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HANDS-ON: Training Simulation in Surgery

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Methods of the teaching-learning binomial in surgery has undergone major transformations in the last decade, moving from purely informational content models of environments that stimulate theoretical "know-how" by incorporating skills and competencies. There has been a paradigm shift in the training of surgical residents from the traditional "apprenticeship" model to a hybrid one, involving simulation training. This shift has been in response to several current challenges in residency training, including time constraints, patient safety concerns, financial costs, and decreasing durations of training programs.[1] During the past several years, major shifts in surgical education have brought into question whether surgical residency programs could truly ensure competency and technical proficiency in these surgeons.[2]

Simulation is an increasingly vital component of graduate medical education and becoming the standard of practice in many residency programs, particularly in surgical specialties, owing to the need for moving basic skill acquisition out of operating rooms into surgical skill laboratories. Deliberate practice is an educational technique that aims to improve performance through intense training and preparation. These steps include repetition, assessment, and feedback, which lead to performance improvement.[3]

Since a wave of innovation using new technologies has introduced a series of procedures with less invasive potential, such as minimally invasive surgery and robotics, training in surgery has become progressively more complex, occupying an important space in surgical treatment. Residents and young surgeons must learn these new techniques in a safe and effective way. Therefore, the advent of several simulators in surgery to practice activities is called "Hands-On."

The "Hands-On" is a different strategy for teaching and learning because it allows for interaction between experts (surgeons with recognized expertise and competence) with surgeons on different learning curve phases including residents, junior surgeons or even those with several years of surgical practice. This strategy differs from other teaching activities once trainees are directly involved in the whole procedure by "using their hands." Trainee is incentivized to observe all steps of operations, perform tactical movements and actions ordered in a logical sequence, or may incorporate new skills. All this happens without the urgency of time and, importantly, under qualified and committed guidance and supervision of experts.

At the same time, it promotes teaching and allows for both correction and evaluation of performance-inducing satisfaction in trainees by creating a pleasant sense of mastery of new skills or consolidation of previous ones that could now be executed with a more refined technique. These new skills are incorporated into the salutary practice of exhaustive repetition, which will automate them. After their final registration in the brain centers that integrate knowledge with motor skills, these new skills emerge automatically when requested, completing the cycle of see-search-understand-perform.[4]

It is also challenging for institutions responsible for training programs because they are expected to offer an efficient and adequate curriculum, which relies on the paradox of providing safe surgical opportunities without compromising postoperative outcomes and excellent patient care. Operating room surgical training has significant limitations: it provides a short time to develop technical skills and has low tolerance for learning mistakes.

Regarding traditional simulation models for surgery training, despite their high fidelity, human cadaver training has been discouraged for two main reasons. First, the corpses are not always available for use under good conditions for preservation. The second reason might be the short period of time spared for training, since those patients have to be handed out to their families for ceremonials.

Conducting training procedures on animal models offers the closest scenario to surgery in humans. However, completion of this kind of training requires sacrificing these animals, culminating in great opposition by animal protection organizations as well as by the general population. This traditional method has well-known limitations, such as the need for a broad framework for hosting, maintaining, and preparing these animals and their subsequent disposal, which, in addition to high costs, also requires involvement of many professionals for the correct execution of these tasks. These facilities are routinely available only in medical schools, to which undergraduate or graduate students usually have restricted access.

Biological models, compared with animal models "*in vivo*", have the advantage of storage capacity for days in the refrigerator, and lower costs, which is very advantageous considering the current financial constraints of most residency training programs. In addition, they enable realistic tissue sensations and excellent anatomical correspondence. In this context, we suggest that incorporating the simulation of biological models in our residency program could improve surgical training and patient safety owing to its potential to avoid surgical technical failure that would compromise the outcomes, bringing more safety, efficacy, and better long-term results.

Recognizing these challenges about technical skills acquisition for cardiovascular surgery, we started our simulation training program. This program was on biological models for the medical residency of cardiovascular surgery at our institution, the "Hands-on" course with biological models in 2015, for cardiovascular surgery residents in the Heart Institute of University of São Paulo Medical School. A practical evaluation of the performance of specific skills was conducted at the end of the training program. The high scores obtained by residents revealed the efficiency of the simulation in the acquisition of skills. In addition, the residents' responses to the subjective analysis revealed high satisfaction with the training program. They highlighted realistic tissue feel and anatomical representation as positive aspects, as well as the possibility of performing a specific technique multiple times, thereby improving skill acquisition. In general, most of the residents reported that the program could provide a realistic experience and be valuable in teaching surgical skills.[5] We observed that biological models with porcine or bovine hearts provided a high degree of realism. In the case of cardiac surgery, where surgical failure may result in patient morbidity and mortality, such a realistic simulation could reproduce better surgical results, which is essential before clinical application.

The incorporation of new training techniques, such as "Hands-on" simulators, allows for improvements in resident preparedness, training of new technologies by practice surgeons, minimizing possible technique failures, and allowing for better efficacy in the procedures and better results. These moments represent a unique opportunity for a desirable interaction, in that the more experienced ones could help qualify this critical mass of professionals eager to attain new knowledge but also willing to incorporate specific technical skills as basic support for their professional performance.[6]

In the cognitive domain, the transmission and retention of essential theoretical knowledge are required and of paramount importance for the judgment and proper handling of each patient. This part has been widely covered by many mini-courses offered at numerous conferences in different areas of the specialty as well as continuing medical education programs carried out by schools and educational institutes created and maintained by specialty societies and supported by pharmaceutical companies for equipment and instruments in surgery.[7]

The congresses of some specialties are modified each year to discuss the incorporation of new technologies by presenting the results of numerous well-designed studies conducted to validate, disseminate, and extend their use in daily practice. Watching an operation, usually a complex case or new procedure, performed at distance in a specialized center and broadcasted to an audience, offers the participating surgeons an opportunity to interact with the team that performs surgery and learn useful surgical aspects. However, this does not endow observers with new skills. In addition, this format has certain limitations, including legal issues. The surgical team responsible for surgery was subjected to stress above the usual levels. They could not repeat the tactical maneuvers performed because of the imperative need for continuing the operation. Unclear steps or details, even if explained well, cannot be repeated. The operation needs to have a normal course and patient must not be subjected to additional risks, such as stopping at each step of the procedure, to allow for controversial debates or opinions. Traditional video sessions, in which procedures can have their technical details presented and discussed, allowing for pauses or repetitions when necessary, are instructive in providing opportunities for learning technical and tactical details without putting pressure on the surgical team without subjecting patients to additional risks. This mode helps understand how to overcome difficulties in their implementation and new ways of executing it. Although it is a useful and attractive format, it does not provide new psychomotor skills to those attending the activity. Therefore, creative and innovative ways of transmitting knowledge, as described above, do not directly involve a community of observers in theatres for surgical procedures. Observers can even assimilate the steps and various tactical maneuvers essential to the operation. However, these do not provide them with the ability to implement them.

The task of producing scientific knowledge and validating it through the current methods of evidence-based medicine belongs primarily to universities. Through their institutes and research laboratories, universities are prepared for this crucial stage in developing medical science. On the other hand, the medical specialty societies must be in charge for the task of training and retraining the graduates of these educational institutions who completed their residency program or fellowship in surgery to maintain excellence in their daily practice.

Some studies have validated the need for simulation in surgery.[8] Surgical simulation allows medical residents to perform surgeries in a less stressful environment and may provide structured graduate training for technical skills. Furthermore, educators recognize this activity as a method by which expertise may be developed and assessed. Another positive aspect of simulation-based skills training in surgery is that educators can spend more time teaching in less stressful environments, promoting a better understanding and retention of skills.

Whether the improved performance in the simulation laboratory is transferable to the operating room is not easily addressed. However, most trainees reported that they felt much better prepared and less anxious about performing each skill in an operating room environment. These findings support those in the published literature that structured teaching sessions improve learners' confidence level.[9]

In addition, concerns have been raised regarding the safety of training surgeons when performing surgeries. In fact, there is a growing demand for improved clinical results and outcomes, with intense public scrutiny of their clinical performance. That is why surgical training in this field requires balance between standard of care delivered to patients and provision of sufficient operative exposure to trainees who are the cardiac surgeons of the future.

The perception that a procedure requires fellowship training is a possible explanation why most core and advanced surgical skills are considered above residency training. Proving competency in a controllable environment may allow residents to gain autonomy in operating rooms. Faculty surgeons may be more at ease because residents have demonstrated their knowledge and skills before entering the operating room. A study conducted in general surgery found that 80% of faculty members did not expect graduating residents to perform complex operations.[10]

There is a pressing need to incorporate simulation-based training into existing and future surgical residency programs. Since mandates for quality measures and shorter training periods emerge, teaching alone, using the traditional "apprenticeship" model in the operating room, is no longer sufficient. High-fidelity, low-technology tools such as fresh tissue cadaver laboratories and virtual operating rooms might be important adjuncts to successful curriculum implementation. Each program should recognize that a needs assessment can help focus on curricular content and that implementation will vary depending on resources, faculty time, and available educational time. These programs could benefit from defining the specific needs that are important for the widespread and local implementation of simulation-based training in surgery.

The combination of patient safety concerns, changes in resident education, and more complex procedures for high-risk patients has generated a greater interest in simulation-based learning in training. Considering the current educational environment and importance of training the next generation of surgeons, simulations represent a feasible alternative. We strongly suggest that simulation may contribute to the development of technical skills and procedural knowledge required for adequate performance in the operating room.

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Determining the relationship between serum acute phase reactants and cervical premalignant lesions: a cohort study

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Cervical cancer screening.

ABSTRACT

BACKGROUND: Acute phase reactants play a role in the progression and prognosis of many malignant and premalignant tumors. This study investigated the diagnostic value of certain reactants as markers for cervical premalignant lesions.

OBJECTIVES: Despite advanced screening and vaccination programs, cervical cancer remains a serious health problem worldwide. We aimed to determine the possible relationship between premalignant cervical disease and serum acute phase reactant levels.

DESIGN AND SETTING: This study included 124 volunteers who underwent cervical cancer screening. We divided the patients into three groups according to cervical cytology and histopathological findings as follows: no cervical lesion, low-grade neoplasia, or high-grade neoplasia.

METHODS: We included women aged 25–65 years with benign smear or colposcopy results, low- and high-grade squamous intraepithelial lesions. The benign group was based only on cytology findings, whereas the other groups were based on histopathology findings. Demographic data and serum albumin, fibrinogen, ferritin, and procalcitonin levels were evaluated in the three groups.

RESULTS: We found significant differences among the three groups in terms of age, albumin level, albumin/fibrinogen ratio, and procalcitonin level. The regression analysis revealed lower serum albumin levels in the low- and high-grade squamous intraepithelial lesion groups compared with the benign group.

CONCLUSION: This is the first study to evaluate the importance of serum inflammatory markers in cervical intraepithelial lesions. Our results indicate that serum albumin level, albumin/fibrinogen ratio, procalcitonin level, and neutrophil values differ among cervical intraepithelial lesions.

INTRODUCTION

Cervical cancer is the third most diagnosed gynecological cancer and cause of death in the United States.[1] Owing to advanced screening programs, cervical cancer currently has lower incidence and mortality rates compared with endometrial and ovarian cancer. However, cervical cancer remains a significant cause of cancer morbidity and mortality in countries with limited access to screening programs. Cervical cancer screening facilitates the detection and treatment of premalignant cervical lesions before cancer develops. Current screening methods include human papillomavirus (HPV) testing, cervical cytology (also known as the Pap test or Pap smear), or both.[2]

HPV is positively detected in 99.7% of patients diagnosed with cervical cancer.[2] The infection of the cervical transformation zone with oncogenic HPV subtypes results in the initiation of carcinogenesis. The development of high-grade cervical intraepithelial neoplasia and invasive cancer from the first infection takes an average of 15 years, although rapid progression has also been reported.[3]

Inflammation reportedly plays an essential role in the formation, progression, and even invasion and metastasis of tumor cells. In reviewing the literature, we noted that numerous inflammatory complete blood parameters and acute phase reactants have been used in tumor diagnosis and prognosis.[4–8]

OBJECTIVE

We aimed to evaluate the relationship between cervical premalignant lesions and serum albumin, fibrinogen, ferritin, and procalcitonin levels. These molecules play essential roles in systemic inflammation, as well as the detection of cervical premalignant lesions to a certain degree, considering the carcinogenesis process begins in the presence of HPV infection.

METHODS

This case-control study included 124 volunteers with cervical cytology and histology results who applied to the Gynecology and Obstetrics department of the University of Health Sciences Bursa Yüksek İhtisas Training and Research Hospital between August 1, 2020, and March 19, 2021.

The University of Health Sciences Bursa Yüksek İhtisas Training and Research Hospital Clinical Research and Ethics Committee approved this study (approval number: 2011-KAEK-25 2020/07-04) on July 22, 2020. All participants read and signed the Informed Volunteer Consent Form.

We included women aged 25–65 years who applied to our gynecology department and had a benign smear or colposcopy result, low-grade squamous intraepithelial lesion (LSIL), or high-grade squamous intraepithelial lesion (HSIL). We categorized participants to the benign group only according to cytology findings and the other groups according to histopathology findings. We included patients who did not smoke or use alcohol or drugs; with no signs of active infection; and no known chronic, autoimmune, inflammatory diseases or cancer.

Patient age, gravidity, parity, polymerase chain reaction-based HPV DNA detection (HPV-DNA), and colposcopy results, if any, were recorded. Approximately 5 ml of blood was collected from each volunteer in four tubes. We determined and recorded the serum albumin, fibrinogen, ferritin, and procalcitonin levels in our patients using the appropriate kits in our hospital's biochemistry laboratory. Results of pretreatment hemogram tests routinely performed upon admission were also obtained from the patient files. Leukocyte, hemoglobin, neutrophil, lymphocyte, mean platelet volume, and platelet levels were recorded. All final pathologies were evaluated by the Pathology department at our hospital. Conization pathology results of the treated patients were obtained and recorded. Patients with smear results showing benign findings (n = 53) were included in the control group.

Participants with low-grade lesions in the final pathology results were included in the LSIL group (n = 40); participants with high-grade lesions were included in the HSIL group (n = 28). Three patients with cervical cancer were excluded from the study. We compared the parameters recorded among the three groups using the appropriate statistical analyses.

Sample calculation

Regarding the number of cases included in this study, we referred to a previous study titled "Diagnostic Value of Albumin to Fibrinogen Ratio in Cervical Cancer."[9] Based on the sample calculation using the fibrinogen and albumin parameters shown in **Table 1**, we included a total of 121 volunteers with a 95% confidence interval [CI] and 80% power. G*Power version 3.1.9.2 software (Erdfelder, Faul, & Buchner, 1996; Heinrich Heine University, Düsseldorf, Germany) was used for the sample calculation.

Statistical analysis

SPSS version 24.0 for Windows (IBM Corp., Armonk, New York, United States) was used for the statistical analyses. Variables were examined visually (histograms, probability graphs) and using analytically (Shapiro-Wilk and Kolmogorov-Smirnov tests) to determine whether the data showed a normal distribution. Variables were defined as the mean ± standard deviation (X ± standard deviation), mean difference between groups, 95% confidence interval (95% CI), median (minimum-maximum), frequency (n), or percentage (%). Student's t-test and the Mann-Whitney U test were used to compare normally and nonnormally distributed variables in the two-group analysis. Analysis of variance and Kruskal-Wallis tests were used to compare variables involving more than two groups. Pearson's and Spearman's tests were performed to determine the relationships between normally and nonnormally distributed variables. According to the cervical cytology and histopathology findings, independent predictors of benign, LSIL, and HSIL outcomes were analyzed using multinomial logistic regression analysis. The model compatibility was considered significant at $P < 0.05$. Receiver operating characteristic (ROC) curve analysis was performed to determine the borderline albumin value in patients who developed cervical intraepithelial lesions.

RESULTS

The descriptive analysis results of the demographic and laboratory characteristics of the cases screened for cervical intraepithelial lesions are shown in **Table 1**. This study included 124 participants. The mean age of all participants was 40.1 ± 9.7 years. We conducted a further evaluation by biopsy in 18 patients with smear results indicating LSIL, 11 patients with HSIL, and 21 patients with atypical squamous cells of undetermined significance. The number of patients with benign cervical cytology findings was 68 (56.2%); 53 patients whose final pathology results were benign were included in the three-group analysis (42.7%). Despite benign smear findings, 15 patients underwent histopathological examinations because they were HPV-positive. Invasive cancer was detected in three patients, although these patients were not included in further analyses (**Table 1**).

We divided the included patients into benign, LSIL, and HSIL groups according to cervical cytology and final histopathology results. There was a statistically significant difference between the groups in terms of age, albumin level, procalcitonin level, and albumin/fibrinogen ratio ($P < 0.01$, $P = 0.006$, $P = 0.006$, and $P = 0.067$, respectively). When we evaluated the groups using binary *post hoc*, a statistically significant difference was observed between the benign

and LSIL groups in terms of age, albumin, and procalcitonin values (P = 0.043, P = 0.05, P = 0.017, respectively). Binary *post hoc* analysis between the benign and HSIL groups showed statistical significance in terms of age, albumin level, and albumin/fibrinogen ratio. Meanwhile, procalcitonin levels did not differ between the two groups. No significant differences were observed in the laboratory parameters between the LSIL and HSIL groups (**Table 1**).

To determine the most compatible independent predictive variable for cervical intraepithelial lesions, multiple regression analysis was performed among the three groups, and the results are presented in **Table 2**. Although the benign cervical lesion group was the reference category, according to the multinomial logistic regression analysis, albumin values were significantly lower in the LSIL and HSIL groups than those in the reference group (P = 0.042 and P = 0.027, respectively). Each one-unit decrease in albumin level caused a 0.8-fold increase in the development of LSIL and HSIL (**Table 2**).

Receiver operating characteristic curves were created for the albumin parameter, and its predictive effect on the development of LSIL and HSIL was determined. The areas under the curve (AUCs), sensitivity, and specificity were calculated. The cutoff value for albumin was based on the values in the benign group.

Table 1. Comparison of demographic characteristics and laboratory parameters in benign and low- and high-grade squamous intraepithelial lesion groups according to cervical cytology and histopathology findings

	Benign (n = 53)	LSIL (n = 40)	HSIL (n = 28)			
	X± SD/Median (min–max)	X ± SD/Median (min–max)	X ± SD/Median (min–max)	P	$P_{Benign\ \&\ LSIL}$	$P_{Benign\ \&\ HSIL}$
Age (years)*	36.4 ± 9.7	41.2 ± 8.4	45 ± 9.2	< 0.01	0.043	< 0.01
Parity#	2 (0–9)	2 (0–9)	2 (0–9)	0.406		
Hemoglobin (g/dl)#	12.8 (9.9–15.1)	12.8 (7.9–15.6)	13 (7.4–15.4)	0.904		
Leukocyte count (mcl)#	7.7 (3.8–12.5)	7.1 (4.4–12)	7.5 (5.3–12.2)	0.536		
Neutrophil count (mcl)#	4.6 (1.6–9.3)	4.2 (2.1–11.8)	4.5 (2.8–8.2)	0.524		
Lymphocyte count (mcl)*	2.2 ± 0.5	2.2 ± 0.5	2.4 ± 0.8	0.462		
Mean platelet volume (fl)*	9.9 ± 0.9	9.9 ± 0.9	10 ± 1	0.834		
Platelet count (mcl)#	299 (113–453)	270 (164–437)	263 (171–498)	0.438		
Albumin (g/l)*	46.2 ± 2.9	44.6 ± 3.3	44 ± 3.4	**0.006**	**0.05**	**0.009**
Fibrinogen (mg/dl)*	309.8 ± 64.8	331 ± 85.7	331.6 ± 64.9	0.276		
Ferritin (ng/ml)#	29 (6–144)	26 (5–259)	26 (2–127)	0.895		
Procalcitonin (ng/ml)#	0.02 (0.01–0.06)	0.03 (0.02–0.32)	0.03(0.02–0.38)	**0.006**	**0.017**	0.149
Albumin/fibrinogen ratio#	14.5 (8.1–23.5)	14.3 (7.9–23.2)	13.6 (8.3–19.7)	**0.067**	0.295	**0.024**
Neutrophil/lymphocyte ratio#	2 (0.9–4.9)	2 (0.9–5.9)	2 (1–3.7)	0.905		
Platelet/lymphocyte ratio#	127 (43.4–206)	119.1 (64.6–238.1)	119.7 (68.5–233.1)	0.788		

Descriptive analyses were performed using the mean and standard deviation (X ± standard deviation) for normally distributed data and median and minimum–maximum values for nonnormally distributed data. Statistical significance was set at P < 0.05. For two-group analyses of the results that were significant in the multiple regression analysis, Gabriel tests were used when variances from *post hoc* tests were homogeneously distributed, and Games-Howell tests when they were not. Homogeneity of variances was evaluated using the Levene's test.

*One-way analysis of variance; #Kruskal Wallis test.

HSIL = high-grade squamous intraepithelial lesion; LSIL = low-grade squamous intraepithelial lesion; min–max = minimum–maximum; SD = standard deviation. g/dl: gram/deciliter, mcl: microliter, fl: femtoliter, g/l: gram/liter, mg/dl: milligram/deciliter, ng/ml: nanogram/milliliter.

P values < 0.05 were considered significant.

Table 2. Multinomial logistic regression analysis in benign and low- and high-grade squamous intraepithelial lesion groups according to cervical cytology and histopathology findings

Diagnosis	Parameters	B	Wald	OR	95% CI	P
Low-grade squamous intraepithelial lesion	Albumin (gr/l)	-0.165	4.144	0.848	0.705–0.957	0.042
	Albumin/Fibrinogen Ratio	-0.39	0.302	0.962	0.838–1.104	0.582
	Procalcitonin (ng/ml)	28.472	2.803			0.094
High-grade squamous intraepithelial lesion	Albumin (gr/l)	-0.198	4.921	0.820	0.689–0977	0.027
	Albumin/Fibrinogen Ratio	-0.79	0.967	0.924	0.789–1.082	0.325
	Procalcitonin (ng/ml)	27.413	2.580			0.108

CI = confidence interval; OR = estimated relative risk. Wald = test statistic value.

Multinomial logistic regression was used because the dependent variable consisted of three groups. The benign group was the reference category. Parameters that were found to be significant in the previous analysis were included in this analysis. The model fit was determined as P < 0.05.

g/l: gram/liter, mg/dl: milligram/deciliter, ng/ml: nanogram/milliliter.

P values < 0.05 were considered significant.

Accordingly, if the patient's albumin level was < 46.05 g/L, a cervical intraepithelial lesion was expected with 65% probability, 65.9% sensitivity, and 60% specificity (AUC: 0.651 [0.553–0.750], P: 0.004) (**Table 3**, **Figure 1**).

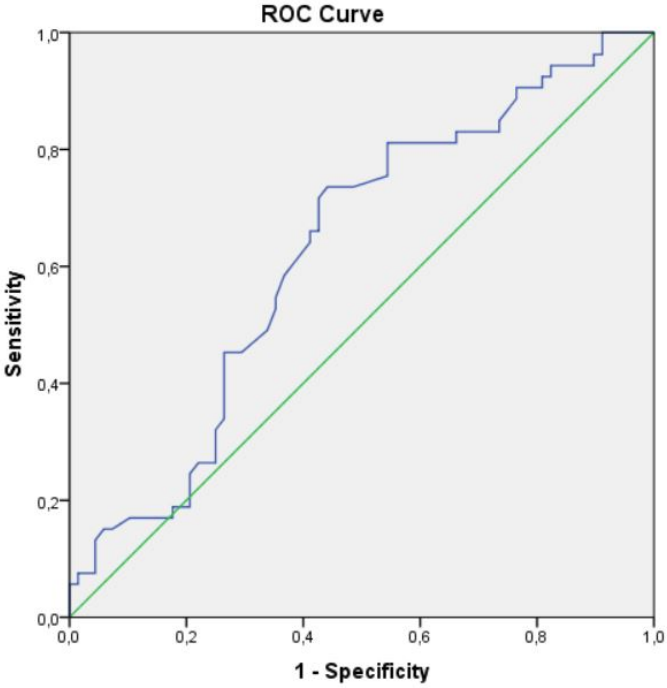
In addition, we divided HPV-DNA-positive patients (n = 68) into two groups: histopathologically-diagnosed LSIL (n = 40) and HSIL (n = 28). Accordingly, high neutrophil levels in women who are positive for HPV were associated with HSIL lesions (P = 0.041) (**Table 4**).

In this study, 32 patients underwent conization for the final diagnosis. We divided these patients into LSIL (n = 13) and HSIL (n = 19) groups after pathological examinations. Comparison tests were performed in terms of laboratory parameters in these two groups. Accordingly, plasma leukocyte and neutrophil levels were statistically significantly higher in the HSIL group than those in the LSIL group (P < 0.05) (**Table 5**).

DISCUSSION

This case-control study aimed to compare inflammatory markers between women with and without cervical intraepithelial lesions. Serum albumin levels were significantly lower in women with premalignant lesions compared with women with benign lesions.

Cervical intraepithelial neoplasms are premalignant squamous lesions of the cervix that are diagnosed by cervical biopsy and histological examination. These premalignant lesions of the cervix have undergone terminological changes over time and have since been revised. In the last classification system, the histological



ROC = receiver curve characteristic.

Figure 1. Receiver curve characteristic analysis of albumin values in patients with cervical intraepithelial lesions.

Table 4. Comparison of human papillomavirus-positive patients diagnosed with low- and high-grade squamous intraepithelial lesions according to laboratory parameters

	LSIL (n = 40)	HSIL (n = 28)	
	X ± SD/ Median (min–max)	X ± SD/ Median (min–max)	P
Hemoglobin (g/dl)#	13.4 (9.7–15.6)	13.1 (10.2–15.4)	0.891
Leukocyte count (mcl)#	7.1 (4.4–9.5)	7.5 (5.3–12.2)	0.075
Neutrophil count (mcl)#	4 (2.1–6.1)	4.5 (2.8–8.2)	**0.041**
Lymphocyte count (mcl)*	2.07 ± 0.6	2.5 ± 0.9	0.101
Mean platelet volume (fl)*	10 ± 1.05	10.1 ± 1.1	0.853
Platelet count (mcl)#	262 (191–331)	256 (181–498)	0.704
Albumin (gr/l) *	45.1 ± 3.1	44.2 ± 3	0.362
Fibrinogen (mg/dl) *	355.1 ± 76.6	330.2 ± 65.4	0.297
Ferritin (ng/ml) #	30 (8–68)	29 (6–84)	0.574
Procalcitonin (ng/ml) #	0.03 (0.02–0.32)	0.03 (0.02–0.38)	0.408
Albumin/fibrinogen ratio#	13.2 (8.2–19.2)	13.1 (8.3–19.7)	0.584
Neutrophil/lymphocyte ratio#	2 (0.9–3.7)	2 (1–3)	0.99
Platelet/lymphocyte ratio#	119.5 (70.3–238.1)	117.8 (68.5–172.8)	0.378

LSIL = low grade squamous intraepithelial lesion; HSIL= high grade squamous intraepithelial lesion; SD = standard deviation, min–max = minimum–maximum.
Descriptive analyses are presented using the mean ± standard deviation (X ± SD), median (minimum–maximum), and (n, %) for normally distributed, nonnormally distributed, and categorical variables, respectively. *Student's t-test; #Mann-Whitney U test; P < 0.05 were considered significant.
g/dl: gram/deciliter, mcl: microliter, fl: femtoliter, g/l: gram/liter, mg/dl: milligram/deciliter, ng/ml: nanogram/milliliter.
P values < 0.05 were considered significant.

Table 3. Receiver operating characteristic curve analysis result for albumin values in patients with cervical intraepithelial lesions following regression analysis results

Area under ROC curve (95% confidence interval)	Negative predictive value	Positive predictive value	Sensitivity	Specificity	Cutoff	P
0.651 (0.553–0.750)	60.1%	67.7%	65.9%	60%	46.05	0.004

ROC = receiver operating characteristic.

Table 5. Comparison of low- and high-grade squamous intraepithelial lesions according to laboratory parameters in patients who underwent conization

	LSIL (n = 13)	HSIL (n = 19)	P
	X ± SD/ Median (min–max)	X ± SD/ Median (min–max)	
Hemoglobin (g/dl)#	12.3 (9.7–15.6)	12.9 (10.2–15.4)	0.570
Leukocyte count (mcl)#	7.1 (4.4–10.6)	8 (5.3–12.2)	**0.030**
Neutrophil count (mcl)#	3.4 (2.1–6.9)	4.8 (2.8–8.2)	**0.014**
Lymphocyte count (mcl)*	2.1 ± 0.7	2.3 ± 0.8	0.497
Mean platelet volume (fl)*	10.2 ± 0.8	10 ± 1	0.509
Platelet count (mcl)#	262 (194–310)	259 (171–498)	0.910
Albumin (gr/l)*	45 ± 3	43.1 ± 3.5	0.126
Fibrinogen (mg/dl)*	362.7 ± 67.3	336 ± 60.4	0.249
Ferritin (ng/ml)#	35 (8–50)	31 (6–127)	0.762
Procalcitonin (ng/ml)#	0.03 (0.02–0.30)	0.03 (0.02–0.15)	0.880
Albumin/fibrinogen ratio#	12.8 (8.2–18.3)	12.7 (8.3–19.7)	0.791
Neutrophil/lymphocyte ratio#	2.1 (0.9–2.6)	2 (1–3.7)	0.323
Platelet/lymphocyte ratio#	118.1 (64.6–238.1)	118.9 (69.7–189.4)	0.910

LSIL = low grade squamous intraepithelial lesion; HSIL= high grade squamous intraepithelial lesion; SD = standard deviation; min–max = minimum–maximum.
Descriptive analyses are presented using the mean ± standard deviation (X ± SD), median (min–max), and (n, %) for normally distributed, nonnormally distributed, and categorical variables, respectively. *Student's t-test; #Mann-Whitney U test; P < 0.05 were considered significant.
g/dl: gram/deciliter, mcl: microliter, fl: femtoliter, g/l: gram/liter, mg/dl: milligram/deciliter, ng/ml: nanogram/milliliter.
P values < 0.05 were considered significant.

findings of the cervix are presented using the same terminology as the cytological findings.[10]

In women in developing countries, cervical cancer is the second most common type of cancer and the third most common cause of cancer-related death.[11] Cervical intraepithelial lesions or invasive tumors are almost entirely caused by HPV infection. Cytological sampling of the cervix or HPV detection is the most effective screening method for cervical cancer. In particular, with the frequent use of HPV vaccines, screening programs have brought forth new perspectives for cervical cancer prevention.[12]

Early diagnosis after screening is vital for controlling the development of cervical cancer. However, an effective tumor marker for the early diagnosis, prognostic evaluation, and follow-up of patients with cervical cancer has not yet been established. The cytology and histological examinations mentioned above can sometimes show low sensitivity.[9] Therefore, there is a need to develop cost-effective specific tumor markers for cervical lesions and early cervical cancer diagnosis. Furthermore, additional tests that can increase the sensitivity of various screening methods can improve their clinical applications.

We found some differences in laboratory values for whole blood markers and biochemical acute phase reactants in patients with cervical LSIL and HSIL compared with those of benign patient groups. Several factors are involved in the pathogenesis of cancer and precancerous lesions. The relationship between cancer and inflammatory processes and the role of inflammation-related parameters in this pathogenesis have been demonstrated in many studies.[13–15]

A study by Sattar et al. determined that serum albumin levels in nonsmall cell lung cancer were lower than those in a healthy population.[16] Moreover, Erlinger et al. reported that serum C-reactive protein levels were higher in patients with colorectal cancer compared with a healthy group.[17] Although studies show that plasma fibrinogen elevation is significantly increased in many malignancies, previous studies and meta-analyses that evaluated the albumin and fibrinogen parameters together revealed that the proportional values of these two molecules differ significantly among cancer patients.[18–23] In a 2016 study, plasma ferritin levels had a significant relationship with prostate cancer.[7] A review published in 2016 that analyzed 15 articles found that serum procalcitonin levels are significantly valuable for the early diagnosis of infection-related complications and exacerbations in cancer patients.[24] This finding indicates that although the procalcitonin molecule is not a direct cancer marker, it may differ significantly in malignancies compared with healthy populations and may be a topic of further study. However, previous studies have shown that serum procalcitonin levels increase significantly in lung, medullary thyroid, and metastatic liver cancer.[25–27]

Complete blood parameters have been extensively studied in many malignancies because they are easy to obtain, readily available, economical, and have pioneered many studies in the literature. Hemoglobin level, white blood cell count, and thrombocyte count and their relative values, which were among the complete blood parameters, also differed significantly in cancer patients compared with a healthy population.[6,28–30] An article published in 2019 showed that serum neutrophil/lymphocyte and platelet/lymphocyte ratios were significantly associated with cervical cancer and cancer stage.[31]

Although studies and reviews have been conducted on the relationship between cancer, inflammation, and inflammatory molecules, the mechanisms that can assist in monitoring and screening cancer and precancerous lesions are unclear. We analyzed inflammation-associated whole blood parameters and other markers to observe cervical intraepithelial lesions exposed to HPV-related infection and inflammation processes.

In our study, serum albumin levels were lower and procalcitonin levels were higher in women who developed cervical intraepithelial lesions compared with a normal population. However, the plasma albumin/fibrinogen ratio was lower in the groups with cervical premalignant lesions than that in the healthy group. We performed a regression analysis to identify the data showing the most significant difference in cervical intraepithelial lesion development based on these three parameters. Serum albumin levels are the most significant laboratory finding with predictive value in women who develop LSIL and HSIL compared with a healthy population. With a sensitivity of 65% and specificity of 60%, the probability of developing cervical premalignant lesions increases in women with serum albumin levels below 46.05 g/l. Although studies have shown that serum albumin levels are low in some malignancies, this is the first analysis to detect significantly lower levels in cervical cancer precursor lesions. Universally accepted cervical smears and HPV tests are available for cervical cancer screening. As this is the first study of its kind, the differences in laboratory markers examined in our study may contribute to improved observation protocols after screening tests, disease prediction, and treatment evaluation, and may also serve as a reference for future studies on this topic.

A previous study reported that plasma albumin values differed significantly among patients with cervical cancer. In our study, we compared a population diagnosed with cervical intraepithelial lesions and a healthy population by observing the cytological and histological results for cervical cancer screening. In this sense, we are the first to describe the detection of low albumin values and albumin/fibrinogen ratios in women diagnosed with LSIL and HSIL in the literature. However, this analysis had some limitations. This study was conducted with volunteers at a single center, and the vaginitis or cervicitis findings of the patients could not be clearly evaluated. However, the number of patients diagnosed with cervical cancer was insufficient; therefore, this group was excluded from the study. A multicenter clinical prospective study with a larger cohort is needed to support the findings of this study.

Serum procalcitonin levels have been previously studied in solid tumors and significant results have been obtained. To our knowledge, our study is the first to correlate cervical lesions with procalcitonin levels. High procalcitonin levels were observed more often in women with LSIL compared with women with a healthy cervix. Previous studies have indicated that procalcitonin is a good indicator of infection in patients with cancer. However, it is not a validated diagnostic method, and the standard limit has not yet been defined. However, we believe that its use in daily clinical practice, preferably in combination with other clinical or laboratory tests, may help detect malignancies or premalignant lesions.

We divided the patients into two groups according to histopathological examination results: LSIL and HSIL groups according to the histopathological examination results of participants who were HPV-DNA positive. We observed that the neutrophil count was higher in the HSIL group. In addition, when we evaluated the conization patients in the LSIL and HSIL groups, we found that the serum neutrophil count was higher in the HSIL group. This increase in cervical lesions and serum neutrophil values indicates that this parameter may be a supportive method for screening or observations. Previous studies have reported a relationship between serum neutrophil and neutrophil/lymphocyte ratio and inflammation. Increased neutrophil concentration is considered to promote neoplastic progression.[31–33]

This study investigated the relationship between inflammatory blood markers and precursor lesions in women screened for cervical cancer. Among these parameters, albumin/fibrinogen ratio and albumin, neutrophil, and procalcitonin levels were significantly associated with cervical intraepithelial lesions. However, these results may not directly indicate the role these molecules play in cervical cancer screening and may not indicate a direct relationship between the disease and its severity. This study was based on the observation of these laboratory parameters in a healthy population and a population with cervical lesions. Our findings may gain further significance by observing a larger group of patients, conducting additional multicenter studies, and incorporating different molecules into the analysis. To the best of our knowledge, this is the first such study in the literature.

CONCLUSION

In conclusion, there is no low-cost, highly-specific diagnostic laboratory marker that can assist the smear and HPV tests used in screening for cervical cancer and intraepithelial lesion precursors to cervical cancer. Low serum albumin levels may be predictive of cervical lesion development. Future studies with more patients and different study designs may provide new data for the prediagnosis and follow-up of premalignant cervical diseases. This study is the first to evaluate the importance of serum inflammatory markers in cervical intraepithelial lesions. According to our results, serum albumin, albumin/fibrinogen ratio, procalcitonin, and neutrophil values were significantly correlated in cervical intraepithelial lesions.

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First facts on the distribution of personal protective equipment during the coronavirus pandemic and facts revealed by medical entities in Brazil: a cross-sectional study

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ABSTRACT

BACKGROUND: The 2019 coronavirus pandemic (COVID-19) has revealed precarious public health conditions worldwide, where serious failures have occurred, similar to the distribution of personal protective equipment (PPE) to physicians in the government of Brazil.

OBJECTIVE: The objective of this investigation was to prove through facts that there have been failures in the distribution of PPE to medical professionals within a reasonable timeframe.

DESIGN AND SETTING: Through a cross-sectional study, we sought to identify the information and data on the subject of "Distribution of PPE" from the official sites of all the national and regional medical representative entities.

METHODS: All medical representative entities, such as unions, councils, and federations, were identified by searching their existing websites, which were active on the World Wide Web, identifying facts, news, and official data regarding the supply of PPE on a daily basis and during the research period.

RESULTS: It was evident from the identification of over 3,900 physician complaints and news reports that there was a failure to distribute PPE to medical professionals in Brazil over a reasonable period. Several physicians obtained PPE through the ruling of the courts.

CONCLUSIONS: There was indeed a failure in the context of health service administration, which compromised the second level of the Maslow Scale, safety needs, and exposed these professionals to a greater risk than necessary, compromised the quality of work life, and directly compromised the doctor-patient relationship. The condition of the physicians cannot be forgotten during the COVID-19 pandemic.

INTRODUCTION

The public management of health services in Brazil can be described as compromised or deficient. In addition to issues with the quality of the services and supply of personal protective equipment (PPE) during the coronavirus disease 2019 (COVID-19) pandemic, poor management has had a negative impact on the quality of work life (QWL) of the medical professionals.

The pandemic officially began in Brazil on February 26, 2020,[1] with the first case of a 61-year-old man, as confirmed by the Ministry of Health. The patient was a businessman and resident of the city of São Paulo, who arrived from the Lombardy region in Italy. According to the health officials, he was unlikely to have been the first patient.[2]

The COVID-19 pandemic that began in Wuhan, a province located in the People's Republic of China, affected almost every country worldwide, leading to a huge effort to meet the demands for health services and ultimately dramatically further compromising the economies of nations,[3] and compromised the world economy by more than US$ 700 billion in 2020, exceeding the global financial crisis of 2008 by 60%.[4]

The impact of the COVID-19 pandemic will be marked in the main economies globally, and in developing countries where two-thirds of the world's population lives, with strong pressure on their financial systems, demanding coordinated actions and help from everyone for the coming months.[5]

Out of respect for physicians who are fellow human beings, the state should not demand irresponsibly that these professionals risk their lives beyond the natural risk of the profession. Such an increase in risk would compromise the QWL and adversely impact the specific and necessary technical activities to be performed during the COVID-19 pandemic. The facts are connected to mysthanasia—silent, little discussed, and causing much less revolt than it deserves: a

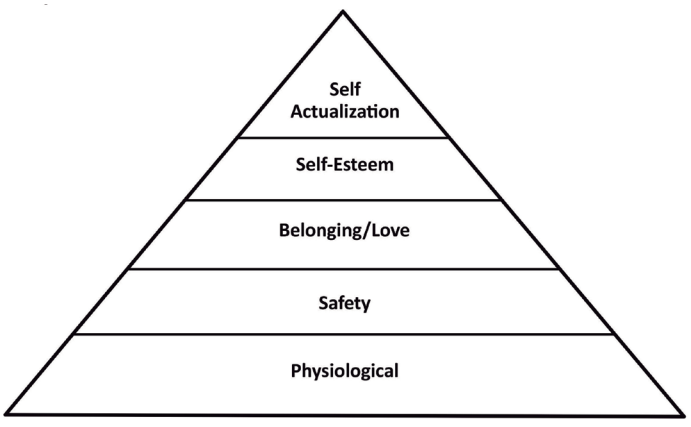
crime not yet typified in the Penal Code, which comes from Greek etymology (mys = unfortunate; thanathos = death; "unfortunate death").[6] It is a miserable, precocious, and preventable death. It is the death facilitated by the three levels of the government, through sustained poverty, lack of infrastructure, and minimum conditions to have a dignified life.[7] Mysthanasia is observed to be part of the context of Bioethics.

The above is evidenced by the following statistics: from February 20, 2020, to June 27, 2020, a total of 19,037 physicians were infected, and 247 of these physicians eventually died.[8] We extended this survey until the last day of August 2020.

In Brazil, where the public sector employs approximately 73.1% of medical professionals, this problem is more serious and the need for a true policy of effective management is evident. As already pointed out, the survey revealed that 21.6% of physicians worked only in the public sector, whereas 26.9% worked exclusively in the private sector. As there is an overlap, 51.5% of physicians work concurrently in the public and private spheres; it can be stated that 78.4% of physicians have ties to the private sector and 73.1% to the public sector.[9]

Maslow scale

We chose Maslow's classical, universal scale (**Figure 1**) as a reference for this study. The lack of PPE distribution to the medical professional class that is on the front line in the fight against the COVID-19 pandemic can lead to a higher exposure of medical professionals to the virus, resulting in a higher risk of pathology, that may be fatal. Thus, concerns about their own safety may lead to a state of mental imbalance in these professionals owing to a greater exposure to the risk of death. During this pandemic, several medical professionals experienced real health impairments, which led to hundreds of work absences, hospitalizations, and numerous deaths.[10]



Adapted from Ferreira et al.[12]

Figure 1. Maslow's scale of needs.

The number of healthcare professionals, including physicians with COVID-19, and the incidence of death were significant in Brazil. According to the Ministry of Health, Brazil has had 31,790 confirmed cases of health professionals with COVID-19. A further 114,000 cases are currently under investigation. Brazil still has the highest rate of death among nurses worldwide because of the COVID-19 pandemic.[11]

The class of medical professionals has a more refined educational level, and the purpose of the profession is supported and grounded with a strong physician-patient relationship and bioethics. Perhaps these reasons have led medical professionals to remain systematically active, even with an increased risk of death. Within the scope of this sample, it is concluded that the Maslow's Hierarchy of Needs, when applied to the work environment, presents an increasing trend of preference in relation to the level of education; that is, the longer the study time, the higher the Maslow scale, and the higher the needs of people.[12]

Regardless of the involvement of the second hierarchical (safety needs) level of the Maslow scale and their educational level, the physicians were inevitably exposed to an increased risk of death by COVID-19 due to the lack of PPE. Therefore, the sophistication of Maslow's needs pertaining to the medical professional class, in proportion to their level of education and the existence of a strong physician-patient relationship, does not result in an absence, *sine qua non,* of their real safety needs. There is a widespread fear of the implications of disease and death. The commitment of the second level of the Maslow scale is due to facts such as complaints about safety and stability at work, the fear of being arbitrarily dismissed, not being able to plan a family budget due to a lack of guarantees regarding one's permanence at work, and arbitrariness of the supervisor with respect to possible indignities to which the individual has to remain at work, his own physical safety in relation to the possible accidents at work, and more efficient and active medical care.[13]

The impairment of the level of safety experienced by the Brazilian medical professionals was evidenced by hundreds of complaints that arrived at representative institutions, which were also reported by the press. If the medical professionals had not felt threatened, there would not have been numerous complaints from all over the country.

The concern and care for the medical professionals compromised the second level of the Maslow Scale, **Figure 1** and, consequently, the QWL. The quality of life (QOL) theory developed by Abraham Maslow's human developmental perspective was presented.

A counterpoint to these statements is the issue of facts reported in this research, where the non-distribution of PPE by the states for the Brazilian medical class simply reached the basic level of the Maslow scale, which compromised their safety and that of the population.

Medical Institutions that fought to get PPE

Institutions from all over Brazil, such as the Brazilian Medical Association (Associação Médica Brasileira, AMB), Federal Council of Medicine (Conselho Federal de Medicina, CFM), National Federation of Physicians (Federação Nacional dos Médicos, FENAM), and the Brazilian Medical Federation (Federação Médica Brasileira, FMB) are in solidarity with Brazilian physicians and other health professionals who contracted COVID-19.[14] Specific pages for complaints were created, such as the one available at the Brazilian Medical Association (Associação Médica Brasileira, AMB).[15] Additionally, several legal actions to obtain PPE, such as in the state of Paraná were undertaken.[16] The same occurred with the regulative institution of the Brazilian medical class, the CFM, which initiated a series of specific recommendations, resolutions, and meetings with representatives of the federal government and made a direct link available on its official website to fill in the form referring to the complaints about the lack of PPE,[17] as was also the case with AMB. The latter was the medical entity that received the most complaints regarding the poor distribution of PPE through the link https://amb.org.br/epi/, which made available a specific form for these complaints. The number of complaints was shown according to the table in **Figure 2**, during the period between February 1 and September 30, 2020.

Some medical unions, through their own link on their official website, redirected complaints regarding the lack of PPE to the official website of the AMB, where a dedicated form for these complaints was found.

There were difficulties in the acquisition and distribution of PPE in the initial phase of the epidemic in Brazil and practically worldwide. The initial inventories, acquisition capacity, and distribution of these PPEs were approached within the context of reasonableness.

Prioritization in the distribution of PPE

The prioritization of health professionals to receive PPE is due to the fact that they are on the front line and are more exposed to COVID-19 than the general population. There is no controversy regarding the risk of contamination when working with pathogens, such as the severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) virus.[18]

The medical professional class is more likely to contract COVID-19 than the general population due to their exposure to the work environment, which includes direct contact with COVID-19 carriers. Our findings could help provide a greater context for previous cross-sectional reports from public health authorities, suggesting that 10–20% of SARS-CoV-2 infections occur among healthcare workers.[19]

Considering the need for the ethical distribution of PPE to medical professionals during the COVID-19 pandemic, there was an unprecedented increase in the consumption of equipment worldwide, which required efforts to meet the demand. It is difficult for clinicians to think about rationing PPE, particularly recognizing that decisions may expose some individuals to a greater risk of infection. However, if these decisions are to be made, they should be based on sound scientific and ethical principles, executed transparently and equitably, and subject to accountability. It is essential to minimize any moral residue from the decisions made during this pandemic such that once it is over, the task of rebuilding may be undertaken.[20] An increase in the PPE supply in response to this new demand will require a large increase in PPE manufacturing, a process that will take time that several healthcare systems do not have, given the rapid increase in ill COVID-19 patients.[21]

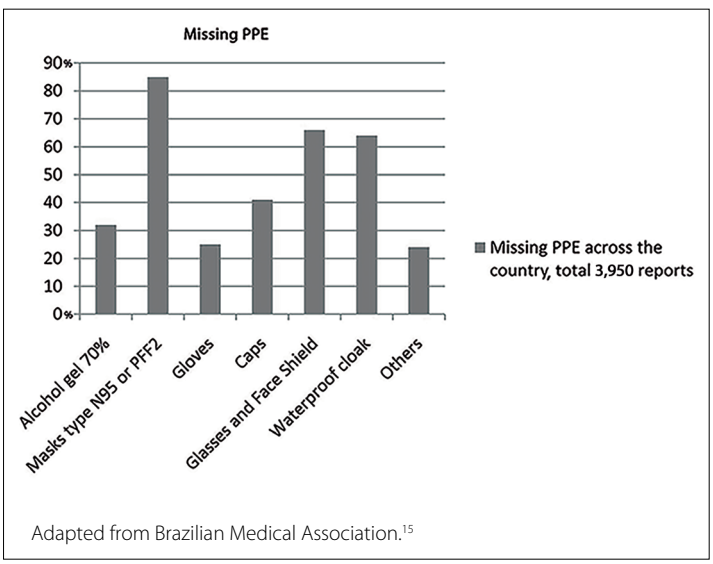
The process of supply and distribution of PPE was not only restricted to the class of medical professionals, but also to all the health professionals who dealt directly with patients affected by COVID-19. It is essential that health workers use PPE during the COVID-19 pandemic; however, it is also essential to coordinate the supply chain for these inputs, implement strategies that minimize the need for PPE, and ensure its proper use.[22]

OBJECTIVE

The objective of this study was to prove through facts that there were failures in the distribution of PPE to Brazilian medical professionals during the time between February 1 and September 30, 2020.

METHODS

This research was approved by the Ethics Committee of the Faculty of Medicine of the University of Porto on June 21, 2021, with opinion 04/CEFMP/2021, and its methodology was approved by the coordinator of PhD in bioethics at the same university.



Adapted from Brazilian Medical Association.[15]

Figure 2. Missing personal protective equipment (PPE).

We identified all the institutions representing the class of Brazilian medical professionals.

The first step of the work consisted of prospecting every day, without exception, with respect to the period defined between February 1 and September 30, 2020, of all facts and all news on their official website via the World Wide Web and searching for the complaints of Brazilian doctors regarding the lack of distribution of PPE as part of the fight against COVID-19. These surveys were conducted when these institutions had official websites and/or were available.

The work verified this fact on consecutive days in all 26 states of the federation and in the Federal District, and its sub-regions.

Data were collected from the websites of all official representative entities of physicians, such as CFM and its 27 regional sites, and the AMB and its 27 federated sites. The two union federations, the FENAM, which brings together the 16 State unions—Amazonas (AM), Bahia (BA), Distrito Federal/Capital (DF), Espírito Santo (ES), Goiás (GO), Maranhão (MA), Minas Gerais (MG), Mato Grosso do Sul (MS), Paraná (PR), Piauí (PI), Rio de Janeiro (RJ), Rio Grande do Norte (RN), Rio Grande do Sul (RS), Sergipe (SE), and five other subregional unions (Juiz de Fora and Zona da Mata/MG, Niterói, São Gonçalo and Região/RJ, Norte do Paraná and Santos, São Vicente, Cubatão, Guarujá, and Praia Grande/SP)—the other trade union, the FMB, which brings together eight other remaining States—Acre (AC), Alagoas (AL), Mato Grosso (MT), Pará (PA), Paraíba (PB), Pernambuco (PE), Santa Catarina (SC), and Tocantins (TO), and three subregional States (Anápolis, Campinas and regions, and Southern Region of Santa Catarina)—were all assessed.

This research was complemented by surveying several national and international publications to provide a theoretical basis for this study.

RESULTS

Table 1 demonstrates the existence of websites of regional representative unions of the Brazilian medical class that have in their own website an announcement about the existence of information on the topic: "Lack of PPE." They provide a "specific link" for these complaints, which redirects the complaining physician to the AMB form. AMB is the only federal medical institution that provides the sum of these national data on the lack of PPE and identifies the total number of complaints from the states where the doctors' complaints are coming from. This information was also accessible to the public. In the case of state councils of medicine (CRM), they provide a "specific link" that redirects to the form on the website of the CFM; however, unlike the AMB, they do not have public access, including for doctors. The unions related to FENAM, which do not have their own form, have a link that redirects them to the AMB website. All complaints, including those made directly on the AMB website (https://amb.org.br/epi/), were presented as aggregated data, and there was no individual identification.

What we refer to as the "specific link," is the one that is identified in a specific page in the site of the accessing institution, and that redirects the complaining physician to the site of the AMB, either through its own homepage or even in an internal page with the subtitle of the main menu as the theme "PPE."

The physicians in states that do not have a specific link for complaints only have the option to do so through the CFM or AMB websites.

The CFM website decided not to present for consultations the totalization of complaints received as complaints of lack of PPE made by physicians.

All state unions that did not have their own website, as well as all those that did, but that did not redirect the physicians' complaints about the lack of PPE to the AMB or CFM websites, are not part of the data in the tables.

The states of Acre and Alagoas did not have a website available on the World Wide Web at the time.

The states of AM, GO, MG, PR, RS, and MT requested PPE distribution in court. To complain regarding the lack of PPE, it is necessary to be accredited as a doctor at AMB, CFM, and others.

The news published on the official sites of the representative entities of the medical class concerning the PPE theme and the failure in its distribution were all selected one by one, day by day, and identified by accessing their respective sites through menus such as: Home Pages, Publications, News or Dialogues, during the proposed period from January 1 to September 30, 2020 (**Table 2**). This specific news was encouraged by the involvement of hundreds of complaints on the official websites of their representative institutions whose data were added together and are shown in **Figure 2**. The data were not included for institutions that did not express specific opinions on the subject, or if the corresponding website was inoperative or non-existent during the period from January 1 to September 30, 2020.

Table 1. Specific link in website: Lack of personal protective equipment (PPE)

State Unions	DF	BA	MG	PR	PI	RJ	RN	RS
Specific link	x	x	x	x	x	x	x	x

DF = Distrito Federal; BA = Bahia; MG = Minas Gerai; PR = Paraná; PI = Piauí; RJ = Rio de Janeiro; RN = Rio Grande do Norte; RS = Rio Grande do Sul.

Table 2. The news published on the official sites of representative entities

Institutions/ State Unions	CFM	AMB	FMB	DF	BA	AM	ES	GO	MG	PR	PI	RN	RS	SE	SC
News about the PPE	10	2	6	7	4	8	2	3	19	4	5	3	6	2	1

PPE = personal protective equipment; CFM = Federal Council of Medicine; AMB = Brazilian Medical Association; FMB = Brazilian Medical Federation; DF = Distrito Federal; BA = Bahia; AM = Amazonas; ES = Espírito Santo; GO = Goiás; MG = Minas Gerais; PR = Paraná; PI = Piauí; RN = Rio Grande do Norte; RS = Rio Grande do Sul; SE = Sergipe; SC = Santa Catarina.

DISCUSSION

The COVID-19 pandemic has been observed to be a testing time in the area of public health management worldwide, and especially in Brazil. In this context, the numbers of physicians, together with nurses and other health professionals,[23] are affected along with those of the general public. All these medical professionals are extremely important for the prevention and in the fight against COVID-19. The need to adopt public health policies worldwide has been placed beyond its conventional limits. This fact persisted well beyond the initial three months of this pandemic, which was officially recognized in Brazil by the government and parliament in February 2020 after the publication of a Federal Law.[24] The frequent lack of PPE numerous times made the medical class struggle to receive them even through lawsuits, such as in the states of AM, GO, MG, PR, RS, and MT. In March 2020, the federal government started releasing extra resources to the states of the federation to combat COVID-19,[25] and consequently to purchase PPE. Despite the low cost of their acquisition, they were not properly distributed to the Brazilian medical class and other health professionals. The absence of PPE for medical activities can cause increased insecurity and individual stress due to the real increase in the risk of death caused by possible contamination with the SARS-CoV-2 virus, which compromises the second level of Maslow's scale. Notably, we must never forget the human condition of the physicians.

In this research, specific news about the theme was identified in the official sites of the physicians' representative institutions, which greatly reinforces the significance of this fact. There were 18 specific news articles from national representative entities, and another 73 news articles, a total of 91 news posts, for their state union representatives only in the research period. During this period, a significant number of physicians made their denouncements, totaling to approximately 4,000 physicians. The denunciations made on the websites of the various state unions and at the federal level were addressed and added to those made directly on the AMB website (**Table 2**).

CONCLUSION

The COVID-19 pandemic, which started in 2019 in the People's Republic of China, spread worldwide and was officially reported in Brazil in February 2020, with its extremely negative aspects becoming more evident in the areas of administrative management involving public health in several countries, including its social and economic consequences. This pandemic also revealed the need for a greater interchange between nations, to stimulate a new proposal to improve the World Health Organization for the practice of data transparency, and for the real need for investments that necessarily transform the management of health services into a higher level and move away from the theme of chronic rhetoric that characterizes some governments. There is an imperative need for more robust national security strategies, as demonstrated by the need to produce our own medical supplies, not depending on other nations for such supplies, efficient logistics to assist in the distribution of equipment and supplies, and so on. Poor management has a negative impact on the QWL of medical professionals. In a global assessment, we cannot forget the human condition of physicians.

Across Brazil, hundreds of complaints about the lack of PPE for the medical class were registered on the websites of representative entities and verified by them. This continued even after the initial phase of the pandemic. Finally, these facts demonstrate the lack of proper management of public services. It was evident that the non-distribution of PPE to health professionals compromised the second level of the Maslow Scale, the level of security, and consequently, the QOL of these professionals. Thus, mysthanasia is a common practice among governments. The states must seek a real reformulation of their posture in relation to bio-laws, which reflect the health of their citizens and health professionals, especially in Brazil, where health is part of the current 1988 Federal Constitution.[26]

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Mortality predictors in a cohort of patients with COVID-19 admitted to a large tertiary hospital in the city of São Paulo, Brazil: a retrospective study

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Predictors.
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Parameters.

ABSTRACT

BACKGROUND: There is discrepant information across countries regarding the natural history of patients admitted to hospitals with coronavirus disease (COVID-19), in addition to a lack of data on the scenario in Brazil.

OBJECTIVE: To determine the mortality predictors in COVID-19 patients admitted to a tertiary hospital in São Paulo, Brazil.

DESIGN AND SETTING: A retrospective analysis of medical records of COVID-19 patients admitted to the Hospital Central da Irmandade da Santa Casa de Misericórdia of São Paulo.

METHODS: Overall, 316 patients with laboratory-confirmed COVID-19 between March 1, 2020, and July 31, 2020, were included. The analysis included the baseline characteristics, clinical progression, and outcomes.

RESULTS: The mortality rate of the sample was 51.27%. Age ≥ 60 years was determined as a risk factor after multivariate logistic regression analysis. Patients with an oxygen (O_2) saturation ≤ 94% upon admission accounted for 87% of the deaths ($P < 0.001$). Vasoactive drugs were used in 92% ($P < 0.001$) of patients who progressed to death, and mechanical ventilation was employed in 88% ($P < 0.001$) of such patients. However, patients who received corticosteroids concomitantly with mechanical ventilation had a better prognosis than those who did not. The progressive degree of pulmonary involvement observed on chest computed tomography was correlated with a worse prognosis. The presence of thrombocytopenia has been considered as a risk factor for mortality.

CONCLUSION: The main predictors of in-hospital mortality after logistic regression analysis were age, O_2 saturation ≤ 94% upon admission, use of vasoactive drugs, and presence of thrombocytopenia.

INTRODUCTION

Coronavirus disease (COVID-19) is a potentially fatal infection caused by the new severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) that was first reported in the city of Wuhan, China, in December 2019. Since then, the disease has achieved a pandemic status, assuming dramatic proportions, thus leading to a global public health emergency.[1-3]

In Brazil, the first case was officially confirmed on February 26, 2020, in the city of São Paulo, which has remained the epicenter of the country's pandemic with the third highest total number of confirmed cases.[4,5]

Reports issued by the World Health Organization (WHO) on July 31, 2020, show that there is a significant difference in prognoses across countries, with a case fatality rate of the disease ranging between 3.53% (90,134/2,552,265 cases) in Brazil, 3.42% (150,054/4,388,566 cases) in the United States of America, and 14.21% (35,132/247,158 cases) in Italy. The reasons for such discrepancies remain to be fully elucidated, with population and genetic aspects, epidemiological control, population testing, and local management of the pandemic seeming to contribute to this situation.[6]

Moreover, in Brazil, approximately 70% of the population relied solely on the services of its National Healthcare System (known as the "Unified Health System," or by its acronym in Portuguese: SUS, Sistema Único de Saúde),[7] which rapidly led to hospital overcapacity and, therefore, possible preventable fatalities. In addition, hospitalization is known to have an array of negative impacts on the overall health of patients, such as secondary infections, needless procedures, psychological distress, and economic fallout of the health system that covers most of the nation's population.

In this context, since most studies so far have focused either on a specific population subset, such as patients admitted to intensive care units or those with a specific disease, for instance or indiscriminately analyze data from public and private services altogether, there is still a gap in the literature on the mortality predictors in the general admitted population in a public hospital setting. Thus, this study aimed to characterize the predictive mortality factors in a cohort of patients admitted with COVID-19 to a tertiary public hospital in the city of São Paulo, Brazil, while also seeking to determine the clinical characteristics and prognostic factors of patients representing the most severe cases of the disease and hence requiring hospitalization.[8]

Therefore, these findings may support the creation and design of scientifically supported clinical management protocol for inpatient admission and hospitalized patient care in large public facilities.

OBJECTIVE

This study aimed to determine the predictors of mortality in patients with COVID-19 admitted to a tertiary hospital in São Paulo, Brazil.

METHODS

Study design

This retrospective study was conducted at the Hospital Central da Irmandade da Santa Casa de Misericordia of São Paulo (ISCMSP), a large tertiary public hospital in São Paulo, Brazil. The Hospital Central has a total capacity of 559 beds, 550 of which are currently in use. At the time of this study, 152 of these beds were intended for COVID-19 patients, of which 72 beds were intended for intensive care.

Data were collected from the electronic medical records of patients with confirmed SARS-CoV-2 infection between March 1, 2020, and July 31, 2020.

The patients were selected from a list generated by the institution's Nosocomial Infection Control Committee (CCIH, the Portuguese acronym for Comissão de Controle de Infecção Hospitalar), which included cases reported during the period of suspected COVID-19 cases due to the presence of respiratory symptoms, regardless of the primary cause of admission.

Of the 1840 selected patients, only 329 patients showed a positive result in the reverse transcription polymerase chain reaction (RT-PCR) assay, serology, or viral panel, performed either by Instituto Adolfo Lutz or the CientíficaLab, a laboratory associated with the institution, and were therefore considered for our analyses.

An electronic form was developed to insert the data collected from the medical records (Sistema Soul MV, Versão SMA-PEP.2019.006. LTS [Recife, Brazil]). The following variables were collected:

- Demographic characteristics and information upon admission: age, sex, ethnicity, comorbidities, saturation (pulse oximetry), pulmonary involvement on chest computed tomography (CT), and indication for admission (due to COVID-19 or any other diagnosis).
- Progression and outcomes: use of vasoactive drugs, mechanical ventilation, hemodialysis, length of hospital stay, complications, and outcome (discharge from hospital or death). All patients who died during their hospital stay, regardless of the cause, were categorized under "death." A total of 13 patients who were transferred or dropped out during hospitalization were excluded from this study. See **Figure 1** for further details.

Older adult patients were those aged over 60 years, as defined by the WHO for developing countries.[9]

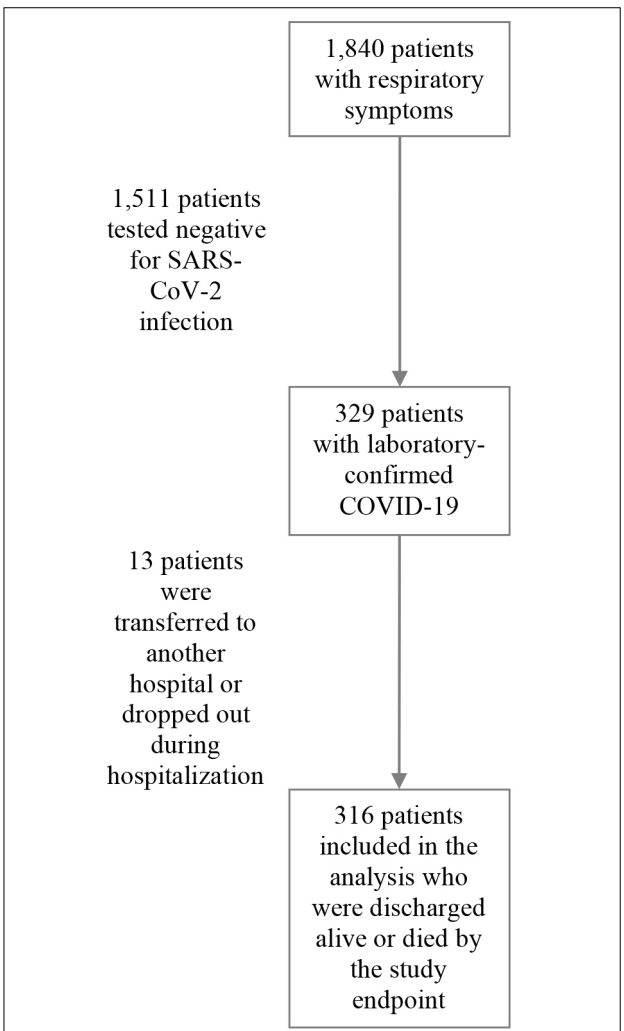

Figure 1. Flowchart for the selection of the study population.

This work was a part of project No. 4,893,387 (August 9, 2021) approved by the Research Ethics Committee (CEP, Portuguese acronym of Comitê de Ética em Pesquisa) at the institution where the study was carried out. Due to the retrospective nature of this study, the requirement for voluntary informed consent form was waived in accordance with the current regulations.

Data collection

Comorbidities were reported on the basis of an initial anamnesis performed with the patient, their accompanying person, or as per the description contained in an electronic medical record from a previous time when the patient received health care services at the institution. The following were considered for analysis: chronic cardiovascular disease, systemic arterial hypertension, chronic kidney disease, use of corticosteroids, transplant recipients, chronic liver disease, chronic neurological disease, chronic neuromuscular disease, chronic lung disease, asthma, tuberculosis, smoking, diabetes mellitus, overweight, obesity, dementia, primary or secondary immunodeficiency, neoplastic disease, chronic hematologic disease, drug use, and pregnant or postpartum women.[10]

The vital signs considered were those upon admission to the COVID-19 department, either at the time of initial care in the emergency room or upon suspicion of nosocomial infection in patients who had previously been admitted to the hospital. A heart rate between 50 and 100 beats per minute was considered as normal,[11] as was a respiratory rate between 12 and 20 breaths per minute.

The patients were considered to have been subjected to hemodialysis in all cases where this procedure had been employed during their hospital stay, whether due to a prior need or not.

The CT scans included in the analysis corresponded to the first study carried out within the first 24 h of patient admission to the COVID-19 sector.

With regard to the laboratory tests, normal values, such as those used by the clinicians at the laboratory where the tests were performed, were used as the parameters. Thus, in relation to the arterial blood gas test, an acid-base disorder was considered when the pH was below 7.35 or above 7.45, whereas hypoxemia was considered when the partial pressure of oxygen (PaO_2) was lesser than 80 mmHg. With respect to the blood count, anemia was considered when the hemoglobin level was less than 12 g/dL, leukocytosis when the leukocyte count was greater than 10,000 cells/mm^3, and thrombocytopenia when the platelet count was lesser than 140,000 platelets/mm^3. In addition, prothrombin time (PT) was classified as normal between 11 and 12.5 s, normal activated partial thromboplastin time (aPTT) between 24 and 40 s, and altered D-dimer when values were above 0.50 μd/mL.

The use of any given medication was considered as positive if at least one dose thereof was administered.

Statistical analysis

Data analyses were performed using the SPSS version 25.0 software (IBM Corporation, Armonk, New York, United States).

The statistical analysis of the study population was based on whether a given variable could be characterized as a mortality predictor.

Thus, several variables related to the clinical characteristics, supplementary tests, and treatments were compared according to patient progression (discharge from hospital or death). The corresponding frequencies were established, and Pearson's chi-square test was used for the analysis, with a level of significance (P value) of 0.05.

Subsequently, to assess the risk factors associated with death, a multivariate logistic regression analysis was performed using the stepwise method, with a P value ≤ 0.05 requirement for data entry.

However, since the number of variables was quite extensive, pre-selection was carried out using bivariate analysis and setting a P value ≤ 0.20, according to Pearson's chi-square test or Fisher's exact test, along with excluding those with a data loss greater than 10%.

RESULTS

A total of 316 patients admitted to the hospital with COVID-19 were included in the analysis. The mortality rate in this population was 51.27% (162/316; 95% confidence interval [CI], 45.75–56.78%).

In addition to the overall mortality rate of the study sample, three other groups were considered (clinical, supplementary, and treatment characteristics) to better elucidate the potential predictors of mortality.

However, it is noteworthy that for each item, the number of patients may vary according to the availability of data.

Clinical characteristics that are mortality predictors

Of the 316 patients, 262 (82.91%) patients were community-acquired, and SARS-CoV-2 infection was the primary cause of hospitalization. The other 54 (17.09%) cases were nosocomial cases.

The average length of stay for the sample was 17.47 days (95% CI 15.13; 19.81), and 174 (55.06%) patients required admission to the intensive care unit during clinical progression, whereas 142 (44.94%) cases remained in the ward during the entire hospital stay.

In **eTable 1** in the Supplement (https://drive.google.com/file/d/1WwAiHPfkpZjC1wvaKArI6FpAoEtR-8e9/view), the data considered valid from 316 patients in the study population were evaluated for mortality predictors according to the hospitalization characteristics.

The mortality predictors were analyzed according to the clinical characteristics. **Table 1** shows the main clinical characteristics of the sample. Most patients were observed to be Caucasian older adult men with comorbidities.

Subsequently, the same patient samples were assessed for vital signs upon admission. Oxygen saturation, as measured by pulse oximetry, had a significance probability of < 0.001; thus, it was

statistically significant. Considering the admission data, patients with saturation ≤ 94% appeared to have a worse prognosis (**Table 2**).

The use of vasoactive drugs, mechanical ventilation, and hemodialysis as potential prognostic indicators was also analyzed, with results shown in **Table 3**. However, after a multivariate logistic regression analysis, only the use of vasoactive drugs could be considered as a predictor of mortality.

In **eTable 2** in the Supplement (https://drive.google.com/file/d/1WwAiHPfkpZjC1wvaKArI6FpAoEtR-8e9/view), symptoms are displayed according to their order of relevance as potential predictors. For this analysis, a report of a subgroup of 307 patients was considered, whereas those from which patient histories could not be retrieved were excluded. Of the symptoms listed, only the absence of fever was higher in the in-hospital mortality group.

Table 1. General clinical characteristics of the study population

Clinical characteristics	Total	Discharge from hospital	Death	P
Age (in years)	316	154	162	< 0.001*
≥ 60	170 (54%)	64 (42%)	106 (65%)	
< 60	146 (46%)	90 (58%)	56 (35%)	
Comorbidity	309	153	156	< 0.001*
Yes	254 (82%)	112 (73%)	142 (91%)	
No	55 (18%)	41 (27%)	14 (9%)	
Sex	316	154	162	0.163 NS
Male	197 (62%)	90 (58%)	107 (66%)	
Female	119 (38%)	64 (42%)	55 (34%)	
Ethnicity	290	140	150	0.347 NS
Caucasian	191 (66%)	96 (69%)	95 (63%)	
Non-Caucasian	99 (34%)	44 (31%)	55 (37%)	

*Statistically significant; NS = not significant.

Supplementary characteristics serving as mortality predictors

To assess the possible associations between supplementary tests and hospitalization outcomes, subgroups were considered according to the available tests. Altogether, a chest CT analysis was performed for 116 patients (detailed in **eTable 3** in the Supplement: https://drive.google.com/file/d/1WwAiHPfkpZjC1wvaKArI6FpAoEtR-8e9/view), who represented the sample with such tests accompanied by their respective reports. In addition, entry oxygen saturation and the degree of impairment, as seen on chest CT, were correlated in a subgroup of 113 patients.

For chest CT analysis, pulmonary involvement was quantified in the imaging study, and the main findings were ground-glass opacity, consolidation, pleural thickening, and reticular opacities, with ground-glass opacity being the most common finding.

Three degrees of pulmonary involvement were considered (< 25%, between 25% and 50%, and > 50%); the greater the alterations, the greater the correlation with death, and therefore, the worse the prognosis. Additionally, when correlated with oxygen

Table 2. Vital signs upon admission

Vital signs upon admission	Total	Discharge from hospital	Death	P
Sat (%)	303	152	151	< 0.001*
≤ 94	240 (79%)	108 (71%)	132 (87%)	
> 94	63 (21%)	44 (29%)	19 (13%)	
Heart rate (bpm)	285	147	138	0.024 NS
Tachycardia	101 (35%)	60 (41%)	41 (30%)	
Normocardia	180 (63%)	87 (59%)	93 (67%)	
Bradycardia	4 (1%)	0 (0%)	4 (3%)	
Respiratory rate (ipm)	281	145	136	0.143 NS
Eupneic	101 (36%)	58 (40%)	43 (32%)	
Tachypneic	180 (64%)	87 (60%)	93 (68%)	

Sat = saturation; bpm = beats per minute; ipm = incursions per minute; NS = not significant; * statistically significant.

Table 3. Hemodynamic progression of the study population

Hemodynamic progression	Total (n = 316)	Discharge from hospital (n = 154)	Death (n = 162)	P
Use of vasoactive drug				< 0.001*
Yes	171 (54%)	22 (14%)	149 (92%)	
No	145 (46%)	132 (86%)	13 (8%)	
Mechanical ventilation				< 0.001*
Yes	166 (53%)	24 (16%)	142 (88%)	
No	150 (47%)	130 (84%)	20 (12%)	
Hemodialysis				< 0.001*
Yes	62 (20%)	13 (8%)	49 (30%)	
No	254 (80%)	141 (92%)	113 (70%)	

*Statistically significant.

saturation upon admission lower or equal to 94%, the progressive severity of the pulmonary imaging findings remained associated with a poorer prognosis; taken together, these two constitute an important set of predictive mortality factors. However, this variable could not be included in the multivariate logistic regression analysis because of excessive data loss.

The laboratory characteristics were also evaluated, as shown in **Table 4**.

The altered levels of PT or aPTT, and anemia, leukocytosis, and thrombocytopenia, were more prevalent in the population that progressed to death. However, the in-hospital mortality was only associated with thrombocytopenia after a logistic regression analysis.

Treatment characteristics

Although the only treatment recommended by the WHO is the use of systemic corticosteroids in severe or critical cases of COVID-19,[12] the use of medications in the sample patients was analyzed, as detailed in **eTable 4** in the Supplement (https://drive.google.com/file/d/1WwAiHPfkpZjC1wvaKArI6FpAoEtR-8e9/view).

None of the evaluated medications showed an association with better prognoses in the study population.

The correlation between patients on mechanical ventilation and corticosteroid use was also evaluated. Thus, patients on mechanical ventilation who received corticosteroids had a mortality rate of 72.73% (40/55), whereas for those who did not receive corticosteroids, the rate was 91.89% (102/111) with a P value of 0.006.

Finally, as shown in **Table 5**, some variables were chosen for the multivariate logistic regression. Therefore, age > 60 years, O_2 saturation ≤ 94%, use of mechanical ventilation without concomitant corticosteroid therapy, thrombocytopenia, and the use of vasoactive drugs were considered as the risk factors for mortality.

DISCUSSION

The COVID-19 pandemic is a serious threat to public health owing to the uncertainty it has brought worldwide. The panorama of a new virus with high transmissibility, high heterogeneity, and pathophysiology has not yet been fully elucidated, with cases ranging from an asymptomatic clinical picture to death,

Table 4. Laboratory test results of the study population

Arterial blood gas test	Total (n = 258)	Discharge from hospital (n = 119)	Death (n = 139)	P
Acid-base disorder				0.320 NS
Yes	158 (61%)	69 (58%)	89 (64%)	
No	100 (39%)	50 (42%)	50 (36%)	
Hypoxemia: PaO_2 < 80 mmHg				0.947 NS
Yes	161 (62%)	74 (62%)	87 (63%)	
No	97 (38%)	45 (38%)	52 (37%)	
Blood count	**Total (n = 292)**	**Discharge from hospital (n = 142)**	**Death (n = 150)**	**P**
Anemia				0.004*
Yes	149 (51%)	60 (42%)	89 (59%)	
No	143 (49%)	82 (58%)	61 (41%)	
Leukocytosis				< 0.001*
Yes	89 (30%)	29 (20%)	60 (40%)	
No	203 (70%)	113 (80%)	90 (60%)	
Thrombocytopenia				0.046*
Yes	24 (8%)	7 (5%)	17 (11%)	
No	268 (92%)	135 (95%)	133 (89%)	
Altered PT and/or aPTT	**Total (n = 254)**	**Discharge from hospital (n = 120)**	**Death (n = 134)**	**P < 0.001**
Yes	96 (38%)	30 (25%)	66 (49%)	
No	158 (62%)	90 (75%)	68 (51%)	
Changed D-Dimer	**Total (n = 255)**	**Discharge from hospital (n = 121)**	**Death (n = 134)**	**P = 0.600 NS**
Yes	39 (15%)	17 (14%)	22 (16%)	
No	216 (85%)	104 (86%)	112 (84%)	

PaO_2 = partial pressure of oxygen; PT = prothrombin time; aPTT = activated partial thromboplastin time; NS = not significant; *statistically significant.

Table 5. Multivariate logistic regression of selected variables with odds ratio values, standard error, and significance probability

First group of variables	Total number of patients	OR	OR, 95% CI lower bound	OR, 95% CI upper bound	SE	P
O_2 saturation	303	3.8	1.2	12.0	0.584	0.022*
Age	316	4.2	1.5	11.5	0.512	0.005*
Thrombocytopenia	292	20.0	4.0	100.5	2.998	< 0.001*
Use of vasoactive drug	316	525.4	122.5	2253.4	0.743	< 0.001*

OR = odds ratio; CI = confidence interval; SE = standard error; O_2 = oxygen; *statistical significance.

achieving a reduction in mortality due to the disease has become a priority in the international scientific community.

Furthermore, reports issued by the WHO show that the mortality rate associated with COVID-19 varies greatly across different countries, indicating that particular geographic features likely play a role in the progression of the disease, and not every study can be extrapolated to individual realities.

In addition, our sample was composed solely of patients from the SUS, the nation's public healthcare services, on which approximately 70% of the population relies. Therefore, protocols designed to prioritize patients for hospital admission are essential to avoid overcapacity and the consequences of avoidable hospitalization.

Hence, the identification of predictive mortality factors that could aid in the establishment of protocols for the care of the studied population is essential, especially in the management of the most severe cases of the disease spectrum requiring hospitalization, and our study was designed with the aim of filling that gap.

Similar to the findings of other studies that analyzed cohorts of in-hospital patients in the same period as this one, such as the one published by Richardson et al., which analyzed 5,700 patients admitted to hospitals with COVID-19 in the New York City (United States) region,[13] and the one published by Bellan et al., with 1,697 patients distributed across hospitals in northern Italy,[14] our study population was characterized by comprising mostly older adult males and patients with comorbidities; being older than 60 years of age can also be considered an independent risk factor for mortality.

Moreover, the mortality rate (51%) in our study was much higher than that reported by Richardson et al.[13] and Bellan et al.[14] (21% and 30%, respectively), but similar to those in other Brazilian studies, such as the one by Santos et al.,[15] a multicenter national study that analyzed 46,285 hospitalized patients due to COVID-19, which reported a 46% mortality rate.

With regard to the characteristics upon admission, an oxygen saturation level ≤ 94%, as measured by pulse oximetry, had an odds ratio of 3.8, i.e, such patients were 3.8-fold more likely to progress to death than those with an oxygen saturation > 94%. The most prevalent symptoms in the sample were dyspnea, coughing, and fever; however, the presence of none may be associated with higher in-hospital mortality.

Although CT scans of the chest accompanied by their respective reports were available for only 37% of patients, they also showed that the greater the degree of pulmonary involvement, the worse the prognosis of the patient. The conclusion remained the same when associated with entry oxygen saturation, i.e., these parameters could be useful for the rapid stratification of cases being admitted to the hospital.

As already explored in other studies,[16] the hypercoagulable state seems to be associated with higher mortality via pathophysiological mechanisms that are yet to be fully elucidated. This phenomenon can also be seen in our study population, as translated by the association between higher mortality and altered PT and activated thromboplastin time, in addition to thrombocytopenia, which can be considered as a risk factor, with an odds ratio of 20.0, as found by logistic regression.

The use of vasoactive drugs and the need for mechanical ventilation were also highly prevalent in the death group, with the former being considered as a risk factor for such outcomes. However, the concomitant use of corticosteroids in mechanically ventilated patients, as recommended by the WHO,[12] could result in better prognoses.

This study has a few limitations, primarily due to its observational and retrospective nature; not all the data initially planned for analysis could be retrieved. Therefore, the total sample, comprising 316 patients, could not be analyzed for all the categories initially envisaged. In addition, variables, such as ethnicity and pulmonary involvement as seen on chest CT scans were not only described by a large number of different professionals, but also by dependent examiners. It is also worth noting that the hospital where this study was carried out is a referral facility located in the central region of the city and receives patients transferred from various other less complex minor hospitals/health care system units, which may indicate that the patient's condition could already be more advanced at the time of the initial care provided by our team and consequently result in worse outcomes and higher mortality.

Our study contributed to determining the phenotype of patients admitted to the hospital with COVID-19 at a higher risk of in-hospital mortality, with the aid of identifying those in need of hospital admission, priority care, case stratification, signs of clinical deterioration, and worse outcomes.

CONCLUSION

According to our findings, age ≥ 60 years, oxygen saturation ≤ 94% upon admission, use of vasoactive drugs, and thrombocytopenia were the main clinical predictors of in-hospital mortality.

In addition, mechanical ventilation, pulmonary involvement as seen on chest CT scans, altered values of PT, aPTT, leukocytosis, and anemia were more prevalent in the death group; however, they could not be considered as risk factors for mortality after adjustments.

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Longitudinal evaluation of the Ophthalmology residents in Brazil: an observational prospective study

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ABSTRACT

BACKGROUND: The longitudinal evaluation of students seems to be a better way to assess their knowledge compared with that of the traditional methods of evaluation, such as modular and final tests. Currently, progress testing is the most consolidated type of longitudinal testing method. However, despite being well consolidated as an assessment tool in medical education, the use of this type of test in residency programs is scarce.

OBJECTIVES: This study aimed to investigate residents' knowledge growth regarding residency training and to describe the implementation of a longitudinal evaluation test in ophthalmological residency training across several medical schools in Brazil. Finally, the study aimed to check whether performance in the tests can be used as a predictor of the results of the specialist title test.

DESIGN AND SETTING: This was a prospective observational study. This study was conducted using an online platform.

METHODS: Online tests were developed following the same pattern as the Brazilian Ophthalmology Council specialist tests. All the residents performed the test simultaneously. The tests were conducted once a year at the end of the school year.

RESULTS: A progress test was conducted across 13 services with 259 residents. Our results demonstrated that resident scores improved over the years ($P < 0.0001$) and had a moderate correlation with the Brazilian Opthalmology Council specialist test ($P = 0.0156$).

CONCLUSION: The progress test can be considered a valuable tool to assess knowledge, meaning their knowledge increased over residency training. In addition, it can be used as a predictor of the result in the specialist title test.

INTRODUCTION

Knowledge assessment plays an important role in medical education since professional expertise development appears to be strongly connected to knowledge.[1] Research has shown that assessment may be used in different ways. For example, studies have demonstrated that assessment drives and stimulates learning,[2,3] provides educational efficacy information to institutions and teachers, and protects patients.[1]

The definitions of "to test" in the dictionary are as follows: to discover the worth of something by trial, to obtain more information about the object of assessment, and to improve the quality of something by trial.[4] Thus, assessment in the broader sense involves testing, measuring, collecting, combining information, and providing feedback.[4]

In many medical residency programs, modular, intermediate, or final tests have been used to measure the knowledge level of trainees.[5,6] However, these types of tests are associated with the promotion of short-term memorization.[5] In addition, residents' performance may not correspond to the real knowledge level since it is merely a one-point measurement, not allowing any extrapolation to the maintained knowledge level over time.[7] To benefit students' long-term retention, longitudinal testing in the form of the progress test, the most known and established kind of longitudinal test, has been suggested.[2,8]

Progress testing aims to measure students' knowledge at the end level and allows the measurement of knowledge growth.[8,9] In addition, progress testing forces students to study over time, encouraging more profound and deep learning[10] since it is impossible for students to cram before the test. Alternatively, students must acquire information continuously in such a way that it is available when required.[11] Progress tests allow for individual learning pathways, which may

provide clues for future performance. Finally, progress testing can be organized at a national level[7] and can be used to compare the results of candidates from different countries.[5]

Progress tests have been used in different ways, such as for providing feedback to students,[12,13] understanding knowledge growth on questions requiring lower and higher order of cognitive processing,[12,13] comparing national[14] and international curricula,[15] and the effectiveness of educational strategies.[16,17] Many medical schools worldwide have already adopted this progress testing as part of their curricula, such as the Netherlands,[18] Canada,[19] Germany,[6] Indonesia, South Africa, the United States,[20] and Brazil.[21,22]

Despite being a well-established assessment tool in the undergraduate context, progress testing is much less widespread in the postgraduate context, where the best test format remains controversial.[23] Some authors believe that, at least in theory, longitudinal tests would also be an interesting approach to knowledge assessment in postgraduate medical education.[7] So far, only a few residency programs have already included the progress test in their curricula, such as in obstetrics and gynecology,[24] radiology, and in general practice,[10,25] demonstrating promising results.

The World Reference Institution in ophthalmology residency programs is the International Council of Ophthalmology (ICO). According to the ICO, medical knowledge is one of the general core competencies expected from ophthalmic specialists (besides patient care, practice-based learning and improvement, communication skills, professionalism, and systems-based practice).[26,27]

Progress testing during residency could play an important role in monitoring the competence progress. Besides, it could be useful for the quality control of residency programs in Brazil, by allowing interventions during the course. In addition, the tests can serve as self-learning tools for residents. Finally, it can be useful to predict residents' results in the specialist test of the Brazilian Opthalmology Council.[28]

OBJECTIVE

This study aimed to investigate residents' knowledge growth during their residency training. This study also describes the implementation of a progress test in ophthalmological residency training across several medical schools in Brazil. Finally, this study aimed to investigate whether there was a correlation between the performance of the progress test and the specialist title test.

METHODS

This was a prospective observational study carried out through an online platform.

This study was approved by the ethics committee of Universidade Estadual de Campinas on December 17, 2018 (CAAE number:02613718.9.0000.5404).

Participants: The study was conducted in 2019. All participants were ophthalmology residents who agreed to participate voluntarily in the study and signed a consent form.

Ophthalmology Residency in Brazil

In Brazil, the ophthalmology residency consists of a 3 years program.

The institution that represents the Brazilian Ophthalmology is the Brazilian Ophthalmology Council (Conselho Brasileiro de Oftomologia, CBO).[28] According to the CBO, the minimum pedagogic program required for the ophthalmology specialization consists of the following content:

1. Basic sciences: 100% in the 1st year and 0% in the 2nd and 3rd year
2. Propaedeutics: 60% in the 1st year, 30% in the 2nd, and 10% in the 3rd year
3. Optometry: 50% in the 1st year, 50% in the 2nd, and 0% in the 3rd year
4. Surgical techniques: 50% in the 1st year, 50% in the 2nd, and 0% in the 3rd year
5. Clinics and surgery: 25% in the 1st year, 50% in the 2nd, and 25% in the 3rd year

Besides this mandatory content, there may be complementary activities, such as clinical case discussions, pathological anatomy sections, and scientific article discussions.[28]

Progress test construction and application

The progress test consisted of 125 multiple-choice questions on clinical and surgical issues in ophthalmology. The blueprint followed the same pattern as the Brazilian Ophthalmology Council specialist test:[28]

- uveitis: 9 questions;
- neuro ophthalmology: 7 questions;
- orbit: 4 questions;
- lacrimal system: 4 questions;
- ocular plastics: 8 questions;
- ocular tumors: 5 questions;
- cornea: 14 questions;
- contact lenses: 4 questions;
- refractive surgery: 2 questions;
- retina: 13 questions;
- cataract: 10 questions;
- glaucoma: 11 questions;
- refraction: 23 questions;
- strabismus: 7 questions;
- low vision: 4 questions.

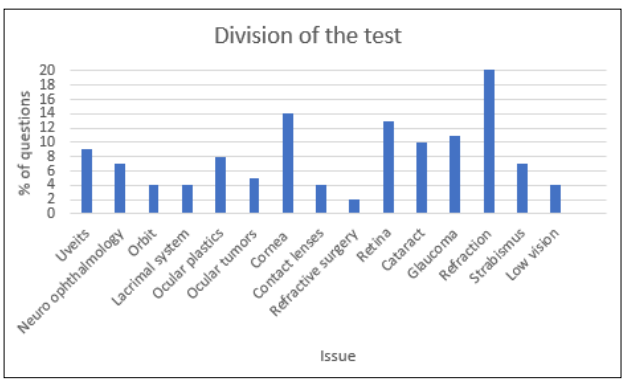
The **Graphic 1** shows the division of the test questions.

As the tests consisted of 125 multiple-choice questions, for the statistical analysis, a 0.08 value corresponds to 10/125 for each

correct answer; thus, it was attributed to a score that could vary from 0 to 10 for each test.

The questions in the tests were taken from the following books: Review Questions in Opthalmology,[29] Clinical Optics and Refraction,[30] and Self-tests in Optic and Refraction.[31] They were chosen according to the issue and level of difficulty (judged by the authors), in a way that there were questions of different issues and levels of difficulty.

As there were residents from many parts of the country, the tests were online, and all the residents from the 1st to the 3rd year of the ophthalmology residency programs performed the tests simultaneously. Therefore, all residents were enrolled in the same test, regardless of whether they were in their 1st, 2nd, or 3rd year of residency. The tests were conducted once a year at the end of the school year.



Graphic 1. Division of the test questions.

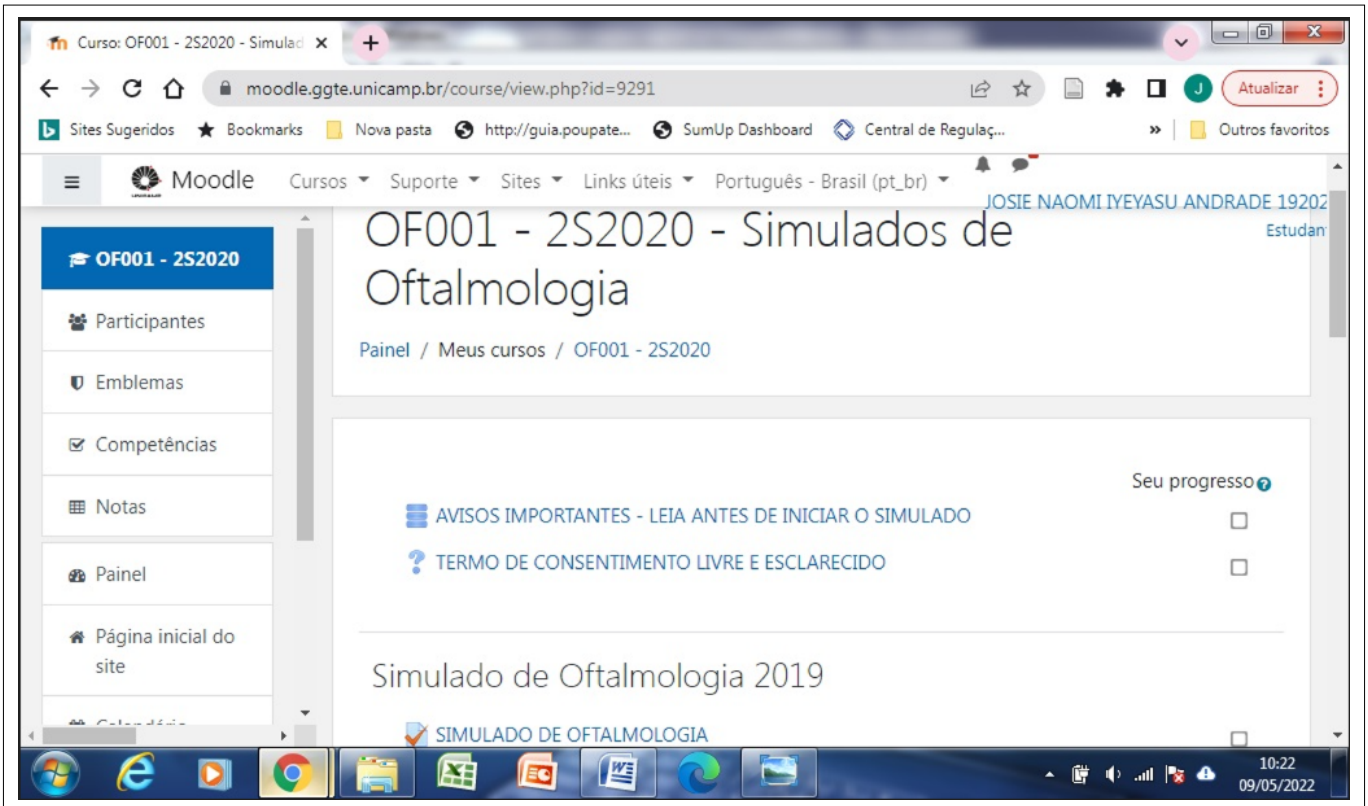
Each service organized the implementation of the tests, and the only requirement was that all residents sat on the test simultaneously. Some services used their own informatic lab rooms, while those that did not have one allowed their residents to use their own computers, either at the service or at home, at a predetermined schedule, as long as there was one computer for each resident.

Site

First, participants had to create an account. Once completed, they were able to access the site. **Figures 1–4** show a small portion of the site.

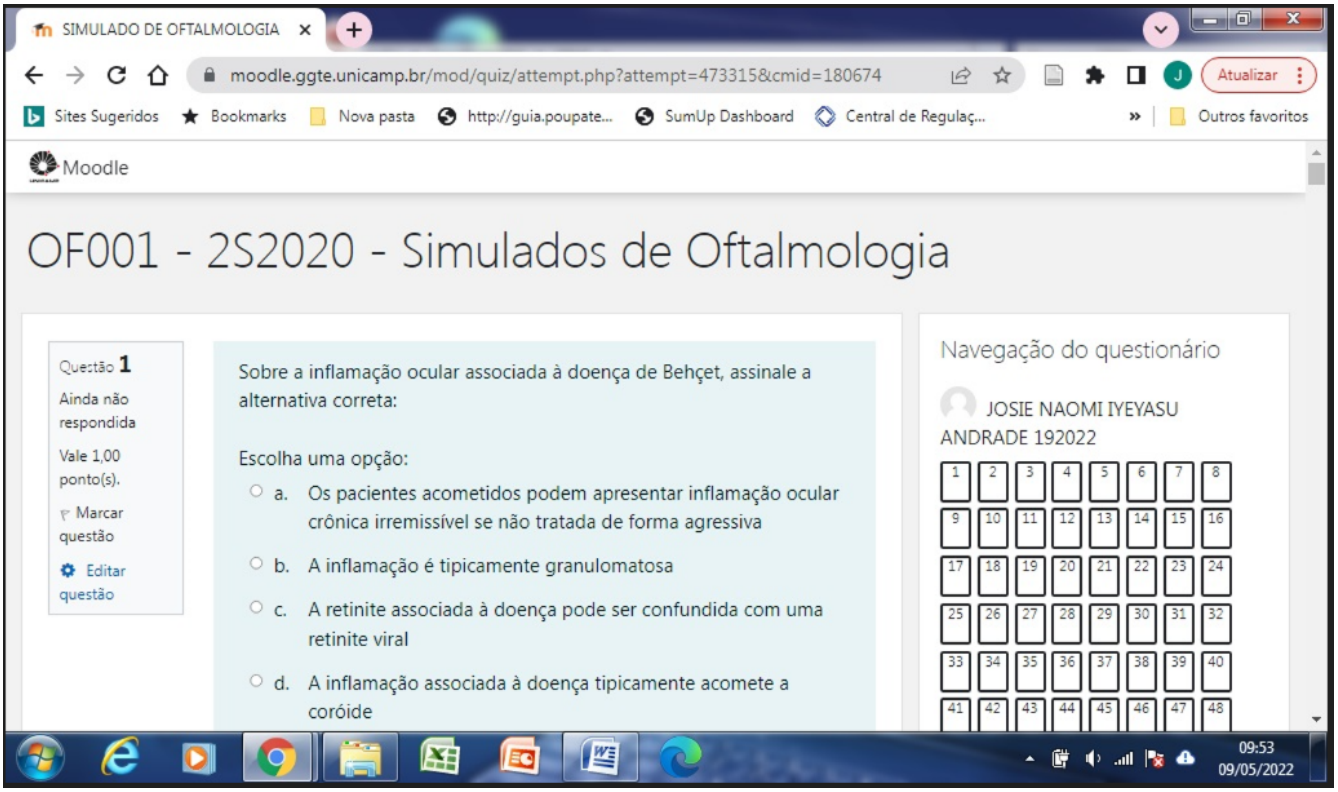
The presentation page contains some important advice to read and the consent term that had to be signed before the test itself (**Figure 1**).

The test page contained the test itself. Once completed, participants had to submit their answers. Immediately after the submission, the participant received feedback (**Figure 2**).



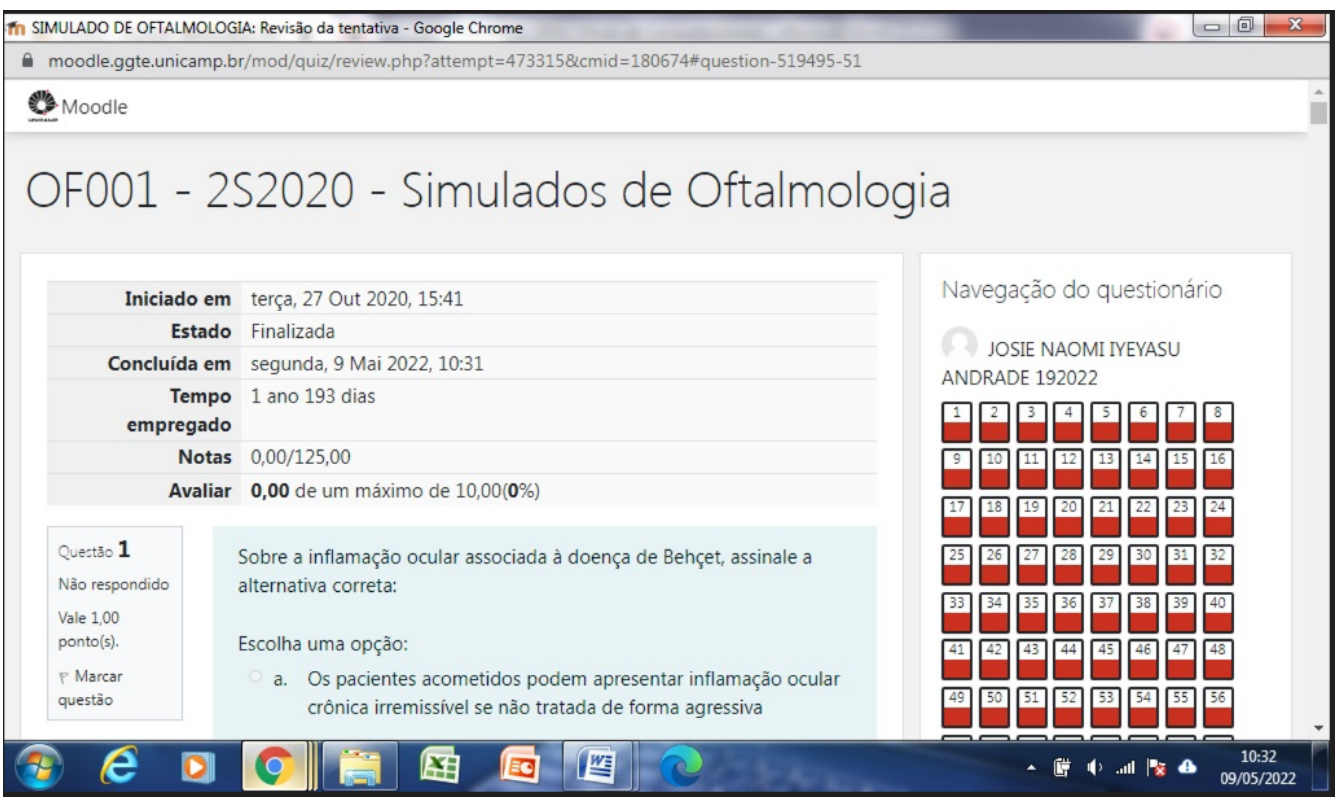
The presentation page contains some important advice to read and the consent term that had to be signed before the test itself.

Figure 1. Presentation page.



The test page contains the test itself. Once done, the participant had to submit the answers. Immediately after the submission, the participant received feedback.

Figure 2. Test page.



The feedback page shows the number of correct and incorrect answers, the time spent performing the test, and the score.

Figure 3. Feedback page.

The feedback page shows the number of correct and incorrect answers, the time spent performing the test, and the score (**Figure 3**).

Figure 4 shows the correct answers and explanations.

Data analysis

Frequency tables were used for the descriptive analysis of categorical variables. Positions and dispersion measures were used for numeric variables. The Kruskal–Wallis test was used to compare the differences between years, followed by Dunn's test to identify significant differences.

The Friedman or Wilcoxon test was used to compare students' knowledge growth.

To investigate the relationship between the progress test and CBO scores, the Spearman linear correlation coefficient and Wilcoxon test for related samples were conducted.

A statistical level of 0.05 was considered significant.

Data were analyzed using the Statistical Analysis Software (SAS) System for Windows (Statistical Analysis System), version 9.4. SAS Institute Inc, 2002-2012, Cary, North Carolina, United States.

RESULTS

Among the many ophthalmology residents all around Brazil invited to join the study, 24 accepted the invitation. A total of 297 residents participated in the progress test. Of these, 100 (33.7%) were from the 1st year, 108 (36.4%) from the 2nd year, and 89 (30.0%) from the 3rd year.

Descriptive analysis and comparison of the scores for each residency year

The mean score of the 1st year residents was 4.3, that of the 2nd year residents was 5.1, and that of the 3rd year residents was 5.4. **Table 1** and **Graphic 2** show the descriptive analysis and comparison of scores for each residency year.

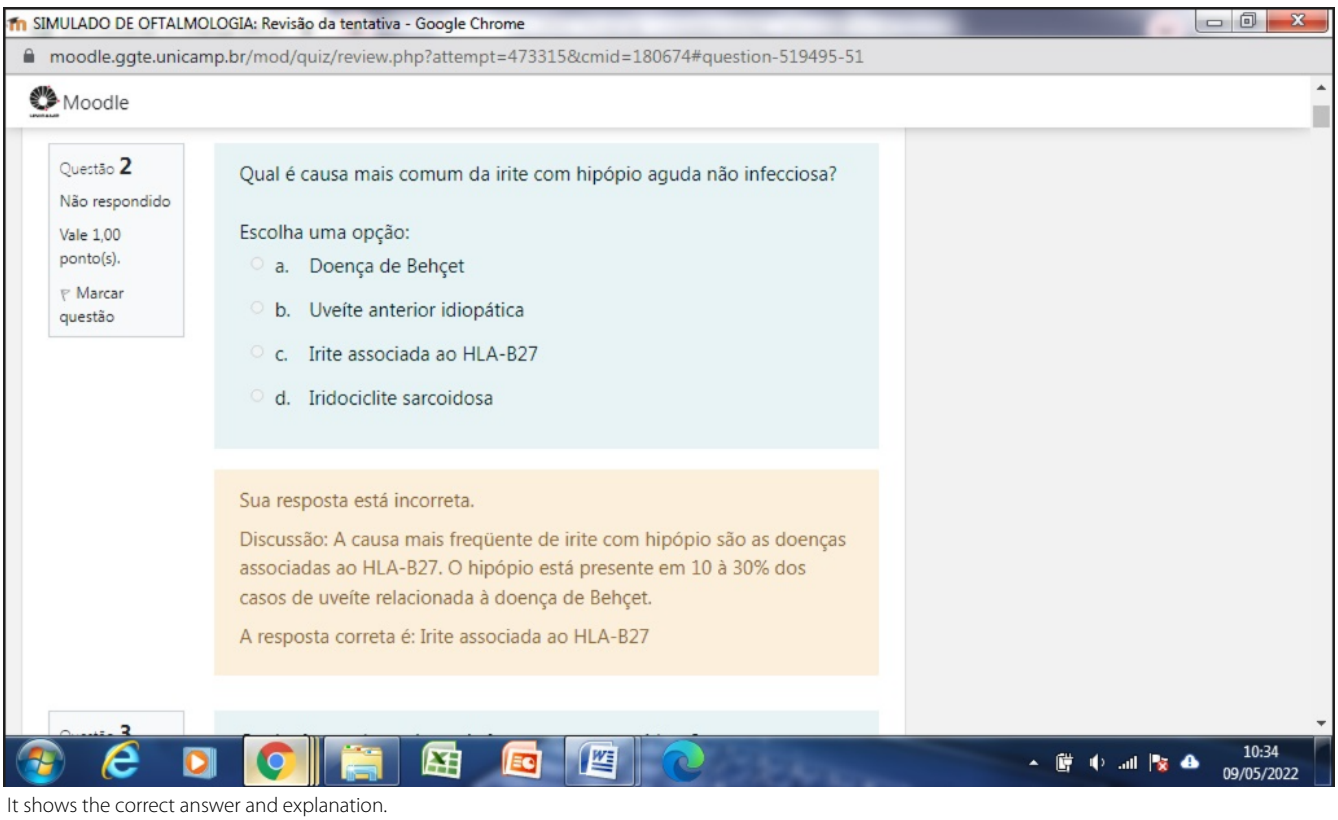
The Kruskal–Wallis test was used to compare the mean scores across the three years of residency. The P value was < 0.0001, which was considered statistically significant. Therefore, it is possible that there was a difference between the mean scores.

The Wilcoxon test was used for multiple comparisons of the mean scores for each pair of the residency years (1st versus 2nd,

Table 1. Descriptive analysis and comparison of the scores for each residency year

Residency year	n	Mean score	SD	Minimum score	Median	Maximum score
1st year	97	4.3	1.0	2.3	4.2	8.0
2nd year	104	5.1	1.2	2.7	5.0	8.2
3rd year	89	5.4	1.1	3.4	5.4	8.5

n = number of participants; SD = standard deviation.



It shows the correct answer and explanation.

Figure 4. Example of a discussion feedback.

1st versus 3rd, and 2nd versus 3rd) to check the difference between the pairs. There was a significant difference between the 1st and 2nd years and the 1st and 3rd years of residency ($P < 0.0001$ in both cases). However, the difference between the 2nd and 3rd years of residency was not significant ($P = 0.0619$). This may be because of the pedagogic program itself since, if we look at it, we can see that almost all the theoretical content was taught in the first two years of residency, with only a small percentage remaining in the 3rd year of residency.

Relationship between the progress test and Brazilian Ophthalmology Council (CBO) scores (Table 2 and Graphic 3)

For this analysis, we had only eight residents from the 3rd year. Correlation analysis demonstrated an association between the progress test and CBO scores. Spearman correlation (**Graphic 3**) showed a positive and significant correlation between these two scores (which was 0.61), which means that the higher the score on the progress test, the higher the score on the CBO test.

DISCUSSION

In this study, we demonstrated that progress tests could be used for ophthalmology residency training. They helped to detect the residents' knowledge growth over time and had a moderate relationship with the CBO test. Our findings are aligned with previous studies in both undergraduate[8,9,32] and residency training.[10,30-33,34]

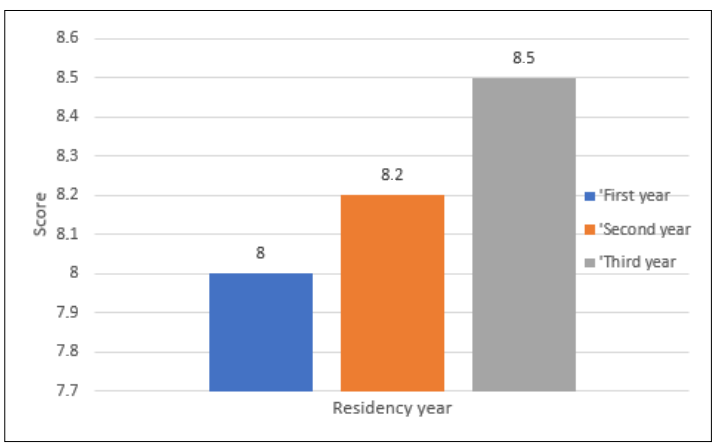
For example, in a study by Tomic et al., 4 years of progress testing were evaluated in a medical school in Brazil and positive results were found, with a continuum of cognitive gain during medical training.[32]

Similarly, previous studies with longitudinal tests on the residency program[10,29,30] found that the progress test was able to detect the difference[33,35] among residency years. Taken together, the knowledge scores increased over the years.[10,35]

Concerning the relationship between the progress and CBO tests, our results were partially in concordance with those of previous studies. For example, in an undergraduate context, a study by Hamamoto Filho et al. found a correlation between students' progress testing scores and their performance in a residency selection process in Brazil.[36]

In the residency context, a descriptive study by Al-Mohammed A et al.[37] compared the residents' performance on the American College of Physicians (ACP) Internal Medicine In-Training Examination (IM-ITE) results and the certification examination of the American Board of Internal Medicine (CABIM) and American Board of Surgery Qualifying Examinations in Qatar, found that the performance on the ITE could accurately predict the performance on both qualifying exams,[31] which is in concordance with our results.

Therefore, our study is in concordance with previous studies performed by residents. What makes our study exclusive is that besides being performed in a country where there are almost no similar studies, it is, as far as we are concerned, the only one performed with ophthalmology residents.

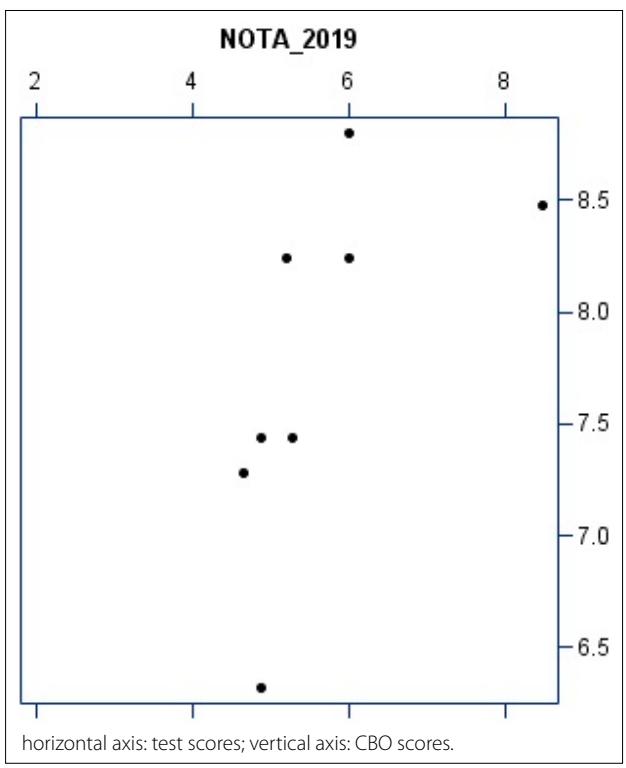


Graphic 2. Descriptive analysis of the scores for each residency year.

Table 2. Relationship between the progress test and CBO scores

Variable	n	Mean score	SD	Minimum score	Median	Maximum score
Test score 2019	8	5.7	1.2	4.6	5.2	8.5
CBO score 2019	8	7.8	0.8	6.3	7.8	8.8
dif		2.1	1.0		2.4	

CBO = Brazilian Ophthalmology Council; n = number of participants; SD = standard deviation; dif = difference between the CBO and progress test scores (CBO score–test score). P value = 0.0156 (Wilcoxon test).



Graphic 3. Spearman linear correlation between the progress test and Brazilian Ophthalmology Council (CBO) scores.

For the future

Two more different tests will be developed, and each test will be used at the end of the school year by all the residents from the 1st to the 3rd year of the ophthalmology residency programs.

All the tests will have the same number of questions (125). They will follow the same division of national testing issues; however, the questions will be completely different from one test to another. In other words, all questions will be changed from the 1st year to another. Thus, at the end of the 3 years of residency, each resident performed three different tests.

After the end of the tests, the tests will be revised, and each resident will receive individual performance feedback through an online program developed with personal login and password.

Limitations of the study

In some services, the residents were allowed to do the test at home because the service did not have informatics labs or an appropriate classroom for them to perform the tests. This can be biased because we cannot guarantee they did not cheat on the test. In addition, as participation in the study was voluntary and the progress test score was not part of the official residency program, some residents did not take it seriously. Finally, our sample size for comparison of the progress and CBO tests was small. However, even with such a small sample size, we found a moderate and significant correlation.

CONCLUSION

Based on the data obtained, it is possible to see that the scores of the residents improved over the years, which means that their knowledge increased. In other words, there was progress along the residency course.

Residents approved the longitudinal test as a self-learning tool and as a tool for improving residency programs. Therefore, we can say that the implementation of a longitudinal evaluation system in ophthalmological residency schools in Brazil was successful and could be implemented in other medical subspecialties.

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Is vitamin D status relevant to psoriasis and psoriatic arthritis? A retrospective cross-sectional study

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ABSTRACT

BACKGROUND: Psoriasis is a systemic, immune-mediated disease characterized by inflammatory manifestations in the skin and joints. Vitamin D deficiency is currently considered a pandemic and is associated with comorbidities including psoriasis and psoriatic arthritis (PsA).

OBJECTIVES: To determine the prevalence of hypovitaminosis D [25(OH)D] in patients with plaque psoriasis, with and without PsA, and of independent predictors of serum 25(OH)D levels.

DESIGN AND SETTING: Retrospective cross-sectional study conducted among 300 patients at an outpatient clinic in a university center in Juiz de Fora, Minas Gerais, Brazil.

METHODS: Demographic and clinical data (psoriasis area and severity index [PASI], family history, age at onset, disease duration, and the presence of PsA according to Classification Criteria for Psoriatic Arthritis), skin phototype, and season of the year were reviewed.

RESULTS: Hypovitaminosis D (< 30 ng/mL) was highly prevalent in patients with psoriasis with and without PsA (82.2% and 74.9%, respectively). An inverse correlation between PASI and vitamin D was found (without PsA r = –0.59 and, PsA r = –0.52, P < 0.001), and multivariate regression revealed that hypovitaminosis D was associated with disease severity, season, and phototype. It was confirmed by binary logistic regression between PASI and vitamin D deficiency (< 30 ng/mL), (odds ratio, OR 1.78 CI: –0.20–0.53, P < 0.001).

CONCLUSION: Hypovitaminosis D (< 30 ng/mL) was highly prevalent in psoriatic patients with and without PsA. Season and skin phototype were associated with 25(OH)D levels. An inverse association between PASI and serum 25(OH)D levels was established.

INTRODUCTION

Psoriasis is a chronic disease with a genetic predisposition. It involves the skin, joints, and immune system,[1] and is characterized by sustained inflammation with alterations in the proliferation and differentiation of keratinocytes.[2] The pathogenesis of psoriasis is still not completely understood. However, it is already known that the development of psoriasis plaques is mediated by Th1, Th17, and Th22 cells, with consequent hyperproliferation of keratinocytes.[2] Vitamin D is considered one of the most important modulators of the immune response, with effects on both innate and adaptive immunity in addition to having antiproliferative actions on keratinocytes.[2,3] Moreover, beneficial effects of ultraviolet radiation in the treatment of psoriasis reinforce this hypothesis.[2-4] The role of vitamin D in psoriasis has been studied for over 60 years, since vitamin D analogs, such as calcipotriol, were first used to treat psoriasis. Currently, vitamin D deficiency is considered a worldwide epidemic with multiple implications for human health because of the roles of vitamin D in various physiological systems. Vitamin D deficiency increases the risk of cardiovascular and metabolic diseases, cognitive and affective disorders, and osteoporosis. Chronic inflammation present in patients with psoriasis and psoriatic arthritis could be related to a higher risk of metabolic syndrome and cardiovascular disease in these individuals.[4-7]

The definition of vitamin D deficiency is still controversial. The Institute of Medicine (IOM) of the National Academy considers vitamin D deficiency 25(OH)D values below 20 ng/mL (or 50 nmol/L) while other societies such as Endocrine Society, National Osteoporosis Foundation, International Osteoporosis Foundation, American Geriatric Society, suggest that the minimum value necessary to reduce the risk of falls and fractures is 30 ng/mL (or 75 nmol/L).[6,7] The World Health Organization advises serum levels above 30 ng/mL (or 75 nmol/L).[8] It is believed that

the recommended serum levels should be higher in psoriasis and psoriatic arthritis than in the general population, as the scientific literature suggests an association between these two diseases and inadequate levels of vitamin D.[9,10]

However, reports of the relationship among vitamin D, psoriasis, and psoriatic arthritis have come from studies with different methodological approaches and demographically different populations from different geographic regions.

OBJECTIVE

In this context, this study aimed to determine the prevalence of hypovitaminosis D [25(OH)D] in patients with plaque psoriasis with and without psoriatic arthritis (PsA) treated at a Psoriasis outpatient clinic. A second aim was to determine independent predictors of serum 25(OH)D levels, such as Fitzpatrick's phototype[11] and season of the year.

METHODS

Sample selection and ethics compliance

We conducted a cross-sectional, comparative, retrospective study that included 300 patients with plaque psoriasis who were treated in psoriasis outpatient clinics of a Dermatology Service between January and December 2016. This study reviewed 350 medical records of patients treated at the psoriasis outpatient clinic and given a standardized medical record that included their serum levels of 25(OH)D. Fifty of the 350 patients were excluded. Patients were excluded due to a lack of accordance with the inclusion and exclusion criteria and missing data in the medical records. As the medical records for this study were obtained from the Dermatology Service of a University Hospital, the data were collected by postgraduate doctors who were also supervised by doctors, and standardized medical records for patients with psoriasis were completed. The inclusion criteria were as follows: patients of both sexes, aged between 18 and 60 years, with clinical and/or histopathological diagnosis of plaque psoriasis, with or without diagnosis of psoriatic arthritis according to the Classification Criteria for Psoriatic Arthritis (CASPAR) criteria.[12] The following were excluded: patients with other clinical forms of psoriasis and those who had data missing from the standardized psoriasis medical record, or with severe and decompensated systemic diseases (hepatic, renal, metabolic, or cardiac), thyroid and parathyroid diseases, malignant neoplasms, acquired immunodeficiency syndrome, and pregnant women; patients with diseases with altered intestinal absorption and other autoimmune and photosensitive diseases; patients using oral supplementation of vitamin D, bisphosphonates, systemic corticosteroids, or calcium; patients undergoing treatment by phototherapy or using sunscreens; and patients using topical vitamin D analogs such as calcipotriol. Data collection began after approval of the investigation by our institution's ethics committee (protocol 3.142.153, approved on November 2, 2019, by the Research Ethics Committee of the University Hospital). All the procedures involved in this study were in accordance with the Declaration of Helsinki of 1975, as updated in 2013.

Clinical, laboratory and radiographic evaluation

Standardized records of patients with psoriasis were used and the following variables were evaluated: sex, age, family history of psoriasis, age at disease onset, duration of the disease, presence of PsA according to CASPAR[12], and disease severity according to the psoriasis area and severity index (PASI).[13] Using PASI, the severity of psoriasis was stratified as mild (PASI < 10) or moderate-to-severe (PASI > 10).[13] Moreover, the patient's phototype and 25(OH)D dosing station were evaluated. The analysis of serum levels of 25(OH)D was performed at the Biochemistry Laboratory of the University Hospital using the chemiluminescence technique (ARCHITECT 25-OH Vitamin D, Abbott Diagnostics, Lake Forest, Illinois, United States) and considered the following parameter definitions: values < 20 ng/mL were considered deficient; ≥ 20 ng/mL and < 30 ng/mL, insufficient; and ≥ 30 ng/mL, sufficient.[14] Rheumatoid factor and radiographic reports were also reviewed.

Statistical analyses

A descriptive data analysis was performed. The Shapiro-Wilk test was used to assess the distributions of variables. Student's t-test was used to test the differences in quantitative variables between two groups and these were confirmed by one-way analysis of variance (F test), followed by the Bonferroni *post hoc* correction. The chi-square test (χ^2), or Fisher's exact test when there were less than five data points were used to test for possible differences in the proportions of qualitative variables.

Pearson's coefficient (r) was used to test the correlations between 25(OH)D and continuous variables. To assess independent predictors of vitamin D levels, a multiple linear regression model was developed using vitamin D levels as the outcome and sex, age, phototype, season of vitamin D blood testing, arthritis, family history, age at diagnosis, duration of psoriasis, and disease severity as determinants, and controlling, if necessary, for confounding variables such as sex and age.

In this context, the presence of arthritis, severity according to PASI, family history, age at diagnosis, evolution time, phototype, and season were used as predictor variables, controlling for sex and age.

In the binary regression, vitamin D was dichotomized as deficient (< 30 ng/mL) or sufficient (≥ 30 ng/mL), and clinical parameters related to psoriasis and psoriatic arthritis were used as predictors of vitamin D levels. The significance level was set at 5% ($P < 0.05$) for all statistical analyses. Analyses were performed

using the R software package for Windows [R Core Team (2019) R, version 3.4.4. (R Foundation for Statistical Computing, Vienna, Austria) and https://www.R-project.org/].

RESULTS

The characteristics of patients with plaque psoriasis with and without arthritis are shown in **Table 1**. Of the 300 patients with plaque psoriasis, 227 (75.67%) had only skin lesions, while 73 (24.3%) had concomitant arthritis. Patients with arthritis had a higher mean age (49.98 ± 11.12 versus 46.34 ± 13.21, P = 0.021). The distribution by sex was similar in both groups, as was the age at diagnosis of the disease, which started, on average, at 34 years (34.60 ± 16.10 years in patients with arthritis versus 34.46 ± 15.58 years without arthritis, P = 0.949). A positive family history was significantly more frequent in patients with arthritis (57.5% versus 30.4%, P < 0.001). The disease duration was longer in the group with arthritis (15.63 ± 12.43 versus 11.85 ± 11.12, P < 0.01). More than 80% of the patients in the study had moderate-severe psoriasis, and the PASI values were significantly higher in the group with arthritis (17.08 ± 4.68 versus 12.79 ± 6.75, P < 0.001) (**Figure 1**). A total of 178 patients (59.4%) with phototype III were evaluated, 105 patients (35 %) with phototype IV, and 17 patients (5.6 %) with phototype V. The serum levels of 25(OH)D were tested more frequently during the summer (164 patients, 54.7%) and to a lesser extent in the winter (23 patients, 7.7%); the two groups did not differ significantly.

Patients with psoriasis and arthritis had significantly lower mean serum 25(OH)D (23.43 ± 6.55 versus 25.39 ± 7.30, P = 0.03) (**Figure 2**).

Vitamin D deficiency (< 20 ng/mL) was present in a greater proportion of patients with arthritis (31.5% versus 23.8%), whereas levels considered sufficient (≥ 30 ng/mL) were proportionally higher in patients with psoriasis without arthritis (25.1% versus 17.8%). The 25(OH)D levels were lower in patients with arthritis in all studied phototypes as well as in all seasons of the year (**Table 2**).

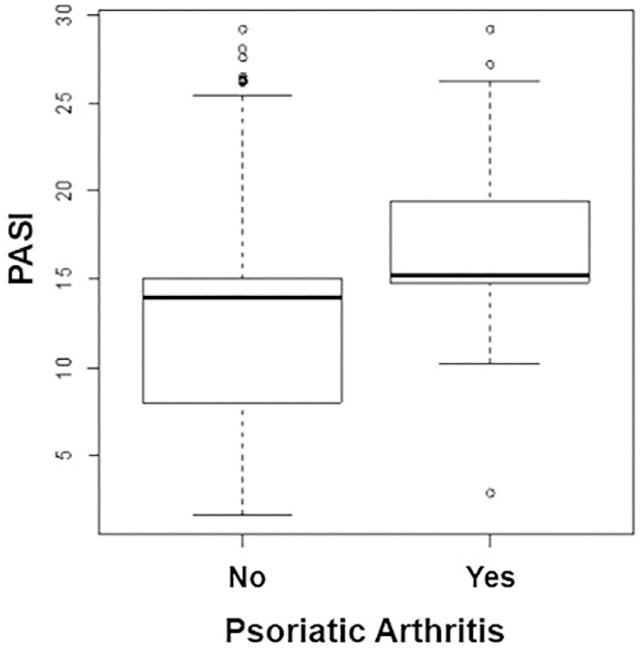
The multivariate linear regression model is presented in **Table 3** (adjusted model, $R^2 = 0.31$, P < 0.001). The presence of arthritis, severity according to the PASI, family history, age at diagnosis, evolution time, phototype, and season of the year were used as predictor variables, controlling for sex and age.

The linear regression results demonstrated an inverse and statistically significant correlation between 25(OH)D levels and disease severity. The presence of moderate-to-severe psoriasis was negatively correlated with serum vitamin D levels (β coefficient = –6.712, CI: –8.51, –4.91, P < 0.0001). Serum vitamin D levels were not correlated with the presence of arthritis, positive family history, age at diagnosis, or disease duration. An association between the season of the year in which the serum measurement was performed and the patients' phototype was evidenced. The positive effect on vitamin D levels, with winter as the reference, increased with the seasons according to the rate of ultraviolet radiation: spring (β Coefficient = 4.512, confidence interval, CI: 1.58 to 7.44,

Table 1. Demographic characteristics of patients with psoriasis according to the presence of psoriatic arthritis

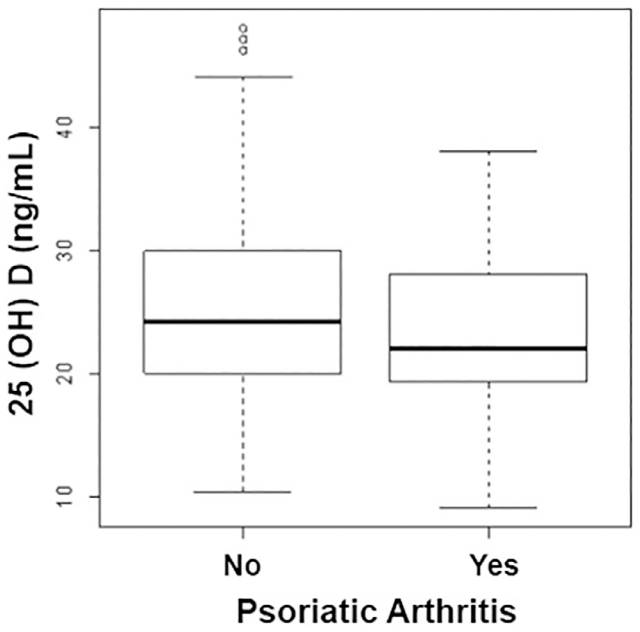
Variables	Psoriasis without arthritis n (%)	Psoriasis with arthritis n (%)	P value
	227 (75.67)	73 (24.33)	
Age, years, (mean ± SD)	46.34 ± 13.21	49.98 ± 11.12	0.021[a]
Male/female (n)	121/106	40/33	-
Prevalence of men (%)	53.3	54.8	0.824
Positive family history [n (%)]	69 (30.4)	42 (57.5)	0.001[**b]
Age of diagnosis, in years (mean ± SD)	34.46 ± 15.58	34.60 ± 16.10	0.949[a]
Duration of psoriasis, in years (mean ± SD)	11.85± 11.12	15.63 ± 12.43	0.002[*a]
PASI (mean ± SD)	12.79 ± 6.75	17.08 ± 4.68	0.001[**a]
Severity [n (%)]			0.001[**b]
Mild	58 (25.5)	1 (1.4)	
Moderate-severe	169 (74.5)	72 (98.6)	
Fitzpatrick skin phototype [n (%)]			0.803[b]
III	134 (59.0)	44 (60.3)	
IV	79 (34.9)	26 (35.6)	
V	14 (6.1)	3 (4.1)	
Season of the year of the test [n (%)]			0.243[b]
Autumn	40 (17.6)	16 (21.9)	
Winter	15 (6.6)	8 (11.0)	
Spring	48 (21.2)	9 (12.3)	
Summer	124 (54.6)	40 (54.8)	

SD = standard deviation; PASI = Psoriasis Area and Severity Index.
[*]P < 0.01; [**]P < 0.001; [a]Student's t-test; [b]χ^2 Test.



PASI was significantly higher in patients with arthritis (P < 0.001).

Figure 1. Comparison of the Psoriasis Area and Severity Index (PASI) between psoriasis patients with and without psoriatic arthritis.



Serum 25 (OH) D concentration was significantly lower in patients with arthritis (23.43 ± 6.55 versus 25.39 ± 7.30; P = 0.033).

Figure 2. Comparison of serum 25(OH)D levels in psoriasis patients with and without psoriatic arthritis.

P = 0.002) and summer (β Coefficient = 8.708, CI: 6.07 to 11.33, P < 0.0001). There was an inverse association between vitamin D levels and the highest phototypes, such as Phototype V (β Coefficient = −3.783, CI: −6.89 to −0.95, P = 0.014) and phototype IV (β Coefficient = 1.56, CI:1.10 to 3.01, P = 0.035).

The 25(OH)D levels were inversely correlated with PASI values (patients without arthritis Pearson's r = −0.59, P < 0.001 and with arthritis r = −0.52, P < 0.001).

To confirm the inverse correlation between vitamin D levels and PASI scores, we developed a binary logistic regression model (**Table 4**). This model confirmed a strong association between PASI and vitamin D deficiency (< 30 ng/mL) (odds ratio, OR 1.78, CI: −0.20 to −0.53, P < 0.001).

DISCUSSION

Hypovitaminosis D (< 30 ng/mL) was highly prevalent in patients with psoriasis with and without PsA (82.2% and 74.9%, respectively). An inverse correlation of PASI with vitamin D was found (without PsA r = −0.59 and with PsA r = −0.52, P < 0.001), and multivariate regression revealed that hypovitaminosis D was associated with the severity of the disease, the season and phototype. An inverse association between PASI and the serum level of 25(OH)D was confirmed by binary logistic regression between PASI and vitamin D deficiency (< 30 ng/mL) (odds ratio, OR 1.78 CI: −0.20–0.53, P < 0.001).

Some previous studies have confirmed the association between vitamin D deficiency and psoriasis[9,10,14-18]; however, in contrast to those studies, a few studies have shown no correlation between them.[19-21] There have been a few studies investigating the comparison between psoriatic patients with and without arthritis.[18,22-24] In situations of low concentrations of 25(OH)D, the immune system favors the development of self-reactive T cells directed against the body's own tissues, and the synthesis of pro-inflammatory cytokines (IL-12 and IFN-γ), predisposing the body to an increased risk of developing autoimmune diseases such as diabetes, rheumatoid arthritis, multiple sclerosis, and inflammatory bowel diseases.[25-27] In psoriasis, the immune system behaves similarly under low concentrations of 25(OH)D and in addition, 25(OH)D is believed to inhibit the production of Th1 and Th17 inflammatory cytokines.[28]

Orgaz-Molina et al.[10] evaluated 43 white patients with plaque psoriasis, 7% of which were associated with psoriatic arthritis with a mean PASI of 4.42, and observed a strong association between psoriasis and vitamin D insufficiency according to logistic regression (< 30 ng/mL) (OR 2.89 CI 95 1.02 to 7.64). However, vitamin D deficiency was not associated with PASI, neither with disease duration nor with the presence of arthritis, which finding differs from our results.[10]

A lack of correlation of vitamin D insufficiency with PASI despite a high prevalence of deficiency in psoriatic patients, was

Table 2. Serum 25(OH)D concentration (mean ± SD) in psoriasis patients with and without psoriatic arthritis according to phototype and season of the year

25 (OH) D	Pso without PsA, n (%) 227 (75.67)	Pso with PsA, n (%) 73 (24.33)	P value
Mean ± SD (ng/mL)	25.39 ± 7.30	23.43 ± 6.55	0.033[a]/0001[b]
Minimum	10.50	9.17	-
Maximum	48.0	38.1	-
25 (OH) D, [n (%)]			0.301[c]
< 20 ng/mL	54 (23.8)	23 (31.5)	
> 20 and ≤ 30 ng/mL	117 (51.5)	37 (50.7)	
≥ 30 ng/mL	56 (24.7)	13 (17.8)	
25 (OH) D			0.265[c]
< 30 ng/mL	171 (75.3)	60 (82.2)	
≥ 30 ng/mL	56 (24.6)	13 (17.8)	
Skin phototype			NA
III	25.62 ± 6.67	23.09 ± 5.61	
IV	26.05 ± 8.24	24.71 ± 7.80	
V	19.42 ±4.72	17.43 ± 5.62	
Season of the year of the test			NA
Autumn	28.00 ± 7.30	25.48 ± 6.41	
Winter	22.74 ± 6.30	22.53 ± 5.24	
Spring	20.86 ± 6.25	15.44 ± 3.88	
Summer	22.28 ± 5.94	22.03 ± 5.93	

25(OH)D = 25-hydroxyvitamin D; Pso = psoriasis; PsA = psoriatic arthritis; SD = standard deviation; [a]Student's t-Test; [b]One-way analysis of variance post hoc Bonferroni; [c]Fisher's Test; NA = not applicable.

Table 3. Multiple linear regression analysis of independent predictors of serum 25(OH)D concentration in patients with psoriasis

Predictors	β coefficient	P value	95% CI
Arthritis			
Absent*			
Present	-0.266	0.759	-1.97 – 1.44
Severity			
Mild*			
Moderate-severe	-6.712	0.000[£]	-8.51 – -4.91
Family history positive	0.194	0.797	-1.29 – 1.68
Age at diagnosis	-0.024	0.383	-0.007 – 0.030
Duration of psoriasis	0.006	0.474	-0.06 – 0.08
Season of the year			
Winter*			
Autumn	3.525	0.017	0.61 – 6.43
Spring	4.512	0.002	1.58 – 7.44
Summer	8.708	0.000[£]	6.07 – 11.33
Skin phototype			
III*			
IV	1.556	.035	1.10 a 3.01
V	-3.783	.014	-6.89 a -0.95

*Reference category: 25(OH)D = 25-hydroxyvitamin D; CI = Confidence Interval; [£]P < 0.0001; adjusted R^2 = 0.31, P < 0.0001.

Table 4. Binary logistic regression model for 25(OH)D deficiency in psoriatic patients

Variable	β Coefficient	OR	CI 95%	P value
Arthritis	0.513	1.67	0.70 – 3.89	0.23
Duration of disease	0.023	1.02	0.99 – 1.05	0.16
Family history positive	0.601	1.82	0.92 – 3.64	0.08
Age at diagnosis	-0.062	0.97	0.96 – 1.01	0.62
PASI	-0.240	1.78	-0.20 – 0.53	0.001*

25(OH)D, 25-hydroxyvitamin D; OR = Odds Ratio; CI = Confidence Interval; PASI = Psoriasis Area and Severity Index. *P < 0.0001.

reported in a study that evaluated 43 patients with psoriasis, 55 with rheumatoid arthritis (RA), and 40 healthy controls; serum levels were significantly lower in patients with psoriasis and RA (P < 0.001).[18]

Our findings were consistent with those of other studies[14,15,17] which demonstrated a higher level of 25(OH)D deficiency in patients with psoriasis and 25(OH)D deficiency was negatively correlated with PASI.

Studies in the southern hemisphere are rare. In places with latitudes above 37^{0}N or below 35^{0}S there is a decrease in the incidence of ultraviolet B radiation during the winter months, and the chances of vitamin D deficiency increase.[27,28]

Zuchi et al.[19] reported a study in Curitiba, South Brazil (25^{0}S 49^{0}W), which compared serum vitamin D levels in 20 psoriasis patients and 20 control patients. Of the 20 psoriasis patients, 15 had plaque psoriasis and 5 had palmoplantar psoriasis. However, the patients studied had low mean PASI (2.4 ± 3.6). There were no differences between the two groups, and the authors reported lower serum vitamin D levels in women than men (20.85 ± 6.70 versus 25.35 ± 2.90; P = 0.031).[19] These data disagree with our study results. This can be explained in part by the fact that our study was conducted in a place located at latitude 21^{0}S 43^{0}W, which theoretically would be related to adequate levels of vitamin D, and they studied

other clinical forms of psoriasis; the phototypes were lower (I and II). It is important to point out that patients with severe psoriasis, with extensive areas of involvement, tend to cover themselves to hide their lesions, which would consequently explain the lower sun exposure and production of vitamin D.

Regarding the comparison between psoriatic patients with and without arthritis: Orgaz-Molina et al.[18] compared 61 patients with psoriatic arthritis and 61 patients without psoriatic arthritis, found no correlation with disease severity, and concluded that 25(OH) D was inversely related to metabolic parameters in patients with psoriasis without arthritis.[18] However, the authors selected patients with mild disease (PASI = 4.76 ± 5.31 in the group without arthritis versus 3.66 ± 3.48 in the group with arthritis).

On the other hand, Kincse et al.[22] found a prevalence of hypovitaminosis D (< 30 ng/mL) in 63% of cases, with inverse correlations between serum vitamin D levels and psoriasis severity (PASI), and arthritis activity.[20] The influence of season and latitude on serum vitamin D levels was investigated by Touma et al.[24] who studied 302 patients with psoriatic arthritis, 201 in Toronto (43° 40' N) and 102 in Israel (32° 46' N), in summer and winter. It was found that levels < 75 nmol/L (30 ng/mL) were 58.7% versus 57.9% in winter in Toronto versus Israel, respectively, and 58.6% versus 64.9% in summer. The authors also evaluated the effect of skin phototype and season, concluding that there were no differences in these variables in each studied group or between the two groups. They also did not find an association between PASI and arthritis activity marker levels. However, the selected individuals had lower PASI averages calculated by rheumatologists (3.59 ± 5.09 in winter and 3.44 ± 5.59 in summer).

In this context, there are reports of inadequate levels of vitamin D, even in individuals with adequate exposure to the sun, due to other related factors, such as high altitudes, obesity, and skin pigmentation.[26-29]

The limitations of our study include the absence of a dietary and sun exposure survey (with time and duration of exposure), and the fact that phototypes I, II, and VI were not represented.

CONCLUSIONS

In conclusion, we emphasize that hypovitaminosis D is highly prevalent in psoriatic patients with and without psoriatic arthritis and in patients with plaque psoriasis with or without arthritis. Furthermore, there was an inverse correlation between 25(OH)D levels and disease severity (PASI). Finally, there were associations between 25(OH)D levels and season of the year and skin phototype. These findings highlight the importance of vitamin D status in these patients and emphasize the need for its regular monitoring in addition to considering vitamin D supplementation, especially in patients with moderate to severe psoriasis, with high phototypes, and during autumn and winter months.

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Prediction and reasons for COVID-19 second dose vaccine hesitation: a cross-sectional study in a municipality of Brazil

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ABSTRACT

BACKGROUND: Hesitation and refusal to take a second dose of the vaccine for coronavirus disease 19 (COVID-19) are prevalent.

OBJECTIVES: We aimed to identify predictive factors for hesitation or refusal and describe groups with higher rates of vaccine hesitancy.

DESIGN AND SETTING: A cross-sectional study in Assis City, Brazil.

METHODS: The study included adults who passed the due date for taking the COVID-19 second dose vaccine. Participants were recruited in December 2021 using a mobile-based text message. Sociodemographic and clinical data and reasons for hesitance were collected. The outcome was the attitude towards completing the recommended second dose of the vaccine. Bivariate and multivariate Poisson analyses were performed to determine the adjusted predictors.

RESULTS: Participants between 30–44 years of age had a 2.41 times higher prevalence of hesitation than those aged 18–29 years. In addition, people who had adverse events or previously had COVID-19 had 4.7 and 5.4 times higher prevalences of hesitation, respectively (P value < 0.05).

CONCLUSION: We found a significant group of adults aged between 30–44 years who refused the second dose of the COVID-19 vaccine. Furthermore, those who reported adverse effects after the first dose and those who had COVID-19 previously were a significant group for refusal.

INTRODUCTION

The high morbidity and mortality due to the coronavirus disease 19 (COVID-19) pandemic pose a challenge to health institutions. All governments need to be prepared to ensure large-scale, balanced access and universal distribution of vaccines. This also requires strategies to increase trust in and acceptance of the vaccine by the population that will receive it.[1]

Before the pandemic, the World Health Organization had defined hesitation in taking vaccines as a or refusal or delay in their acceptance, despite the availability of services.[2] Hesitation can vary in form and intensity according to the place and time in which the vaccine is offered. Concerns about vaccine hesitancy are growing worldwide, with misinformation being a substantial barrier in many countries and constituting an obstacle to immunization and community immune coverage.[2-4]

Moreover, the anti-vaccine movement remains a significant health threat, and new social forces have been set into motion because of COVID-19. The anti-vaccine movement's new conspiracy theories and alliances have possibly grown stronger worldwide.[5]

Since 2020, after the approval of vaccines for emergency use, most vaccine schemes for COVID-19 have recommended at least two doses at predetermined intervals. However, studies have pointed to a relatively high number of people who do not return for the second dose. In a multicenter study conducted in the United States with 14.2 million people in different locations of the country and different ethnicities the hesitancy rate for the second dose varied between 1–25%.[6]

Currently, there is a great concern about non-acceptance and abstention from taking vaccines made available by government campaigns, including about hesitancy and delay regarding taking the second dose of the vaccine for COVID-19.[7] In the municipality of Assis, Brazil, official data provided by the Health Department showed that in December 2021 there were 4,667 people with a delay of more than 30 days in taking the second dose of the vaccine, corresponding to approximately 12% of abstention.

OBJECTIVE

The primary objective of this study was to identify predictive factors for hesitation, delay, or refusal to take a second dose of anti-COVID-19 vaccines by the population of the municipality of Assis.

As specific objectives, we aim to describe groups with higher rates of abstention from the second vaccine dose, and thus contribute to the development and promotion of interventions aimed at reducing rates of hesitation or refusal of the second vaccine dose.

METHODS

An analytical cross-sectional study was conducted in the Municipality of Assis, Brazil, by the Faculty of Medicine of the Educational Foundation of the Municipality of Assis. Assis is a city in São Paulo state with an estimated population of 105,000 inhabitants and a Human Development Index of 0.805. The study focused on the adult population that passed the due date for taking the second dose of the COVID-19 vaccine. On December 3, 2021, cases with at least 30 days delay in receiving the second vaccine dose were selected from information provided by epidemiological surveillance of the municipality. The study was approved on 29th November 2021, by the Research Ethics Committee (CAAE:51936621.8.0000.8547/Statement:5,135,036).

Eligibility criteria: All adults overdue for more than one month to take the second dose of the COVID-19 vaccine were included; Exclusion criteria: Death from any cause after taking the first vaccine dose.

All participants received an invitation letter via a mobile phone-based text message. Those who consented to participate subsequently received an anonymous, confidential electronic form with questions related to sociodemographic data and the reason for their hesitation in taking the second dose of the vaccine.

We applied questions extracted and adapted to Portuguese from the questionnaire reported by the COVID-SCORE study[8] regarding vaccine acceptance. Participants answered vaccine safety and efficacy questions and provided age, gender, and education demographic variables.[8] We also asked about the history of previous COVID-19 infections. The first-dose vaccine's brand name and date were provided by the census of the epidemiological surveillance of Assis. Finally, participants were asked about the reasons for not having taken the second dose of the vaccine, in a multiple-choice question where they could answer one or more of the following alternatives: difficulty in time or access to the place where the vaccine was administered; forgetfulness; lack of confidence in the vaccine; having had adverse events after the first dose; having had COVID-19 previously; being pregnant; being sick; the desired vaccine was not available; and fear of vaccine side effects.

The outcome was analyzed according to the following question: 'What is your best guess whether you will take the second dose of the coronavirus vaccine?' Responses were collected on a five-point Likert psychometric scale: I will take it, I will probably take, no opinion or neutral, I probably will not, I definitely will not.

Age in years was collected and then categorized into 18–24, 25–40, 41–50, 51–60, 61–70, 71–80, and 80 years or older. The patient gender was collected as male, female. Education level was divided into three categories: elementary school, high school, and higher education. The participants were asked if they belonged to the general population or were employed as a healthcare worker. Overall health was self-rated as good or fair/poor, having any comorbidity. We also asked whether the participants reported a history of COVID-19 infection. The data collection period was one week in December 2021. The researchers were responsible for all collection procedures. Text messages were sent twice per week. Data were tabulated and analyzed for comparison between groups and for statistical analysis using bivariate and multivariate Poisson models to meet the objectives proposed by the research. IBM SPSS Statistics for Windows (version 23.0, released in 2015 (Armonk, New York, United States) was used. Categorical variables are presented as frequencies and percentages. Comparisons of these variables were made using the chi-squared test or Fisher's exact test. The significance level was set at $P < 0.05$. Crude odds ratios were obtained using bivariate Poisson regression, and the significance level was set at $P < 0.20$. Adjusted odds ratios considering the significant binary variables for refusing to complete the second vaccine dose were obtained using multivariate Poisson regression, using a significance level of $P < 0.05$.

The primary outcome was the participants' preference for not completing the second-dose vaccination. We included those respondents in an 'indecisive group' with those who responded that they probably or definitively will not take the second dose.

Sample size calculation: We considered a significance level of 5%, absolute error of 5%, and population size of 3,547 people eligible for the study. The resultant sample size was 347 individuals.

RESULTS

Official data from the municipality of Assis showed that 4,667 adults had been vaccinated for more than 30 days at the start of the study, totaling 12% abstention. Of these, 908 received the first dose of CoronaVac (Sinovac), 2,075 ChAdOx1 (Oxford–AstraZeneca), and 1,684 BNT162b2 (Pfizer, BioNTech) provided by the Brazilian Ministry of Health since January 2021. Unfortunately, 1,120 records were discarded because of invalid or nonexistent phone numbers. A total of 3,547 participants were selected to receive a text message containing the letter of invitation to participate in the research and in cases of acceptance of the free and informed consent form, the form with the questionnaire via Google Forms. The mean age was 35.05 years (range 18–97 years).

After one week following the invitation 354 people had responded to the questionnaire. An invitation was sent twice per week to each participant. Of the 354 responses, eight were excluded because of reports sent by family members of people who died before taking the second dose of the vaccine. The causes of death were not obtained because this was not the purpose of the study. **Table 1** presents the sample profiles of the 346 cases included in the study. Of these, 195 were male and 151 were female. The 18–29, 30–44, 45–59, and over 60 years old groups were represented by 179, 96, 51, and 20 participants, respectively. Regarding education, 80 participants had higher education levels. Forty-seven people self-declared that they had any comorbidities or were older than 60 years. In addition, 36 participants reported having previously had COVID-19. The first dose of vaccine was CoronaVac (Sinovac) in 79 participants, ChAdOx1 (Oxford–AstraZeneca) in 91, and BNT162b2 (Pfizer–BioNTech) in 176. The most common reasons for hesitation to accept the second dose of vaccine were related to difficult access, logistics, or lack of time (56.36%) and forgetting or not paying attention to the delay (24.28%). When asked whether they intended to take the second dose, 285 participants responded positively (82.37% of responses). The delay since the first dose of the vaccine ranged from 30 to 287 days, with a mean of 91.39 days.

Table 1. Sample characteristics (n = 346)

	Total	%
Sociodemographic		
Male (%)	195	56.36
Age in years		
18–29	179	51.7
30–44	96	27.7
45–59	51	14.7
≥ 60	20	5.8
Education level		
Elementary	97	28.0
High school	169	48.8
Higher	80	23.1
Healthcare worker	9	2.60
Health status		
Self-rated comorbidities or elder	47	13.58
Belongs to general population	294	84.97
Previous COVID-19	36	10.40
First dose vaccine		
CoronaVac (Sinovac)	79	22.83
ChAdOx1 (Oxford–AstraZeneca)	91	26.30
BNT162b2 (Pfizer–BioNTech)	176	50.87
Reasons for the hesitance		
Logistics, time or difficult access	195	56.36
Forgetfulness	84	24.28
Lack of confidence in the vaccine	10	2.89
Had adverse events after the first dose	7	2.02
Previous COVID-19 and consider yourself immune	2	0.58
Pregnancy	3	0.87
Sickness	14	4.05
There was no vaccine of the desired brand	5	1.45
Afraid of vaccine side effects	30	8.67
Preferred not to answer	9	2.60
Attitude towards completing the vaccine scheme		
I will take it	262	75.72
Probably will take it	23	6.65
Indifferent or indecisive	16	4.62
Probably will not take it	8	2.31
Definitely will not take it	13	3.76
Prefer not to answer	23	6.65
Tendency to refuse vaccination	60	17.34

COVID-19 = coronavirus disease 2019.

The associations of the variables in **Table 1** with participants' refusal to take the second dose of the vaccine were subjected to bivariate analysis. Participants aged 30–44 years, with higher education, comorbidities or advanced age, a declared lack of confidence in vaccines, already had COVID-19, afraid of the vaccine, and adverse side effects after taking the first dose were identified in the bivariate association ($P < 0.20$) as most likely to refuse to complete the vaccination schedule (**Table 2**).

Based on the results shown in **Table 2**, we developed multivariate Poisson models to explain the prevalence of refusal as a function of the following variables: age, education, having comorbidity or being elderly, not having confidence in the vaccine, having had an adverse event with the first dose, having already had COVID-19, and being afraid of side effects. We assessed the association between the independent variables using the homoscedasticity test (**Table 3**).

We observed heterogeneity of variance in the following variables: education, comorbidities, not feeling confident, and fear of side effects; these can be explained by age so they were not included in the model. Thus, model proposals included the variables with homoscedasticity: age, already had an adverse event, and already had COVID-19, as shown in **Table 4**.

According to the adjusted model people between 30 and 44 years of age had a 2.41 times higher prevalence of hesitation in taking the second dose than people between 18 and 29 years of age. People who had adverse events had a 4.7 times higher prevalence of hesitation in taking the second dose, and people who had already had COVID-19 had a 5.4 times higher prevalence of hesitation in taking the second dose (P value < 0.05).

DISCUSSION

In the city of Assis, Brazil, where 12% of the adult population was more than 30 days later for the second dose of the vaccine for COVID-19, we identified that the independent variables that were most associated with increased risk were the population aged 30–44 years, those who experienced adverse effects after the first dose, and those who had previously had COVID-19. Vaccine hesitancy is a worldwide phenomenon, with a variety of reasons

Table 2. Bivariate Poisson distribution. Associations between sociodemographic variables, health status, and reasons for not taking the second dose with refusal to take the second dose. (n = 346)

Variable	Second dose refusal				Total	P
	Not		Yes			
	n	%	n	%	n	
Sociodemographic						
Gender						
Female	124	82.1	27	17.9	151	1.000
Male	161	82.6	34	17.4	195	
Age in years						
18–29	158	88.3	21	11.7	179	0.002
30–44	67	69.8	29	30.2	96	
45–59	44	86.3	7	13.7	51	
≥ 60	16	80.0	4	20.0	20	
Education						
Elementary	79	81.4	18	18.6	97	0.037
High	147	87.0	22	13.0	169	
Higher	59	73.8	21	26.3	80	
Health worker						
No	277	82.2	60	17.8	337	0.001
Yes	8	88.9	1	11.1	9	
Belongs to the general population						
No	40	76.9	12	23.1	52	0.322
Yes	245	83.3	49	16.7	294	
Self-rated overall health						
Comorbidities or elder						
No	250	83.6	49	16.4	299	0.148
Yes	35	74.5	12	25.5	47	
First dose vaccine brand						
CoronaVac (Sinovac)						
No	220	82.4	47	17.6	267	1.000
Yes	65	82.3	14	17.7	79	
ChAdOx1 (Oxford–AstraZeneca)						
No	208	81.6	47	18.4	255	0.529
Yes	77	84.6	14	15.4	91	
BNT162b2 (Pfizer–BioNTech)						
No	142	83.5	28	16.5	170	0.672
Yes	143	81.3	33	18.8	176	
Previous COVID-19						
No	258	83.2	52	16.8	310	0.247
Yes	27	75.0	9	25.0	36	
Reasons for the hesitance/delay						
Logistic, lack of time or access						
No	102	67.5	49	32.5	151	0.001
Yes	183	93.8	12	6.2	195	
Forgetfulness						
No	205	78.2	57	21.8	262	0.001
Yes	80	95.2	4	4.8	84	
Lack of confidence						
No	283	84.2	53	15.8	336	0.001
Yes	2	20.0	8	80.0	10	
Adverse events in the first dose						
No	284	83.8	55	16.2	339	0.001
Yes	1	14.3	6	85.7	7	

Continue...

Table 2. Continuation.

Variable	Second dose refusal				Total	P
	Not		Yes			
	n	%	n	%	n	
Due to prior COVID-19						
No	285	82.8	59	17.2	344	0.031
Yes	0	0.0	2	100.0	2	
Pregnancy						
No	283	82.5	60	17.5	343	0.442
Yes	2	66.7	1	33.3	3	
Sickness						
No	275	82.8	57	17.2	332	0.282
Yes	10	71.4	4	28.6	14	
Not desired vaccine brand						
No	282	82.7	59	17.3	341	0.214
Yes	3	60.0	2	40.0	5	
Afraid of side effects						
No	275	87.0	41	13.0	316	0.001
Yes	10	33.3	20	66.7	30	
Did not answer						
No	285	84.6	52	15.4	337	0.001
Yes	0	0.0	9	100.0	9	

Chi-square and Fisher's exact test. P-value < 0.20; COVID-19 coronavirus disease 2019.

Table 3. Homoscedasticity test for the independent variables

	Higher-level	Comorbidities	Lack of confidence	Previous adverse effects	Previous COVID-19	Afraid of collateral effects
Age	0.001	0.001	0.003	0.329	0.001	0.001
Educational level		0.214	0.842	0.534	0.487	0.001
Comorbidities			0.142	1.000	1.000	0.781
Lack of confidence				1.000	1.000	0.007
Previous adverse effects					1.000	0.473
Previous COVID-19						1.000

P < 0.05; COVID-19 = coronavírus disease 2019.

Table 4. Multivariate Poisson Models adjustment to explain the vaccine's second dose's refusal

Variable	PR	95% CI		P
≥ 60 years	1.56	0.53	4.58	0.416
45–59 years	1.27	0.54	3.00	0.583
30–44 years	2.41	1.37	4.23	0.002
Age (Reference: 18–29 years)				
Adverse events after the first dose	4.72	2.00	11.11	0.001
Previous COVID-19	5.44	1.31	22.49	0.019

P < 0.05; PR = prevalence risk; CI = confidence interval; COVID-19 = coronavirus disease 2019.

for refusing to accept the vaccine. Common reasons include perceived risks versus benefits, religious beliefs, and lack of knowledge and awareness.[8,9] In this study we found that the main reasons for not returning to take the second dose were forgetfulness, difficulties accessing the site, or lack of time to get vaccinated. Despite the full and free availability of vaccines in the municipality, we believe that logistic reasons were associated with socioeconomic status. Studies suggest that public misinformation about COVID-19 may be contributing to hesitancy to get the vaccine.[10] The findings highlight the need for measures to address public acceptability, such as measures to increase trust and reduce concern about the safety and benefit of approved vaccines.[11] A study conducted in Ghana, Africa, reported that participants 36–45 years old were the most hesitant, similarly to our study results.[12]

In an online survey in Brazil with 173,178 respondents the overall vaccine hesitancy was 10.5%, similar to our study (12%) and this was considered low compared to other countries.[13]

Although the results of other studies provided empirical support for the benefits of being able to choose a vaccine in increasing willingness,[14] our study did not show significant differences among the associations of the three varieties of vaccines used in the municipality with refusal or hesitance.

There was high vaccine acceptability among health care professionals, with only nine from more than 2,000 with this profile who did not take the second dose of the vaccine. This result was

similar to that of a study in Mozambique, where the acceptability of the vaccine was 86.6% among health professionals.[15]

Study limitations: Little information exists in the literature to explain why adults aged between 30 and 44 refuse the vaccine. In addition, cross-sectional studies are susceptible to research bias owing to inadequate responses and possible misclassifications. We used a questionnaire based on COVID-SCORE questions;[8] however, it was not validated in Portuguese. Furthermore, we did not assess the associations of ethnicity, marital status, political view, or socioeconomic status with vaccine hesitancy.

In our study the response rate to a mobile phone-based text message was 9.99%. In addition, we have already published a secondary study concerning the representativeness and efficacy of the phone-based text message survey in a population that hesitated in taking the COVID-19 vaccination.[16] The mean age of the respondent group was 33.97 (standard deviation 14.99). In comparison with the characteristics of our eligible population, Cohen's d coefficient was 0.0754, corresponding to a small effect size between the respondents and the eligible population as a reference. Thus, we suppose that a mobile phone-based survey is a feasible and representative strategy during the pandemic in Brazil.

Moreover, older respondents were representative.[16] Furthermore, we received feedback with commentaries from several respondents, most of whom requested further information on the vaccination campaign and acknowledging the advice to complete the proposed scheme. Thus, we consider strengths of our study to be not only the survey strategy, but also the acceptance of the population after receiving the text message and self-reported commitment to get more orientation regarding the vaccination.

Despite the parochial context of our study, we believe that our findings can be generalized to other populations nationwide and worldwide, particularly to low-income populations.

CONCLUSION

We found a significant group of adults between 30 and 44 years of age, intending to refuse the second dose of the COVID-19 vaccine. Furthermore, those who experienced adverse effects after the first dose and those who had COVID-19 previously were representative and independent groups for refusing the second dose.

The scientific community must detect the reasons for hesitation or non-acceptance of vaccines and focus on these predictor risk groups when developing campaigns to raise awareness about the benefits of adequate immunization for the population.

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Frailty is associated with sociodemographic and health factors and related to the care context of older caregivers: a Brazilian cross-sectional study

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ABSTRACT

BACKGROUND: The task of caring can arise suddenly without guidance or support, resulting in psychological tension and health impairment, which can culminate in the development of frailty.

OBJECTIVE: To analyze the relationship between frailty and sociodemographic and health aspects related to the care context of older caregivers.

DESIGN AND SETTING: A cross-sectional study was conducted on 65 older caregivers registered in family health units in the interior of the state of São Paulo.

METHODS: The participants were interviewed individually using the following instruments: a characterization questionnaire, Fried's frailty phenotype, Zarit Burden's Interview, Mini-Mental State Examination, Geriatric Depression Scale, Katz Index, and Lawton Scale. In addition, the following statistical tests were applied: Pearson's chi-squared test, Fisher's exact test, and Mann–Whitney test. A significance level of 5% was considered to be statistically significant.

RESULTS: Women who took care of their spouses predominated without prior training or the help of other people. Most of the patients were pre-frail (72.3%). Frailty was significantly related to marital status (P = 0.016), depressive symptoms (P = 0.029), cognitive decline (P = 0.029), the degree of kinship (P = 0.015), and burden (P = 0.004).

CONCLUSION: Older caregivers without a partner, with severe depressive symptoms and cognitive changes, who cared for their parents, and had higher levels of burden, presented a higher proportion of frailty.

INTRODUCTION

In view of the formation of new family arrangements and the reduction in the number of children, older adults may be taking on the role of caregivers for other older adults. However, these older adults usually assume the task of caring suddenly, without any preparation or support, which can result in a burden. Thus, chronic stress could lead older caregivers to experience physical and emotional exhaustion, making them more vulnerable and enabling greater chances of developing frailty syndrome.[1]

Scholars point out that frailty is a relevant public health problem that deserves investigation because it has a high prevalence, its incidence increases with age, can negatively impact the quality of life of older adults and their families, and may result in undesirable adverse events that can lead to increased health care costs, in addition to high social costs.[2] Furthermore, researchers point out that its prevalence is higher in developing countries.[3] Thus, it is justified to conduct research related to frailty.

Studies that sought to analyze the relationship between frailty and sociodemographic and health aspects related to the care context of older caregivers are scarce in the literature and have demonstrated inconsistent results. A cross-sectional study was conducted in Campinas with 148 older caregivers recruited for health services. There was a higher chance of frailty only in the group of older caregivers with multimorbidity, regardless of the burden.[1]

In Belgium, researchers conducted a case-control study of 79 older spousal caregivers and 79 controls (older non-caregivers). The authors concluded that older spousal caregivers showed an increased risk of becoming frail, using antidepressants, and having greater difficulty maintaining their social contacts compared with that of older non-caregivers. However, the caregiver

burden did not increase the chances of frailty among older caregivers.[4] A cross-sectional study was conducted in São Carlos with 328 older caregivers from the community, which identified that 58.8% of the participants were pre-frail, and 21.1% were frail. Frailty was associated with advanced age, female sex, depressive symptoms, pain, and the absence of a partner.[5]

There are little data available in the literature on frailty syndrome in older adult caregivers and its relationship with the care context.[5] Therefore, it is necessary to investigate it, considering that older adult caregivers with advanced age may present a higher risk of frailty[4] because they face aging, health problems, and increasing demands related to the care process.[5] Furthermore, in view of the above, it is relevant to know the relationship between frailty and sociodemographic and health aspects related to the care context of older caregivers, especially in poverty, since the presence of this syndrome may impair both the quality of life and well-being of these individuals.

OBJECTIVE

To analyze the relationship between frailty and sociodemographic and health aspects related to the care context of older caregivers.

METHODS

Design, period, and place of study

It is an observational, cross-sectional, quantitative research, part of a larger project carried out in the city of São Carlos, state of São Paulo, Brazil, from July 2019 to March 2020, with older caregivers treated in five family health units (FHU) inserted in a context of high social vulnerability. All guidelines of the Strengthening the Reporting of Observational Studies in Epidemiology (STROBE) were included.

Criteria of inclusion and exclusion

The study included all the older caregivers who met the following inclusion criteria: 60 years of age or older; being the primary caregiver of an older adult; being a relative of the older in care, who was dependent on at least one basic activity (BADL, evaluated using the Katz Index) or instrumental activities of daily living (IADL, assessed using the Lawton and Brody scale); informally performed the care; and living in the same household as the older being cared for, and registered at an FHU inserted in a context of high social vulnerability. The exclusion criteria were as follows: communication difficulties due to severe hearing or visual deficits, perceived at the time of data collection; being classified as independent of all older adults in the household, both for BADL and IADL; death of one of the older adults in the dyad; change of address; and not being found after three attempts of contact on different days and times.

The sample was selected from a list provided by the professionals of the five FHUs, with 168 households comprising at least two older adults. All older adults received a visit. Among them, 49 did not participate in the study, 32 were not found after three attempts of contact on different days and times, 18 no longer lived at the address reported, 3 died, and 1 of the households had independent older adults for BADL and IADL. Therefore, the final sample comprised 65 older caregivers. Considering the 168 older adult caregivers registered in the aforementioned FHUs, the 65 participants of this study constituted a sample with a degree of confidence of 95% and a margin of error of 10%, as calculated using the Survey Monkey platform.

Study protocol

Initially, the researchers contacted the five FHUs to identify the homes to be visited. They prepared a list with the names and addresses of older caregivers with the support of nurses and community health agents in the FHUs. They then visited all older caregivers at home to verify their compliance with the inclusion and exclusion criteria. At that moment, the purpose of the study was presented, and related ethical issues and the Katz Index and Lawton Scale instruments were applied to establish who was the older caregiver and the older adult. Those who were dependent for a greater number of activities were considered older adults who received care. Researchers invited those who met the inclusion criteria to participate in the study and, in case of acceptance, scheduled a new home visit for the signing of the informed consent statement and the beginning of the evaluation. Eight previously trained undergraduate and graduate students performed data collection, which took place in the residence of the older adults individually and lasted approximately 2 hours.

The researchers prepared a questionnaire and applied it to characterize older caregivers and their care context. The information included sex, age, marital status, education, race/color, retirement, family and individual income, number of people residing in the home, private health plan, number of medications in use, multimorbidity, pain, degree of kinship, how long the care was exercised, how many hours and days in the week they spent on this care, if they underwent any preparatory course, and if they received help for the task of caring. In addition, the following instruments were used.

To evaluate frailty in older caregivers, the study adopted the phenotype proposed by Linda Fried based on five elements:

1. Unintentional weight loss – "Do you think you have lost weight without dieting in the last 12 months?" If yes, if this weight loss was equal to or greater than 4.5 kg or 5% of body weight in the previous year, the older adults scored this criterion.
2. Fatigue – "How often did you feel that everything you did required a lot of effort in the last week"? and "How often did you feel

that you could not carry on with your things in the last week"? The older adults who answered "always" or "most of the time" for either of these two questions scored on this criterion.

3. Low palmar grip strength: The researchers measured it using a portable hydraulic dynamometer in the dominant hand. They performed three consecutive measurements of palmar grip strength using the arithmetic mean. Then, the results were adjusted to complete the criteria according to sex and body mass index (BMI).
4. Low level of caloric expenditure: adapted question. It was assessed by self-report based on the following question: "Do you think you perform less physical activity than you did 12 months ago?" If so, older adults scored this criterion.
5. Slow gait: This is indicated by the average time spent traveling a distance of 4.6 m, with adjustments according to sex and height. Three gait speed measurements were performed using the arithmetic mean. The presence of three or more of the five characteristics of the phenotype indicates a frail older adult; one or two means pre-frailty, and none of these characteristics indicates robust or non-frail older adults.[6]

The study used the Katz Index and Lawton and Brody scale to evaluate the functional capacity of both older caregivers and adults who receive care. The Katz Index for BADLs was validated for the Brazilian context and was used to evaluate six areas of everyday life of self-care and presented as response options: "independent" or "dependent." Ultimately, the interviewer should check the number of activities the older adults are independent in and how many activities they are dependent on.[7] Lawton and Brody's scale of IADLs aimed to evaluate the degree of independence of the interviewee in seven activities. The final score can vary between 7 and 21 points; 7 points indicate total dependence, 8 to 20 points indicate partial dependence, and 21 points indicate independence.[8]

The research used the Zarit Burden Interview to assess the burden of older caregivers, consisting of 22 Likert questions. The result obtained at the end of the questionnaire was the sum of all the questions answered, ranging from 0 to 88 points. The higher the score obtained, the greater the burden perceived by the caregiver.[9] The cut-off point suggested using the international study by Ferreira et al.:[10] little burden (0–20), moderate burden (21–40), moderate to severe burden (41–60), and severe burden (61–88).

The Mini-Mental State Examination was used to assess cognition in older caregivers. The instrument consisted of 12 items with a maximum score of 30 points. The cut-off score adopted to indicate possible evidence of cognitive impairment varies according to the respondent's education, of which 17 points were for illiterate, 22 points for individuals with 1–3 years of education, 24 points for 4–7 years of study, and 26 points for people with 8 years of education or more.[11]

Researchers used the Geriatric Depression Scale to screen depressive symptoms in older caregivers, a 15-items version. Finally, we used it to calculate the sum of the scores obtained. A score between 0 and 5 points indicates an absence of depressive symptoms, 6 to 10 points indicate mild depressive symptoms, and 11 to 15 points indicate severe depressive symptoms.[12]

Ethical aspects

The study followed all the ethical aspects contained in Resolution 466/12. Data collection began only after authorization from the Municipal Health Department and subsequent approval from the ethics committee of Human Research of the Universidade Federal de São Carlos (UFSCar) [CAAE:08175419.5.0000.5504; number 3.275.704; approval date: April 22, 2019].

Analysis of results and statistics

The Kolmogorov–Smirnov test was used to verify the normality of the variables. It helped to estimate the frequency distributions, means, and minimum and maximum values for the numerical variables of the study for descriptive analysis of the data. The proportions of categorical variables were also estimated. Pearson's chi-square, Fisher's exact, and Mann–Whitney tests were used to identify differences between the groups. Pearson's chi-square test or Fisher's exact test was used to compare categorical variables, which were sociodemographic and health characteristics of the frailty groups. The Mann–Whitney test was used to compare numerical variables: care time, daily hours, and weekly day of care in the frailty groups. A significance level of 5% was used. The data obtained were encoded and typed in an electronic spreadsheet using two different digitizers and analyzed with the support of the statistical package Stata (version 13.0; StataCorp, College Station, United States).

RESULTS

The study sample consisted of 65 older caregivers. Of these, 72.3% were pre-frail, 24.6% were frail, and 3.1% were robust. Regarding frailty criteria, reduction in physical activity was the most prevalent component (75.4%), followed by fatigue (38.5%), weakness (35.4%), weight loss (24.6%), and slow gait (21.5%). **Table 1** presents the sociodemographic characteristics of the older caregivers in the context of high social vulnerability according to frailty.

The proportion of frailty was higher among older caregivers who did not have a partner than among those with a partner (P = 0.016). **Table 2** presents the health characteristics of older caregivers in the context of high social vulnerability according to frailty.

The study indicated that the proportion of frailty was higher among older caregivers with severe depressive symptoms when compared with that of the others (P = 0.029). Statistically significant differences were also identified between cognitive decline and

Table 1. Sociodemographic characteristics of older caregivers in a context of high social vulnerability according to frailty in the city of São Carlos, state of São Paulo (SP), Brazil, 2019–2020 (n = 65)

Variables	n (%)	Frailty		P
		No n (%)	Yes n (%)	
Sex				
Male	28 (43.1)	20 (71.4)	8 (28.6)	0.520
Female	37 (56.9)	29 (78.4)	8 (21.6)	
Age group				
60 to 74 years	51(78.5)	39 (76.5)	12 (23.5)	0.698
75 years or older	14 (21.5)	10 (71.4)	4 (28.6)	
Marital status				
With companion	61 (93.9)	48 (78.7)	13 (21.3)	**0.016**
No companion	4 (6.1)	1 (25.0)	3 (75.0)	
Retired				
No	17 (26.2)	14 (82.4)	3 (17.6)	0.438
Yes	48 (73.8)	35 (72.9)	13 (27.1)	
Years of study				
Medium (min–max)	3 (0-14)	3 (0–11)	4 (0–14)	0.950
Race/color				
White	21 (32.3)	19 (90.5)	2 (9.5)	0.098
Black	7 (10.8)	5 (71.4)	2 (28.6)	
Brown	34 (52.3)	24 (70.6)	10 (29.4)	
Indigenous people	1 (1.5)	0 (0.0)	1 (100.0)	
Yellow	2 (3.1)	1 (50.0)	1 (50.0)	
Personal income				
Medium (min–max)	998 (0–6.000)	998 (0–6.000)	998 (0–2.700)	0.379
Family income				
Medium (min–max)	2.090 (300–6.998)	2.000 (300–6.998)	2.094 (980–3.700)	0.949
Number of residents in the household				
Medium (min–max)	2 (2–9)	2 (2–5)	2 (2–9)	0.372

min–max = minimum–maximum.

frailty (P = 0.029). Among older caregivers with cognitive changes, the percentage of frailty was higher when compared with that of older adults without cognitive impairment. **Table 3** presents the characteristics related to the care conditions of older caregivers in the context of high social vulnerability according to frailty.

The results showed that the proportion of frailty was higher among older adults who cared for their parents when compared with that of other categories (P = 0.015). Moreover, the majority of the older caregivers who scored for the absent or moderate burden were not frail, while older caregivers who scored for moderate to severe or severe burns were frail (P = 0.004).

DISCUSSION

Older pre-frail caregivers were predominant (72.3%), followed by frail caregivers (24.6%). Although they present different proportions, it also identified a higher prevalence of pre-frailty in a national survey conducted with caregivers of older adults from São Paulo municipalities.[1] This divergence in proportion may have occurred because of the use of different instruments to assess frailty. An international study also observed a predominance of older pre-frail caregivers.[4]

Being an older caregiver may favor their entry into the cycle of frailty because of the greater exposure to stressors due to aging associated with the presence of morbidities. In addition, the older caregiver undergoes intense changes in their daily routine that can negatively reflect their physical and psychological health, making them more vulnerable to adversity, which would facilitate the installation of the syndrome.[5] Researchers point out that the risk of an older caregiver becoming frail may be partially related to the lower propensity of these caregivers to engage in preventive health behaviors.[4]

The present study found that older caregivers who did not have a partner had a higher proportion of frailty. A case-control study conducted in Belgium showed divergent data.[4] However, a national investigation conducted with 328 older caregivers identified that participants without partners had 11.03 and 14.39 times more chances of developing pre-frailty and frailty, respectively, when compared with those with partners.[5]

Table 2. Health characteristics of older caregivers in a context of high social vulnerability according to frailty in the city of São Carlos, state of SP, Brazil, 2019–2020 (n = 65)

Variables	n (%)	Frailty		P
		No n (%)	Yes n (%)	
Health care plan				
No	56 (86.2)	44 (78.6)	12 (21.4)	0.207
Yes	9 (13.8)	5 (55.6)	4 (44.4)	
Pain				
No	6 (9.2)	4 (66.67)	2 (33.33)	0.631
Yes	59 (90.8)	45 (76.27)	14 (23.73)	
Multimorbidity				
No	3 (4.6)	3 (100.0)	0 (0.0)	0.311
Yes	62 (95.4)	46 (74.2)	16 (25.8)	
Use of medicines				
None	8 (12.3)	6 (75.0)	2 (25.0)	0.107
A	10 (15.4)	10 (100.0)	0 (0.0)	
Two or more	47 (72.3)	33 (70.2)	14 (29.8)	
Depressive symptoms				
Severe	5 (7.7)	2 (40.0)	3 (60.0)	**0.029**
Light	15 (23.1)	9 (60.0)	6 (40.0)	
Absence	45 (69.2)	38 (84.4)	7 (15.6)	
Cognitive decline				
No	18 (27.7)	17 (94.4)	1 (5.6)	**0.029**
Yes	47 (72.3)	32 (68.1)	15 (31.9)	
BADL				
Independence	48 (73.9)	36 (75.0)	12 (25.0)	1.000
Dependence on an activity	16 (24.6)	12 (75.0)	4 (25.0)	
Dependence on two activities	1 (1.5)	1 (100.0)	0 (0.00)	
IADL				
Partial dependence	41 (63.1)	29 (70.7)	12 (29.3)	0.373
Independence	24 (36.9)	20 (83.3)	4 (16.7)	

BADL = Basic Activities of Daily Living; IADL = Instrumental Activities of Daily Living.

According to the literature, being married is a positive condition for general health. Evidence shows that having a partner raises the feeling of well-being, works as a protective factor against loneliness, and exposes the couple to healthier lifestyle habits, which are extremely important for physical, mental, and cognitive maintenance. Therefore, older adults without a partner can become frail due to insufficient physical activity and food inadequacy, which are factors that contribute to sarcopenia.[13]

In the present study, the proportion of frailty was higher among older caregivers with severe depressive symptoms. The data we found corroborate those of other investigations.[5,13-15] Scholars state that older adult caregivers may manifest more depressive symptoms than non-caregivers and that a possible explanation would be the high demand for care and emotional pressure derived from the solitary performance of the task of caring.[16] Evidence from the literature indicates similarity in the pathophysiological changes of both conditions, which suggests a bidirectional relationship between frailty and depression.[17]

Older adults with severe depressive symptoms demonstrate a lack of energy, reduced physical activity, and inappetence, which are recognized as open doors to the cycle of frailty. On the other hand, frail older adults may also present depressive symptoms in the presence of multimorbidity and possible functional limitations that may arise.[18]

Older caregivers with cognitive impairment had a higher proportion of frailty than those without cognitive impairment. Scholars have dedicated themselves to investigating a new condition conceptualized as cognitive frailty, identified based on cognitive impairment related to the criteria of frailty syndrome without the diagnosis of neurodegenerative diseases.[19]

There is also controversy among researchers regarding the inclusion of cognitive impairment as one of the criteria for frailty,[19] given that both conditions are multifactorial, have a higher incidence in older adults, and seem to share similar pathophysiological mechanisms. In addition, female sex, low education, and sedentary lifestyle are possible risk predictors for both conditions.[20]

Table 3. Characteristics related to the care context of older caregivers in a context of high social vulnerability according to frailty in the city of São Carlos, state of SP, Brazil, 2019–2020 (n = 65)

Variables	n (%)	Frailty		P
		No n (%)	Yes n (%)	
Who gets the care				
Spouse	58 (89.3)	46 (79.3)	12 (20.7)	**0.015**
Parent	3 (4.6)	0 (0.0)	3 (100.0)	
Father-in-law/mother-in-law	1 (1.5)	1 (100.0)	0 (0.0)	
Brother/sister	1 (1.5)	1 (100.0)	0 (0.0)	
Others	2 (3.1)	1(50.0)	1 (50.0)	
Care time (years)				
Medium (min–max)	5.0 (0.05–50)	5.0 (0.05–50)	8.0 (0.5–45)	0.799
Daily hours of care				
Medium (min–max)	24 (1–24)	24 (1–24)	24 (2–24)	0.549
Weekly days of care				
Medium (min–max)	7 (4-7)	7 (4–7)	7 (7–7)	0.415
Previous training				
No	63 (96.9)	47 (74.6)	16 (25.4)	1.000
Yes	2 (3.1)	2 (100.0)	0 (0.0)	
Get help in care				
No	38 (58.5)	29 (76.3)	9 (23.7)	0.836
Yes	27 (41.5)	20 (74.1)	7 (25.9)	
Burden				
Small	27 (41.5)	24 (88.9)	3 (11.1)	**0.004**
Moderate	27 (41.5)	21 (77.8)	6 (22.2)	
Moderate to severe	9 (13.9)	4 (44.4)	5 (55.6)	
Severe	2 (3.1)	0 (0.00)	2 (100.0)	

min–max = minimum–maximum.

From this perspective, the context of high social vulnerability can be configured as a risk factor for older caregivers because the profile of these individuals reveals low education, financial and support scarcity, greater exposure to psychosocial stressors, and low adherence to the treatment of diseases, as well as physical and cognitive impairments.[21] Thus, cognitive impairment due to physical conditions has the potential for reversibility. Therefore, the sooner interventions are identified, the more effective they may be.[22]

Older adults who cared for their parents presented a higher percentage of frailty than that of the others. Scholars point out that the responsibility of care can be considered an obligation, given that parents have previously devoted care to their children.[23] Thus, the feeling of obligation combined with uninterrupted care could trigger symptoms of exhaustion and lack of time for oneself, discouraging older adults from performing leisure activities and increasing the possibility of falling within the criteria of the phenotype.[5] This explanation is in line with the context of care in the present study.

In the present study, most older caregivers who scored little or moderate burden were not frail, while most of those who scored moderate to severe or severe burden were frail. These findings confirm the results of a national study.[1,14] Assuming the role of caregiver of another older adult requires a high degree of vigilance and attention, which can generate physical and psychological tension over time, especially in the face of unpredictable situations and the lack of social support.[1] In addition, cohabiting with the recipient of care exposes the caregiver to continuous and uninterrupted demand, favoring low insertion in social, physical, and leisure activities.[21] Such conditions interact with each other, leading to the entry of older adults into the cycle of frailty.

Frailty syndrome results from a series of changes in biological mechanisms that culminate in the deregulation of multiple systems and, consequently, in homeostatic imbalance. Therefore, the body cannot tolerate stressors in the face of the reduced available energy, which triggers a progressive decline in physical functioning,[24] contributing to the individual feeling overwhelmed. In contrast, burns can also cause homeostatic imbalance and favor the occurrence of frailty, considering that, in the care context, there are high demands and an excess of tasks that need to be performed. It could generate a feeling of fatigue and exhaustion in addition to the short time for self-care, which would contribute to physical inactivity, a known path to the cycle of frailty. Thus, this explanation route has a double meaning; that is, a weakened organism may have a more impactful view of the care context, leading to a higher

perception of burden, just as a burdened individual may present dysfunction of multiple systems and become frail.

In the face of such reflections, this study suggests that primary healthcare professionals should develop psychosocial and psychoeducational actions that aim to reduce the impact of tension involved in the task of care. Therefore, group interventions can contribute to the exchange of experiences, stimulate social interaction, and offer support to caregivers inserted in this context[25] since the absence of support and education can subject the older caregiver to the worsening of already installed morbid conditions. Integrating health promotion and disease prevention behaviors can prevent the burden from being added to other occurrences, thus reducing the chances of the caregiver becoming frail and presenting unfavorable health outcomes, such as falls, early institutionalization, hospitalization, and death.[1]

The study recommends the development of new research with this theme since high levels of burden can culminate in the development of the syndrome and lead to adverse outcomes. Thus, intervention studies can contribute to minimizing the impact of burden and frailty in older caregivers. The inclusion of new variables, such as social support, can enhance a more comprehensive understanding of the profile of older adults and fill gaps in the literature.

The present study has some limitations. The cross-sectional design did not allow us to assign causality between variables. In addition, the small sample size and the specific context of the social vulnerability of older caregivers limit the generalization of the findings.

CONCLUSION

Older caregivers without a partner, with severe depressive symptoms and cognitive changes, who cared for their parents, and had higher levels of burden, presented a higher proportion of frailty.

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Four weeks of exercise regimen for sedentary workers with rounded shoulder posture: a randomized controlled study

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ABSTRACT

BACKGROUND: Rounded shoulder (RS) posture causes neck and shoulder pathologies. Mechanical correction taping (MCT) is often incorporated into postural corrective therapies; however, its effects on muscle stiffness are unclear.

OBJECTIVE: We investigated the effect of MCT with different tape fabrics, along with exercise, on upper trapezius and pectoralis minor muscle stiffness and the posture of sedentary workers.

DESIGN AND SETTING: A randomized controlled study was performed at Aydın Adnan Menderes University, Aydın, Turkey.

METHODS: The study included 39 workers with RS posture. Two intervention groups (performance tape: PT and classic tape: CT) were taped twice a week and administered a home exercise program for 4 weeks. The control (C) group performed only home exercises. RS was measured using an acromion-testing table (AT), stiffness using shear wave elastography ultrasound, and shoulder angle (SA) using a smartphone application at baseline and 4 weeks. Time and group interactions were determined using 3 × 2 mixed analysis of variance.

RESULTS: Intragroup analyses revealed a significant main effect of time on AT distance ($\eta^2 = 0.445$) and SA ($\eta^2 = 0.325$) in the PT and C groups ($P < 0.05$) and left upper trapezius stiffness ($\eta^2 = 0.287$) in the CT and C groups ($P < 0.05$). In the post hoc analyses, no difference was noted between the groups from baseline to 4 weeks ($P > 0.05$).

CONCLUSION: Scapular MCT added to postural exercises did not show any difference between the intervention groups and controls in terms of muscle stiffness and posture in sedentary workers.

INTRODUCTION

Posture is defined as the sequence of body parts required to maintain musculoskeletal balance.[1-3] Rounded shoulder (RS) posture is a postural disorder in which the line of gravity shifts anteriorly. This shift causes the head and shoulder positions to be inconsistent with the vertical line of the body, leading to "poor" posture.[1,2,4] Poor posture of the head and shoulders is associated with the risk of increased muscle load, degenerative disc disease, back pain, and chronic shoulder pathologies.[3,5] RS posture also develops with alignment impairments in the scapular position. A protracted and anteriorly tilted scapula creates excessive stress and increases muscle tone.[6,7] According to the literature, the muscles with the highest increase in tone are the upper trapezius and pectoralis minor.[2,3]

Prolonged sitting in a static position increases poor posture. Therefore, the possibility of developing poor posture is especially concerning in desk workers. Working in a static environment exacerbates the RS posture over time, causing[8,9] loss of function[10] and work efficiency in workers.[11]

Several different applications used for posture correction have been described in the literature.[12,13] Among these, scapular mechanical corrective taping with elastic tape is a popular technique.[14-16] In a study using corrective taping, it was shown that this application significantly improved shoulder posture.[9] In a systematic review, scapular corrective taping was suggested to improve scapular posture in both healthy individuals and patients with shoulder problems.[17]

Muscle stiffness is considered valuable information in the diagnosis of neck and shoulder problems.[18] The shear wave elastography method has high reliability and provides objective data by converting the stiffness of the muscle in a localized area into numerical data.[19] In the literature, there is no study explaining the effectiveness of scapular mechanical correction taping (MCT)

on shoulder muscle stiffness using the shear wave elastography method. Therefore, it remains unclear whether corrective taping regulates muscle stiffness in the long term.

OBJECTIVE

Our primary hypothesis was that MCT applied in addition to exercise would decrease the stiffness of the upper trapezius and pectoralis minor muscles and fix shoulder posture in workers with RS deformity. The secondary aim of this study was to determine whether different tape fabrics affected the application results.

METHODS

Participants

This study was conducted at a university hospital with 45 sedentary workers aged 18–34 years. Participants were included if they had RS posture with reference to a prior screening using lateral acromion-testing table distance (AT distance) measurement. Based on the results of this test, individuals with a result of 3 cm or more were considered to have RS posture, as shown in a previous study.[9,20] The participants were excluded if they had a musculoskeletal system injury in the past 6 months or any neurologic or orthopedic disorder or cervical radiculopathy, received physical therapy in the last 6 months, participated in professional sports, or had an allergic skin reaction to the tape material. All procedures were explained to the participants, and written informed consent was obtained. Ethical approval for the study was obtained from the Ethics Committee of Aydın Adnan Menderes University, Faculty of Health Sciences Non-Interventional Clinical Investigations (No. 92340882-050.04.04; protocol: 2018/14), dated April 25, 2018.

Study design

This study was a randomized controlled, single-blinded clinical study. The participants were randomized using a computer-assisted randomization method. For this process, the sequence generator available at "www.random.org" was used. The participants did not have any information about the groups formed or which group they belonged to. Therefore, a single-blinded study was performed. The study included two intervention groups, classic tape (CT, n = 15) and performance tape (PT, n = 15), and one control group (C, n = 15). Data were collected using a smartphone-based photographic analysis application, Dr. Goniometer (CDM S.r.L, Milano, Italy), for shoulder angle (SA) and using shear wave elastography for muscle stiffness. Elastographic evaluations of the participants were performed by a radiologist at the Radiology Department of the same university. Worker height (cm), weight (kg), and age (years) were recorded as demographic information.

Sample size

Assuming that a strong degree of effect size (f = 0.5) was obtained for the difference between the three groups as a result of the power analysis conducted a priori in the direction of hypothetical expectations with reference to a similar study,[9] at least 42 individuals (14 for each group) were required to obtain 80% power with 95% confidence.

Intervention procedures

At the first visit, all the participants underwent baseline measurements. Immediately after the first visit, the tape was applied to the participants in the CT and PT groups. CT is a classical corrective tape made with a regular corrective fabric. PT is a new form of corrective tape developed by the same brand for the same purpose although with a different fabric. There is a difference in weaving between the different fabrics of the tape, allowing them to be thicker or thinner. The tapes of the participants in these groups were reapplied twice a week for a total of 4 weeks. The workers continued their home exercise program for 4 weeks. The workers in the control group performed only the home exercise program. Measurements were repeated in the same order at the end of 4 weeks. The tape was removed during the final measurement.

MCT application

The tape application was performed by a physiotherapist with 12 years of experience, who was a certified corrective taping practitioner. First, an I-shaped tape was measured and cut in a personalized manner for each participant. The anchor of the tape was applied on the anterior aspect of the glenohumeral joint without any tension as the participant sat upright. Subsequently, the participant was asked to retract the scapula bilaterally. While the participant was maintaining this position, the tape was diagonally applied to the inferior border of the scapula with 50–75% tension and the last anchor was applied with no tension.[14,21] The tape was applied to left and right shoulder girdle. The same taping technique was applied to the CT and PT groups using different tape fabrics (**Figure 1**).

Exercise program

The home exercise program prescribed to all participants consisted of basic postural exercises. These exercises were performed to strengthen the scapular muscles and provide healthy posture. Participants followed the home exercises as indicated in **Table 1**.

Outcome measures

RS assessment (AT distance)

In the supine position, the acromion was palpated and marked, and the vertical distance between this point and the testing table

Table 1. Exercise program

Exercise	Explanation	Intensity
'W' wall slides	At the edge of the wall, when the back is in full contact with the wall, the arms are first opened to the side and bent by the elbows (making a W), dragging upward on the wall without interrupting the arm contact with the wall, and subsequently returning to the initial W position.	3 sets × 15 Twice a day 4 weeks
Shoulder retraction	Elbows are bent at 90° with arms adjacent to the body. In this position, the shoulder blades are squeezed for 5 s and held close to each other and then loosened. Concurrently, care should be taken not to pull up the shoulders. It is recommended to perform this exercise in front of the mirror if possible.	3 sets × 15 Twice a day 4 weeks
Backward shoulder rolls	While the arms are adjacent to the trunk, and the elbows are bent, the shoulders are rolled up first, then backward, and downward. The shoulder is required to make a full circle movement. This exercise is continued for 2 min.	3 sets × 2 min Twice a day 4 weeks

These exercises were provided to both the intervention groups and control group.

was measured using a ruler. The measurements were recorded in centimeters. The reliability of this test was demonstrated in a previous study (intraclass correlation coefficient = 0.95).[22,23] In this study, individuals with a measurement result of > 3 cm were considered to have RS.[9]

Postural angle assessment (Dr. Goniometer application)

Photogrammetry is the most commonly used noninvasive postural measurement because it eliminates possible exposure to harmful radiation during the radiographic method and does not require printing of photographs. Grading is performed by marking the reference bone points and measuring the distance or angle between the specified points.[1] Before the measurement, the reference bone points (the acromion and seventh vertebra) were marked using a pen or a reflective marker to be clearly observed on the photograph. The camera was set up to take a photograph of the participant from the right lateral side. The participant was subsequently asked to lean forward and backward three times to relax and assume a comfortable standing position. While the participants breathed properly and stood still, a point was marked on the wall directly opposite the participant's eye level to maintain posture. After taking the photo, the cursors on the application screen were adjusted, and the desired angle was recorded (**Figure 2**). Validity and reliability studies of this smartphone application were conducted, and the intraclass correlation coefficient value was found to be 0.92.[24]

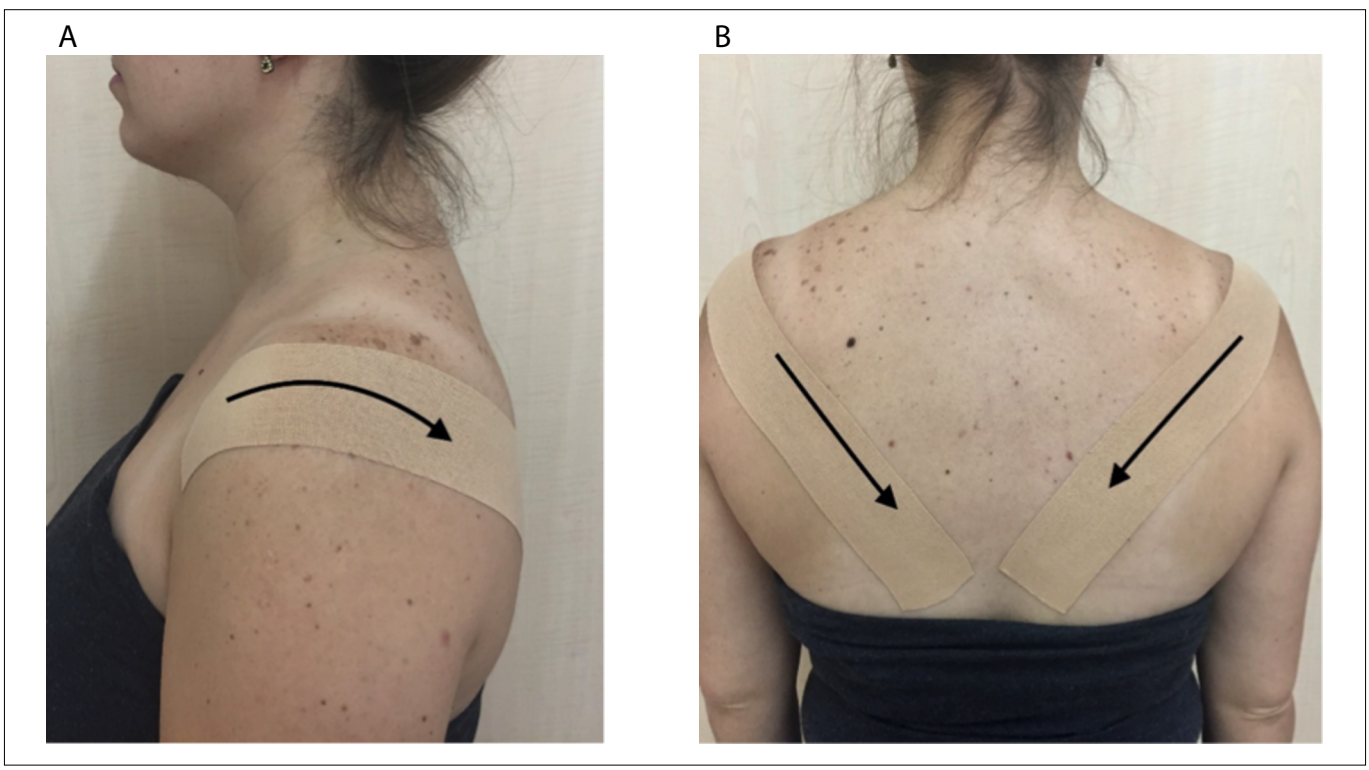


Figure 1. Scapular correction taping. **(A)** Taping technique from the lateral view. **(B)** Taping technique from the posterior view.

SA

This angle occurs at the point where the line joining the seventh cervical spinous process with the acromion of the shoulder intersects the horizontal line. This angle decreases as the shoulder protraction increases.[1,2]

Shear wave elastography

Evaluations were performed using a Samsung RS80 Ultrasound Device (Gyeonggi-do, Republic of Korea), and the stiffness of the upper trapezius and pectoralis minor muscles was examined. A 4 cm transducer and a 9 MHz linear probe were used for imaging. The 'musculoskeletal present' setting was used. The probe was placed parallel to the muscle fibers. At least 10 consecutive measurements were performed for each muscle, and the median was obtained. For standardization, measurements with a quality factor of 0.4–1.0 reliability measurement index were used in each muscle. Measurements below the 0.4 reliability measurement index are omitted. The test for the upper trapezius muscle was performed while the participant was in a sitting position with the hands resting on the thigh. For the pectoralis minor test, the participant was in the supine position with the arms resting on both sides. The muscle shear modulus was recorded in kilopascals (kPas), considering that each assessment was taken at the same point, and the level of probe pressure was equal.[25]

Figure 2. Shoulder angle assessment using Dr. Goniometer

Data analysis

The Statistical Package for Social Sciences (SPSS) (version 22.0; SPSS Inc., Chicago, Illinois, Unites States) was used for data analysis. For the three groups (CT, PT, and C) at two different times of assessment (at baseline and 4 weeks), time and group interactions were determined using 3 × 2 mixed analysis of variance. For significant P values, Bonferroni corrections were used for post hoc analysis. Effect sizes were interpreted using partial eta squared (η^2) and Cohen's d. Partial eta squared (η^2) values were accepted as follows: 0.01 = small, 0.06 = medium, and 0.14 = large.[26] Cohen's d values were accepted as follows: < 0.20 = small, 0.21–0.50 = small and medium, 0.50–0.80 = medium and large, and > 0.80 = large.[27] Significance level was set at $P < 0.05$.

RESULTS

A total of 52 sedentary workers were assessed, of whom four did not meet the inclusion criteria and three declined to participate. Forty-five eligible individuals were randomized into three groups. Six participants dropped out for various reasons. Final analyses were conducted using data from 39 individuals (**Figure 3**).

The demographic characteristics of the 39 participants with RS posture (PT group, n = 15; CT group, n = 14; C group, n = 10) included in the study are shown in **Table 2.** The mean age of the participants was 23.3 ± 3.6, 22.5 ± 4.1, and 23.3 ± 5.4 years for the PT, CT, and C groups, respectively. The mean height was 164.06 ± 6.3,

Table 2. Demographic characteristics of the groups

Groups	Variable	Min	Max	Mean ± SD
PT (n = 15)	Age (year)	19.00	32.00	23.3 ± 3.6
	Weight (kg)	48.00	95.00	63.3 ± 12.6
	Height (cm)	145.00	170.00	164.06 ± 6.3
CT (n = 14)	Age (year)	18.00	33.00	22.5 ± 4.1
	Weight (kg)	48.00	86.00	63.2 ± 13.9
	Height (cm)	158.00	176.00	164.7 ± 5.07
C (n = 10)	Age (year)	19.00	34.00	23.3 ± 5.4
	Weight (kg)	43.50	65.00	57.1 ± 6.3
	Height (cm)	155.00	170.00	163.3 ± 4.96

Min = minimum; Max = maximum; SD = standard deviation; PT = performance tape; CT = classic tape; C = control.

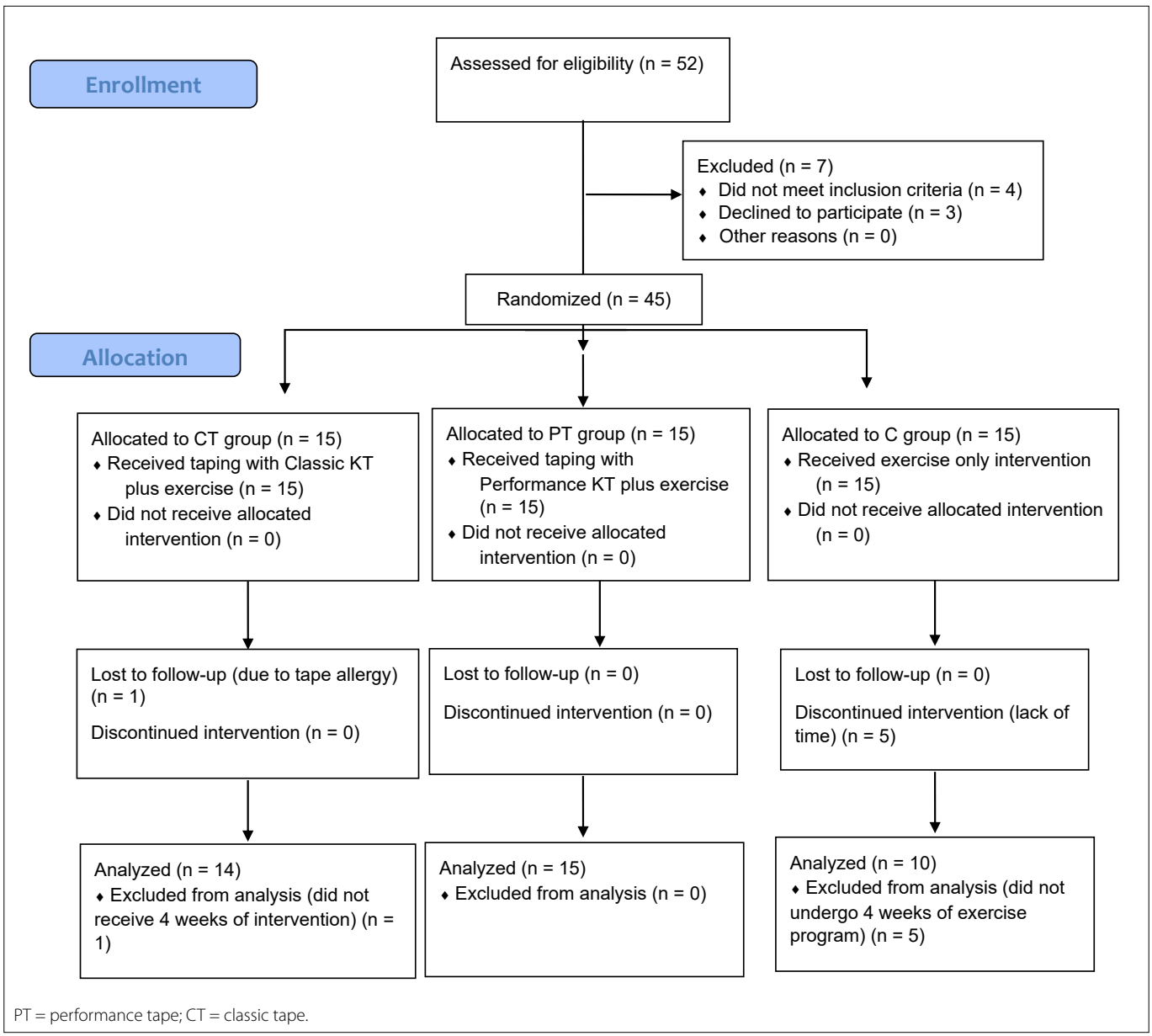
164.7 ± 5.07, and 163.3 ± 4.96 cm for the PT, CT, and C groups, respectively. The mean weight was 63.3 ± 12.6, 63.2 ± 13.9, and 57.1 ± 6.3 kg for the PT, CT, and C groups, respectively (**Table 2**).

The effect sizes of the mean differences, 95% confidence intervals, P values of the SA, and stiffness values of the upper trapezius and pectoralis minor muscles at baseline and 4 weeks are shown in **Table 3**. In intragroup analyses, a significant main time effect was noted in AT distance (F [1, 36]: 28.860, P < 0.001, partial η^2: 0.445) and SA degrees in the PT and C groups (F [1, 36]: 17.348, P < 0.001, partial η^2: 0.325) and in left upper trapezius stiffness in the CT and C groups (F [1, 36]: 14.462, P = 0.001, partial η^2: 0.287) (P < 0.05). However, in the post hoc analyses, none of the evaluated parameters showed differences among the groups from baseline to 4 weeks (P > 0.05) (**Table 3**).

DISCUSSION

To our knowledge, this is the first randomized controlled study to investigate the effects of MCT on muscle stiffness. After 4 weeks of mechanical scapular correction taping application, the results showed that the RS posture significantly decreased in all groups; however, the SA was corrected only in the PT and C groups. Improvement in muscle stiffness was only observed in the left upper trapezius in the CT and C groups. No superiority was observed among the intervention groups and controls in terms of the evaluations.

Deformities in soft tissue stiffness, muscle activity, and bone alignment may cause alterations in scapular and humeral movement. Consequently, several conditions, such as



PT = performance tape; CT = classic tape.

Figure 3. Flow diagram.

Table 3. Baseline and fourth week results of the group

Parameter	Group	Baseline	At 4 weeks	Difference (95% CI)	P value	Cohen's d
		Mean ± SD	Mean ± SD			
SA (degrees)	PT	61.25 ± 8.93	68.19 ± 9.10	6.94 (2.53–11.35)	**0.003**	0.76
	CT	63.84 ± 9.35	65.84 ± 5.21	1.99 (–2.57–6.56)	0.382	0.26
	C	57.91 ± 9.39	66.09 ± 5.40	8.18 (2.78–13.580)	**0.004**	1.06
AT distance (cm)	PT	6.10 ±1.21	5.05 ± 0.80	1.05 (0.49–1.61)	**0.001**	1.02
	CT	6.40 ±1.28	5.55 ± 1.15	0.850 (0.27–1.43)	**0.005**	0.69
	C	6.48 ±1.40	5.58 ± 1.26	0.900 (0.21–1.59)	**0.012**	0.67
Trapezius Stiffness Right (kPa)	PT	43.38 ± 13.79	37.55 ± 12.72	5.83 (–0.78–12.43)	0.082	0.43
	CT	41.64 ± 14.44	38.94 ± 19.01	2.70 (–4.14 to 9.54)	0.429	0.15
	C	38.98 ± 9.73	34.71 ± 12.96	4.27 (–3.82–12.36)	0.292	0.37
Trapezius Stiffness Left (kPa)	PT	46.24 ± 17.26	42.41 ± 13.43	3.83 (–1.82–9.49)	0.177	0.24
	CT	47.94 ± 16.82	40.52 ± 16.08	7.42 (1.58–13.27)	**0.014**	0.45
	C	42.59 ± 17.33	33.83 ± 8.64	8.76 (1.84–15.68)	**0.015**	0.63
PecMinor Stiffness Right (kPa)	PT	18.83 ± 14.26	15.13 ± 10.28	3.69 (–5.23–12.62)	0.407	0.29
	CT	22.38 ± 11.65	21.33 ± 13.22	1.05 (–8.19–10.29)	0.819	0.08
	C	26.99 ± 31.13	17.12 ± 12.95	9.87 (–1.06–20.80)	0.075	0.41
PecMinor Stiffness Left (kPa)	PT	15.42 ± 8.39	13.51 ± 8.39	1.91 (–11.70–15.51)	0.778	0.22
	CT	20.63 ± 12.60	19.88 ± 12.38	0.75 (–13.33–14.83)	0.915	0.06
	C	34.40 ± 49.49	18.22 ± 14.81	16.18 (–0.48–32.84)	0.057	0.44

SD = standard deviation; SA = shoulder angle; PT = performance tape; CT = classic tape; C = control; kPa = kilo pascal; P < 0.05.

impingement, rotator cuff disease, joint instability, and capsulitis, may occur.[15,28] To prevent these shoulder problems during repetitive overhead movements, a stable scapula and coordinated activity of the scapulohumeral muscles are required. Impairments in scapular movements during activities are associated with shoulder pain because they cause excessive stress and microtrauma to soft tissues.[29,30] Scapular taping is one of the most useful methods for increasing joint stability by providing biomechanical realignment of the scapula and glenohumeral joint during several activities. With this technique, which is applied using an elastic therapeutic tape, both the normal healing of soft tissues and the stability of the joints are supported without restricting the range of motion.[14] In a systematic review, it was suggested that scapular corrective taping could be used to improve scapular posture in both healthy individuals and patients with shoulder problems.[17] A placebo-controlled study also reported a reduction in supine AT distance measurement for RS posture with mechanical scapular correction taping.[9] On the contrary, in a study investigating the acute effect of bilateral scapular mechanical correction technique by using corrective and rigid tapes on posture in university students with significant shoulder protraction, no significant effect was reported.[31] Similarly, Gulpinar et al. used the mechanical correction technique with both corrective and rigid tapes to determine the acute effect on RS posture.[32] They positioned the glenohumeral joint in external rotation using the mechanical correction technique. They found an increase in the total range of motion of the shoulder in acute measurements; however, no change in posture was noted.[32] The use of this technique is controversial in the literature. In these studies, posture was generally measured immediately after taping. In contrast, we evaluated the long-term effects in our study. The results were inconsistent with different fabricated tapes. The SA did not change in the CT group; however, it significantly increased in the PT group. Intergroup analyses also showed that no superiority of scapular MCT on the SA over the controls was noted. Since the numerical increase in the SA was mostly in the control group, we cannot conclude that the angular change was due to taping. We postulate that the exercise program had the necessary effect.

Overactivation and stiffness of the upper trapezius and pectoralis minor muscles associated with weakness of the lower trapezius and rhomboid muscles may cause a relatively protracted shoulder and disrupt normal posture.[33,34] In desk workers, upper trapezius stiffness was shown to increase as the inclination angle of the head changes.[6,35,36] Like the upper trapezius, proper tension–length relationship and pectoralis minor stiffness are also associated with optimal scapular posture.[9,37] Average stiffness values of the upper trapezius were calculated as follows: 40–47 kPa in the sitting position and 0° neutral cervical position and 60–83 kPa in 50° cervical forward flexion in healthy participants using the shear

wave elastography method.[38] Average pectoralis minor stiffness was also measured as 12.7 ± 3.6 kPa in healthy individuals in another study.[39] In our study, in the baseline measurements, upper trapezius stiffness measured in the neutral position was found to be between 40 and 47 (±9–17) kPa in all groups, whereas pectoralis minor stiffness ranged between 15 and 34 (±14) kPa, similar to the study by Zhang et al.[38] In this situation, scapular taping may be a useful technique to reduce the symptoms. The tape can adjust the muscle activity through proprioceptive feedback.

It was reported that upper trapezius activity decreased and proprioception improved in individuals who underwent scapular corrective taping.[15] In our study, instead of reducing the muscle stiffness using a direct application, we expected a decrease in stiffness that may occur secondary to posture correction with proprioceptive feedback. After 4 weeks of scapular MCT, a significant decrease in left upper trapezius muscle stiffness in the CT and C groups was noted; however, no intergroup superiority was observed. The pectoralis minor stiffness in the C group also numerically decreased; however, this was not statistically significant. The decrease in the stiffness level of the upper trapezius muscle in both the CT and C groups indicated that this decrease was not caused by MCT. Thus, we can argue that a 4-week home exercise program regulated muscle stiffness by improving shoulder posture. In addition, although the participants included in this study had an RS posture, the initial stiffness values were similar to those in studies on healthy individuals. This may be another reason why the decrease in stiffness levels was not significant. While there are studies showing the effectiveness of exercise on postural angles in the literature, none have evaluated muscular properties using shear wave ultrasonography. Kim et al. showed that McKenzie exercises were effective in increasing the craniovertebral angle and decreasing RS posture.[40] Likewise, in another study, similar exercises were performed while MCT was added to the intervention group. In that study, it was shown that the greatest improvement in craniovertebral angle occurred in the exercise group, and a well-planned exercise program was concluded to help improve posture.[41] In the present study, the exercise program prescribed to all participants included simple postural corrective exercises. The fact that no difference was noted between the groups showed that even a 4-week posture training with simple exercises could achieve the same effect.

Our study had some limitations. First, we performed pre-screening using supine AT distance measurement instead of angular measurement, while similar studies used angular measurements as the inclusion criteria of the participants. We recommend using postural angle data obtained by the photogrammetric method as an inclusion criterion in future studies. Second, a healthy group was not included in the study for comparison. Thus, in future studies, the baseline measurements can also be compared with those of healthy individuals.

CONCLUSION

Scapular mechanical correction using corrective taping in addition to a postural exercise program was not found to be effective for muscle stiffness and posture in workers with RS posture. Different fabrics of tape materials did not result in significant changes. Therefore, prescribing corrective postural exercises will be more effective for the treatment of muscle stiffness that develops secondary to postural disorders. Based on our study results, we do not recommend the use of scapular MCT with the expectation of corrective and muscle stiffness regulatory effects in the long term.

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Occult hepatitis B virus infection in patients with chronic liver disease of different etiology in a Brazilian referral center: comparison of two different hepatitis B virus deoxyribonucleic acid amplification protocols: a cross-sectional study

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AUTHORS' KEY WORDS:
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Chronic liver disease.
Nested-PCR.

ABSTRACT

BACKGROUND: Occult hepatitis B virus infection (OBI) is defined as the presence of hepatitis B virus (HBV) deoxyribonucleic acid (DNA) in the liver of individuals with undetectable hepatitis B virus surface antigen (HBsAg) in the serum. The actual prevalence of OBI and its clinical relevance are not yet fully understood.

OBJECTIVE: To evaluate the prevalence of HBV DNA in liver biopsies of HBsAg-negative patients with chronic liver disease of different etiologies in a referral center in Brazil and compare two different HBV DNA amplification protocols to detect HBV.

DESIGN AND SETTING: This cross-sectional observational study was conducted at the Liver Outpatient Clinic, Hospital das Clínicas, Universidade Federal de Minas Gerais, Belo Horizonte, MG, Brazil, between January 2016 and December 2019.

METHODS: HBV DNA was investigated in 104 liver biopsy samples from individuals with chronic liver disease of different etiologies, in whom HBsAg was undetectable in serum by nested-polymerase chain reaction (nested-PCR), using two different protocols.

RESULTS: OBI, diagnosed by detecting HBV DNA using both protocols, was detected in 6.7% of the 104 individuals investigated. Both protocols showed a good reliability.

CONCLUSION: In addition to the differences in the prevalence of HBV infection in different regions, variations in the polymerase chain reaction technique used for HBV DNA amplification may be responsible for the large variations in the prevalence of OBI identified in different studies. There is a need for better standardization of the diagnostic methods used to diagnose this entity.

INTRODUCTION

Hepatitis B virus (HBV) infection is one of the most prevalent infections worldwide and is an important cause of morbidity and mortality. It often progresses to chronic hepatitis, liver cirrhosis, and hepatocellular carcinoma (HCC) and is responsible for approximately 780,000 deaths annually.[1-4]

HBV infection is usually diagnosed based on the presence of the HBV surface antigen (HBsAg) in the serum. However, the possibility of persistence of the HBV genome in HBsAg-negative individuals has been demonstrated. This entity termed occult hepatitis B virus infection (OBI), is defined by the presence of HBV deoxyribonucleic acid (DNA) in the liver (in some cases, also in the serum) in the absence of circulating HBsAg.[1,5,6] When HBV DNA is detectable in the serum, its levels are usually very low (< 200 IU/mL). It has been hypothesized that OBI is related to strong suppression of viral activity by host immune surveillance.

From a biomolecular perspective, different mechanisms may be involved in OBI development: mutations in the HBsAg gene, epigenetic changes, host immune responses, human immunodeficiency virus (HIV) and hepatitis C virus (HCV) coinfections, metabolic factors, HBV immune complexes, and genomic integration.[7-12] Moreover, there is evidence that microRNAs (miRNAs) are differentially expressed in patients with OBI compared to healthy controls.[13]

The exact magnitude, pathogenesis, and clinical relevance of OBI are not completely understood. Individuals with this entity can transmit HBV through blood transfusion or organ transplantation.[1,5,6,11,14,15] In the setting of immunosuppression, the suppressed state of viral activity observed in OBI can be discontinued, leading to the development of typical hepatitis B, which often has a severe course.[16,17] Observational data suggest that OBI may favor or accelerate the progression of other chronic liver diseases, such as HCV infection,[18] and HCC development.[1,6,19,20]

The diagnosis of OBI has been established using polymerase chain reaction (PCR) to amplify HBV DNA. Modifications to the PCR technique (nested-PCR and real-time PCR) were used to increase the sensitivity of the method. PCR assays vary in sensitivity and specificity, and the factors associated with the biological material in which the DNA is probed may affect HBV detection rate. Thus, the diagnosis of OBI remains challenging because there is no standard method or protocol for the detection of occult HBV DNA.[21]

In Brazil, few studies have evaluated the prevalence of OBI using current case definition criteria.[24-27]

OBJECTIVE

In this context, the present study aimed to investigate the frequency of OBI in patients with chronic liver disease who underwent liver biopsy as part of the investigation of their disease and to compare two different HBV DNA amplification protocols for HBV detection.

METHODS

This is a cross-sectional observational study approved by the Research Ethics Committee of the Universidade Federal de Minas Gerais (UFMG) (CAAE 32140914.0.0000.5149) on October 1, 2014. All the patients signed an informed consent form.

Patients

Liver biopsy samples were selected from 104 adult patients, HBsAg-negative, with chronic liver disease of any etiology, who had undergone liver biopsy as part of the investigation of their disease and were followed up at the Liver Outpatient Clinic, Hospital das Clínicas, UFMG, between January 2016 and December 2019.

In addition to the paraffin-embedded biological samples, data from medical records were collected, including the results of markers of previous HBV infection, collected at the time of biopsy, that is, antibodies anti-HBV core antigen (anti-HBc) and antibodies anti-HBV surface antigen (anti-HBs), this last marker from unvaccinated patients. The exclusion criteria were HIV infection, use of immunosuppressive drugs, and hematological malignancies.

Patients were grouped according to the etiology of the underlying liver disease as follows: chronic liver disease associated with HCV, nonalcoholic steatohepatitis, autoimmune liver disease (autoimmune hepatitis, primary biliary cholangitis, and primary sclerosing cholangitis), cryptogenic liver disease and hemochromatosis.

Representativeness of liver biopsies

The representativeness of liver biopsies was assessed based on fragment size and number of portal tracts. The size distribution of the fragments was very close to a normal curve, with a mean size of approximately 13 mm.

The distribution of the number of portal tracts, unlike the biopsy size, showed wide variability with a skewed distribution, despite the higher concentration around the eight portal tracts (**Figure 1**).

The quality of the DNA present in the samples was analyzed using the A260/A280 ratio. Nucleic acids absorb light with a wavelength of 260 nm. Proteins absorb light with a wavelength of 280 nm. Thus, the A260/A280 ratio provides a parameter for evaluating the quality of nucleic acid preparation. DNA was considered pure when the A260/A280 ratio was between 1.8 and 2. Values lower than 1.8 indicate protein contamination. **Figure 2** shows that the DNA was not of good quality.

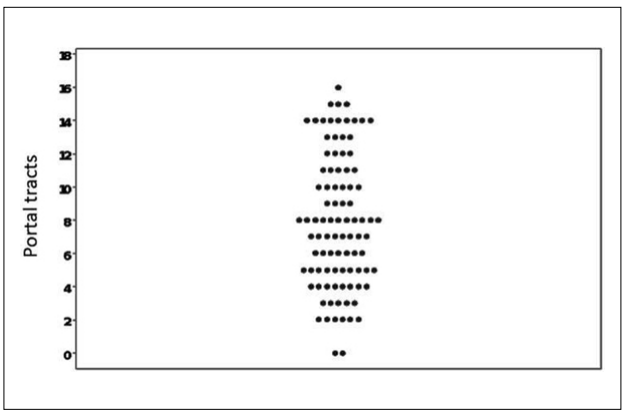

Figure 1. Number of portal tracts.

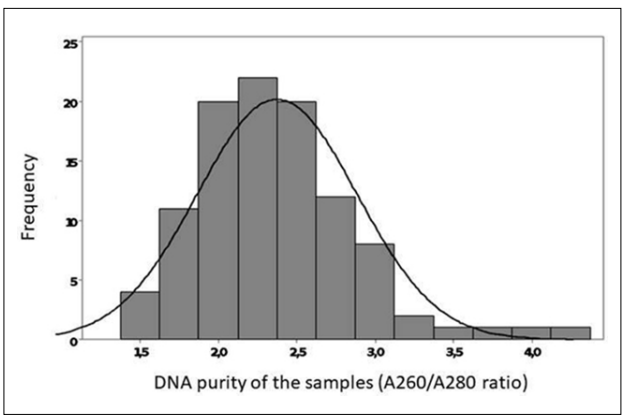

Figure 2. Deoxyribonucleic acid (DNA) purity in the samples (A260/A280 ratio).

DNA extraction and amplification

DNA was extracted from paraffin-embedded samples using the Qiamp DNA FFPE Tissue Kit (QIAGEN, Hilden, Germany), as recommended by the manufacturer. DNA was extracted from three negative and positive controls. DNA from all samples was amplified according to two previously published protocols: the protocols described by Raimondo et al.[5] (protocol 1) and Chapel et al.[28] (protocol 2).

According to protocol 1, DNA was amplified using nested PCR and the primers employed were complementary to four conserved regions of the viral genome (pre-S/S, pre-core/core, polymerase, and region X), as described in **Table 1**. A programmable thermal controller PTC-100™ thermal cycler (MJ Research, Inc., St. Bruno, Canada) was used for PCR.

For internal and external reactions, a SuperMix Kit (PCR SuperMix, Invitrogen, Fisher Scientific, Inc., Fair Lawn, United States) was used. The reaction conditions were as follows: initial denaturation at 94 °C for two minutes, followed by 35 cycles of denaturation at 94 °C for 30 s, primer binding at 56 °C for 45 s, extension at 72 °C for 90 s, and a final step of 10 min at 72 °C.

The primers used in protocol 2 are listed in **Table 2**. DNA was amplified by nested PCR, using the same kit for internal and external reactions. Primers for the S and Pol regions of the viral genome were used in the following order: in the first amplification step, primers 14/13 were used to amplify a 416 bp sequence located in a conserved region of the polymerase (Pol) and surface (S) genes. For the second step, the primers 06/03 were used to re-amplify a 128 bp segment located in the 416 bp sequence. The external reaction parameters (primers 14/13) were as follows: initial denaturation at 90 °C for seven min, 40 cycles of 20 s at 94 °C, 60 s at 47 °C, 60 s at 74 °C; and a final extension at 74 °C for seven min. Five microliters of the products from the first reaction were subjected to 35 cycles of a second PCR reaction using the primers 06/03; the parameters of this second step (internal reaction) were: 20 s at 94 °C, 60 s at 57 °C, and 60 s at 74 °C for each cycle, with an initial denaturation at 90 °C and a final extension step at 72 °C.

Polyacrylamide gel electrophoresis was performed to verify whether the fragment of interest was amplified by PCR.

Table 1. Initiators for hepatitis B virus deoxyribonucleic acid detection by nested-polymerase chain reaction - protocol 1[5]

Hepatitis B virus genomic regions	Nucleotide positions
S region	
S1- F: 5′-CATCAGGATTCCTAGGACCCCT-3′	[168–189]
S2- F: 5′-CTTGTTGACAAGAATCCTCACA-3′	[214–235]
S3-R: 5′- AGGACAAACGGGCAACATAC-3′	[478–458]
S4-R:5′- CCAACAAGAAGATGAGGCATA-3′	[442–420]
C region	
C5-F: 5′- TCACCTCTGCCTAATCATC-3′	[1825–1843]
C6-F: 5′- TTCAAGCCTCCAAGCTGTGCC-3′	[1862–1882]
C7-R: 5′- GAGGGAGTTCTTCTTCTAGG-3′	[2391–2371]
C8-R: 5′- AGGAGTGCGAATCCACACTCC-3′	[2277–2267]
Polymerase region (Pol)	
P9-F: 5′- CGTCGCAGAAGATCTCAATC-3′	[2420–2439]
P10-F: 5′- CCTTGGACTCATAAGGT-3′	[2463–2479]
P11-R:5′- TCTTGTTCCCAAGAATATGGT-3′	[2845–2825]
P12-R: 5′- TCCCAAGAATATGGTGACCC-3′	[2839–2820]
X region	
X13-F: 5′- CGCCAACTTACAAGGCCTTTC-3′	[1100–1120]
X14-F: 5′- CCATACTGCGGAACTCCTAG-3′	[1266–1685]
X15-R: 5′-GGCGTTCACGGTGGTCTCCAT-3′	[1628–1608]
X16-R: 5′- CGTAAAGAGAGGTGCGCCCC-3′	[1540–1521]

Statistical analysis

For this study, OBI cases were considered in individuals in whom DNA amplification was obtained using the two protocols.

Categorical variables are presented as numbers and percentages. Continuous variables were expressed as mean ± standard deviation, as they presented a normal distribution according to the Shapiro-Wilk test. Pearson's chi-square or Fisher's exact test was used to analyze the differences between qualitative data when appropriate. The Student's t-test was used to compare quantitative data. The degree of agreement between tests was calculated using the kappa coefficient of agreement. Statistical significance was set at P value < 0.05.

RESULTS

Epidemiological and clinical data

Of the 104 patients investigated, the mean age was 47.8 (range, 18–73). The patients' demographic, clinical, and laboratory characteristics are shown in **Table 3**.

The most common underlying liver disease was chronic hepatitis C (41.3%). No patient had HCC. In 84 cases, total anti-HBc data were available, of which 14 (16.7%) were positive. Anti-HBs were analyzed in 83 unvaccinated individuals and were positive in 37 (44.6%). Fourteen patients were positive for both markers, and 47 had negative markers.

Table 2. Initiators for hepatitis B virus deoxyribonucleic acid detection by nested-polymerase chain reaction - protocol 2[28]

Primer sequences	Oligonucleotides position
External reaction	
Primer 14″ F: 5′- ATCTTCTTATTGGTTCTTCT-3′	[430–449; pol]
Primer 13″ R: 5′- GTTAGGGTTTAAATGTATAC-3′	[845–826; S]
Internal reaction	
Primer 06 F: 5′-CTTGGATCCTATGGGAGTGG-3′	[632–651; pol]
Primer 03 R: 5′-CTCAAGCTTCATCATCCATATA-3′	[759–738; S]

Table 3. Characteristics of the 104 HBsAg-negative patients included in the study

Characteristic	Numerical value (n = 104)
Gender (F/M)	57 (54.8%)/47 (45.2%)
Age (mean age in years ± SD)	47.8 ± 12.6
Blood transfusion* yes/no	19 (23.5%)/62 (76.5%)
Anti-HBc positive¶ yes/no	14 (16.7%)/70 (83.3%)
Anti-HBs positive§ yes/no	37 (41.3%)/46 (58.7%)
Fibrosis grade on liver biopsy†	
F0	42 (40.4%)
F1	24 (23.1%)
F2	16 (15.4%)
F3	11 (10.6%)
F4	11 (10.6%)

HBsAg = surface antigen of hepatitis B virus; F/M = female/male; SD = standard deviation, anti-HBc = antibody anti-hepatitis B virus core antigen; anti-HBs = antibody anti-hepatitis B virus surface antigen.
Data are presented as number (percentage) and mean ± standard deviation.
*Data available for 81 patients; ¶data available for 84 patients; §data available for 83 patients.
†F0, no fibrosis; F1, portal fibrosis without septa; F2, few septa; F3, numerous septa without cirrhosis; F4, cirrhosis.[29]

Table 4. Amplification of HBV DNA according to two different protocols

HBV DNA	Protocol 1	Protocol 2
Positive	13 (12.5%)	9 (8.7%)
Negative	91 (87.5%)	95 (91.3%)
Total	**104 (100.0%)**	**104 (100.0%)**

HBV = hepatitis B virus; DNA = deoxyribonucleic acid.
Protocol 1: Raimondo et al., 2008;[5] protocol 2: Chapel et al., 1995.[28]
Data are presented as numbers (percentage).

Table 5. Distribution of OBI cases according to the etiology of the underlying liver disease

Etiology	HBV DNA		Total
	Negative	Positive	
Chronic HCV infection	39 (90.7%)	4 (9.3%)	**43 (100.0%)**
NASH	21 (95.5%)	1 (4.5%)	**22 (100.0%)**
Autoimmune	26 (96.3%)	1 (3.7%)	**27 (100.0%)**
Cryptogenic	9 (90.0%)	1 (10.0%)	**10 (100.0%)**
Hemochromatose	2 (100.0%)	0 (0.0%)	**2 (100.0%)**
Total	**97 (93.3%)**	**7 (6.7%)**	**104 (100.0%)**

OBI = occult hepatitis B infection; HBV = hepatitis B virus; DNA = deoxyribonucleic acid; HCV = hepatitis C virus; NASH = nonalcoholic steatohepatitis.
Data are presented as numbers (percentage).

OBI diagnosed by nested-PCR

HBV DNA was amplified in 13 (12.5%) of the 104 patients evaluated using protocol 1 and in nine (8.7%) using protocol 2 (**Table 4**). Considering the cases identified by both protocols, the frequency of OBI was seven in 104 individuals (6.7%). In six cases, HBV DNA was amplified only by the Raimondo et al. protocol,[5] and in two, only by the Chapel et al. one.[28]

The value of the kappa coefficient of agreement, considering the comparison of protocols 1 and 2, was 0.595 (95% confidence interval [CI], 0.487–0.696), showing that there was a substantial agreement between the results obtained in both tests.

No difference was found in the mean age (P = 0.244) or sex distribution (P = 0.698) between patients with and without OBI. No association was found between OBI and any underlying liver disease (P = 0.169). **Table 5** summarizes the distribution of OBI cases according to the etiology of underlying liver disease.

No association was observed between the occurrence of OBI and presence of anti-HBc antibodies (P = 0.086). However, such an association was observed when HBV DNA cases were identified using protocol 1. When comparing the patients with positive and negative PCR results (protocol 1) and the presence of HBV markers (anti-HBs and/or anti-HBc), it was observed that among the 13 individuals with positive HBV-PCR results, only one presented all negative markers, and 12 (92.3%) had at least one positive marker. Among 71 individuals with negative PCR results for HBV, 46 (64.8%) presented all negative markers and 25 (35.2%) presented with at least one positive antibody (anti-HBc and/or anti-HBs) (P = 0.000). No association was observed between the presence of HBV and hemotransfusion history (P = 1.000).

DISCUSSION

OBI was detected in 6.7% of 104 individuals with HBsAg-negative chronic liver disease, considering only those cases in which HBV DNA was detected by both protocols. The presence of HBV in individuals with chronic liver disease varies from 0.7-73% in different countries.[18,28,30-34] In Brazil, the range is 2%[35] to 19.5%.[23] This variation is probably due to differences in the prevalence of HBV infection in different regions of Brazil and the world and in the methodology used for HBV detection.

In a previous study conducted at the same institution where the current study was developed, the authors found 4.4% of OBI in explanted livers from patients with HBsAg-negative cirrhotic who underwent liver transplantation.[26] In that study, the protocol of Raimondo et al. was employed,[5] and the investigators analyzed only fresh liver tissue removed from the explanted liver, which provides larger fragments for analysis, facilitating HBV DNA detection.[26] Conversely, in the present study, we used fragments obtained by percutaneous liver biopsy stored in paraffin blocks. However, contrary to expectations, considering the nature of the material, the frequency of OBI found in the current study was approximately three times higher using the same protocol. It is noteworthy that in the study cited above,[26] sequencings were

performed, and only cases in which the HBV genome was identified were considered OBI cases.

Although nested PCR is considered an efficient molecular tool to detect HBV,[36] false-positive results may occur when this technique is used to diagnose OBI. It is possible to question whether the presence of cirrhosis makes it difficult to detect HBV DNA. Arguments against this hypothesis are the fact that all patients in the study by Ferrari et al.,[26] were cirrhotic, and in the current study, only 21.2% showed advanced fibrosis or cirrhosis on histology. Furthermore, in studies by Cacciola et al.,[18] Sagnelli et al.[37] and Squadrito et al.,[34] OBI was also associated with more severe stages of liver fibrosis or cirrhosis. We found no association between the occurrence of OBI and the etiology of the underlying liver disease. The association between OBI and chronic HCV infection has been observed in some investigations.[18,22,37,38] The small number of OBI cases in our study may explain the lack of this finding in the current study.

The presence of markers of prior HBV infection (anti-HBc and/or anti-HBs) was associated with OBI only when employing the protocol of Raimondo et al.[5] Previous studies confirm this association,[14,18,39,40] and some authors suggest that anti-HBc could be considered a sentinel marker of OBI.[14]

The analysis of DNA quality showed that this quality was adequate in only 16.3% of the samples, which may have interfered with the results. The use of paraffinized tissue in molecular biology tests, despite being inferior to the use of fresh material,[41] allowed for OBI detection in our study.

A difference was found between the two protocols in HBV DNA detection, which reinforces the need for better standardization of the method to diagnose OBI. The protocol by Raimondo et al.[5] allowed the identification of HBV DNA in more cases when compared with the protocol by Chapel et al.[28] These authors described a nested-PCR protocol for HBV DNA detection in paraffin-embedded tissue using primers complementary to a conserved region of the S and Pol genes.[28] However, in the protocol by Raimondo et al.,[5] primers were used for four conserved regions of the viral genome. It is possible to question whether the large number of primers used in protocol 1 could generate nonspecific binding, resulting in false-positive results. Thus, to increase specificity, we considered actual cases of OBI in which HBV DNA was detected using both protocols.

The low prevalence of OBI in this study limited the comparative analysis of the characteristics of patients with and without OBI. Another limitation of the study was the inability to perform gene sequencing of the positive samples, which occurred due to a technical issue because the tissue samples from several patients were too small. Our results may also be biased when considering the universe of patients with chronic liver disease, as we selected only cases that underwent biopsy.

Of the phases of HBV infection, the least understood phase is OBI.[42] Several aspects need further investigation, such as the possible influence on the course of associated liver disease, the role of genetic polymorphisms in its development, and the diagnostic value of viral markers. In this context, it was observed that genetic variants of HLA-DP and the presence of anti-HBc may be important predictors of OBI.[43] On the other hand, Daef et al.[44] demonstrated that total anti-HBc is an ineffective marker of OBI. The association with HCV infection has been studied by different authors, but the results have been controversial. In some studies, the absence of an interaction between OBI and chronic hepatitis C was observed,[45,46] while others have identified that some mutations in HBV may favor its occult phenotype in chronic HCV carriers.[47]

OBI has been suggested to be associated with hepatocarcinogenesis. An increasing number of prospective studies and meta-analyses have demonstrated a higher incidence of HCC in patients with HCV infection and OBI, as well as more advanced tumor histological grades and earlier age of HCC presentation compared to patients without OBI. The suggested pathogenic mechanisms of OBI-related HCC include the influence of HBV DNA integration on the hepatocyte cell cycle, production of pro-oncogenic proteins, and persistent low-grade necroinflammation.[48,49]

CONCLUSION

This study showed a difference in the results of the two protocols, reinforcing the need for better standardization of the method for diagnosing OBI. Additional studies with larger sample sizes are needed to standardize diagnostic methods for OBI. Furthermore, it is important to conduct prospective studies to clarify the actual impact of OBI on the progression of chronic hepatopathies of different etiologies and the role of occult HBV in hepatocarcinogenesis.

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Effectiveness of a SNAPPS in psychiatric residents assessed using objective structured teaching encounters: a case-control study

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ABSTRACT

BACKGROUND: Residents play the role of teachers in almost one-quarter of their activities in residency programs.
OBJECTIVE: To evaluate whether a 45-minute class using summarize, narrow, analyze, probe, plan, and select (SNAPPS) could improve psychiatry residents' case discussion skills in diverse practical learning settings.
DESIGN AND SETTING: This case-control, randomized, blinded study was conducted in a psychiatry hospital at Fortaleza-Ceará.
METHODS: Using "resident as teacher" (RaT), objective structured teaching encounters (OSTEs), and SNAPPS, we conducted a study with 26 psychiatry residents. We analyzed video footage of psychiatric cases in three settings: outpatient, nursing, and emergency. An intervention was held two months later with the residents, who were then assigned to two groups: group A (lecture on SNAPPS) and group B (lecture on a topics in psychiatry). Shortly after the lectures, they were video recorded while discussing the same cases. Three blinded examiners analyzed the videos using an instrument based on the Stanford Faculty Development Program (SFDP-26).
RESULTS: We found high internal consistency among external examiners and an interaction effect, group effect, and moment effect ($P < 0.05$). The residents who received the SNAPPS lecture scored significantly higher than their counterparts who received a traditional case presentation.
CONCLUSION: This study indicates the efficacy of SNAPPS over traditional case presentation in all three settings as assessed by OSTEs and supports its implementation to improve the teaching of clinical reasoning.

INTRODUCTION

Residents play the dual role of learners and teachers for up to one-quarter of their time in residency programs.[1] Nevertheless, formal training in teaching-learning techniques developed for residents, or at the least specific recommendations and regulations for those activities are scant. In addition, teaching skills are difficult to correlate directly with clinical diagnostic and recognized competences. Thus, residents are likely to adopt ineffective teaching strategies.[2]

In the United States, more than 50% of residency programs have already implemented "Resident as Teacher" (RaT) training.[2] More recently, a study of program directors in the United States showed that RaT has been implemented in 80% of residency programs, representing a 26.34-point increase from 2001 to 2016.[3] Often, residency programs use a variety of methodologies to teach RaT techniques, including workshops, lectures, seminars, and teaching retreats. These programs have been shown to improve residents' teaching skills[4] and satisfaction with programs, promoting positive changes in their attitudes toward teaching. A systematic review conducted in 2008 analyzed 13 studies carried out with residents of programs in different fields, demonstrating an improvement in residents' teaching skills in the most diverse techniques employed.[5] More recently, a review of RaT in general surgery found that changes in attitude toward teaching was the most frequent outcome of assessment,[6] and a resident-as-teacher consensus guideline has been developed to provide a road map for program directors and institutions and to enhance the culture of teaching and learning.[7]

After the implementation of an RaT curriculum, it might be beneficial to use objective structured teaching encounters (OSTEs) in conjunction with these pedagogical strategies to allow the standardized assessment of skills over time.[8] OSTEs have proven to be an effective method to assess both residents and medical students,[9] has and have been used to assess and improve the teaching performance of faculty members.[10]

There are benefits of RaT programs for different participants: Residents, by acquiring practical knowledge and skills, are more likely to engage in teaching and learning activities. The students will be able to perceive the educational potential in their institution. The institution may build multi-level capacities in education, alleviating the increasing demands on senior faculty members.[2]

Although it is not included in the three most popular RaT models (namely, the One-Minute Preceptor, the clinical teaching program of the Stanford Faculty Development Center, and Irby's domains), role-modeling is the most frequently identified method for residents engaged in teaching.[11]

An example of a good technique used in medical education for clinical case presentation is the summarize, narrow, analyze, probe, plan, and select (SNAPPS) technique.[12] Initially proposed by Wolpaw,[13] this technique is based on constructive learning wherein students as active participants are able to develop new knowledge and teachers are partners in the learning process.[14] The use of this technique in the teaching-learning process might help students effectively and efficiently verbalize higher-level thinking skills and improve their technical skills.[12] In addition, SNAPPS can improve clinical reasoning in the diagnosis and treatment of common diseases[14] and has the theoretical advantage of placing greater emphasis on self-directed learning.[15] There have been no previous studies using modified models of SNAPPS for teaching preceptors.

OBJECTIVE

This paper aims to evaluate whether a 45-minute class using the SNAPPS technique can improve psychiatry residents' case discussion skills in diverse practical learning settings.

METHODS

This study was conducted in a psychiatric hospital in the city of Fortaleza, Ceará, Brazil, from March 2017 to December 2018. The study included all 27 residents of the psychiatry training program and 15 interns (i.e., medical students from the last two of the six years of medical school in Brazil).

Before data collection, approval from the Research Ethics Board was obtained on 09/01/2017 (No. 2.255.068), and all the participants provided written informed consent.

The study proceeded as follows: Three psychiatric cases were simulated in three different settings: an outpatient clinic, a ward, and the emergency department. The researcher video recorded the 27 residents in the three settings. First, each resident was told to simulate a clinical case supervision with an intern. All the interns received basic instruction lasting around 20 minutes on how to discuss the clinical cases previously prepared by the researchers. They had access to the details of each case on a sheet to better guide the residents as the discussion deepened. Second, they were asked to discuss the cases for up to six minutes. Finally, the cases were provided to the interns to be used when they play the learner-actor role.

Two months after the first phase of the study (pre-intervention), the residents were invited to attend a didactic activity. The residents were randomly assigned to two groups of 11 residents, with each group including equal numbers of first-year (R1), second-year (R2), and third-year residents (R3) (**Figure 1**). The intervention group (group A) attended a 45-minute lecture on the teaching technique using SNAPPS. Videos of simulated cases were shown, and the residents were taught how to give effective feedback. Contrariwise, the control group (group B) attended a 45-minute lecture on a general topic in the field of psychiatry. Note that unlike the traditional method, only teachers (in this case, the residents) were taught this technique. The interns did not attend the class.

After the lectures, the groups of residents were taken to different places in the hospital and did not meet each other. Thereafter, the residents had another six minutes of discussion in the same three simulated cases and were video recorded again (**Figure 1**). All the pre- and post-intervention videos were coded, grouped, and recorded. Only 1 out of 144 video files was found to be corrupted

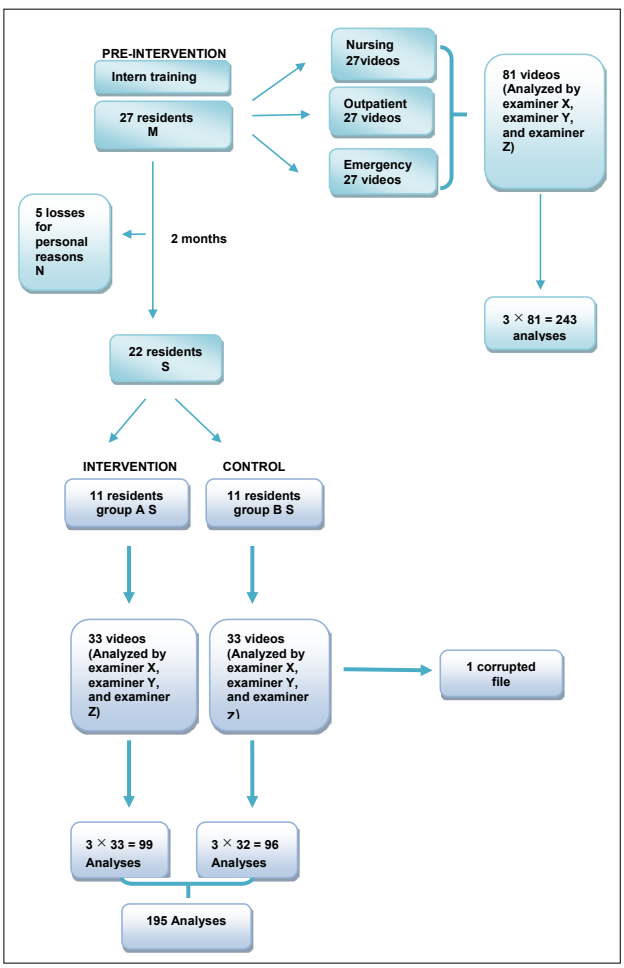

Figure 1. Study design.

and, therefore, could not be evaluated. The videos were analyzed by three blinded assessors who did not have access to the decoding of the study phases. These invited assessors are clinician-educators in another medical school with extensive teaching experience.

After the intervention day, group B residents were invited to attend the 45-minute lecture on the SNAPPS teaching technique. Only one resident did not attend the lecture, for personal reasons.

Each video was assessed three times—outpatient, emergency, and ward—by the three blinded assessors using the Stanford Faculty Development Program (SFDP)-26 tool (validated in Brazil by Fakhouri Filho SA).[16]

A sociodemographic questionnaire was used to collect and assess the residents' gender, year of residency, previous teaching experience, medical school methodology (traditional or active learning), perceived importance of the resident's teaching role, and the approximate amount of time spent teaching during the residency program.

The following analyses were performed: 1) Cronbach's alpha was calculated between the results gathered from the assessors in each stage (pre- and post-intervention); 2) the generalized estimating equation (GEE) approach with gamma distribution and unstructured correlation structure was used to compare the scores in the outpatient, ward, and emergency settings; 3) a chi-squared test or Fisher's exact test (F) was used, as appropriate, for the comparison of demographic characteristics between the two groups of residents. Finally, the Mann–Whitney U test was used for the comparison of variables when there were two groups and the Kruskal–Wallis test where there were more than two. All the tests were performed with a significance level of 5%.

RESULTS

Internal consistency between external examiners was high in all three settings (outpatient, ward, and emergency), with values of Cronbach's alpha above 0.70. The values obtained in the pre-intervention and post-intervention settings were 0.850 and 0.910 (outpatient), 0.691 and 0.934 (emergency), and 0.701 and 0.885 (nursing), respectively.

An interaction ($P < 0.001$) in the three settings was observed when comparing the overall score between Group A and Group B. In the outpatient setting, the overall scores ranged from 2.30 ± 0.77 to 6.00 ± 6.76 in Group A and 2.85 ± 0.82 to 2.85 ± 0.78 in Group B. In the emergency setting, they ranged from 2.18 ± 0.82 to 5.06 ± 1.14 in Group A and 2.45 ± 0.85 to 2.36 ± 0.57 in Group B. In the ward setting, the scores ranged from 2.12 ± 0.82 to 5.45 ± 0.67 in Group A and 1.79 ± 0.82 to 2.40 ± 0.81 in Group B.

The analysis of each item separately revealed that some items differed significantly in the outpatient setting (**Table 1**).

The items that differed significantly in the emergency setting are given in **Table 2**.

The items that differed significantly in the ward setting are given in **Table 3**.

Comparison of the associations between sociodemographic variables (gender, year of residency, previous teaching experience, time spent teaching, teaching role perceived importance, and medical training methodology) between the two groups—intervention (A) and control (B)—revealed no statistically significant differences ($P > 0.05$). Most participants (81.8%) were female.

Of the 432 recorded videos, only 1 file was corrupted (Group B in the post-intervention phase in the nursing setting). This loss was discrete and highlighted the statistical data of our study.

DISCUSSION

In a training program of only 45 minutes, followed by practice, SNAPPS served to consistently improve residents teaching skills. Many studies have also specifically tested and proven the effectiveness of this method in RaT programs.[12,17–22] Despite their small samples, the results of other studies in psychiatry match the findings of this study, as they demonstrated significant improvements in skills and attitudes.[23–25]

Table 1. Mean scores in each item in the outpatient setting

	Group A pre	Group A post	Group B pre	Group B post	Interaction effect	Moment effect	Group effect
Teaching environment							
Wakened students' interest in the topic.	1.24 ± 0.70	4.06 ± 0.71	1.58 ± 0.53	2.18 ± 1.46	P = 0.005	----	----
Encouraged students to actively participate in the discussion.	1.61 ± 1.11	4.85 ± 0.17	2.03 ± 1.52	2.45 ± 1.51	P = 0.008	----	----
Promotion of understanding and retention							
Assessed students' level of previous knowledge.	1.21 ± 0.48	3.91 ± 0.91	1.45 ± 1.01	2.18 ± 1.44	P = 0.012	----	-----
Promotion of self-directed learning							
Explicitly encouraged further study.	1.00 ± 0.00	4.24 ± 0.56	1.21 ± 0.60	1.21 ± 0.40	P < 0.001	----	----
Politely encouraged students to read while not in the institution.	1.00 ± 0.00	4.42 ± 0.52	1.12 ± 0.31	1.21 ± 0.40	P < 0.001	----	----
Made sure the students understood what was being taught.	1.12 ± 0.31	1.82 ± 0.87	1.03 ± 0.10	1.09 ± 0.30	P = 0.018	----	----

RaT is an easy-to-implement and inexpensive model. Furthermore, unlike traditional methods, our study modified the technique by teaching the preceptors, i.e., the residents. To the best of our knowledge, there are no similar published studies. This is the first study to use a modified model of SNAPPS.

The intervention lasted approximately 45 minutes, which is similar to that in the original SNAPPS study by Wolpaw and other studies,[12,13] which prevented the activity from becoming tiresome, thereby reducing participant withdrawal rates as video recordings took place in different shifts. No particular mode or duration of RaT programs can be considered better than others. The programs may include simple lectures, teaching retreats lasting several days, didactic classes, and even online modules.[3,4]

Similar to the study by Connor, the SNAPPS technique was also evaluated shortly after the lecture.[20] As in other studies,[26] the residents were independently assessed by three blinded assessors. Reliability was guaranteed by the standardization of the assessment, which allowed the external examiners to assess the residents with high internal consistency.

The SNAPPS technique had a positive impact on the residents. It improved their skills in managing a case discussion session with interns. The individual items specifically related to awakening the interest of interns in the topic, encouraging their active participation, and assessing their level of previous knowledge were found to be significantly different between Group A and Group B. These items refer to primordial skills taught in the SNAPPS lecture that were properly learned and put into practice by the residents.

Items such as listening carefully to the students (interns), showing respect, not ridiculing them, and answering their questions clearly and politely did not present any interaction effects in any of the three settings. Those attitudes are probably already part of the residents' behavior in psychiatry and may have been acquired throughout life or properly modeled during undergraduate studies.

The sociodemographic variables did not differ significantly between Group A and Group B. Third-year residents have similar teaching skills as first-year residents. Our findings suggest that, without proper training, the residents did not necessarily improve their teaching skills regardless of their year of residency. They need specific training to acquire such skills. Similar results were reported by Sawanyawisuth et al.,[18] in which the differences found in the SNAPPS group resulted due to maturation over time, as fifth-year students performed better than sixth-year students on basic attributes, having more diagnoses in their differential, more justified diagnoses, and initiating more diagnosis.[18]

When asked about the amount of time spent teaching in medical residency, most residents (25 out of 27) reported spending 25% of their time teaching interns or fellow residents. Isenberg-Grzeda et al. [27] found that 86% of respondents reported that teaching is a common activity during a typical week. In another study, 50% of the residents reported teaching daily, 40% reported teaching only a few times a week, and 10% reported teaching a few times a month.[28]

With regard to the importance of residents as teachers, only 1 of the 27 participants did not find this role important. While it was not possible to attest this statistically, it is clear that the subject is of great importance to residents and to interns, who usually

Table 2. Mean scores in each item in the emergency setting

	Group A pre	Group A post	Group B pre	Group B post	Interaction effect	Moment effect	Group effect
Promotion of understanding and retention							
Assessed students' level of previous knowledge	1.85 ± 1.49	4.21 ± 0.75	1.70 ± 1.39	1.76 ± 0.84	P = 0.029	----	----
Management of the session							
Efficiently used the time for teaching	2.42 ± 1.40	4.06 ± 0.59	2.21 ± 1.20	2.06 ± 0.84	P = 0.024	----	----

Table 3. Mean scores in each item in the ward setting

	Group A pre	Group A post	Group B pre	Group B post	Interaction effect	Moment effect	Group effect
Teaching environment							
Awakened students' interest in the topic.	1.73 ± 1.27	4.06 ± 0.96	1.70 ± 1.15	2.00 ± 1.20	P = 0.046	----	----
Encouraged students to actively participate in the discussion.	1.94 ± 1.36	4.48 ± 0.77	1.76 ± 1.15	1.90 ± 1.66	P = 0.048	----	----
Promotion of self-directed learning							
Explicitly encouraged further study.	1.33 ± 0.77	4.33 ± 0.80	1.30 ± 1.01	1.70 ± 1.16	P = 0.009	----	----
Politely encouraged students to read while not in the institution.	1.33 ± 0.77	4.33 ± 0.80	1.30 ± 1.01	1.70 ± 1.16	P = 0.009	----	----
Motivated students to study own their own.	1.21 ± 0.48	3.88 ± 1.10	1.30 ± 1.01	1.50 ± 0.97	P = 0.002	----	----
Communicating goals							
Presented the expected level of competence.	1.21 ± 0.40	2.97 ± 0.96	1.09 ± 0.30	1.27 ± 0.49	P < 0.001	----	----

start learning from the residents shortly before starting residency. Similar data have been found in a study that reported that most participants (87%) found teaching to be pleasant or rewarding, 79% wished to continue teaching after residency, and 72% believed that RaT programs should be mandatory.[27] These findings are also supported by a study of psychiatry residents that reported a score of 4.53 out of 5 for the item "I think teaching medical students is an important role of residents."[29] The residents who had experienced active teaching methodologies during their undergraduate studies were expected to present better scores than those who had learned from traditional teaching methods. However, the scores were practically the same in the three settings, and there were no statistically significant differences.

This is the first study to use the SNAPPS teaching technique in Brazil. It tested the technique only on teachers (residents) and found statistically significant results in three different settings; moreover, it found the residents' interest and willingness to participate to be quite significant.

Although there were many assessments of the residents due to the analysis of three settings by three examiners, the number of residents who participated in this study was relatively small and were drawn from only one medical specialty, thus impairing the generalizability of the results. Furthermore, we did not reassess the residents' performance a few months after the intervention, which would be highly useful for evaluating the retention and effectiveness of the method applied. Further, the interns' perceptions as actors were not assessed nor those of the residents of their role as clinician-educators.

Medical education has undergone an important and substantial evolution since last century. Frenk identified and described three phases of this evolution, as shown in the **Chart 1**.[30]

Current evidence suggests that some active learning methodologies show a significant improvement in student learning over traditional teaching methods. Meta-analyses of flipped classrooms,[31] team-based learning (TBL),[32] simulation-based medical education (SBME)[33] with deliberate practice (DP), and problem-based learning (PBL)[34] seem to be more effective in improving students' knowledge, attitudes, and skills. There has been no meta-analysis comparing RAT or SNAPPS to traditional training methods.

Recently, we have achieved an improvement of medical education by the implementation of new types of learning such as e-learning (since the emergence of the Internet) and blended learning that show significantly better knowledge outcomes than those for traditional learning, as shown in the meta-analysis by Vallée in 2020.[35] They can transcend the previous restrictions of space and time as well as improve collaborative and individualized learning effectiveness.[35]

As a promising tool for medical learning in the future, Free Open Access Med(ical edu)cation, FOAMed is a dynamic collection of articles, apps, and audio and video materials produced to support clinicians' lifelong learning. It began in emergency medicine (EM) but has spread to critical care (CC), pediatrics, and toxicology to become a large repository of Internet-based resources provided by a large social media community as a means of delivering high-quality medical education to anyone with a device.[36]

Some advantages of PBL were described in the study by Jones in 2006, and can illustrate the benefits of many other active learning methodologies: facilitating trainees in becoming responsible for their own learning, making curriculum content relevant by building learning around clinical, community, or scientific problems, and increasing the motivation of trainees to learn by focusing the learning on "real-life" scenarios.[34] In practical learning settings, preceptors' view of the traditional presentation identify generic skills such as history-taking and presentation skills. Lack of time and objective feedback is also recognized as a deficit of traditional clinical training.[37]

Disadvantages of new learning methods can also be pointed out: The knowledge acquired through PBL is less organized than that acquired through traditional learning; more time is required of trainees to fully engage in new learning methods; the replacement of the traditional teacher role by the facilitator may make it difficult for trainees to emulate good teachers as role models; and significant costs, resources, and time are required to train effective facilitators.[34]

CONCLUSION

Generally, the SNAPPS group had significantly higher scores than the traditional case presentation group in the outpatient, ward, and emergency settings, as assessed by OSTE using SFDP-26. There were no correlations of the results with sociodemographic variables, such as gender, year of residency, previous experience in teaching, or undergraduate medical school methodology.

Chart 1. Medical education evolution

A global review identified the following three phases in the evolution of medical education: (1) A formative phase characterized by didactic teaching, phenomenological and memory learning, and a focus on the scientific basis for medicine during the first 70 years of the 20th century; (2) A performative phase characterized by problem-based instructional innovations focused on concepts in biology as applied to medicine, data retrieval, and integration of knowledge during the latter decades of the 20th century; (3) A transformative phase starting in the 21st century to improve the performance of health systems by adapting core professional competencies to specific contexts while drawing on global knowledge.[30]

Adapted from Frenk et al.[30]

Despite being targeted only at residents who performed teaching functions, the lecture on the SNAPPS technique has proven effective and can be useful in medical teaching for the improvement of skill acquisition. As in peer learning, where the use of two-way processes and reciprocal learning activities is important, SNAPPS involves the sharing of knowledge, ideas, and experience among participants for mutual learning in undergraduate medical schools. This type of activity can have an impact on medical practice in Brazil and other countries, where studies on RaT and OSTE are still emerging. If implemented systematically as part of an RaT program, the residency will benefit from an approach that can improve the teaching of clinical reasoning. Further studies using SNAPPS and other case presentation techniques are needed to consolidate such active teaching methodologies. Pedagogical surveys to identify residents' opinions about the method are also important.

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Associated factors of professional burnout among faculty members of graduate *stricto sensu* programs in language teaching and linguistics: a cross-sectional study

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ABSTRACT

BACKGROUND: The burnout syndrome can be avoided and/or have its signs and symptoms reduced by knowing the five associated factors that help identify the health and working conditions of the professors of graduate programs.

OBJECTIVE: To analyze the factors associated with burnout among faculty members of graduate *stricto sensu* programs.

DESIGN AND SETTING: A cross-sectional study was conducted among 585 faculty members of Graduate Programs in Language Teaching and Linguistics in Brazil.

METHODS: Data were collected through an online questionnaire. The outcomes were the dimensions of burnout and its related factors identified through multiple templates of logistic regression.

RESULTS: Faculty members with increased chances of emotional exhaustion and depersonalization mentioned the use of medications due to labor activities. The negative influence of pace and intensity of work, thoughts about quitting the program, and having to produce three or more scientific articles were associated with higher chances of emotional exhaustion, while having to achieve nine hours per week in undergraduate programs was related to reduced personal accomplishment. Having a conjugal relationship, satisfaction with health and work, post-doctoral degree, autonomy, and good interpersonal relationships with faculty members of the program reduced the chances of emotional exhaustion. Reduced chances of depersonalization occurred among those who were satisfied with work, had good interpersonal relationships with advisees and faculty members, and received productivity funding.

CONCLUSION: Sociodemographic, health, and occupational factors related to the dimensions of burnout were identified.

INTRODUCTION

Work, defined as an essential activity and a constituent of human identity, as well as stressful conditions inherent to it, have been associated with imbalances and psychosocial phenomena such as the development of burnout syndrome as an aftermath of transformations, demands, and intensification of the labor process in several professional categories and organizations.[1-3]

Burnout syndrome is defined as a phenomenon characterized by a set of signals and symptoms arising from a chronic reaction to interpersonal emotional stressors at work that results in exhaustion or depletion of the worker.[4,5]

The syndrome is a result of the interconnectedness of aspects from the work environment and individual characteristics, in which the phenomenon is pointed out as an issue that affects mainly workers, who have direct contact with other people as part of their job, such as faculty members.[4]

Burnout is a singular occupational phenomenon affecting the worker's health since it refers specifically to the occupational context and is not used to describe experiences in other areas of life, according to the definition in the new International Classification of Diseases (ICD-11) on January 1, 2022.[6]

Burnout affects workers as their emotional resources are reduced, showing signals and symptoms related to emotional exhaustion, depersonalization, and reduced personal accomplishment.[4,5]

Emotional exhaustion is a response characterized by the worker's impoverishment of physical and emotional resources and generally includes the first signals and symptoms related to burnout, such as chronic fatigue sensations and emotional distress. When it appears, workers have minimal physical and emotional resources and m ay feel insufficiently energetic to face new problems or demands related to work.[5]

Depersonalization represents the imbalances related to the interpersonal context of burnout and, when present, workers mention insensibility in their interpersonal relations and excessive disinterest in several aspects related to work. On the other hand, reduced levels of personal accomplishment refer to self-evaluation of burnout once the phenomenon includes several cognitive-attitudinal variables, such as reduced personal accomplishment at work.[5]

Burnout also results in high costs to the organizations and employers. Thus, it is conceivable that there is a need to comprehend the complexity between the 'self' of the worker and the context of work, as greater the difference or incompatibility between worker-work contexts, the greater the probability of emotional exhaustion or depletion.[5]

In teaching, factors related to the work environment and conditions, and the organization of work are considered possible agents of health and psychological imbalances of faculty members who work in undergraduate[3,7-8] and graduate programs.[9]

Postgraduate professors' work-related processes and conditions can result in their dissatisfaction and health problems,[9] since the activities performed have their own complexity due to the specificities of the work process and high workload.[10]

However, there are no studies on burnout and its associated factors among faculty members of *stricto sensu* graduate programs in Language Teaching and Linguistics in Brazil, characterizing the uniqueness of this investigation.

Once the phenomenon studied is avoided and/or its signals and symptoms are reduced,[5] knowing the factors associated with burnout can enable the identification of the work conditions of institutions in which faculty members of graduate programs work, their health conditions, and support can be provided for the development of strategies and assertive interventions within the organizational context.

This study addresses the following research question: "What are the associated factors related to burnout dimensions among faculty members of graduate *stricto sensu* programs in Language Teaching and Linguistics in Brazil?". This study hypothesized that burnout dimensions were associated with sociodemographic, health, occupational, and lifestyle variables.

OBJECTIVE

The objective of this research was to analyze the dimensions of burnout and explore the factors associated with it among faculty members of graduate *stricto sensu* programs in language teaching and linguistics in Brazil.

METHODS

Design of the study, description of the sample and places

A cross-sectional study was conducted with 585 faculty members of Graduate Programs in Language Teaching and Linguistics (GPLTL).

The inclusion criteria was permanent faculty members registered on the GPLTL in 2018. Faculty members who were on any sort of leave during 2018 were excluded from this study.

Measurements

To locate the faculty members, a manual search was conducted between January and April 2019 on *Sucupira* Platform.[11] To collect the contact information of each faculty member, the information available on each program's website and a list of e-mails received from the program coordinators were used.

A total of 2,270 professors belonging to GPLTL were identified. To define the study sample, the formula $n \geq 50+(8 \times m)$ (m: number of independent variables) was used to test multiple associations.[12] Thus, the minimum number of 370 participants ($50+(8 \times 40)$) was obtained based on 38 sociodemographic, health, occupational, and lifestyle variables, and the dimensions of burnout.

Procedures

Data were obtained between February and August 2019 on a virtual platform called Mubble. This platform had a semi-structured questionnaire[13] that included items of sociodemographic, health, lifestyle, and occupational variables, especially the typical elements of a faculty member's working process. All questions were mandatory to answer to minimize possible losses or failures during data collection.

The information collected was imported into a database enabling statistical analysis of the following variables: marital status (yes/no), health satisfaction (yes/no), usage of medication due to labor activities (yes/no), having a post-doctoral degree (yes/no), time working on undergraduate courses (in years), autonomy at work (yes/no), work satisfaction (yes/no), negative influence of the pace and intensity of work on life (yes/no), thoughts about quitting the GPLTL (no or sometimes/frequently), number of research articles being developed (≤ 2 or ≥ 3), relationship with faculty members from the current GPLTL (bad/regular or excellent/good), having productivity funding (yes/no), working hours in undergraduate teaching (in hours per week), number of books and/or journal chapters published during the last year (≤ 2 or ≥ 3), and the relationship with the advisees (bad/regular or excellent/good).

Burnout syndrome was evaluated using the *Maslach Burnout Inventory*™ - *Human Services Survey* (MBI™-HSS), composed of

22 items distributed in three dimensions: emotional exhaustion (nine items), depersonalization (five items), and reduced personal accomplishment (eight items). The responses were measured on a seven-point Likert scale, ranging from 0 to 6.[14]

To analyze the responses, the three dimensions must be analyzed and considered equally as a construct, with the objective of identifying the potential of development of the syndrome and not as a diagnosis of it.[14] Therefore, when an individual showed higher scores of emotional exhaustion and depersonalization and lower scores on professional accomplishment they might have higher chances of developing the burnout syndrome.[4]

Statistical analyses

SPSS version 20.0 (IBM, Chicago, Illinois, United States) was used for the data analyses. The outcomes of this study were the dimensions of the MBI™-HSS and the associated factors identified through multiple logistic regression models. In this step, univariate analysis was used to verify the relationship between the dependent and independent variables (sociodemographic, health conditions, and occupational characteristics).

The *stepwise forward* method was used during the multiple model elaboration, in which the independent variables were inserted individually following the order of decreasing values of significance, established by existing research. The final models of regression showed variables with statistical significance of $P < 0.05$ according to Wald's test and adjusted for gender and age variables, considering that previous works indicated these aspects to be controlled,[15] as well as years of teaching experience at an undergraduate level and as a senior professor, once they are considered as possible misleading factors in the data analysis.

The variation explained in terms of outcomes was verified using the Nagelkerke R-Squared test. The results were presented as raw odds ratios (OR) and adjusted with 95% confidence intervals (CI).

Ethical considerations

The study followed the ethical standards, including an approval from the Research Ethics Committee under the legal opinion no. 2,347,839, CAAE:79006017.0.0000.5231. Dated: October 25, 2017.

RESULTS

This study included teachers from all regions of Brazil. Of the 585 participants, 396 (67.69%) were married. Regarding health satisfaction, 209 (35.73%) were not satisfied, and 278 (47.52%) mentioned the usage of medication due to symptoms they believed was related to their labor activity.

Regarding the educational qualification and teaching experience, 339 (57.95%) faculty members had a post-doctoral degree, 85 (14.58%) received productivity funding, 508 (86.84%) mentioned professional autonomy, 490 (83.76%) were satisfied with their work, and 467 (79.83%) were satisfied with their performance within the GPLTL. However, 345 (58.95%) participants mentioned that they had already thought about quitting activities related to the GPLTL.

Regarding interpersonal relationships, 106 (18.12%) reported not having a good relationship with their colleagues, and 392 (67.01%) believed that the pace and intensity of work negatively influenced their lives.

The participants who informed the usage of medications due to the effect of their labor activity, negative influence of pace and intensity of work in their personal life, thoughts on quitting GPLTL, and having three or more scientific articles being produced, showed increased chances of emotional exhaustion. Reduced chances of emotional exhaustion were shown by faculty members who were in a marital relationship, satisfied with their health, had a post-doctoral degree, autonomy, work satisfaction, and a good interpersonal relationship with their colleagues, as shown in **Table 1**.

Faculty members who mentioned the use of medications related to their labor activities showed an increased chance of high depersonalization. On the other hand, those who mentioned being satisfied with work, having good interpersonal relationships with advisees and other faculty members, and having productivity funding showed decreased chances of depersonalization (**Table 2**).

With respect to reduced professional accomplishment, **Table 3** shows that satisfaction with work and GPLTL, good relationships with advisees and faculty members, and presentation of more than three books and/or publication of journal chapters during the last year decreased the levels of reduced professional accomplishment. Faculty members with a workload of more than nine hours per week in undergraduate teaching demonstrated associations with higher chances of reduced professional accomplishment.

DISCUSSION

The profiling of the participants showed a predominance of faculty members with marital relationships, which was associated with reduced levels of emotional exhaustion. Although burnout is strongly identified and significantly associated with situational and occupational factors, identifying individual characteristics of the workers is also important and essential to comprehend the development of the syndrome.[4,16-19]

Regarding the dimensions and associated factors of burnout, it is evident in this study that faculty members who have mentioned the use of medications related to symptoms arising from their professional activities, negative influence from the pace and intensity of work on personal life, thoughts about quitting the program, and publication of three or more scientific articles, showed higher chances ($P < 0.05$) of emotional exhaustion.

Largely, the emotional exhaustion within faculty members comes from their responsibilities, duties, and tasks in which the workload is increased based on the need to guarantee quality

Table 1. Multiple model with factors associated with emotional exhaustion among faculty members of graduate *stricto sensu* programs in Language Teaching and Linguistics. Brazil, 2020

Multiple model	P value	Odds ratio[raw] (95% CI)	P value	Odds ratio [adjusted*] (95% CI)
Marital status (yes/no)	**0.011**	1 0.524 (0.319–0.861)	**0.013**	1 0.533 (0.325–0.877)
Health satisfaction (dissatisfied/ satisfied)	**< 0.001**	1 0.411 (0.256–0.660)	**< 0.001**	1 0.419 (0.261–0.675)
Usage of medication due to labor activities (yes/no)	**< 0.001**	1 2.189 (1.403–3.416)	**< 0.001**	1 2.278 (1.448–3.585)
Post-doctoral degree (yes/no)	**0.020**	1 0.584 (0.371–0.919)	**0.030**	1 0.598 (0.376–0.951)
Autonomy at work (yes/no)	**0.014**	1 0.519 (0.308–0.875)	**0.016**	1 0.526 (0.312–0.887)
Work satisfaction (yes/no)	**< 0.001**	1 0.365 (0.223–0.599)	**< 0.001**	1 0.363 (0.221–0.596)
Negative influence of the pace and intensity of work on life (yes/no)	**< 0.001**	1 9.416 (5.432–16.320)	**< 0.001**	1 8,406 (4.737–14.914)
Thoughts on quitting the GPLTL (no or sometimes/ frequently)	**0.002**	1 2.054 (1.297–3.252)	**0.003**	1 2.047 (1.284–3.264)
Research articles produced (≤ 2 x ≥ 3)	**< 0.001**	1 2.146 (1.371–3.361)	**< 0.001**	1 2.082 (1.326–3.269)
Relationship with most of the faculty members from the program (bad/regular or excellent/good)	**0.049**	1 0.671 (0.469–0.960)	**0.030**	1 0.672(0.469–0.963)

*Adjusted for gender, age, being a senior professor, and years of teaching experience at an undergraduate level; Nagelkerke R Square:0.553.
CI = confidence interval; GPLTL = Graduate Programs in Language Teaching and Linguistic.

Table 2. Multiple model with factors associated with depersonalization among faculty members of graduate *stricto sensu* programs in Languages and Linguistic. Brazil, 2020

Multiple model	P value	Odds ratio[raw] (95% CI)	P value	Odds ratio[adjusted*] (95% CI)
Usage of medication due to labor activities (yes/no)	**0.011**	1 2.033 (1.173–3.525)	**0.011**	1 2.066 (1.179–3.622)
Work satisfaction (yes/no)	**0.004**	1 0.425 (0.239–0.756)	**0.005**	1 0.434 (0.243–0.774)
Relationship with most of the advisees (bad/regular or excellent/good)	**< 0.001**	1 0.312 (0.184–0.530)	**< 0.001**	1 0.321 (0.189–0.547)
Receives productivity funding (yes/no)	**0.022**	1 0.312 (0.115–0.845)	0.052	1 0.365 (0.132–1.011)
Relationship with most of the faculty members from the program (bad/regular or excellent/good)	**< 0.001**	1 0.455 (0.304–0.679)	**< 0.001**	1 0.452 (0.302–0.675)

*Adjusted for gender, age, being a senior professor, and years of teaching experience at an undergraduate level; Nagelkerke R Square:0.296.
CI = confidence interval.

education during the training of new professionals.[20] It is also associated with the achievement and continuous participation in research, management, and interpersonal relations in the workplace. Emotional exhaustion results in lower capability and/or lower levels of internal resources of emotional intelligence and empathy, attitudes from cynicism, depersonalization, professional inefficiency, sleeplessness, and other health imbalances,[21] which may explain the factors identified.

Most of the time, faculty members endured unfavorable situations in their workplace due to individual and/or collective protections, avoiding becoming sick to keep working.[22] In the case of teaching practice in graduate programs, a study reflects upon the hypotheses that should be discussed regarding the work and health conditions of professors.[23] One of which is that the work of faculty members in graduate programs and the related activities such as tutoring, reporting, managing journals, examining committee, and attending seminars, when intensified, might harm their health.

The other hypotheses referred to the submission of work and productivity ethics as possible causes of becoming sick. Moreover, the social perspective of the incapacity of a faculty

Table 3. Multiple model with factors associated with reduced professional accomplishment among faculty members of graduate *stricto sensu* programs in Languages and Linguistic. Brazil, 2020

Multiple model	P value	Odds ratio[raw] (95% CI)	P value	Odds ratio[adjusted*] (95% CI)
Work satisfaction (yes/no)	**< 0.001**	1 0.337 (0.201–0.565)	**< 0.001**	1 0.341 (0.203–0.572)
Workload (hours) of teaching undergraduate courses (≤ 8 x ≥ 9)	**0.006**	1 1.872 (1.196–2.929)	**0.005**	1 1.907 (1.209–3.007)
Relationship with most of the advisees (bad/regular or excellent/good)	**0.007**	1 0.560 (0.366–0.855)	**0.008**	1 0.561 (0.366–0.861)
Satisfaction with the GPLTL (yes/no)	**< 0.001**	1 0.381 (0.222–0.657)	**< 0.001**	1 0.374 (0.215–0.648)
Number of published book and/or journal chapters during the last year (≤ 2 x ≥ 3)	**0.008**	1 0.507 (0.306–0.840)	**0.015**	1 0.533 (0.321–0.885)
Relationship with most of faculty members from the program (bad/regular or excellent/good)	**< 0.001**	1 0.577 (0.411–0.810)	**< 0.001**	1 0.566 (0.402–0.796)

*Adjusted for gender, age, being a senior professor, and years of teaching experience at an undergraduate level; Nagelkerke R Square:0.334. CI = confidence interval; GPLTL = Graduate Program in Language Teaching and Linguistics.

member to work while dealing with a personal problem was considered one of the factors that aggravated health,[23] physical, and mental conditions even more.

It is worth stressing that amongst the faculty members' activities recommended by Coordination of Improvement of Higher Education Personnel (Coordenação de Aperfeiçoamento de Pessoal de Nível Superior [CAPES]) to a graduate *stricto sensu* professor, there are those related to teaching within the program's courses, development of research and gathering resources from funding agencies, leadership of research groups, tutoring of doctoral and master's students, participation in in undergraduate thesis and scientific initiation of students from other degrees, elaboration of research papers, emission of reports to scientific journals as a reviewer, and working on administrative and undergraduate teaching activities, among other activities.[24]

A study conducted with 550 faculty members from northern Italy found that work overload and conflicts with colleagues and students were positively associated (P < 0.05) with emotional exhaustion. Beyond that, excessive demand from students was considered a stressful factor for faculty members.[25]

Regarding the negative influence of the pace and intensity of work on a person's life, the intense pacing of work was one of the factors that faculty members were exposed to, and when associated with a higher level of stress, showed variations in life quality and health imbalance.[26]

As an example of imbalances related to health, signals and symptoms related to occupational factors such as burnout stand out, and may affect the psycho-affective, musculoskeletal, nervous, digestive, dermatological, cardiovascular, and urogenital systems.[27] In faculty members, symptoms such as vocal fatigue due to extensive use of voice, hoarseness, dysphonia, and musculoskeletal pain are considered health issues resulting from their working process,[7] which may justify the use of medications due to professional activities. In this study, faculty members who mentioned the use of medications due to their professional activities also showed 2.066 times higher chances (P = 0.011) of depersonalization due to exhaustion and emotional overload.[5]

Regarding thoughts on quitting the GPLTL, a study[28] affirms that faculty members show increasing demotivation and emotional distress. It reveals a need for the organizations' managers to think about actions and strategies to identify the levels of exhaustion of their workers[5] similar to the ones identified in this study.

Aggravation of the professors' physical and mental health conditions is among the possible causes for them leaving the profession and/or related activities. Hence, it is essential to concentrate efforts on workers who are generally asymptomatic and healthy,[5] and improve their capacity of work.[7] From this aspect, adoption of burnout intervention programs may become strategies for preventing and/or reducing the signals and symptoms of the syndrome and also broadening their effects on GPLTL at the individual, collective, and organizational levels, with the potential to implement changes in the workplace.

Concerning the amount of research in preparation as a risk factor for emotional exhaustion, it stood out that Brazil, the country in which the study was developed, published more than half of all scientific production registered in 2018 in Latin America and showed productivity standards being constantly changed due to academic production goals related mainly to the graduate level.[23]

The criteria to evaluate a faculty member's work and production are mostly associated with a capitalist historical model that permeates college education institutions. Physical and emotional distress related to faculty members' production occurs from a numerical evaluation of non-measurable aspects, such as the quality of the accomplished activities.[29] Moreover, it is noted that occupational

factors such as quantitative demands, workload, number of working hours, low autonomy during the working process, and absence of social support are strongly related to distress and emotional exhaustion as a response to stress.[30-31]

In contrast, marital status, satisfaction with health and work, autonomy at work, and good relationships with most of the program's faculty members were protective factors ($P < 0.05$) against emotional exhaustion as found in this study.

It is noteworthy that the level of wellness of a worker influences the quality of work. In this sense, the significance received by workers based on their professional activities, beneficial interpersonal relations in the workplace, and social support are the factors that contribute to the acknowledgment of their identity, motivation, satisfaction, and professional efficiency,[29] minimizing the emotional exhaustion and risk of burnout, which potentializes engagement at work.[25]

Individual factors such as marital status, motivation, and self-efficacy should also be considered as improvers or protectors to stress and the phenomena that might be triggered by it, such as burnout. Thus, identifying positive occupational aspects, having satisfactory relationships with colleagues, having flexibility in terms of working hours, coexisting and sharing of experiences with students, having autonomy, and the being capable of expansion and construction of knowledge are factors that improve the feeling of pleasure and satisfaction at work[22] and minimize the signals and symptoms of burnout syndrome.

Being satisfied with the work, having a good relationship with the majority of the program's faculty members and advisees, and receiving productivity funding were associated with lower levels of depersonalization ($P < 0.05$). However, satisfaction in teaching varies according to the organization of work and its conditions.[7]

Faculty members who mentioned having more than nine hours of undergraduate teaching showed higher chances ($P < 0.05$) of development of reduced professional accomplishment. From this result, it is defended that high workload is among the main factors of negative influence in the professional life of faculty members, who work on GPLTL, by showing intense working hours within undergraduate courses, validating the note on how performing faculty members' activities most of the time is challenging. Furthermore, the faculty members' work does not constitute a workload of more than nine hours for demands and activities, which might result in reduced professional accomplishment.

The number of hours worked, especially the extra hours, is considered a factor that influences fatigue and injury risks, and interferes with motivation and self-evaluation of the professional accomplishment of workers. In cases of a reduced sense of professional accomplishment, and lack of institutional resources, social support and opportunities for professional development, it is possible to intensify perceptions about faculty members' identity and professional competence, productivity, working hours, and achievement.[5]

A study about work and health conditions among faculty members and high school teachers in Mendoza, Argentina, showed that faculty members with higher professional qualifications demonstrated higher levels of emotional and physical distress arising from demands and conditions they endured at work.[32] On the other hand, it was highlighted that being satisfied with work at the GPLTL, having good relationship with most of the faculty members, and having at least three books and/or journal chapters published within the last year were protective factors of reduced professional accomplishment.

Hence, it stands out that burnout has, as possible consequences, implications on: personal as well as interpersonal relationships between workers and colleagues, physical health, family issues, increasing usage of substances, and higher chances of depression and suicide ideation.[5]

Once present, besides the development of feelings and negative perceptions as personal anguish,[33] workers may mention dissatisfaction with their professional achievements,[34] physical exhaustion, sleeplessness, and adversities with family and interpersonal relationships.[16] It happens from the imbalance of one or more areas of professional life that are centrally associated with burnout such as, workload, control, rewards, community, justice, and values.[4]

It was observed that due to the uniqueness of the research conducted, studies that did not show differentiation between the levels of teaching in which faculty members worked constituted a limitation that could be the base of the discussion on the findings. In addition, the cross-sectional establishment of this study allowed the identification of associated factors, but not the causal nexus between these factors and the dimensions of higher levels of burnout. Moreover, any type of leave was also considered a limitation because knowing the health and work conditions of faculty members who were off work on medical leave could enhance this investigation. However, the advancement of knowledge through the study of this phenomenon in a group of workers has rarely been explored.

The results support the implementation of strategies at the organizational and individual levels to prevent and/or reduce symptoms related to the three burnout dimensions in different GPLTLs in Brazil.

CONCLUSION

Sociodemographic, health, and occupational factors related to the dimensions of burnout were identified in this study. The participants who informed the usage of medications due to their labor activity, negative influence of pace and intensity of work on their personal life, thoughts on quitting GPLTL, and having three or more scientific articles being produced, showed increased

chances of emotional exhaustion. Faculty members who mentioned the use of medications due to their labor activities showed an increased chance of high depersonalization. Faculty members with a workload of more than nine hours per week in undergraduate teaching demonstrated associations with higher chances of reduced professional accomplishment.

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Association between multimorbidity, intensive care unit admission, and death in patients with COVID-19 in Brazil: a cross-section study, 2020

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ABSTRACT

BACKGROUND: Multimorbidity can influence intensive care unit (ICU) admissions and deaths due to coronavirus disease (COVID-19).

OBJECTIVE: To analyze the association between multimorbidity, ICU admissions, and deaths due to COVID-19 in Brazil.

DESIGN AND SETTING: This cross-sectional study was conducted using data from patients with severe acute respiratory syndrome (SARS) due to COVID-19 recorded in the Influenza Epidemiological Surveillance Information System (SIVEP-Gripe) in 2020.

METHODS: Descriptive and stratified analyses of multimorbidity were performed based on sociodemographic, ventilatory support, and diagnostic variables. Poisson regression was used to estimate the prevalence ratios.

RESULTS: We identified 671,593 cases of SARS caused by COVID-19, of which 62.4% had at least one morbidity. Multimorbidity was associated with male sex, age 60–70 and ≥ 80 years, brown and black skin color, elementary education and high school, ventilatory support, and altered radiologic exams. Moreover, all regions of the country and altered computed tomography due to COVID-19 or other diseases were associated with death; only the northeast region and higher education were associated with ICU admission.

CONCLUSION: Our results showed an association between multimorbidity, ICU admission, and death in COVID-19 patients in Brazil.

INTRODUCTION

The coronavirus disease (COVID-19), caused by severe acute respiratory syndrome coronavirus-2 (SARS-CoV-2), rapidly spread worldwide, causing approximately 185 million cases and more than 4 million deaths between December 31, 2019, and June 30, 2021.[1]

In Brazil, COVID-19 cases that progress to severe acute respiratory syndrome (SARS), leading to hospitalizations and deaths, are monitored using clinical samples analyzed in reference laboratories. Case notification is mandatory, and records are stored in the Influenza Epidemiological Surveillance Information System (SIVEP-Gripe) from the SARS Surveillance network, initially implemented to monitor the influenza epidemic in 2000.[2]

Since the emergence of COVID-19, scientific literature has addressed the virological characteristics of SARS-Cov-2 and clinical complications arising from its infection in different populations. Although severity is high in older individuals and males, some studies have shown a relationship between COVID-19 and pre-existing morbidities[3,4] (e.g., cardiovascular diseases),[5-7] which are associated with increased intensive care unit (ICU) admissions and deaths.

Studies have also shown an association between morbidity and COVID-19; however, only a few have investigated multimorbidity (i.e., the co-occurrence of two or more chronic diseases for a specific period[8]) as a factor predisposing patients to ICU admission and death.[5,9]

Brazil had the highest number of COVID-19 cases in Latin America and currently it also has a high prevalence of diabetes, hypertension, and cardiovascular diseases.[5-7] Therefore, studies on association between multimorbidity, and ICU admissions and deaths due to COVID-19, are needed to provide basic knowledge for more complex studies establishing multicausality.[5-7] Therefore, this study aimed to analyze the association between multimorbidity, ICU admission, and death due to COVID-19 in Brazil.

METHODS

Study design and data source

This cross-sectional study was conducted using data from hospitalized patients with SARS, reported in SIVEP-Gripe (base population) between February 20 and December 31, 2020. SIVEP-Gripe is a Brazilian epidemiological surveillance information system implemented in 2000 to monitor the influenza virus. However, during the H1N1 pandemic (2009), SARS surveillance was implemented in the Brazilian hospital network[2] which became important for the notification of SARS cases during the COVID-19 pandemic.

We considered SARS in patients diagnosed with COVID-19 when they presented with flu-like syndrome followed by dyspnea, respiratory distress, persistent chest tightness, oxygen saturation < 95%, or cyanosis (i.e., bluish discoloration of lips or face).[2] Moreover, cases should have been be reported in the SIVEP-Gripe, according to the Epidemiological Surveillance Guidance: Public Health Emergency of National Concern due to COVID-19.[2] All patients with SARS due to COVID-19 were included (study population), except pregnant women, because pregnancy is a temporary condition that affects physiological functions independent of the disease[10] and should be studied separately. Pregnant women represented 0.97% of the patients with SARS due to COVID-19 and were identified using Question 11 of the notification form.[2]

The database of SARS cases from 2020 was obtained from the openDataSus platform of the Brazilian Ministry of Health on May 3, 2021 (https://opendatasus.saude.gov.br/). We also obtained a dictionary of variables and SARS notification form. Unspecified SARS cases accounted for 37.3% of the total records.

Variables

Outcome variables were ICU admission (yes or no), and death due to COVID-19, which were based on the progression of cases to "yes" (death due to COVID-19) or "no" (cure or death due to other causes) answers.

The independent variable, multimorbidity, was addressed using Question 36 ("Do you have risk factor or comorbidities?") on the SIVEP-Gripe notification form, which had 14 answer options (puerperium, Down syndrome, asthma, diabetes mellitus, obesity, immunodeficiency or immunosuppression, cardiovascular, hematological, neurological, liver, kidney, or lung disease, among others). However, the puerperium option was not evaluated. We also identified other morbidities in option "others". After identification and grouping, the following morbidities were included in the study: cancer, diabetes mellitus, dyslipidemias, obesity, systemic arterial hypertension, hypothyroidism, immunodeficiency or immunosuppression, and cerebrovascular, cardiac, hematologic, psychiatric, neurological, respiratory, liver, and kidney diseases. Multimorbidity was defined as a case (presence of at least two morbidities) and non-case (one morbidity). The number of morbidities (from one to five or more) was also included.

Independent variables were the following:

A – Sociodemographic variables:

- Sex (female or male);
- Age (days, months, years). Patients were categorized into age groups (20–39, 40–59, 60–79, and ≥ 80 years) based on the age distribution according to chronic morbidities from the National Health Survey 2019.
- Race or skin color (white or yellow, black, and brown). We excluded the indigenous category because it represented only 0.38% of the SARS cases due to COVID-19.
- Educational level, categorized as no education, complete elementary education (1st to 9th year), high school (1st to 3rd year), or higher education
- Brazilian regions (midwest, northeast, north, southeast, and south) were categorized based on data from the states of residence (including the Federal District) of patients.

B – Ventilatory support and diagnostic variables:

Invasive ventilatory support (yes, no)

- Positive radiologic examinations for COVID-19, collected in six categories (normal, infiltrated, consolidated, mixed, other, or not performed) and dichotomized into normal and altered (infiltrated, consolidated, mixed, and other).
- Computed tomography (CT) was categorized as negative or positive for COVID-19 or other diseases. We did not assess the "not performed" category for radiologic examinations and CT.

Statistical analysis

R software 4.0.4 (R Foundation, Vienna, Austria)[11] was used to analyze the data. The absolute and relative frequencies were calculated for each morbidity and outcome.

We calculated the number of morbidities and estimated the prevalence (P%), prevalence ratio (PR), and 95% confidence interval (95% CI) for ICU admission and death due to COVID-19.

The association between multimorbidity and outcomes was investigated using raw (number of morbidities) and stratified (multimorbidity) analyses, according to sociodemographic, ventilatory support, and diagnostic variables.

Hierarchical adjusted analysis, associated multimorbidity and sociodemographic, ventilatory support, and diagnostic variables, with ICU admission and death. Three blocks were considered: country region, sociodemographic, and support and diagnostic variables.

Poisson model with robust variance was used to estimate PR and 95% CI since outcomes of interest had prevalence of > 10%.[12] We selected variables using bivariate analysis between outcomes and region, sociodemographic, ventilatory support, and diagnosis variables; $P \leq 0.20$ was set as cutoff point for initial model selection.

The model was adjusted to retain variables with the lowest Akaike information criterion values and theoretical criteria. We then assessed the influential point (i.e., absolute value of standardized errors > 3) and collinearity between predictor variables (i.e., positive variables with values > 10). The Hosmer-Lemeshow test determined the goodness of fit of the final model, considering a good fit when $P \geq 0.05$.

Ethical aspects

This study used anonymous information from the public domain. Thus, authorization for data collection and approval by the research ethics committee were not required.

RESULTS

A total of 671,593 (59.7%) out of 1,121,601 hospitalized patients with SARS recorded in the SIVEP-Gripe in 2020 were diagnosed with COVID-19 (≥ 20 years and not pregnant). Of these, 216,055 patients were admitted to the ICU (38.1%) and 219,405 (35.7%) died. Moreover, 62.4% (419,425) of the patients with COVID-19 had at least one morbidity, and 97.0% with up to three morbidities were hospitalized due to SARS.

Table 1 shows the frequency distribution of morbidities according to ICU admission and mortality. The frequency of morbidities ranged from 34.1% (systemic arterial hypertension) to 47.1% (kidney diseases) in patients admitted to the ICU, and from 16.0% (hypothyroidism) to 62.8% (cancer) in those who died.

We observed that 29.5% (57,331) of the patients admitted to the ICU and 25.2% (57,359) of the patients who died had no morbidities. The prevalence and prevalence ratio of ICU admissions and deaths increased with an increase in number of morbidities (**Table 2**).

Table 1. Bivariate analysis between isolated morbidities, intensive care unit (ICU) admission, and deaths in patients hospitalized for COVID-19 in Brazil, 2020

Morbidities	ICU admissions			Deaths		
	n[a]	n[b]	%	n[a]	n[b]	%
Diabetes mellitus	29,798	10,498	35.2	31,841	11,257	35.4
Dyslipidemias	409	156	38.1	396	64	16.2
Systemic arterial hypertension	20,227	6,905	34.1	21,566	7,042	32.7
Hypothyroidism	1,839	637	34.6	1,808	290	16.0
Immunodeficiency	3,775	1,368	36.2	3,965	1,646	41.5
Obesity	11,696	5,202	44.5	11,871	2,959	24.9
Cancer	616	228	37.0	721	453	62.8
Stroke	249	108	43.4	276	164	59.4
Cardiac diseases	80,063	31,032	38.8	83,150	30,647	36.9
Hematologic diseases	881	307	34.8	903	359	39.8
Liver diseases	1,027	443	43.1	1,104	597	54.1
Neurological diseases	6,174	2,472	40.0	6,603	3,642	55.2
Mental health disorders	942	325	34.5	953	231	24.2
Kidney diseases	3,312	1,560	47.1	3,582	1,931	53.9
Respiratory diseases	9,035	3,103	34.3	9,283	2,755	29.7

[a]Total for occurrences of COVID-19; [b]COVID-19 cases that progressed to ICU admission or death.

Table 2. Bivariate analysis between number of morbidities, intensive care unit (ICU) admission, and deaths in patients hospitalized for COVID-19 in Brazil, 2020

Number of morbidities	ICU admissions		
	n[a]	n[b] (P%)	PR (95% CI)
1	170,043	64,344 (37.8)	1.00
2	130,825	57,419 (43.9)	1.16 (1.15; 1.17)
3	53,215	26,706 (50.2)	1.33 (1.31; 1.34)
4	14,940	8,035 (53.8)	1.42 (1.39; 1.45)
5 or more	3,864	2,220 (57.4)	1.52 (1.47; 1.57)
	Deaths		
	n[a]	n[b] (P%)	PR (95% CI)
1	178,022	64,037 (36.0)	1.00
2	135,662	59,778 (43.9)	1.22 (1.21; 1.23)
3	54,287	27,513 (50.7)	1.41 (1.39; 1.42)
4	15,110	8,539 (56.7)	1.57 (1.54; 1.59)
5 or more	3,917	2,379 (60.7)	1.68 (1.63; 1.74)

[a]Total for occurrences of COVID-19; [b]COVID-19 cases that progressed to ICU admission or death.
P% = prevalence; PR = prevalence ratio; 95% CI = 95% confidence interval.

Stratified analysis indicated a higher prevalence of ICU admissions and deaths in patients with multimorbidity at all types of sociodemographic variables (**Table 3**).

The prevalence of ICU admission (48.6%) and death (49.0%) were high in males with multimorbidity. Moreover, patients with multimorbidity aged 60–79 years and ≥ 80 years had 48.0% and 48.5% prevalence of ICU admission, respectively. Patients aged ≥ 80 years also had a high mortality rate (64.2%).

The prevalence of ICU admission was higher in patients with multimorbidity, with higher educational levels (49.7%) than in those with lower educational levels (40.1%). However, deaths were more frequent in patients with a lower educational level (60.8%)

Table 3. Stratified analysis between multimorbidity, intensive care unit (ICU) admission, and death in patients hospitalized due to COVID-19 according to sociodemographic characteristics in Brazil, 2020

Variable	MMB	ICU admission			Deaths		
		n[a]	P%	PR (95% CI)	n[a]	P%	PR (95% CI)
Sex							
Female	No	26,070	35.5	1.00	26,420	34.2	1.00
	Yes	43,319	44.3	1.25 (1.23; 1.26)	45,138	44.7	1.30 (1.29; 1.32)
Male	No	38,268	39.6	1.00	37,606	37.3	1.00
	Yes	51,056	48.6	1.23 (1.21; 1.24)	52,860	49.0	1.31 (1.30; 1.33)
Age (years)							
20–39	No	5,516	33.5	1.00	2,828	16.7	1.00
	Yes	3,736	41.8	1.25 (1.20; 1.29)	2,405	26.7	1.60 (1.52; 1.68)
40–59	No	18,345	33.6	1.00	12,089	21.5	1.00
	Yes	21,882	42.9	1.28 (1.26; 1.30)	16,776	32.4	1.50 (1.47; 1.53)
60–79	No	28,596	40.2	1.00	30,664	41.1	1.00
	Yes	49,433	48.0	1.19 (1.18; 1.21)	51,961	48.9	1.19 (1.17; 1.20)
≥ 80	No	11,887	42.7	1.00	18,456	61.0	1.00
	Yes	19,329	48.5	1.14 (1.12; 1.15)	26,867	64.2	1.05 (1.04; 1.06)
Education							
No education	No	1,607	33.3	1.00	2,910	57.0	1.00
	Yes	2,597	40.1	1.20 (1.14; 1.26)	4,111	60.8	1.07 (1.03; 1.10)
Elementary school	No	10,142	34.3	1.00	13,037	42.3	1.00
	Yes	17,835	43.9	1.28 (1.26; 1.30)	21,984	52.6	1.24 (1.22; 1.26)
High school	No	6,307	33.1	1.00	5,793	29.4	1.00
	Yes	9,151	45.9	1.39 (1.35; 1.42)	9,038	44.4	1.51 (1.47; 1.55)
Higher education	No	3,843	38.3	1.00	2,404	23.8	1.00
	Yes	4,896	49.7	1.30 (1.26; 1.34)	3,806	38.8	1.63 (1.56; 1.70)
Race or skin color							
White/yellow	No	26,397	37.7	1.00	25,132	34.5	1.00
	Yes	40,987	46.2	1.23 (1.21; 1.24)	42,028	46.3	1.34 (1.33; 1.36)
Brown	No	20,369	35.9	1.00	23,754	39.8	1.00
	Yes	28,505	45.1	1.25 (1.24; 1.27)	32,626	49.7	1.25 (1.23; 1.26)
Black	No	2,872	35.8		3,390	40.0	
	Yes	4,920	45.9	1.28 (1.24; 1.33)	5,783	51.7	1.29 (1.25; 1.33)
Brazilian region							
Midwest	No	5,871	37.3	1.00	5,091	31.0	1.00
	Yes	8,597	46.3	1.24 (1.21; 1.27)	8,118	43.1	1.39 (1.35; 1.43)
Northeast	No	15,094	39.5	1.00	16,841	41.8	1.00
	Yes	23,157	48.3	1.22 (1.21; 1.24)	25,050	50.2	1.20 (1.18; 1.22)
North	No	3,889	29.8	1.00	6,457	45.1	1.00
	Yes	4,427	38.8	1.31 (1.26; 1.35)	6,658	55.2	1.22 (1.19; 1.25)
Southeast	No	34,198	38.9	1.00	31,140	34.0	1.00
	Yes	47,913	46.8	1.20 (1.19; 1.22)	48,076	45.7	1.34 (1.33; 1.36)
South	No	5,288	35.1	1.00	4,502	29.4	1.00
	Yes	10,277	45.5	1.30 (1.26; 1.33)	10,098	44.1	1.49 (1.46; 1.54)

[a]Number of people affected by COVID-19.

MMB = multimorbidity; P% = prevalence; PR = prevalence ratio; 95% CI = confidence interval.

than in those with a higher educational level (38.8%). Black and brown patients presented with ICU admissions at 45.9 and 45.1%, respectively. They also presented a high prevalence of death (black patients, 51.7%; brown patients, 49.7%). The northeast region had a prevalence of 48.3% for ICU admissions, whereas the northern region had 55.2% of deaths (**Table 3**).

Regarding the associations between multimorbidity and outcomes according to support and diagnostic variables, the prevalence of ventilatory support was high in patients admitted to the ICU (52.7%) and those who died (51.1%). We also found that a high prevalence according to imaging tests; altered radiologic exams were associated with ICU admission (49.3%) and death (48.6%), while CT positivity for COVID-19 or other diseases was associated with ICU admission (50.3%) and death (41.5%) (**Table 4**).

The hierarchical adjusted analysis (**Table 5**) showed an association between multimorbidity and ICU admission and death after inclusion of variables (distal to proximal). These outcomes were also associated with male sex (ICU admission: PR = 1.15, 95% CI: 1.06–1.24; death: PR = 1.34, 95% CI: 1.24–1.46), 60–79 years (ICU admission: PR = 1.42, 95% CI: 1.21–1.66; death: PR = 2.96, 95% CI: 2.47–3.53), ≥ 80 years (ICU admission: PR = 1.55, 95% CI: 1.30–1.85; death: PR = 7.02, 95% CI: 5.76–8.56), brown color (ICU admission: PR = 1.14, 95% CI: 1.04–1.24; death: PR = 1.37; 95% CI: 1.23–1.51), black skin color (ICU admission: PR = 1.20, 95% CI: 1.03–1.41; death: PR = 1.77, 95% CI: 1.50–2.08), elementary education (ICU admission: PR = 1.34, 95% CI: 1.13–1.56; death: PR = 1.31, 95% CI: 1.12–1.55), high school (ICU admission: PR = 1.69, 95% CI: 1.43–1.99; death: PR = 1.38, 95% CI: 1.16–1.64), ventilatory support (ICU admission: PR = 5.50, 95% CI: 4.85–6.23; death: PR = 4.02, 95% CI: 3.53–4.58), and altered radiologic exams (ICU admission: PR = 1.63, 95% CI: 1.38–1.93; death: PR = 1.65, 95% CI: 1.38–1.96). Positive CT for COVID-19 or other diseases had a protective effect against death (PR = 0.65, 95% CI: 0.55–0.76).

We did not find associations between the three Brazilian regions and positive CT findings for COVID-19 or other diseases and ICU admission, or between higher education and death. Collinearity was not observed between variables. The most influential point was no lower than 0.005. Furthermore, the goodness-of-fit test indicated a good fit in both ICU admission (P = 0.358) and death (P = 0.105).

DISCUSSION

We aimed to analyze the association between multimorbidity, ICU admission, and death due to COVID-19 in Brazil. We found associations between multimorbidity, male sex, black skin color, ventilatory support, and altered radiologic exams.

The high percentage of morbidities in the studied population was expected and corroborated the literature[13] since individuals, with some morbidity and COVID-19, are more likely to be admitted to the ICU or they may expire.

The frequency of morbidities analyzed in this study (e.g., diabetes mellitus, systemic arterial hypertension, obesity, and cardiac diseases) was higher than those in the literature,[13,14] even compared to a study conducted in the Brazilian population.[15] We also obtained more robust results due to the size and national scope of the SIVEP-Gripe database, which is different from previous studies.[13-15]

The simultaneous effects of morbidities explain the increase in hospitalizations and deaths due to COVID-19. Therefore, assessing

Table 4. Stratified analysis between multimorbidity, intensive care unit (ICU) admissions, and deaths in hospitalized patients due to COVID-19 according to support and diagnostic variables in Brazil, 2020

Variables	MMB	ICU admissions			Deaths		
		n[a]	P%	PR (95% CI)	n[a]	P%	PR (95% CI)
Ventilatory support							
No	No	6,662	17.1	1.00	6,672	17.5	1.00
	Yes	7,564	21.0	1.23 (1.19; 1.26)	8,789	25.0	1.43 (1.39; 1.47)
Yes	No	52,886	44.8	1.00	46,429	40.5	1.00
	Yes	81,340	52.7	1.18 (1.17; 1.19)	76,960	51.1	1.26 (1.25; 1.27)
Radiologic exams							
Normal	No	1,158	31.5	1.00	1,003	27.9	1.00
	Yes	1,524	38.4	1.22 (1.14; 1.30)	1,481	37.9	1.36 (1.27; 1.45)
Altered	No	21,343	39.6	1.00	19,184	36.2	1.00
	Yes	34,541	49.3	1.25 (1.23; 1.26)	33,519	48.6	1.34 (1.32; 1.36)
Tomography							
Negative	No	1,180	39.2	1.00	1,023	35.2	1.00
	Yes	2,041	45.3	1.16 (1.09; 1.22)	1,956	44.8	1.27 (1.20; 1.35)
Positive for COVID-19 or other diseases	No	21,612	41.4	1.00	14,651	29.3	1.00
	Yes	33,781	50.3	1.21 (1.20; 1.23)	26,783	41.5	1.41 (1.39; 1.44)

[a]Number of patients with COVID-19.

MMB = multimorbidity; P% = prevalence; PR = prevalence ratio; 95% CI = 95% confidence interval.

Table 5. Hierarchical adjusted analysis for intensive care unit (ICU) admission and death in hospitalized patients due to COVID-19 according to independent variables in Brazil, 2020

Variables	ICU admissions			Deaths		
	Model 1[a]	Model 2[b]	Model 3[c]	Model 1[a]	Model 2[b]	Model 3[c]
	PR (95% CI)	PR[a] (95% CI)[b]	PR[a] (95% CI)[b]	PR[a] (95% CI)[b]	PR[a] (95% CI)[b]	PR[a] (95% CI)[b]
Multimorbidity						
No	1.00	1.00	1.00	1.00	1.00	1.00
Yes	**1.42 (1.40; 1.44)**	**1.51 (1.48; 1.54)**	**1.46 (1.35; 1.57)**	**1.60 (1.57; 1.61)**	**1.58 (1.54; 1.62)**	**1.61 (1.48; 1.75)**
Region						
Midwest	**1.06 (1.03; 1.09)**	0.95 (0.91; 1.01)	1.03 (0.87; 1.21)	0.99 (0.96; 1.03)	**1.11 (1.05; 1.17)**	**1.75 (1.46; 2.10)**
Northeast	**1.15 (1.13; 1.18)**	**1.12 (1.07; 1.17)**	**1.59 (1.35; 1.86)**	**1.44 (1.40; 1.47)**	**1.57 (1.51; 1.64)**	**1.31 (1.10; 1.55)**
North	**0.76 (0.74; 0.79)**	**0.73 (0.70; 0.77)**	0.86 (0.71; 1.03)	**1.66 (1.65; 1.77)**	**2.13 (2.01; 2.24)**	**2.39 (1.94; 2.93)**
Southwest	**1.10 (1.08; 1.13)**	**1.10 (1.06; 1.13)**	1.08 (0.98; 1.20)	**1.12 (1.09; 1.15)**	**1.52 (1.47; 1.58)**	**1.22 (1.09; 1.36)**
South	1.00	1.00	1.00	1.00	1.00	1.00
Sex						
Female		1.00	1.00		1.00	1.00
Male		**1.22 (1.19; 1.25)**	**1.15 (1.06; 1.24)**		**1.31 (1.28; 1.34)**	**1.34 (1.24; 1.46)**
Age (years)						
20–39		1.00	1.00		1.00	1.00
40–59		1.04 (0.99; 1.09)	1.07 (0.91; 1.26)		**1.34 (1.30; 1.46)**	1.18 (0.98; 1.41)
60–79		**1.44 (1.38; 1.51)**	**1.42 (1.21; 1.66)**		**3.12 (2.96; 3.30)**	**2.96 (2.47; 3.53)**
≥ 80		**1.55 (1.47; 1.63)**	**1.55 (1.30; 1.85)**		**6.90 (6.52; 7.31)**	**7.02 (5.76; 8.56)**
Race or skin color						
White/Yellow		1.00	1.00		1.00	1.00
Brown		0.99 (0.96; 1.02)	**1.14 (1.04; 1.24)**		**1.20 (1.17; 1.23)**	**1.37 (1.23; 1.51)**
Black		1.02 (0.98; 1.07)	**1.20 (1.03; 1.41)**		**1.33 (1.27; 1.39)**	**1.77 (1.50; 2.08)**
Education						
No education		1.00	1.00		1.00	1.00
Elementary education		**1.15 (1.10; 1.20)**	**1.34 (1.14; 1.56)**		**0.88 (0.85;.0.93)**	**1.31 (1.12; 1.55)**
High school		**1.26 (1.21; 1.33)**	**1.69 (1.43; 1.99)**		**0.77 (0.73; 0.81)**	**1.38 (1.16; 1.64)**
Higher education		**1.48 (1.40; 1.56)**	**1.84 (1.53; 2.21)**		**0.59 (0.56; 0.63)**	1.15 (0.95; 1.40)
Ventilatory support						
No			1.00			1.00
Yes			**5.50 (4.85; 6.23)**			**4.02 (3.53; 4.58)**
Radiologic exams						
Normal			1.00			1.00
Altered			**1.63 (1.38; 1.93)**			**1.65 (1.38; 1.96)**
Computed tomography						
Negative			1.00			1.00
Positive for COVID-19 or other diseases			1.05 (0.90; 1.22)			**0.65 (0.55; 0.76)**

[a]Model 1: block 1 (region); [b]Model 2: model 1 + block 2 (sex, age, race or skin color, and education); [c]Model 3: model 2 + block 3 (ventilatory support, radiologic examinations, and computed tomography).
PR = prevalence ratio; 95% CI = 95% confidence interval.

multimorbidity is important because some COVID-19 patients are expected to have other morbidities. Studies associated with metabolic syndrome and COVID-19 showed worsening of patients' conditions that led to ICU admission or death when two or three additional conditions (e.g., hyperglycemia, dyslipidemia, or arterial hypertension) were considered to classify this syndrome.[16,17]

The P% and PR of ICU admission and death due to COVID-19 increased with increase in the number of morbidities. This result was expected;[17] however, the increase was significant in the presence of two or three morbidities. These data indicate a worse prognosis for patients with COVID-19 and multimorbidity, raising concerns for health services due to the high costs and increased demand of the health care personnel and technological support.

Analysis by age groups suggested that younger individuals were less affected by COVID-19 than adults and older individuals.[14,18] We also found associations between age group and ICU admission or death in patients with multimorbidity. Age is an essential factor to assess the time to ICU admission or death due to COVID-19.[19]

Also, the time to ICU admission of older individuals may have been underreported since individuals belonging to this group are more likely to die before ICU admission.

This is the first study to report an increase in the P% of patients with multimorbidity admitted to the ICU with an increase in educational level. This result may be associated with better jobs, higher income, and better social living conditions in individuals with higher educational levels, suggesting availability of better healthcare. However, decrease in P% of deaths among individuals with higher education levels with multimorbidity was an inverse result. A study analyzing the socioeconomic aspects of COVID-19 lethality in Brazil showed that patients with higher education who had a more severe disease presented a lower prevalence of death than those with less education.[20]

Black and brown patients with multimorbidity have a high mortality rate. Another study also demonstrated that non-white patients, especially black patients, were more likely to develop severe conditions due to COVID-19, require ventilatory support in the ICU, and/or pass away.[21]

Regional disparities in socioeconomic development directly affected the number of COVID-19 cases. We observed that the northeast and north regions had the highest prevalence compared to other macro-regions of Brazil. Even considering that presence of, and access to specialized healthcare facilities for treating COVID-19 reduces the number of outcomes investigated in this study, access to health care must be considered in the most affected regions.

Complementary tests, such as radiologic and CT examinations, showed an relevant prevalence of ICU admission and death. Although these tests have good sensitivity, studies investigating complementary tests for COVID-19 have revealed low specificity compared with the reference diagnostic test (i.e., the reverse transcriptase real-time polymerase chain reaction). Nevertheless, some studies recommend using imaging tests to assess the extent of the disease and investigate possible complications,[22,23] particularly in patients receiving ventilatory support in the ICU.[24]

Multivariate analysis indicated associations between male sex, age 60–70 and ≥ 80 years, black and brown skin color, elementary education, high school, ventilatory support, and radiological examinations. These findings corroborate with recent studies[25-27] suggesting that sociodemographic factors are important predictors of ICU admission and death due to COVID-19.

This study had some limitations. Data may have been underreported, considering the lack of data regarding non-mandatory questions on the form. However, the sample size evaluated allowed us to demonstrate situations that were not revealed by other studies. Another limitation could be related to cases of SARS due to COVID-19 not detected by the Brazilian healthcare system, mainly those who did not have time to be treated in emergency care units or ambulances. Moreover, unreliable records may have influenced the results. Linking different databases may yield robust results. Finally, the SARS notification form did not inform whether deaths were caused during the disease or later due to post-disease complications. Similarly, the length of stay in the ICU may be a relevant factor in the assessment of cases.

In this study we highlight the assessment performed with the morbidities and outcomes, since it may be more expressive when considering isolated, dyad, and triad morbidities.

From the present study, we concluded that the prevalence of ICU admission and death was high in patients with morbidities, and that the increment in number of morbidities increased the prevalence and prevalence ratio of outcomes. An association between multimorbidity and ICU admissions due to COVID-19 was observed when adjusted for male sex, black and brown skin colors, age between 18 and 40 years, patients with some degree of education, use of ventilatory support, and altered radiological examinations. Regarding deaths due to COVID-19, multimorbidity was associated with male sex, black and brown skin colors, age ≥ 60 years, ventilatory support, altered radiologic exams, and CT findings indicating COVID-19 or other diseases.

Our findings may help train healthcare personnel to offer specialized care to patients with morbidities and COVID-19. Furthermore, we expect competent healthcare groups in the three spheres of the government to disseminate knowledge about multimorbidity and COVID-19 to reduce the spread of the disease and its impact on the healthcare system.

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INSTRUCTIONS FOR AUTHORS

Scope and indexing

São Paulo Medical Journal (formerly Revista Paulista de Medicina) was founded in 1932 and is published bimonthly by Associação Paulista de Medicina, a regional medical association in Brazil.

The Journal accepts articles in English in the fields of evidence-based health, including internal medicine, epidemiology and public health, specialized medicine (gynecology & obstetrics, mental health, surgery, pediatrics, urology, neurology and many others), and also physical therapy, speech therapy, psychology, nursing and healthcare management/administration.

São Paulo Medical Journal's articles are indexed in MEDLINE, LILACS, SciELO, Science Citation Index Expanded, Journal Citation Reports/Science Edition (ISI) and EBSCO Publishing.

Editorial policy

Papers with a commercial objective will not be accepted: please review the Journal's conflicts of interest policy below.

São Paulo Medical Journal accepts manuscripts previously deposited in a trusted preprint server.

São Paulo Medical Journal supports Open Science practices. It invites reviewers to join Open Peer Review practices through acceptance that their identities can be revealed to the authors of articles. However, this is purely an invitation: reviewers may also continue to provide their input anonymously.

São Paulo Medical Journal is an open-access publication. This means that it publishes full texts online with free access for readers.

São Paulo Medical Journal applies a publication fee in the form of an article processing charge (APC) for all studies conducted outside of Brazil. This rate will be charged to the corresponding author when the study has been accepted on the grounds of its scientific merit. This fee is US$ 500.00 and is independent of the length of the text. The corresponding author should wait to receive the journal's invoice before making the payment. The article will only be published after presentation of the proof of payment. Submission is free for all. Associação Paulista de Medicina provides financial support for the Journal.

Articles accepted for publication become the Journal's property for copyright purposes, in accordance with Creative Commons attribution type BY.

Transparency and integrity: guidelines for writing

The Journal recommends that all articles submitted should comply with the editorial quality standards established in the Uniform Requirements for Manuscripts Submitted to Biomedical Journals,[1] as updated in the Recommendations for the Conduct, Reporting, Editing and Publication of Scholarly Work in Medical Journals. These standards were created and published by the International Committee of Medical Journal Editors (ICMJE) as a step towards integrity and transparency in science reporting and they were updated in December 2018.[1]

All studies published in *São Paulo Medical Journal* must be described in accordance with the specific guidelines for papers reporting on clinical trials (CONSORT),[2] systematic reviews and meta-analyses (PRISMA),[3,4] observational studies (STROBE),[5,6] case reports (CARE)[7] and accuracy studies on diagnostic tests (STARD).[8,9] These guidelines ensure that all methodological procedures have been described, and that no result has been omitted. If none of the above reporting guidelines are adequate for the study design, authors are encouraged to visit the EQUATOR Network website (http://www.equator-network.org/) to search for appropriate tools.

Conflicts of interest

Authors are required to describe any conflicts of interest that may exist regarding the research or the publication of the article. Failure to disclose any conflicts of interest is a form of misconduct.

Conflicts of interest may be financial or non-financial. The Journal recommends that the item "Conflicts of interest" at http://www.icmje.org should be read to obtain clarifications regarding what may or may not be considered to be a conflict of interest. The existence and declaration of conflicts of interest is not an impediment to publication at all.

Acknowledgements and funding

Grants, bursaries and any other financial support for studies must be mentioned separately, after the references, in a section named "Acknowledgements." Any financial support should be acknowledged, always with the funding agency name, and with the protocol number whenever possible. Donation of materials used in the research can and should be acknowledged too.

This section should also be used to acknowledge any other contributions from individuals or professionals who have helped in producing or reviewing the study, and whose contributions to the publication do not constitute authorship.

Authorship

The Journal supports the position taken by the ICMJE (http://www.icmje.org) regarding authorship. All authors should read ICMJE's recommendations to obtain clarifications regarding the criteria for authorship and to verify whether all of them have made enough contributions to be considered authors.[10]

All authors of articles published in *São Paulo Medical Journal* need to have contributed actively to the discussion of the study results and should review and approve the final version that is to be released. If one author has not contributed enough or has not approved the final version of the manuscript, he/she must be transferred to the Acknowledgement section.

The corresponding author is the primary guarantor of all ethical issues relating to the manuscript, before, during and after its

publication. However, *São Paulo Medical Journal* and ICMJE consider that all authors are held fully responsible for the study, regarding the accuracy or integrity of data and data interpretation in the text. Contributions such as data collection only do not constitute authorship.

The addition or deletion of authors' names in the manuscript byline is possible only if the corresponding author provides the reason for the rearrangement and a written signed agreement from all authors. Modifications to the order of the authors are possible, but also need to be justified. Authors whose names are removed or inserted must agree with this in writing. Publication of the article cannot proceed without a declaration of authorship contributions signed by all authors.

São Paulo Medical Journal supports the ORCID initiative. All authors should create an ORCID identification (ID) record (in www.orcid.org) before submitting their article and should link the submission to their existing ORCID ID in the electronic submission system. ORCID identifications help to distinguish researchers with similar names, give credit to contributors and link authors to their professional affiliations. In addition, this may increase the ability of search engines to retrieve articles.

São Paulo Medical Journal supports Open Science practices. Authors must therefore complete an open science compliance form, which is available from: https://wp.scielo.org/wp-content/uploads/Open-Science-Compliance-Form_en.docx.

Redundant or duplicate publication

São Paulo Medical Journal will avoid publishing redundant or duplicate articles. The Journal agrees with the ICMJE definition of redundant publication,[11] i.e. an attempt to report or publish the same results from a study twice. This includes but is not limited to publication of patient cohort data that has already been published, without clear reference to the previous publication. In situations in which authors are making a secondary analysis on data that has already published elsewhere, they must state this clearly. Moreover, the outcomes assessed in each analysis should be clearly differentiated.

The Journal's peer review policy and procedures

After receipt of the article through the electronic submission system, it will be read by the editorial team, who will check whether the text complies with the Journal's Instructions for Authors regarding format. The Journal has adopted the *CrossRef Similarity Check* system for identifying plagiarism and any text that has been plagiarized, in whole or in part, will be promptly rejected. Self-plagiarism will also be monitored.

When the general format of the manuscript is deemed acceptable and fully compliant with these Instructions for Authors, and only then, the editorial team will submit the article to the Editor-in-Chief, who will firstly evaluate its scope. If the editor finds that the topic is of interest for publication, he will assign at least two reviewers/referees with expertise in the theme, to evaluate the quality of the study. After a period varying from one to several weeks, the authors will then receive the reviewers' evaluations and will be required to provide all further information requested and the corrections that may be necessary for publication. These reviewers, as well as the Editorial Team and the Editor-in-Chief, may also deem the article to be unsuitable for publication by *São Paulo Medical Journal* at this point.

At the time of manuscript submission, the authors will be asked to indicate the names of three to five referees. All of them should be from outside the institution where the authors work and at least two should preferably be from outside Brazil. The Editor-in-Chief is free to choose them to review the paper or to rely on the *São Paulo Medical Journal's* Editorial Board alone.

Articles will be rejected without peer review if:

- they do not present Ethics Committee approval (or a justification for the absence of this);
- they fail to adhere to the format for text and figures described here.

After peer review

Peer reviewers, associated editors and the Editor-in-Chief may ask for clarifications or changes to be made to the manuscript. The authors should then send their article back to the Journal, with the modifications made as requested. Changes to the text should be highlighted (in a different color or using a text editor tool to track changes). Failure to show the changes clearly might result in the paper being returned to the authors.

The modified article must be accompanied by a letter answering the referees' comments, point by point. The modified article and the response letter are presented to the editorial team and reviewers, who will verify whether the problems have been resolved adequately. The text and the reviewers' final evaluations, along with the response letter, will then be sent to the Editor-in-Chief for a decision.

Manuscripts that are found to be suitable for publication through their scientific merit will be considered "provisionally accepted". However, all articles will subsequently be scrutinized to check for any problems regarding the reporting, i.e. sentence construction, spelling, grammar, numerical/statistical problems, bibliographical references and other matters that may arise, especially in the Methods section. The adherence to reporting guidelines will be checked at this point, and the staff will point out any information regarding methodology or results that the authors should provide. This is done in order to ensure transparency and integrity of publication, and to allow reproducibility.

The editorial team will then provide page proofs for the authors to review and approve. No article is published without this final author approval. All authors should review the proof, although the Journal asks the corresponding author to give final approval.

Submission

Articles should be submitted only after they have been formatted as described below. Texts must be submitted exclusively through the Internet, using the Journal's electronic submission system, which is available at http://mc04.manuscriptcentral.com/spmj-scielo. Submissions sent by e-mail or through the post will not be accepted.

The manuscript should be divided into two files. The first of these, the main document ("blinded"), should contain the article title, article type, keywords and abstract, article text, references and tables, but must omit all information about the authors. The second of these, the "title page", should contain all the information about the authors.

To format these documents, use Times New Roman font, font size 12, line spacing 1.5, justified text and numbered pages.

The corresponding author is responsible for the submission. However, all authors should approve the final version of the manuscript that is to be submitted and should be aware of and approve any changes that might be made after peer review.

Covering letter

All manuscripts must be submitted with a covering letter signed at least by the corresponding author. The letter must contain the following five essential items relating to the manuscript:

1. a declaration that the manuscript is original and that the text is not under consideration by any other journal;
2. a statement that the manuscript has been approved by all authors, who agree to cede the copyrights to the Journal, disclose all sources of funding and declare all potential conflicts of interest;
3. a statement that the study protocol was endorsed by an Internal Review Board (Ethics Committee), including the date and number of the approval (in the case of original articles). This is required for absolutely all studies involving human subjects or patient data (such as medical records), in accordance with the Committee on Publication Ethics (COPE) guidelines, and even for case reports. A copy of the approval document must be submitted to the Journal;
4. each author should indicate a valid, up-to-date email address for contact;
5. a list of a minimum of five potential referees outside of the authors' institutions, who could be invited, at the Editor-in-Chief's discretion, to evaluate the manuscript.

General guidelines for original articles

The following are considered to be full-text original articles: clinical trials; cohort, case-control, prevalence, incidence, accuracy and cost-effectiveness studies; case series (i.e. case reports on more than three patients analyzed together); and systematic reviews with or without meta-analysis. These types of article should be written with a maximum of 3,500 words (from the introduction to the end of the conclusion).

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.

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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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III CONGRESSO PAULISTA DE DOR 2023

28 a 30 setembro

VENHA SE ATUALIZAR NO DIAGNÓSTICO E TRATAMENTO DA DOR NAS DIVERSAS ESPECIALIDADES

Chegamos a terceira edição do Congresso Paulista de Dor, desta vez totalmente presencial e com muitas novidades, como as oficinas "A dor de Ouvir a Dor" e um módulo de introdução aos conceitos básicos de dor para alunos de medicina e residentes.

CONFIRA ALGUNS TEMAS

- Anestesiologia;
- Fisiatria;
- Termografia;
- Medicina Aeroespacial;
- Medicina do Esporte;
- Psiquiatria & Dor;
- Oficinas Dor de Ouvir a Dor;
- Ortopedia;
- Cefaleia;
- Sono;
- Neurologia;
- Cannabis;
- Geriatria;
- Endocrinologia;
- Acupuntura;
- Reumatologia.

GARANTA SEU LUGAR!

VAGAS LIMITADAS

Local do evento: Associação Paulista de Medicina
Av. Brigadeiro Luís Antônio, 278 - Bela Vista,
São Paulo - SP | CEP: 01318-901

Médico Técnico Científico responsável pelo evento:
Dra. Telma Regina Mariotto Zakka / CRM 33741 SP

Realização e comercialização: APM Associação Paulista de Medicina

Apoiador Institucional: SBOT Sociedade Brasileira de Ortopedia e Traumatologia

Patrocinador Master: ENDOGEN Ciência para vida

Simule seu plano

ou ligue (11) 31884200

*ANSs e condições no site.

APM ASSOCIAÇÃO PAULISTA DE MEDICINA

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