abbreviations of authors' names must not be used; therefore, we ask that names be stated in full, without using abbreviations;
4. Place or institution where the work was developed, city and country;
5. Each author should indicate the way his/her name should be used in indexing. For example: for "João Costa Andrade", the indexed name could be "Costa-Andrade J." or "Andrade JC", as preferred;
6. The author's professional background (Physician, Pharmacist, Nurse, Dietitian or another professional description, or Undergraduate Student); and his/her position currently held (for example, Master's or Doctoral Student, Assistant Professor, Associate Professor or Professor), in the department and institution where he/she works, and the city and country (affiliations);

7. Each author should present his/her ORCID identification number (as obtained from HYPERLINK "http://www.orcid.org/" www.orcid.org);
8. Each author must inform his contribution, preferably following the CRediT system (see above in Authorship);
9. Date and venue of the event at which the paper was presented, if applicable, such as congresses, seminars or dissertation or thesis presentations.
10. Sources of financial support for the study, bursaries or funding for purchasing or donation of equipment or drugs. The protocol number for the funding must be presented with the name of the issuing institution. For Brazilian authors, all grants that can be considered to be related to production of the study must be declared, such as fellowships for undergraduate, master's and doctoral students; along with possible support for postgraduate programs (such as CAPES) and for the authors individually, such as awards for established investigators (productivity; CNPq), accompanied by the respective grant numbers.
11. Description of any conflicts of interest held by the authors (see above).
12. Complete postal address, e-mail address and telephone number of the author to be contacted about the publication process in the Journal (the "corresponding author"). This author should also indicate a postal address, e-mail address and telephone number that can be published together with the article. *São Paulo Medical Journal* recommends that an office address (rather than a residential address) should be informed for publication.

Second page: abstract and keywords

The second page must include the title and a structured abstract in English with a maximum of 250 words. References must not be cited in the abstract.

The following headings must be used in the structured abstract:

- Background – Describe the context and rationale for the study;
- Objectives - Describe the study aims. These aims need to be concordant with the study objectives in the main text of the article, and with the conclusions;
- Design and setting – Declare the study design correctly, and the setting (type of institution or center and geographical location);
- Methods – Describe the methods briefly. It is not necessary to give all the details on statistics in the abstract;
- Results – Report the primary results;
- Conclusions – Make a succinct statement about data interpretation, answering the research question presented previously. Check that this is concordant with the conclusions in the main text of the article;
- Clinical Trial or Systematic Review Registration – Mandatory for clinical trials and systematic reviews; optional for observational studies. List the URL, as well as the Unique Identifier, on the publicly accessible website on which the trial is registered.
- MeSH Terms - Three to five keywords in English must be chosen from the Medical Subject Headings (MeSH) list of Index Medicus, which is available at http://www.ncbi.nlm.nih.gov/sites/entrez?db=mesh.These terms will help librarians to quickly index the article.
- Author keywords - The authors should also add three to six "author keywords" that they think express the main article themes. These keywords should be different from the MeSH terms and preferably different from words already used in the title and abstract, so as to improve the discoverability of the article by readers doing a search in PubMed. They provide an additional chance for the article to be retrieved, read and cited. Combinations of words and variations (different wording or plurals, for example) are encouraged.

References

For any manuscript, all statements in the text that do not result from the study presented for publication in the *São Paulo Medical Journal* but from other studies must be accompanied by a quotation of the source of the data. All statements regarding health statistics and epidemiological data should generally be followed by references to the sources that generated this information, even if the data are only available electronically.

São Paulo Medical Journal uses the reference style known as the "Vancouver style," as recommended by the International Committee of Medical Journal Editors (ICMJE). Follow the instructions and examples at www.icmje.org, item "References", for the format.

In the text, the references must be numbered in the order of citation. The citation numbers must be inserted after periods/full stops or commas in sentences, and in superscript (without parentheses or square brackets). References cited in the legends of tables and figures must maintain sequence with the references mentioned in the text.

In the list of references, all the authors must be listed if there are up to and including five authors; if there are six or more, the first three should be cited, followed by the expression "et al." For books, the city of publication and the name of the publishing house are mandatory. For texts published on the internet, the complete uniform resource locator (URL) or address is necessary (not only the main home page of a website or link), so that by copying the complete address into a computer internet browser, the Journal's readers will be taken to the exact document cited, and not to a general website.

At the end of each reference, please insert the "PMID" number (for papers indexed in PubMed) and the link to the "DOI" number if available.

Authors are responsible for providing a complete and accurate list of references. All references cited in the text must appear in the reference list, and every item in the reference list must be cited in the text. Also, citations must be in the correct sequence.

Manuscripts that do not follow these guidelines for references will be returned to the authors for adjustments.

The reference list should be inserted after the conclusions and before the tables and figures.

Figures and tables

Images must be submitted at a minimum size that is reproducible in the printed edition. Figures should be sent at a resolution of 300 DPI and minimum size of 2,500 pixels (width) and be recorded in ".jpg" or ".tif" format. Images submitted in inadequate formats will not be accepted.

Images must not be embedded inside Microsoft PowerPoint or Microsoft Word documents, because this reduces the image size. Authors must send the images separately, outside of .doc or .ppt documents. Failure to send the original images at appropriate sizes leads to paper rejection before peer review.

Flowcharts are an exception: these must be drawn in an editable document (such as Microsoft Word or PowerPoint), and should not be sent as an image that can't be changed.

Figures such as bars of line graphs should be accompanied by the tables of data from which they have been generated (for example, sending them in the Microsoft Excel spreadsheets, and not as image files). This allows the Journal to correct legends and titles if necessary, and to format the graphs according to the Journal's style. Graphs generated from software such as SPSS or RevMan must be generated at the appropriate size, so that they can be printed (see above). Authors must provide internal legends/captions in correct English.

All the figures and tables should be cited in the text. All figures and tables must contain legends or titles that precisely describe their content and the context or sample from which the information was obtained (i.e. what the results presented are and what the kind of sample or setting was). The reader should be able to understand the content of the figures and tables simply by reading the titles (without the need to consult the text), i.e. titles should be complete. Acronyms or abbreviations in figure and table titles are not acceptable. If it is necessary to use acronyms or abbreviations inside a table or figure (for better formatting), they must be spelled out in a legend below the table or figure.

For figures relating to microscopic findings (i.e. histopathological results), a scale must be embedded in the image to indicate the magnification used (just like in a map scale). The staining agents (in histology or immunohistochemistry evaluations) should be specified in the figure legend.

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