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Monument in honor of 100 years of Japanese immigration to Brazil – Santos (SP), Brazil
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Federada da AMB Associação Médica Brasileira

Global Summit TELEMEDICINE & DIGITAL HEALTH 2023

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Robotic surgery training

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Robot-assisted surgery emerged in the 2000s and has grown almost exponentially in the last decade. The use of robotic-assisted surgery has increased 10–40-fold more than that of laparoscopic surgery for general routine procedures.[1] The continuous improvement of robotic platforms has allowed surgeons to overcome the limitations of conventional laparoscopy, such as 2D visualization and long instruments that do not accurately reproduce human wrist movements. Robotic systems provide high-definition 3D visualization, giving control of the camera to the surgeon. Robotic platforms have surgical instruments with intracavitary joints that reduce tremors, reproducing the movements of the surgeon on the console with great accuracy. Combined with these technical advantages, the clinical results consistently demonstrated in scientific articles seem to corroborate the great growth of robotic surgery in several specialties.[2]

The increasing use of robotic systems has raised concerns about the safety of patients operated on by surgeons on a learning curve. This demand resulted in a standardized curriculum for training new surgeons. A few years ago, robotic training was controlled and certified by Intuitive, the company that manufactured the only robotic platforms then available in Brazil. The significantly increased demand for robotic surgery led the Brazilian Medical Association (AMB), the Specialty Societies, and the Federal Council of Medicine (CFM) to regulate robotic surgery in Brazil, establishing a structured training curriculum[3,4] consisting of a basic and an advanced stage. The basic or pre-clinical stage includes acquiring theoretical knowledge about robotic equipment and how the robot works, online training on the fundamentals of robotic surgery, watching videos and attending some robotic surgeries in person, training on a robotic simulator, and training on the robot console simulating real surgery movements and procedures (in-service training). In the advanced stage, the apprentice performs the robotic procedure as the main surgeon under the supervision of a surgeon-instructor (proctor) with extensive experience in the technique. After supervising at least ten specialty procedures, the proctor will be able to certify the apprentice surgeon's competence to perform robotic surgery. Next, we will describe the stages of the structured curriculum in more detail.

ONLINE TRAINING

The Fundamentals of Robotic Surgery (FRS) is an online program on the principles of robotic surgery developed by more than 80 experts. Actually, it is not just an online program because it included other training stages. It is divided into an introduction to the robotic surgical system, didactic instructions on robotic surgical systems, psychomotor skills curriculum and training, communication skills training, and staff training. However, the program that is currently mostly used is the Technology Training Pathway, developed by Intuitive Surgical for its platform. This website provides videos and documents about the principles of the da Vinci system, especially about robotic instruments and accessories, port placement, docking, intraoperative configuration, surgical console manipulation, troubleshooting, and safety resources.[5]

BEDSIDE EXPERIENCE

This stage allows the apprentice surgeon to consolidate some of the concepts taught in the online stage. Watching and, ideally, participating in robotic surgeries in theater as a supervised assistant, the apprentice practices proper patient positioning, port placement, docking, and handling

the robot's arms and instruments, in addition to learning how to solve system problems. Live observation of an experienced surgeon allows the apprentice to become more familiar with the main standard procedures in their specialty and learn some critical points and technical tricks.[6]

SIMULATION

The apprentice surgeon uses simulators to practice the skills required for robotic procedures. The exercises include handling articulated and 3D optic instruments, improving forceps movements, suturing, tying surgical knots, dissecting structures, and using different forms of energy. The most used 3D simulators are the dVSS da Vinci Simulator (3-D Systems/Simbionix), adapted to the surgeon's console on the da Vinci platform, and the DV-Trainer (Mimic Technologies). In both models, the apprentice receives scores that evaluate different aspects of their movements throughout the exercises, helping to improve their weaker points.

In addition to virtual reality simulators, there are also physical simulators in which the surgeon performs exercises to develop skills such as suturing, cauterizing, and closing planes in organic tissues and anatomical parts. For an experience even closer to reality, animal organs such as porcine models can be used inside domes and manikins. However, due to their high costs, they are reserved for more advanced training stages or for the final evaluation of the pre-clinical part of robotic certification. A cadaveric human model is also a very realistic option, but it is very expensive.[6]

SUPERVISED PROCEDURES

After being certified in the pre-clinical/basic stage, the apprentice surgeon can begin the clinical/advanced stage. This stage consists of at least ten robotic procedures supervised by an instructor surgeon with extensive robotics experience. Ideally, the first surgeries should be simpler procedures, and as the apprentice gains confidence with robotic technology, they move on to more complex procedures. When this progression is not possible, the apprentice can begin by receiving help from the instructor in the more technically difficult stages of complex procedures, gaining more autonomy as they gain experience. At the end of the advanced stage, the apprentice surgeon will be able to continue independently, as long as the proctor deems that they are ready to do so.

SYSTEMS AVAILABLE IN BRAZIL

In Brazil, we currently have platforms produced by three companies. Most of the robotic systems are produced by Intuitive Surgical, the American company that pioneered robotics. The available platforms are the da VinciÒ Si, X, and Xi, with the Si model being discontinued over the next few years and gradually replaced by the VinciÒ X and Xi models. One hundred and three da VinciÒ systems are distributed in 88 hospitals across all Brazilian regions. The second company that came to Brazil was CMR Surgical, a British company that produces the VersiusÒ platform. At the moment, there are six VersiusÒ systems installed in six different hospitals in the South and Southeast regions. Finally, we have the HugoÒ RAS platform, produced by Medtronic, already available in two hospitals in São Paulo, SP. However, to date, the HugoÒ system is only validated for urological and gynecological surgeries.

The increased number of new platforms requires structured curriculum adaptations because even accredited surgeons will require training to use each of the different systems. Furthermore, an increasing number of surgeons will begin their experience directly on the new platforms. In the near future, the ideal structured curriculum should cover even broader skills, enabling new surgeons to work across all different platforms. However, predicting how training will be affected by an increasing number of robotic systems is difficult.

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Reallocation of time spent on sedentary behavior by time spent on physical activity reduces dynapenia in older adults: a prospective cohort study

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Sedentary time.

ABSTRACT

BACKGROUND: Dynapenia is characterized by mobility limitations in the older population when combined with aggravating behavioral factors that can increase the risk of morbidity and mortality.

OBJECTIVE: To investigate the hypothetical effects of reallocation of time spent on sedentary behavior (SB), moderate-to-vigorous physical activity (MVPA), and sleep on dynapenia in older adults.

DESIGN AND SETTING: A prospective cohort study using exploratory surveys in Alcobaça City, Bahia State, Brazil.

METHODS: In total, 176 older adults (≥ 60 years) of both sexes participated in this study. Dynapenia was assessed using the handgrip strength test with cutoff points of < 27 kg for men and < 16 kg for women. MVPA and SB were assessed using the International Physical Activity Questionnaire, and sleep was assessed using the Pittsburgh Sleep Quality Index.

RESULTS: Effects on reallocation were found for the shortest times, such as 10 minutes (odds ratio (OR) 0.92; 95% confidence interval (CI): 0.85–0.99); substituting MVPA with SB increased the chances of dynapenia by 58.0% (95% CI: 1.01–2.49). Analyzing the substitution of 60 minutes/day of SB with 60 minutes/day of MVPA revealed a protective effect, with a lower OR for dynapenia of 37.0% (OR 0.63; 95% CI: 0.40–0.99). The reallocation of sleep time did not significantly reduce dynapenia.

CONCLUSIONS: Substituting the time spent sitting with the same amount of time spent on MVPA can reduce dynapenia, and a longer reallocation time confers greater health benefits in older adults.

INTRODUCTION

Aging is commonly accompanied by a significant reduction in muscle performance, since skeletal muscle mass and strength are affected by this process.[1] The age-related decline in muscle strength is termed dynapenia. This condition exposes older adults to a greater risk of mobility limitations.[2] It is directly influenced by behavioral factors such as the level of physical activity (PA), exposure to sedentary behavior (SB), and quality and duration of sleep.[3]

Moderate-to-vigorous physical activity (MVPA) is an established component of healthy aging and can improve the health and longevity of the population.[4] Insufficient levels of physical activity are prevalent worldwide; in older adults, this prevalence reportedly ranges from 4.9% (Sweden)[5] and 29.0% (Portugal)[5] to 33% in Brazil.[6] PA levels among older adults remain below the minimum 150 to 300 minutes per week recommended by the World Health Organization.[7] These low levels induce several deleterious muscle adaptations, including reductions in muscle volume, power, and strength, which are aggravating factors for older adults.[8]

Concomitantly, advancing age has been associated with high SB,[3] with an estimated sedentary time of older adults of 9.4 hours per day, ranging from 8.5 to 10.7 hours per day, according to a systematic review of 22 studies.[9] Consequently, SB is independently associated with reduced muscle strength, which contributes to reducing the functionality and autonomy of older adults.[10]

Therefore, exposure to dynapenia may play a role in the relationship between PA, MVPA, and SB. Establishing and quantifying the associations between such variables is thus a priority for informing potential lifestyle guidelines and interventions, ultimately mitigating poor health outcomes.[11]

Regarding sleep, its relationship with aging and strength and its close association with the development of adverse health conditions have been described.[12] A study found that low handgrip strength was independently associated with poor sleep quality in middle-aged and older adults.[13]

Although the association between SB, PA, and sleep has been investigated in the literature,[14,15] studies examining the relationship between dynapenia and SB, PA, and sleep, especially their effects when assessing the reallocation of the exposure time of older individuals to these activities, are lacking. Therefore, investigating sleep hour time, MVPA, and SB in relation to dynapenia is relevant; an isotemporal substitution modeling shows the ability not only to control the effect between activities but also the effect of substitutions of time spent, reducing the heterogeneity of associations, thus facilitating public health recommendations.[16] We hypothesized that the hypothetical reallocation of time in MVPA by SB would increase the odds of dynapenia.

OBJECTIVE

To investigate the hypothetical effects of the reallocation of time spent on SB, MVPA, and sleep on dynapenia in older adults.

METHODS

Study design

This was a prospective and observational cohort study, part of the Longitudinal Study of Elderly Health in Alcobaça (ELSIA, as per its Portuguese acronym) conducted between 2015 and 2020 in the municipality of Alcobaça, located in the extreme south of state of Bahia, Brazil. It comprised 743 older adults aged 60 years and over who lived in urban areas and were registered in the Family Health Strategy (FHS). This program comprises a care model to access public health, aiming to promote the integration of social security services with the public health services of states and municipalities.[17]

Participants

For the survey, individuals registered in the FHS of the Health System of the Brazilian government, conducted in Alcobaça, were selected. Alcobaça has 743 older adults enrolled in the FHS; 54 of whom refused to participate in the survey, 58 were excluded because they did not meet the inclusion criteria, and 158 could not be located, resulting in a final sample of 473 individuals.[18] The exclusion criteria were severe cognitive impairment according to the Mini-Mental State Examination (MMSE), adapted for the Brazilian population,[19] severe difficulty in visual and hearing acuity, use of wheelchairs, severe sequelae of stroke with localized loss of strength, or terminal illness. For home visits, the researchers used data provided by the Municipal Health Department of Alcobaça as a reference. Contact was made with the older adults through home visits, informing them of the objectives, and requesting their participation in the research voluntarily.[20]

In February 2020, 249 participants were excluded due to a lack of information (59 due to death, 36 due to relocation to another city, 18 due to refusal to participate, 25 due to not meeting the inclusion criteria, and 105 due to not being locatable); 48 were excluded because they already had dynapenia at the beginning of the study, and 6 were excluded due to a lack of information on handgrip strength, resulting in a final study population of 176 individuals (**Figure 1**).

Ethical consideration

This study complied with the procedures and protocols of the Declaration of Helsinki and was approved by the Research Ethics Committee of the Universidade Federal do Triângulo Mineiro (no. 966.983/2015; date: February 25, 2015) and the Universidade do Estado da Bahia (no. 3.471.114/2020; date: July 26, 2019). Participation was voluntary and all participants provided informed consent.

Dynapenia

Dynapenia was assessed using the handgrip strength test with a Jamar portable hydraulic dynamometer (SAEHAN, SH5001, Korea). The participants were instructed to remain standing, with their elbows extended, then press the handle of the dynamometer with the highest force possible and hold it for 6 seconds. The recovery time between attempts was 1 minute. Three measurements were obtained in kilograms/force (kgf). The highest value of attempts for the dominant hand (self-reported by the subject) was used in the analysis.[21]

Dynapenia was classified as < 27 kgf for men and < 16 kgf for women, according to the criteria of Dodds et al.[22]

Physical activity and sedentary behavior

PA and SB were assessed using the long form of the International Physical Activity Questionnaire (IPAQ), validated for Brazilian older adults.[23,24]

PA was determined based on activities with MVPA for at least 10 continuous minutes during one day of the week. To characterize older individuals, a cutoff point of 150 minutes/week of MVPA was used (≥ 150 minutes/week = sufficiently active and < 150 minutes/week = insufficiently active),[7] and for the reallocation analysis, the time of MVPA was used continuously.

SB was determined by the time spent sitting during one day in the week and one day on the weekend. The total time spent sitting (minutes/day) was determined based on the weighted arithmetic mean [(time sitting on a weekday × 5 + time sitting on a weekend Day × 2)/7].[25] The 50th percentile of sitting time, corresponding to 391.78 minutes/day, was used as the cutoff point to characterize older individuals with high SB (≥ 50th percentile). For isotemporal analyses, total continuous values were used.

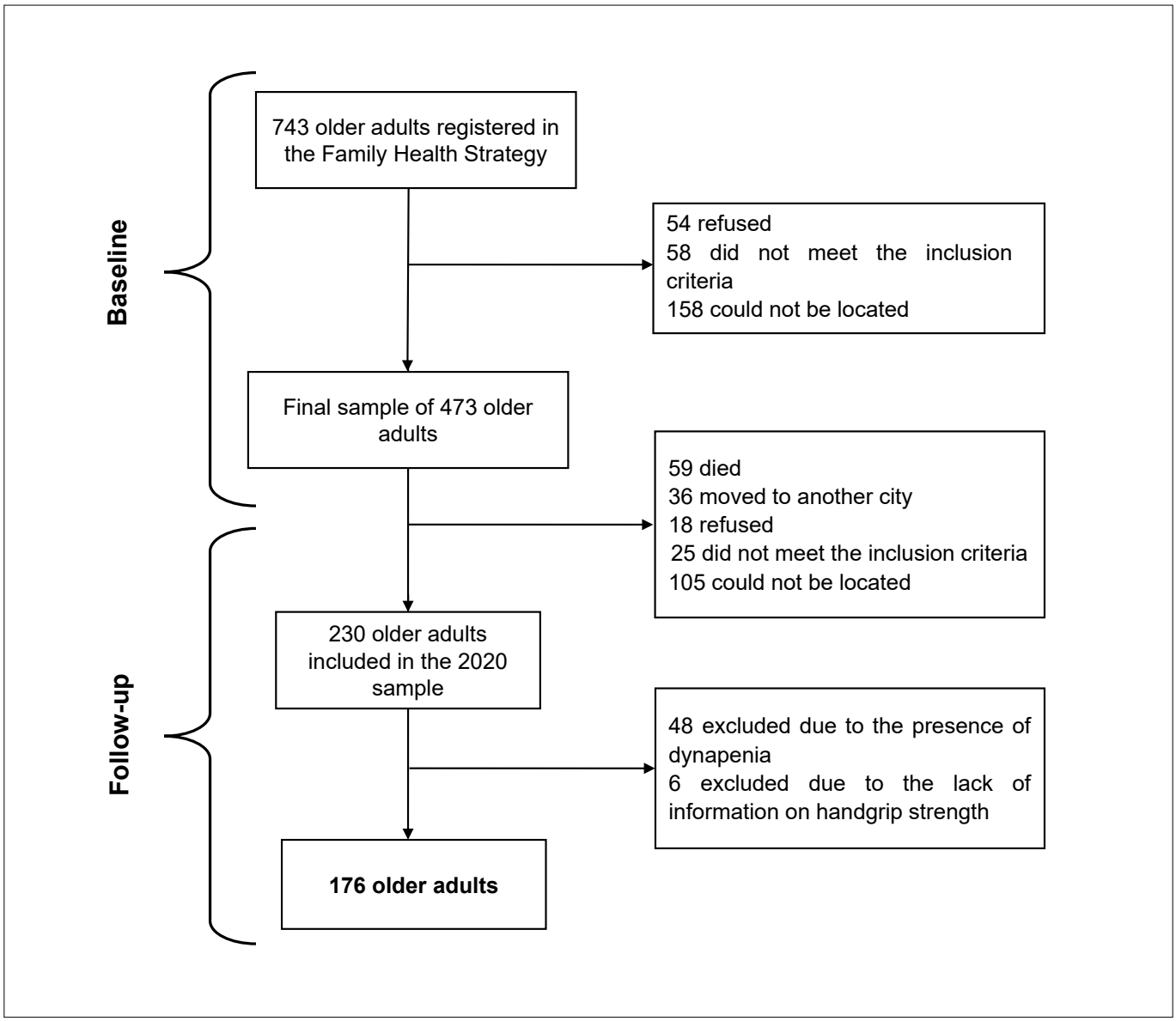

Figure 1. Longitudinal Study of Elderly Health in Alcobaça, 2015–2020, Sample flowchart.

Sleep

The time spent on nocturnal sleep was measured by the question, "During the past month, how many hours did you sleep at night?," from the Pittsburgh Sleep Quality Index,[26] translated and validated for Brazilian Portuguese.[27] It refers to the amount of sleep an individual has per night. Continuous values expressed as minutes per day (minutes/day) were considered for the construction of the isotemporal substitution models.

Covariables

Data on socioeconomic and general health variables were collected using a structured questionnaire. The variables consisted of sex (male and female), age group (60–69, 70–79, and ≥ 80 years), marital status (with a partner and without a partner), occupation (paid work and without paid work), income (value in financial unit BRL converted to American dollars U$) and schooling (years of study), polypharmacy (0 to 4 medicines ≥ 5 medicines), Basic Activities of daily living (BADL) (score) was assessed by using the Katz Index,[28] number of diseases (amount), smoking (yes or no) self-reported by the participant. The body mass index (BMI) was calculated as body mass/height^2 (kg/m^2). The waist-hip ratio (WHR) was determined by measuring the circumference in centimeters (cm) and was defined as waist to umbilical scar and hip at the largest circumference of the gluteal bone through the ratio of one measure to the other (cm waist/hip cm).[29]

Data analysis

Epidata software, version 3.1b, was used to prepare the database, and the analyses were performed using SPSS software (version

23.0; SPSS, Inc. Chicago, Illinois, United States). The Kolmogorov–Smirnov test was used to test the normality of the data.

Descriptive statistics were used to identify the sample, including the distribution of absolute and relative frequencies, medians, means, standard deviations (SDs), and interquartile ranges. The difference between groups with and without dynapenia was measured using the Mann–Whitney *U* test. For the association between the covariables and dynapenia, inferential statistics were used (Pearson's chi-square test).

To determine the hypothetical effects of the reallocation of time spent on sleep, SB, and PA on dynapenia, the isotemporal substitution approach was used.[30] Isotemporal substitution analyses were performed using logistic regression, with an estimate of odds ratio (OR) and 95% confidence interval (CI). The effects of substituting the times of 10, 20, 30, 40, 50, and 60 minutes spent on sleep, SB, and MVPA for the presence of dynapenia were also checked. The models were adjusted for sex, basic activities of daily living scores, income, smoking, number of diseases, polypharmacy, schooling, body mass index, and waist-hip ratio. A significance level of 5% was used.

RESULTS

This study included 176 older adults of both sexes, with a median age of 66.0 years. The incidence of dynapenia during the follow-up period was 17% (n = 30). **Table 1** displays the characteristics of the participants and their associations with the covariables at baseline, according to the incidence of dynapenia at follow-up.

The mean times of the measured variables included in the hypothetical isotemporal substitution model were a mean of 64 minutes/day (SD 76.57; IRQ 73.21) for MVPA, a mean of 413.94

Table 1. Characteristics of participants and associations according to the presence and absence of dynapenia. Alcobaça-BA, Brazil, 2020

Variables	Total n (%)	Dynapenia		P
		Absence n (%)	Presence n (%)	
Sex				
Male	63 (35.8)	50 (79.4)	13 (20.6)	0.404
Female	113 (64.2)	96 (85.0)	17 (15.0)	
Age group				
60–69 years	120 (68.2)	106 (88.3)	14 (11.7)	**0.003**
70–79 years	46 (26.1)	35 (76.1)	11 (23.9)	
≥ 80 years	10 (5.7)	5 (50.0)	5 (50.0)	
Marital status				
Without partner	87 (49.4)	69 (79.3)	18 (20.7)	0.233
With partner	89 (50.6)	77 (86.5)	12 (13.5)	
Occupation				
Employed	48 (27.3)	42 (87.5)	6 (12.5)	0.376
Unemployed	128 (72.7)	104 (81.3)	24 (18.3)	
Polypharmacy				
0–4 medicines	148 (84.1)	128 (86.5)	20 (13.5)	**0.011**
≥ 5 medicines	28 (15.9)	18 (64.3)	10 (35.7)	
Smoking				
No	160 (90.9)	133 (75.6)	27 (16.9)	0.739
Yes	16 (9.1)	13 (81.3)	3 (18.8)	
Level of physical activity				
≥ 150 minutes/week	114 (64.8)	98 (86.0)	16 (14.0)	0.207
< 150 minutes/week	62 (35.2)	48 (77.4)	14 (22.6)	
Sedentary lifestyle				
< 535 minutes/day	142 (80.7)	120 (84.5)	22 (15.5)	0.309
≥ 535 minutes/day	34 (19.3)	26 (76.5)	8 (23.5)	
	Median (IQR)	**Median (IQR)**	**Median (IQR)**	**P**
Income (Dollars)	322.81 (326.96)	326.96 (284,54)	322.81 (326.96)	0.179
Number of Diseases	3.00 (4.00)	3.00 (4.00)	3.50 (4.00)	0.379
Schooling (years)	4.00 (6.00)	4.52 (5.00)	3.50 (6.00)	0.828
BMI (kg/m²)	27.01 (6.93)	27.03 (6.54)	26.78 (7.61)	0.196
WHR (cm)	0.98 (0.10)	0.98 (0.10)	0.99 (0.13)	0.406

Data are expressed as absolute and relative frequencies for categorical variables and as medians and interquartile ranges for quantitative variables.
IQR = interquartile range; BMI = body mass index; WHR = waist-to-hip ratio.

minutes/day (SD 149.48; IRQ 173.04) for sedentary behavior and a mean of 414.00 minutes/day (SD 98.36; IRQ 120.00) for sleep.

In the isotemporal substitution analyses (**Table 2**), it was observed that the substitution of MVPA time for time spent on SB resulted in a higher OR of dynapenia at all tested times of 10, 20, 30, 40, 50, and 60 minutes among the surveyed older individuals ($P < 0.05$).

The reduction in SB and increase in MVPA were shown to have a protective role, where the longer the substitution time, the greater the protective effect. Substituting short times, such as 10 minutes/day of SB, with 10 minutes/day of MVPA was associated with an 8% reduction in dynapenia. In comparison, at the maximum time of 60 minutes/day, reallocation was associated with a 37% reduction in the development of dynapenia (95% CI: 0.40–0.99). Substitutions of sleep time with SB and MVPA times did not result in significant differences.

DISCUSSION

The main findings show that reallocations of SB by MVPA at all times tested reduced the chances of developing dynapenia. The inverse mode also occurs where the reallocation of time in MVPA by SB is a risk factor for the conservation of muscle strength in older adults.

Recent investigations have shown the possible effect of physical activity on muscle strength.[31,11] Consistent with these studies, the results of the current study reinforce this positive association, showing PA as a protective factor for reducing muscle strength in the aging process. Cooper et al.,[32] with a sample of more than 66,000 English citizens aged ≥ 60 years, identified a linear and positively associated behavior of handgrip strength and PA, the older adults whose handgrip strength increased spent more minutes per day on MVPA.

Despite its health benefits, PA levels among older adults remain below the recommended 150 minutes/week.[33] It has been shown that even at low levels, small changes in the inactive profile can improve and maintain the health of older adults.[3] These results reinforce that changes in small amounts of time (10 and 20 minutes/day) in the increase of PA showed benefits by significantly reducing the chances of developing dynapenia.

Conversely, SB contributes to an unhealthy lifestyle[34] associated with declines in performance and muscle strength in older adults.[1] Accordingly, the results of the current study highlight the risks of time increments in SB for dynapenia from the short times of 10 to 30 minutes per day, in addition to the fact that the reallocation of an additional hour (60 minutes daily) of SB, there was a 58% increase of dynapenia, corroborating the results reported by Gianoudis et al.[35] for each additional hour.

This factor has been assessed by sedentary activity; the study by Hammer and Stamatakis[10] addressed the daily time spent on TV and internet use and its inverse association with muscle strength, highlighting that older adults who watched TV for ≥ 6 hours per day had less handgrip strength than older individuals who watched TV for < 2 hours per day.

In older adults, sleep and muscle strength vary according to the aging process. As modifiable parameters, they can interact and influence each other.[36] The results of the current study did not show significant changes in the reallocations of sleep time by SB or MVPA, which can be explained by the mean sleep rate of the population, which was of the recommended regular amount (~7 hours). However, recent investigations have identified strong evidence between the quality and amount of sleep and muscle strength.[36,37] Pourmotabbed et al. showed that both short (< 6 hours) and long (> 8 hours) periods of sleep could lead to an increase in the risk of sarcopenia (decline in muscle mass, strength, and performance).[37]

In the isotemporal substitution model, no studies reported on dynapenia as an outcome; however, with sarcopenia and its

Table 2. Isotemporal substitution model of the association among sleep time reallocation, sedentary behavior, and moderate to vigorous physical activity in the risk of dynapenia in older adults. Alcobaça-BA, Brazil, 2020

Substitution Models	Dynapenia		
	OR (95% CI)	OR (95% CI)	OR (95% CI)
	MVPA	SB	Sleep
10 minutes			
MVPA Substitution	-	1.08 (1.01–1.16)*	1.05 (0.95–1.14)
SB Substitution	0.92 (0.85–0.99)*	-	0.97 (0.92–1.02)
Sleep Substitution	0.95 (0.87–1.04)	1.02 (0.97–1.08)	-
20 minutes			
MVPA Substitution	-	1.16 (1.01–1.35)*	1.10 (0.92–1.31)
SB Substitution	0.85 (0.73–0.99)*	-	0.94 (0.84–1.05)
Sleep Substitution	0.90 (0.75–1.08)	1.05 (0.95–1.17)	-
30 minutes			
MVPA Substitution	-	1.26 (1.01–1.58)*	1.15 (0.88–1.51)
SB Substitution	0.79 (0.63–0.99)*	-	0.91 (0.78–1.07)
Sleep Substitution	0.86 (0.66–1.13)	1.09 (0.92–1.28)	-
40 minutes			
MVPA Substitution	-	1.36 (1.01–1.83)*	1.21 (0.84–1.74)
SB Substitution	0.73 (0.54–0.99)*	-	0,89 (0.71–1.10)
Sleep Substitution	0.82 (0.57–1.18)	1.12 (0.90–1.39)	-
50 minutes			
MVPA Substitution	-	1.47 (1.01–2.14)*	1.27 (0.81–2.00)
SB Substitution	0.68 (0.46–0.99)*	-	0.86 (0.66–1.13)
Sleep Substitution	0.78 (0.50–1.23)	1.15 (0.88–1.51)	-
60 minutes			
MVPA Substitution	-	1.58 (1.01–2.49)*	1.33 (0.77–2.29)
SB Substitution	0.63 (0.40–0.99)*	-	0.84 (0.61–1.16)
Sleep Substitution	0.74 (0.43–1.28)	1.18 (0.86–1.64)	-

CI = confidence interval; OR = odds ratio; MVPA = moderate to vigorous physical activity; SB = sedentary behavior. Adjusted for sex, basic activities of daily living score, income, smoking, number of diseases, polypharmacy, years of study, body mass index, and waist-hip ratio; *P < 0.005.

components, Sánchez-Sánchez et al.[38] found that the reallocation of 60 minutes/day of MVPA by time spent on SB was associated with a reduction in the risk of sarcopenia (OR = 0.522; 95% CI: 0.367–0.726). Furthermore, when its components were assessed separately, reallocation was also associated with higher handgrip strength values (β = 0.888; 95% CI: 0.145–1.631).

MVPA is an important predictor for the maintenance of muscle physiology,[12] especially in aging, contributing to the increase of systemic inflammation, improving its oxidative power, and decreasing the loss of motor units, thus helping to conserve muscle strength.[1] On the other hand, the systems directly involving SB and dynapenia remain unclear; however, physiological processes explain that staying sedentary can influence systemic inflammation, which contributes to the infiltration of adipocytes into muscle tissue,[39] reducing the contractile capacity of the skeletal muscle that entails, among other outcomes, decreased muscle power and strength,[35] thus revealing similar paths between SB and dynapenia.

The use of isotemporal substitution modeling demonstrates a valuable avenue for the development of research within the epidemiological area owing to its ability to interdependently identify activities of different intensities, making more realistic assumptions that an increase in a behavior will be accompanied by a decrease in the equal duration of the others while the total time in all behaviors is kept constant.[40] These findings may be important in preparing specific recommendations for PA and SB in older adults. This can be useful for primary health and health professionals on how to use discretionary time in a way that is beneficial to health in daily practice.

With the need for future studies that complement our results, monitoring the high exposure to SB already present in the population can influence the development of dynapenia, even if PA levels remain above the recommended parameters.

Among the limitations of this study is the isotemporal substitution method, which is hypothetically applied, and the lack of estimating the change in behavior via a direct assessment. Moreover, we implemented an instrument that indirectly assesses PA and SB, which does not estimate mild intensity, which is considered important for the composition of the day in 24 hours. Nevertheless, the strengths of the study should be highlighted, such as its representative sample, the follow-up having been performed by the same assessors throughout the study period, in addition to the measurement of muscle strength with the hydraulic dynamometer, considered the gold standard for large populations, its originality, and its configuration in a longitudinal design that no other studies have utilized.

CONCLUSION

Substitution of the time spent on MVPA with the same amount in SB is associated with an increased risk of dynapenia. The opposite also occurs; longer time spent on MVPA correlates with greater benefits, drastically reducing the risk of developing dynapenia, thus directly reflecting on the reduction of the limiting impacts of the decline in muscle strength.

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Age, skin color, self-rated health, and depression associated with co-occurrence of obesogenic behaviors in university students: a cross-sectional study

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ABSTRACT

BACKGROUND: The university context plays an important role in the health-disease process since students are potentially vulnerable to obesogenic behaviors that can influence long-term health.

OBJECTIVE: To estimate the prevalence of and factors associated with the co-occurrence of obesogenic behaviors among university students.

DESIGN AND SETTING: This was a cross-sectional study at a Brazilian public university.

METHODS: This study was conducted with all university students in the first and second semesters of 2019 at Universidade Federal de Ouro Preto, Minas Gerais, Brazil. Data were collected between April and September 2019, using a self-administered questionnaire. The outcome was the co-occurrence of obesogenic behaviors, measured as the sum of three risk behaviors: inadequate eating practices, leisure-time physical inactivity, and sedentary behavior. A Venn diagram was used to evaluate the simultaneous occurrence of risk behaviors. Pearson's chi-square test and multivariate logistic regression were used for statistical analyses.

RESULTS: A total of 351 students participated in the study. Inadequate eating practices constituted the most prevalent isolated risk behavior (80.6%), which was also the most prevalent when combined with sedentary behavior (23.6%). University students aged 20 years or younger, with non-white skin color, poor self-rated health, and symptoms of depression had increased chances of simultaneous occurrence of obesogenic behaviors.

CONCLUSION: These findings highlight the importance of developing and implementing actions to reduce combined obesogenic behaviors in the university environment. Institutions should focus on creating an environment that promotes health-protective behaviors such as physical activity and healthy eating.

INTRODUCTION

The prevalence of obesity has increased rapidly in recent decades in both developed and developing countries, reaching the status of a global pandemic. This condition is characterized as both a disease and a risk factor for other chronic non-communicable diseases (NCDs). The etiology of this condition is multifactorial, resulting from a complex interaction between genetic, individual, sociocultural, economic, environmental, and behavioral factors. Epidemiological studies have demonstrated the relationship between important risk factors associated with this morbidity, which represents one of the biggest public health problems today.[1-5]

Many health risk behaviors, such as inadequate eating practices, low levels of physical activity, and sedentary behavior (SB), are considered independent risk factors for being overweight, contributing to increased morbidity and mortality due to NCDs.[6-8] However, exposure to these risk factors does not occur in an isolated manner[9] but in a group or simultaneously, increasing the risk of becoming overweight and obese.[10,11]

Although studies have evaluated the aggregation of multiple health risk behaviors, especially in the general adult population,[12] few studies have focused on university students.[13,14] University enrollment represents a period of health risk for young adults, as it results in numerous changes in the student's life, including increased opportunities to initiate and establish unhealthy behaviors that favor weight gain.[15] Additionally, it is observed that other factors are associated with obesogenic behaviors among university students during academic life, with emphasis on those related to sociodemographic, individual, social, and environmental characteristics.[16]

Understanding potentially obesogenic behavioral risk factors among university students is imperative for identifying more susceptible groups and recognizing the health effects of these factors, to facilitate the development of prevention and health promotion strategies targeted at the university environment. Additionally, this information can contribute to more effective public policies to reduce the rates of obesity- and overweight-related NCDs.

OBJECTIVE

This study therefore aimed to estimate the prevalence of co-occurrence of obesogenic behaviors and their associated factors in university students.

METHODS

Study design and population

This cross-sectional study was integrated with a project on anxiety and depression among university students titled "Symptoms of Anxiety and Depression among University Students of Minas Gerais: a longitudinal study" (Projeto sobre Ansiedade e Depressão em Universitários - PADu). This study was approved by the Research Ethics Committee of the Universidade Federal de Ouro Preto (UFOP) under CAAE no. 19467919.5.0000.5150 on December 19, 2019.

PADu is a longitudinal study conducted with university students entering undergraduate courses offered at the campi of Ouro Preto and Mariana of the UFOP. Data will be collected at three different time points (T0—in the first semester of the undergraduate course; T1—after attending two years; T2—after attending four years) to verify behavioral changes during academic life. For the present study, data from the baseline (T0) were used.

The study population included all university students entering the first and second semesters in the 2019 undergraduate courses in architecture and urbanism, performing arts, law, physical education, civil engineering, production engineering, geological engineering, pharmacy, history, journalism, mathematics, medicine, nutrition, and pedagogy. The students' lists were made available through the UFOP's teaching sections.

Students who met the following inclusion criteria participated in the research: regularly enrolled in the first period of the undergraduate courses evaluated in the study and aged 18 years or older.

The PADu sample comprised 355 university students. However, the final sample of this study consisted of 351 university students, since four participants did not answer all the questions related to the co-occurrence of obesogenic behaviors.

Data collection

Data were collected between April and September 2019 by project members who were previously trained to apply the instrument and clarify possible doubts of the students. A pilot study was conducted with students attending the eighth period of the nutrition course in the second semester of 2018 who would therefore not participate in the sample.

The questionnaires were administered during class hours, after taking prior appointments, and the teacher's presence in each selected course. The researchers oriented the university students about the study, risks, and benefits. They were also informed that their participation was voluntary and anonymous. Those who agreed to participate signed the informed consent form and answered a questionnaire consisting of socioeconomic characteristics, lifestyle habits, and health conditions.

Variables of the study

The outcome variable (co-occurrence of obesogenic behaviors) was obtained from the sum of three risk behaviors: inadequate eating practices, leisure-time physical inactivity, and SB. The responses were categorized as none to three obesogenic behaviors. These behaviors are justified because they are considered health risk factors and are associated with the most significant burden of NCDs and mortality.[17]

The variable "inadequate eating practices" was obtained through a scale developed and validated by Gabe and Jaime for adults, which measures adherence to healthy eating practices based on the recommendations of the second edition of the Food Guide for the Brazilian Population.[18,19] For classification purposes, the cut-off points proposed by Gabe and Jaime were used, wherein eating practices were classified as "inadequate" when the sum of the individual scores assigned to the responses for each alternative resulted in a score of up to 31 points, at "risk" when the score was between 32 and 41 points, and "adequate" when it was greater than 41 points.[20,21] Subsequently, for the present study, eating practices were recategorized as "adequate" and "inadequate."

Leisure-time physical inactivity was assessed using the study Surveillance System for Risk and Protective Factors for Chronic Diseases by Telephone Survey (VIGITEL), with questions such as: "In the last three months, did you practice any physical exercise or sport? (Do not consider physical therapy)."[22] Participants who answered "no" were classified as "inactive in leisure time," and those who answered "yes" were considered "active in leisure time."

SB was included in the study because a growing number of studies characterize it as a health risk factor, different from and independent of physical inactivity, and associated with the occurrence of adverse health effects, such as metabolic syndrome.[9,23] SB was determined in the questionnaire using the following question: "In your free time, that is, when you are not studying or working, how much time (in hours) do you dedicate to using the cell phone, television, computer, or tablet?" This question was adapted from two questions from VIGITEL.[22] For each of the screen types

evaluated, eight answers were possible: "I don't use," "less than an hour," "between one to two hours," "between two to three hours," "between four to five hours," "between five to six hours," and "more than six hours." For analysis purposes, SB was analyzed as a continuous variable and responses were coded as 0, 0.5, 1.5, 2.5, 3.5, 4.5, 5.5, and 6.5 hours, respectively. Subsequently, the responses of the time spent on each type of screen were summed, and the classification of SB was established according to the median. University students with screen time ≤ 6 h were classified as "non-sedentary," while those with screen time > 6 h were considered "sedentary."

The explanatory variables included in this study were grouped into two domains: sociodemographic characteristics and health conditions. The variables assessed in the sociodemographic domain included sex (male and female), age (≤ 20 years and > 20 years), skin color (white and non-white—yellow, brown, mulatto, or black), sexual orientation (heterosexual and others—homosexual, bisexual, or asexual), marital status (single and others—married, stable union, widowed, or divorced), and total monthly family income (< three minimum wages and ≥ three minimum wages). The wage value considered in this study refers to the minimum wage in force in Brazil in 2019 (R$ 998.00). The sociodemographic domain comprised the following variables: housing (without and with family members), area of knowledge (life sciences, exact sciences, humanities, and social and applied sciences), and work (no and yes).

In the health condition domain, the following variables were evaluated: self-rated health, categorized as "good" (good and very good) and "bad" (regular, bad, and very bad); anthropometric profile (not overweight or overweight); use of medication for chronic diseases (no and yes); anxiety symptoms (no and yes); depression symptoms (no and yes); and stress symptoms (no and yes).

The anthropometric profile was evaluated by calculating the body mass index (BMI) through the anthropometric measurements of weight and height, self-reported by the participants. The classification was made according to the BMI reference values established by the World Health Organization for adults[24] and adolescents.[25] Individuals classified as underweight and eutrophic (BMI < 24.9 kg/m^2) were grouped in the "not overweight" category and those classified as overweight and obese (BMI ≥ 25 kg/m^2) in the "overweight" category. Additional details on the anthropometric profile classification methodology can be found in a previous publication.[26]

The variables "anxiety symptoms," "depression symptoms," and "stress symptoms" were obtained through the reduced version of the Depression Anxiety Stress Scale-21 (DASS-21).[27] The scale is composed of a set of three subscales, designed to estimate in a self-reported way the symptoms of anxiety, depression, and stress in the week before data collection. The response scale to the items is a four-point Likert scale ranging from 0 (not applicable) to 3 (applicable most of the time), generating scores that allow the classification of anxiety, depression, and stress symptoms as "normal," "mild," "moderate," "severe," and "extremely severe." In the present study, symptoms of mental disorders were re-classified as absence ("no"; normal and mild) and presence ("yes"; moderate, severe, and extremely severe).

Statistical analysis

The variables were descriptively analyzed using frequency distribution. A Venn diagram was used to represent the simultaneous occurrence of obesogenic behaviors among the evaluated university students. This representation method allows for the comparison and visualization of the overlap and differences among the datasets being analyzed based on the intersections of the graphical shapes.[28,29]

Initially, the chi-square test was performed between the explanatory variables and the co-occurrence of obesogenic behaviors, and those with a P value < 0.20 in the bivariate analysis were included in the multivariate model. Multivariate logistic regression was used to verify the association between the co-occurrence of obesogenic behaviors and explanatory variables. In this analysis phase, three models were structured to represent the co-occurrence of the obesogenic behaviors evaluated: Models 1, 2, and 3 included no behavior versus one behavior, no behavior versus two behaviors, and no behavior versus three behaviors, respectively. For this, we used a reference category for university students with no obesogenic behavior versus the number of obesogenic behaviors (1, 2, or 3). To select sociodemographic and health condition variables, the backward method was adopted, and only the variables that presented a P value of < 0.05 remained in the multivariate model. All the models were adjusted for the variable "sex." The odds ratio (OR) was used to measure the association with the respective 95% confidence intervals (95% CI). The level of statistical significance was 5%. The analyses were performed using Stata version 13.0 (Stata Corporation, College Station, Texas, United States).

RESULTS

Of the 351 university students included in this study, 57.6% were female and 65.8% were 20 years or younger, ranging from 18 to 31 years. Most participants self-reported their color or race as white (51.1%), single (95.4%), heterosexual (79.5%), living without family members (66.4%), and not employed (89.2%). Regarding family income, slightly more than half (56.7%) of the students reported a family income higher than or equal to three minimum wages. Regarding the distribution by area of knowledge, 41.0% were from life sciences courses, 34.5% from the humanities and social and applied sciences, and 24.5% from the exact sciences (**Table 1**).

Regarding health conditions, 41.0% of the university students self-rated their health as bad, 22.3% were overweight, and 13.7% reported using medications for chronic diseases. Anxiety, depression, and stress

Table 1. Number of obesogenic behaviors in university students entering the Universidade Federal de Ouro Preto in 2019, according to sociodemographic characteristics and health conditions. Ouro Preto, Minas Gerais, 2019 (n = 351)

Variables	n	%	% of obesogenic behaviors				P value*
			0	1	2	3	
Sex							
Male	149	42.4	8.0	40.3	38.3	13.4	**0.013**
Female	202	576	10.9	24.7	43.1	21.3	
Age (n = 348)							
≤ 20 years	229	65.8	6.5	33.6	41.1	18.8	**0.040**
> 20 years	119	34.2	16.0	27.7	40.3	16.0	
Skin color (n = 350)							
White	179	51.1	14.5	31.3	36.9	17.3	**0.015**
Non-white (yellow, brown, mulatto, or black)	171	48.9	4.7	31.0	45.6	18.7	
Sexual orientation							
Heterosexual	279	79.5	9.7	32.3	41.2	16.8	0.729
Others (homosexual, bisexual, or asexual)	72	20.5	9.7	27.8	40.3	22.2	
Marital status							
Single	335	95.4	9.3	31.6	40.9	18.2	0.584
Others (married, stable union, widowed, or divorced)	16	4.6	18.7	25.0	43.8	12.5	
Total monthly family income**							
< 3 minimum wages	152	43.3	5.9	35.5	38.2	20.4	0.077
≥ 3 minimum wages	199	56.7	12.6	28.1	43.2	16.1	
Housing							
Without family members	233	66.4	9.9	35.6	38.2	16.3	0.091
With family members	118	33.6	9.3	22.9	46.6	21.2	
Area of knowledge							
Life Sciences	144	41.0	11.1	31.2	41.0	16.7	0.365
Exact Sciences	86	24.5	12.8	33.7	40.7	12.8	
Humanities and Social and Applied Sciences	121	34.5	5.8	29.8	41.3	23.1	
Work							
No	313	89.2	10.5	32.0	39.6	17.9	0.268
Yes	38	10.8	2.6	26.3	52.7	18.4	
Self-rated health							
Good (very good and good)	207	59.0	12.6	33.3	40.1	14.0	**0.024**
Bad (regular, bad, and very bad)	144	41.0	5.6	28.5	42.3	23.6	
Anthropometric profile (n = 346)							
Not overweight	269	77.7	10.4	30.9	39.4	19.3	0.365
Overweight	77	22.3	6.5	35.1	45.4	13.0	
Use of medication for chronic diseases							
No	303	86.3	9.9	32.7	39.9	17.5	0.519
Yes	48	13.7	8.3	22.9	47.9	20.9	
Anxiety symptoms (n = 350)							
No	201	57.4	11.9	32.8	44.8	10.5	**< 0.001**
Yes	149	42.6	6.7	28.9	36.2	28.2	
Depression symptoms (n = 349)							
No	232	66.5	12.1	32.3	44.4	11.2	**< 0.001**
Yes	117	33.5	5.1	28.2	35.1	31.6	
Stress symptoms (n = 349)							
No	222	63.6	13.1	32.4	41.9	12.6	**0.001**
Yes	127	36.4	3.9	28.3	40.2	27.6	

*P value obtained using Pearson's Chi-Square test; **The minimum wage in force in Brazil in 2019 = R$ 998.00.
In bold: the statistically significant variables in the bivariate analysis.

symptoms were observed to be 42.6%, 33.5%, and 36.4% of the interviewed university students, respectively (**Table 1**).

Regarding isolation, the most prevalent obesogenic behavior was inadequate eating practices (80.6%; 95% CI: 76.5%–84.8%), followed by SB (49.2%; 95% CI: 44.0–54.5%) and leisure-time physical inactivity (37.3%; 95% CI: 32.2–42.4%).

Figure 1 shows the co-occurrence of obesogenic behavior. The adoption of inadequate eating practices and SB (23.6%) was observed to be the most prevalent combination of risk behaviors among students, followed by inadequate eating practices, leisure-time physical inactivity, and SB (17.9%), and inadequate eating practices and leisure-time physical inactivity (15.7%). The absence of risk factors was observed in 9.7% of university students.

The prevalence distribution of obesogenic behaviors according to sociodemographic characteristics and health conditions is presented in **Table 1**. In the bivariate analysis, sex, age, skin color, self-rated health, anxiety, depression, and stress symptoms remained associated with the co-occurrence of obesogenic behaviors among university students.

Table 2 presents the results of the multivariate analysis. In the final adjusted models, the following variables maintained a significant association (P value < 0.05) with the co-occurrence of obesogenic behaviors: age, skin color, self-rated health, and depression symptoms. Age and skin color remained associated, in the three evaluation models.

In model 1 (no behavior versus one behavior), individuals aged 20 years or younger [OR: 3.68 (95% CI: 1.58–8.59)] and those who reported colored skin [OR: 3.09 (95% CI: 1.23–7.74)] were more likely to have obesogenic behavior. In model 2 (no behavior versus two behaviors), students who were 20 years or younger [OR: 2.77 (95% CI: 1.23–6.26)], colored skin [OR: 4.61 (95% CI: 1.88–11.31)], and self-rated their health as bad [OR: 2.70 (95% CI: 1.09–6.71)] were more likely to have two obesogenic behaviors simultaneously. In model 3 (no behaviors versus three behaviors), those aged 20 years or younger [OR:3.34 (95% CI: 1.23–9.05)], colored skin [OR: 3.31 (95% CI: 1.15–9.58)], and reported symptoms of depression [OR: 6.15 (95% CI: 2.10–18.05)] had an increased chance of having three obesogenic behaviors.

DISCUSSION

The findings of this study indicate that obesogenic behaviors are highly prevalent among university students and tend to co-occur, with more than 80.0% of students presenting at least one obesogenic behavior and 17.9% presenting three behaviors simultaneously. We found a higher chance of one or more obesogenic behaviors in students aged 20 years or younger who self-reported colored skin, self-rated their health as bad, and reported symptoms of depression.

Adopting inadequate eating practices was the single most prevalent risk behavior among university students and was associated

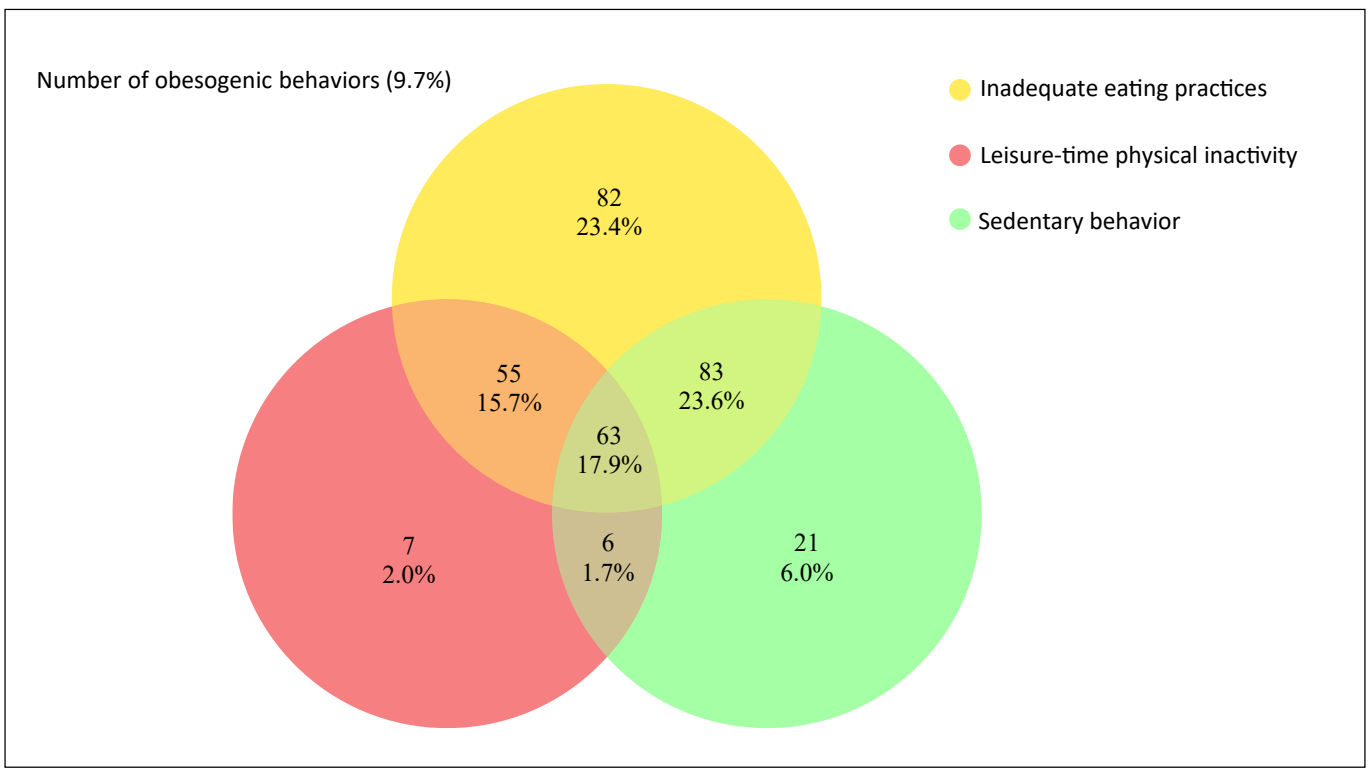

Figure 1. Co-occurrence of obesogenic behaviors (inadequate eating practices, leisure-time physical inactivity, and sedentary behavior) in university students entering the Universidade Federal de Ouro Preto in 2019. Ouro Preto, Minas Gerais, 2019 (n = 351).

with the co-occurrence of two or more obesogenic behaviors. With the transition from high school to higher education, university students face many changes, such as lack of time due to studies, overlapping activities, and new responsibilities, which may interfere with adopting healthy eating practices.[30] In addition, many factors, such as socioeconomic status, lack of ability to make healthy food choices, difficulty cooking, lack of healthy food in university cafeterias, and "environmental barriers," such as opening hours of nearby food stores, influence the availability of food, and negatively affect students' eating behaviors.[30,31]

Table 2. Odds ratio (OR) and 95% confidence interval (95% CI) for one or more obesogenic behaviors; multivariate model of sociodemographic characteristics and health conditions associated with the co-occurrence of obesogenic behaviors in university students entering the Universidade Federal de Ouro Preto in 2019. Ouro Preto, Minas Gerais, 2019 (n = 351)

Model one: No obesogenic behavior versus one obesogenic behavior			
Variables	**OR**	**95% CI**	**P value**
Age (n = 348)			
> 20 years	1		0.003
≤ 20 years	3.68	(1.58–8.59)	
Skin color (n = 350)			
White	1		0.016
Non-white (yellow, brown, mulatto, or black)	3.09	(1.23–7.74)	
Model two: No obesogenic behavior versus two obesogenic behaviors			
Variables	**OR**	**95% CI**	**P value**
Age (n = 348)			
> 20 years	1		0.014
≤ 20 years	2.77	(1.23–6.26)	
Skin color (n = 350)			
White	1		0.001
Non-white (yellow, brown, mulatto, or black)	4.61	(1.88–11.31)	
Self-rated health			
Good (very good and good)	1		0.033
Bad (regular, bad, and very bad)	2.70	(1.09–6.71)	
Model three: No obesogenic behavior versus three obesogenic behaviors			
Variables	**OR**	**95% CI**	**P value**
Age (n = 348)			
> 20 years	1		0.018
≤ 20 years	3.34	(1.23–9.05)	
Skin color (n = 350)			
White	1		0.027
Non-white (yellow, brown, mulatto, or black)	3.31	(1.15–9.58)	
Depression symptoms			
No	1		0.001
Yes	6.15	(2.10–18.05)	

OR = odds ratio; CI = confidence interval.

These factors may favor new eating habits, reflected in unhealthy eating practices and health-related problems, including being overweight.[32-34] Thus, health promotion strategies, including promoting healthy eating in the university environment, are vital, as numerous health behaviors are developed and established during this period[30] and tend to continue into adulthood, increasing the risk of developing chronic diseases in subsequent years.[15]

Exposure to health-risk behaviors has been described in studies with young populations.[9] Studies that evaluated the aggregation of inadequate eating practices and SB showed that these factors share contextual determinants and influence each other.[35] In the present study, we found that the most prevalent combination of risk behaviors among university students was the coexistence of inadequate eating practices and SB. In contrast, in a study of adults, SB, including the habit of watching television, using a computer, reading books, or magazines, remained associated with the consumption of healthy and unhealthy foods.[36] However, comparisons between the risk factors analyzed should be interpreted with caution, given the various methods used to assess food intake. It is noteworthy that the instrument used in the present study included other dimensions of adequate and healthy eating and food intake.

Scientific evidence shows that SB reduces energy expenditure and favors inadequate food consumption, including increased intake of foods rich in fat and sugars and decreased consumption of healthy foods such as fruits and vegetables.[35,36] Moreover, besides being risk factors for becoming overweight, this association between high screen time and inadequate eating habits may increase susceptibility to other health-risk behaviors,[35] resulting directly in series of unfavorable health outcomes.[37]

The simultaneous occurrence of the three risk behaviors assessed, characterized by inadequate eating practices, leisure-time physical inactivity, and SB, was prevalent in 17.9% of university students. Few studies have investigated the clustering of health risk behaviors among university students.[13] In a study conducted with Brazilian university students, a high prevalence was observed for the simultaneous occurrence of the four primary behavioral risk factors for NCDs: physical inactivity, inadequate fruit and vegetable consumption, excessive alcohol consumption, and smoking.[38] The study did not include SB in its analyses since this risk factor has been less studied than other risk behaviors already established in the literature, such as food intake and physical activity. It is worth noting the importance of investigating the aggregation of traditional and emerging risk behaviors among young people, especially university students, to provide information on which to base future actions.[13]

In this study, the co-occurrence of obesogenic behaviors was associated with students' skin color, differing from the findings of Cureau, Duarte, and Teixeira,[38] who found no association between the simultaneous presence of three or more behavioral risk factors and skin color of university students. Studies that have evaluated this association are scarce, making comparisons difficult. However, there is evidence showing that ethnic and racial minorities, the black community in particular, have a high prevalence of obesity and obesogenic behavior. Social inequalities make access to health difficult for groups that live in the same environment, such as universities. In this context, studies highlight the urgent need for broad-based, affirmative actions and policies to overcome racial disparities.[39,40]

In this study, we also observed that university students who self-rated their health as bad had a higher chance of one, two, or three obesogenic behaviors than those who self-rated their health as good. Studies show that individuals who perceive their health as bad tend to present more health risk behaviors,[41] such as inadequate intake of fruits and vegetables, physical inactivity, and SB. These behaviors are determinants of NCDs and are related to the negative subjective assessment of health.[42] Thus, these findings highlight the importance of considering how health is perceived by university students since perceptions of health can influence the adoption of healthy lifestyle behaviors. [43]

The presence of depressive symptoms was associated with the co-occurrence of obesogenic behaviors among university students, corroborating the findings of Champion et al.,[13] who evaluated 18-year-old Australian youth and observed a significant association between the clustering of multiple health-risk behaviors and mental health outcomes such as anxiety and depression. One hypothesis to justify this association is that individuals may engage in unhealthy behaviors to help cope with mental health problems.[44] In addition, stress and mental health disorders may interfere with a person's choice to adopt healthy lifestyle behaviors such as physical activity, while also exposing themselves to health-risk behaviors.[45]

There was a greater chance of exposure to multiple obesogenic behaviors among university students aged 20 years or younger. Evidence shows that the prevalence of simultaneous exposure to health risk behaviors increases with age,[9,46] since young people acquire greater autonomy and economic independence with advancing age.[9] However, this association has not been well established in the literature. In a systematic review of the co-occurrence of multiple risk behaviors, older age groups were considered risk factors for aggregating multiple risk behaviors.[12]

Although the findings of this study are consistent with those reported in the literature, some limitations should be considered when interpreting the results. Students from a single university were included, limiting comparisons with students from other higher education institutions. Another limitation of the study is the methodological design, which does not establish a cause-effect relationship between the variables and temporal relationships on the associations found. In addition, as the students were evaluated in their initial semester at the university, their recent entry into academic life may not have set their lifestyles.

It is important to highlight that this study was based on self-reported behaviors, which may have generated information bias, as young people tend to overestimate or underestimate their exposure to health risk behaviors. Despite these limitations, the findings obtained add essential evidence regarding the prevalence and factors associated with the co-occurrence of obesogenic behaviors among university students.

CONCLUSION

The findings from this study showed that a high proportion of university students with simultaneous obesogenic behaviors, especially among those who self-reported colored skin, rated their health as bad, and reported depressive symptoms. These findings contribute to a better understanding of the associations between various obesogenic behaviors, highlighting the need for interventions directed at university students. In addition, these results highlight the importance of health promotion in the university environment, with actions aimed at a healthy lifestyle. Public policies that target risk behaviors in groups and stimulate a healthy food environment and physical activity in universities are essential for reducing the risk of major chronic diseases related to excess weight.

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Quality analysis of prior systematic reviews of carpal tunnel syndrome: an overview of the literature

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ABSTRACT

BACKGROUND: Carpal tunnel syndrome (CTS) is a common condition greatly affects patients' quality of life and ability to work. Systematic reviews provide useful information for treatment and health decisions.

OBJECTIVE: This study aimed to assess the methodological quality of previously published systematic reviews on the treatment of CTS.

DESIGN AND SETTING: Overview of systematic reviews conducted at the Brazilian public higher education institution, São Paulo, Brazil

METHODS: We searched the MEDLINE and Cochrane Library database for systematic reviews investigating the treatment of CTS in adults. The Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) and measurement tool to assess systematic reviews **(**AMSTAR) were applied by two independent examiners.

RESULTS: Fifty-five studies were included. Considering the stratification within the AMSTAR measurement tool, we found that more than 76% of the analyzed studies were "low" or "very low". PRISMA scores were higher when meta-analysis was present (15.61 versus 10.40; P = 0.008), while AMSTAR scores were higher when studies performed meta-analysis (8.43 versus 5.59; P = 0.009) or when they included randomized controlled trials (7.95 versus 6.06; P = 0.043). The intra-observer correlation demonstrated perfect agreement (> 0.8), a Spearman's correlation coefficient of 0.829, and an ICC of0.857. The inter-observer correlation indicated that AMSTAR was more reliable than PRISMA.

CONCLUSION: Overall, systematic reviews of the treatment of CTS are of poor quality. Reviews with better-quality conducted meta-analysis and included randomized controlled trials. AMSTAR is a better tool than PRISMA because it has a better performance and should be recommended in future studies.

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INTRODUCTION

Median nerve compression in carpal tunnel syndrome (CTS) affects 1–3 people per 1,000 according to studies in the United States. This syndrome leads to pain, decreased sensitivity, and hand strength, and has a significant detrimental economic impact.[1] The initial treatment of the condition is usually non-operative, and surgical treatment is reserved for cases in which non-surgical treatment fails or when facing advanced disease.[2]

In this context, the aims of CTS treatment include the achievement of more efficient resolution of symptoms and earlier return to work. In recent decades, many studies have been conducted to establish the best treatment for this disease. The advent of systematic reviews and modern methods of statistical evaluation is currently pushing research towards more reliable evidence. However, systematic reviews do not always follow the necessary methodological concepts, leading to imprecision and erroneous conclusions.[3] Recent studies have shown, both in hand surgery as a whole,[4] and specifically in carpal tunnel syndrome treatment,[5] that systematic reviews are often lacking in quality.

To identify poorly conducted systematic reviews, objective tools and questionnaires have been developed to improve the methodological robustness of reviews and to provide a parameter for data collection, analysis, and synthesis of the evidence achieved. These protocols[6-9] act as safeguards for systematic reviews, and numerous studies in the literature have supported their systematic usefulness.

OBJECTIVE

This study aimed to assess the methodological quality of previously published systematic reviews on the treatment of CTS, as well as to verify the reproducibility of the A Measurement Tool to Assess Systematic Reviews (AMSTAR) and Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) scores in this scenario, as no study in the literature has previously used these two tools for this purpose.

METHODS

The methodology of this review is registered in the PROSPERO database CRD42020172328 (https://www.crd.york.ac.uk/PROSPERO/display_record.php?ID=CRD42020172328).

Literary search

A comprehensive literature search was performed in the MEDLINE and Cochrane Library databases for articles published from January 1950 to February 2020, with the only restriction being articles in the Mandarin language. The search strategy was performed using two methods.

Method 1 – Search for the terms "carpal tunnel syndrome" and "systematic review" in the "Clinical Queries" section of the PubMed platform. ("carpal tunnel syndrome" AND "systematic review") AND (Therapy/Broad[filter])

Method 2 – Search with the keyword "carpal tunnel syndrome" and "systematic review" in the Cochrane Library platform with the filter "Other reviews" (Epistemonikos)

("carpal tunnel syndrome" AND "systematic review") AND (Epistemonikos[filter])

The results of both search strategies were independently analyzed by two researchers (M.C.C. and G.L.O.), and any discrepancies and disagreements were resolved with the help of a senior third author (V.Y.M.). We selected the MEDLINE and the Cochrane Library databases for their worldwide audience and to include relevant research data.

Inclusion criteria

Systematic reviews (with or without meta-analysis) that included any studies (Randomized Clinical Trials or non-Randomized Clinical Trials) evaluating the treatment of CTS in an adult population (18 years or older).

Exclusion criteria

Reviews lacking a transparent literature search and strategy for their data approach, those that were diagnostic-focused, involved anesthetic procedures, or were clearly narrative.

Methodology evaluation (internal validity) and quality reports

The data from all evaluated studies were considered for the elaboration of a descriptive table presenting the various characteristics of the systematic reviews on the topic.

The following were included in the data analysis: journal impact factor (high impact versus low impact), performed a meta-analysis or not, number of institutions involved, total number of patients, total number of words, presence of conflicts of interest, country of origin of the study, citation of PRISMA, and inclusion or exclusion of randomized controlled trials.

Impact factor stratification

The impact factor is expressed as the average number of weighted citations received in the last three years of articles published in the journal. This calculation yields a number, and all grades are ranked in quartiles according to the criteria of the SCImago Journal and Country Rank (https://www.scimagojr.com/journalrank.php). The evaluated journals were dichotomized between those in the first quartile (Q1), defined as high-impact publications, and those outside of this quartile (not Q1), which were defined as low-impact.

Tools to assess quality

AMSTAR[8] was used to assess the quality of the systematic reviews. This tool covers 16 dichotomous questions relevant to the internal validity of systematic reviews related to study design (Q1), research and study inclusion/exclusion (Q2-5), study characteristics (Q6), internal validity of systematic reviews (Q7-15), and conflicts of interest (Q16). AMSTAR has a maximum score of 16 points, with higher scores indicating better quality. This tool further grades the quality of the analyzed studies as "very low", "low", "medium", or "high".

PRISMA[7] (https://www.prisma-statement.org/PRISMAStatement/) is a tool comprising 27 items that aids in the formulation and analysis of systematic reviews and meta-analyses. For this analysis, we considered all 27 items and the sum of answers as the final score. Although the overall aim of PRISMA is to help ensure the transparency of systematic reviews, in this study, it was used as a tool in which the sum of its items denoted better quality in the studies, as has been performed in previous studies.[10,11]

The acquisition of study data and application of the AMSTAR and PRISMA questionnaires were performed in duplicate. A senior author (V.Y.M.) mediated any cases of disagreement between the examiners.

Data analysis

We defined *a priori* subgroups for a comparative analysis of the quality of systematic reviews: high-impact journal (Q1) versus low impact (non-Q1), presence of meta-analysis versus non-meta-analysis, randomized controlled trials versus non-randomized clinical trials, statement of interest versus non-declaration, whether PRISMA was cited, country of origin, and number of words.

We defined *a priori* subgroups for a comparative analysis of the quality of systematic reviews, as follows: high-impact journals (Q1)

versus low-impact journals (non-Q1), presence of meta-analysis versus its absence, systematic reviews of randomized clinical trials versus studies that did not employ them, presence of a declaration of interest versus its absence, whether PRISMA was mentioned, country of origin of the study, total number of words, total number of patients, and number of institutions involved.

Statistical analysis

Continuous variables were compared using the Mann-Whitney U test. Categorical variables were compared using the Wilcoxon's test. Intraobserver agreement was assessed using Spearman's correlation coefficient and the intraclass correlation coefficient. Interobserver agreement was performed according to the Blant Altman and Kappa coefficient, with a score of more than 0.8 indicating perfect agreement; 0.61–0.8, substantial agreement; 0.60–0.41, moderate agreement; and scores below 0.4 indicating low agreement.[12]

RESULTS

In this systematic review, we considered 55 studies.

The PRISMA flowchart, including the reasons for exclusion at each stage, is outlined in **Figure 1.**Studies characteristics are detailed in **Table 1**,[13-66] and quantitative data are presented in **Table 2**.

The mean values of the two examiners (Examiner E1 and Examiner E2) for the PRISMA and AMSTAR scores were compared with the following covariates: impact factor, conflict of interest, country of origin, meta-analysis, cite PRISMA, and design of the included studies.

Considering the stratification within the AMSTAR, 87% of the studies evaluated by E1 had "low" or "very low" quality, whereas for E2, this value was 76.4%. Thus, only 2.7% of the studies were classified as having "high" quality (**Table 3**).

PRISMA resulted in the highest scores when the studies included meta-analysis (15.61 versus 10.40; P = 0.008). There were no differences in the other variables analyzed, as shown in **Table 4**.

AMSTAR resulted in higher scores when the studies performed meta-analysis (8.43 versus 5.59; P = 0.009) or when they included randomized clinical trials (RCT) (7.95 versus 6.06; P = 0.043), as presented in **Table 5**.

Journals with the greatest impact did not influence most variables, except for the PRISMA citation statement. In publications that cited PRISMA, 47.6% were low-impact journals and 20.6% were high-impact journals. Among those that did not mention PRISMA, 52.4% were low-impact journals, whereas 79.4% were high-impact journals (P = 0.035), as shown in **Table 6**.

By assessing the correlation of the country of origin with the same qualitative covariates, we observed a positive correlation between Chinese studies and those that performed meta-analysis (100% in Chinese studies versus 51% in non-Chinese studies) (P = 0.022), as presented in **Table 7**.

We identified that the intraobserver correlation for E1 and E2 in the AMSTAR and PRISMA scores was above 0.8, with perfect agreement between the pairs, as presented in **Table 8**.

The inter-observer correlation between the two examiners, using the Blant–Altman model, showed that PRISMA has low reliability, unlike AMSTAR, as the values of the latter were closer to zero, as shown in **Table 9**.

Applying the Kappa coefficient to assess inter-observer agreement in AMSTAR, revealed substantial agreement (0.61–0.8) when grouping this tool into two variables: "low" or "medium/high" quality studies, as presented in **Table 10**.

Multivariate analysis using the linear regression model showed a greater impact factor for a journal when a study used meta-analysis, and further showed that multicenter studies have significantly increased PRISMA and AMSTAR scores, as presented in **Table 11**.

DISCUSSION

Systematic reviews on CTS are mostly of low quality. Several factors are related to better methodological quality, including study design, studies that mention PRISMA, and meta-analyses. Factors such as conflicts of interest, country of origin, and multicenter studies did not have the same influence.

Similar studies have shown consistent results regarding the intra-observer correlation of the PRISMA and AMSTAR scores. In agreement with our study, these studies found the influence of the presence of meta-analysis on the score values. They also pointed out that there was no difference in the AMSTAR score in terms of the presence of conflicts of interest and impact factor.[11]

Other studies have indicated that reviews including only RCTs have better AMSTAR scores, which is similar to the findings of our study. They also observed differences in the PRISMA results of studies that presented declared conflicts of interest. In our study, we did not observe this difference.[67]

There have been relatively few studies on the quality of systematic reviews of specific hand and upper limb diseases in orthopedics. However, several of these studies have pointed out that the quality of systematic reviews in leading journals in orthopedics is suboptimal,[68-70] despite having substantially improved following publication of PRISMA.[71]

Taking into account the same area of knowledge of hand surgery, an overview of the quality of systematic reviews of the treatment of fractures of the distal radius[9] also showed that studies only including randomized clinical trials and those that performed meta-analyses had better quality.

AMSTAR scores had greater inter-observer agreement than PRISMA scores, especially when dichotomously dividing the qualitative results into high- and low-quality studies. Our findings therefore suggest that AMSTAR is more robust, although improvements are still possible.

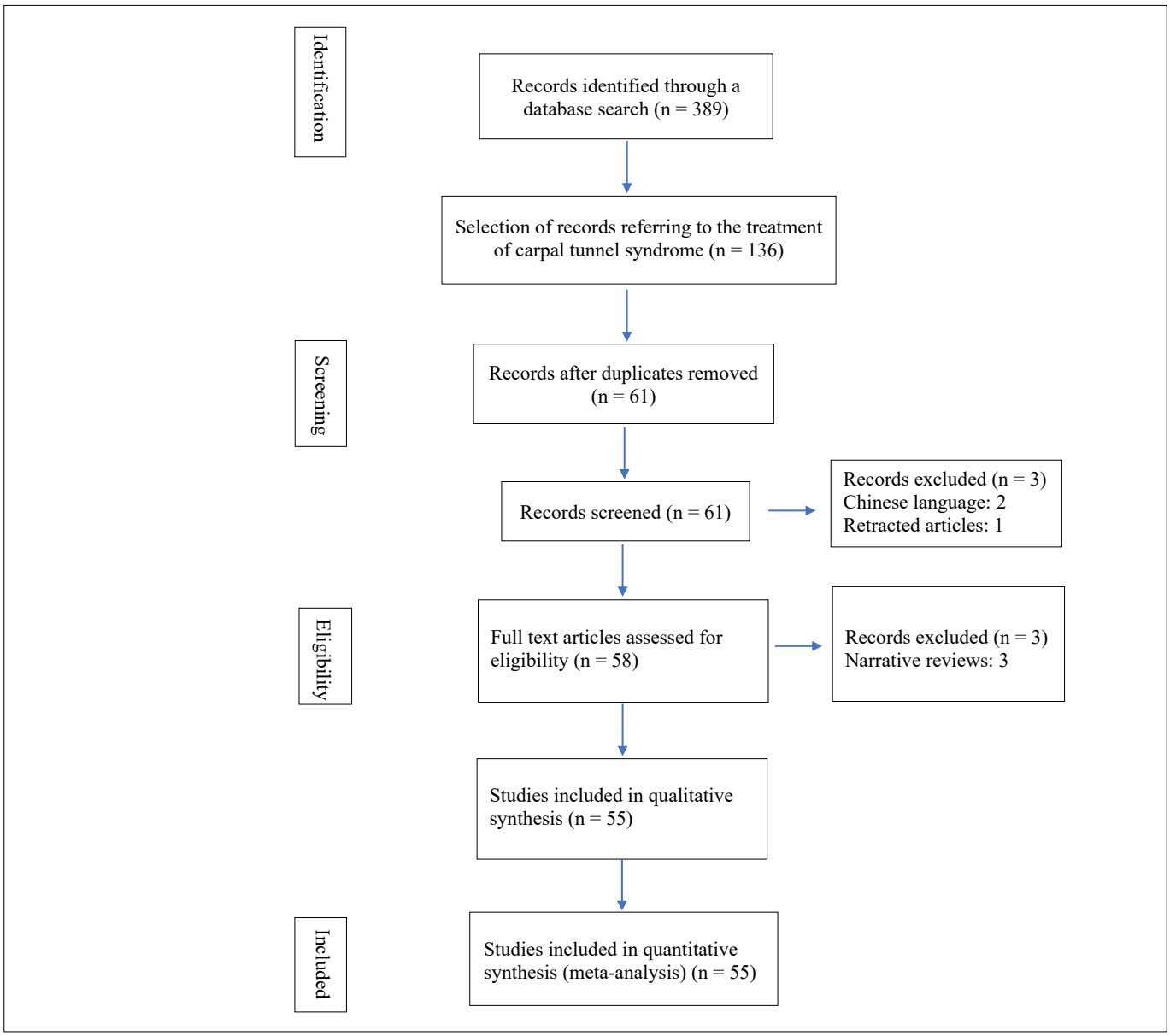

Figure 1. The Preferred Reporting Items for Systematic Reviews and Meta-Analyzes (PRISMA) flowchart of this study.

PRISMA has emerged as a guideline for systematic reviews with better technical quality, which differs from the AMSTAR scores. We speculate that this is one explanation for the lower agreement between observers and the lower robustness of this score. In addition, AMSTAR generally presents more detailed items.[7-9,67]

Observing the relationship between the same covariates and country of origin, we noted that Chinese studies performed meta-analyses more consistently: 100% of Chinese studies included in this study performed meta-analyses, while only 51% of non-Chinese studies performed meta-analyses in their systematic reviews, which supports the current trend of high-quality Chinese studies.[11]

Studies citing PRISMA were more common in journals with a lower impact factor. Although this finding is not intuitive, many high-impact journals endorse PRISMA, and we inferred that many high-quality studies rely on the items in this questionnaire despite not explicitly quoting it (i.e. they have a high PRISMA score despite not mentioning it).

Systematic reviews on CTS have consistently revealed recurrent imperfections. Many lost points on PRISMA for presenting an incomplete, unstructured summary, not presenting a review protocol, not presenting a detailed search strategy, not presenting the data combination methods in detail, and not presenting the

Table 1. Study characteristics

Author, Year	Impact factor	Conflict of interest	Country of origin	What comparison?	Number of institutions	Total number of patients	Number of words	Study design	Meta-analysis	Quoted PRISMA?
Alvayay et al.,[13] 2008	Q4	NO	CHILE	Different CTS physiotherapeutic treatments	1	1,415	1,702	RCT, SYSTEMATIC REVIEW	NO	NO
Babaei-Ghazani et al.,[14] 2017	Q1	NO	IRAN	Corticosteroid injection into the carpal tunnel: guided ultrasound versus guided landmark	3	137	3,502	RCT	YES	NO
Ballestero-perez et al.,[15] 2016	Q1	YES	SPAIN	Effectiveness of nerve glide exercises in CTS	5	733	2,420	RCT, CT	NO	YES
Bekhet et al.,[16] 2017	Q2	YES	EGYPT	Low frequency laser versus placebo	6	473	2,731	RCT	YES	YES
Burger et al.,[17] 2017	Q2	YES	SOUTH AFRICA	Low frequency laser versus placebo	5	614	4,897	RCT	NO	NO
Burton et al.,[18] 2016	Q1	YES	UNITED KINGDOM	Clinical course and prognostic factors of conservative treatment CTS	1	2.639	4,490	COHORT	NO	NO
Chapell et al.,[19] 2003	Q1	YES	UNITED STATES	Neurolysis and epineurotomy versus placebo in surgical treatment	1	390	2,925	RCT	YES	NO
Chen et al.,[20] 2014	Q1	NO	CHINA	Open versus endoscopic release	1	1.395	2,481	RCT	YES	NO
Chen et al.,[21] 2015	Q2	YES	TAIWAN	Different local infiltrations of corticosteroids in the carpal tunnel	4	633	4,728	RCT	YES	NO
Choi et al.,[22] 2018	Q1	YES	SOUTH KOREA/ UNITED STATES	Acupuncture and related interventions for placebo treatments	2	869	13,354	RCT/QUASI-RCT	YES	YES
Dunn et al.,[23] 2017	Q2	YES	UNITES STATES	Labor compensation versus no labor compensation in the treatment of CTS	2	4,367	2,006	PROSPECTIVE, RETROSPECTIVE	NO	NO
Franke et al.,[24] 2017	Q1	YES	NETHERLANDS	Benefits of low frequency laser therapy for CTS	2	1,048	4,923	REVIEWS, RCT	YES	NO
Gerritsen et al.,[25] 2001	Q1	YES	NETHERLANDS	Surgical treatment of CTS	3	1,264	5,021	RCT	NO	NO
Gerritsen et al.,[26] 2002	Q1	YES	NETHERLANDS	Non-surgical treatment carpal tunnel syndrome	4	639	3,189	RCT	NO	NO
Goodyear-Smith et al.,[27] 2004	Q1	YES	NEW ZEALAND	Non-surgical treatment carpal tunnel syndrome	1		2,536	RCT	NO	NO

Continue....

Table 1. Continuation

Author, Year	Impact factor	Conflict of interest	Country of origin	What comparison?	Number of institutions	Total number of patients	Number of words	Study design	Meta-analysis	Quoted PRISMA?
Hamamoto filho et al.,[28] 2009	Q3	YES	BRAZIL	Anti-inflammatory drugs in the treatment of CTS	1	323	3,078	RCT	NO	NO
Hu et al.,[29] 2016	Q2	YES	CHINA	Open versus endoscopic release	2	142	3,052	RCT	YES	YES
Huisstede et al.,[30] 2010	Q1	YES	NETHERLANDS	Effects of non-surgical treatment on CTS	1	4,596	5,822	SYSTEMATIC REVIEW / RCT	NO	NO
Huisstede et al.,[31] 2010	Q1	YES	NETHERLANDS	Effects of surgical treatment on CTS	1	2,957	9,127	SYSTEMATIC REVIEW / RCT	NO	NO
Huisstede et al.,[32] 2017	Q1	YES	NETHERLANDS	Effectiveness of physiotherapy and electrophysical modalities in CTS	2	1,617	5,273	REVIEWS, RCT	NO	NO
Huisstede et al.,[33] 2017	Q1	YES	NETHERLANDS	Comparison between different treatment modalities and post-surgical interventions	2	9,566	7,352	REVIEWS, RCT	NO	NO
Huisstede et al.,[34] 2018	Q1	NO	NETHERLANDS	Oral pain medications versus placebo/ oral steroids versus splinting/ corticosteroid versus placebo	2	1,760	5,171	SYSTEMATIC REVIEW / RCT	NO	NO
Hunt et al.,[35] 2009	Q3	YES	UNITED KINGDOM	Chiropractic manipulation CTS	1	91	2,513	RCT	NO	NO
JImenez Del Barrio et al.,[36] 2016	Q2	YES	SPAIN	Effectiveness of non-surgical carpal tunnel syndrome treatment	2	1,818	2,505	"CLINICAL TRIALS"	NO	SIM
Kim et al.,[37] 2019	Q2	YES	SOUTH KOREA	Shockwave therapy versus non-therapy - CTS	1	281	2,341	RCT	YES	YES
Kim et al.,[38] 2015	Q2	NO	SOUTH KOREA	Effectiveness of nerve and tendon slip exercises in CTS	1	261	1,697	RCT	NO	YES
Klokkari et al.,[39] 2018	Q3	YES	GREECE/ CYPRUS	Surgical versus non-surgical treatment	2	1,787	5,194	RCT, CT, PROSPECTIVE, RETROSPECTIVE	YES	YES
Kohanzadeh et al.,[40] 2012	Q2	YES	UNITED STATES	Open versus endoscopic release	3	4,178	1,846	RCT, RETROSPECTIVE	NO	NO
Lai et al.,[41] 2019	Q1	YES	CHINA	Surgical treatment with reconstruction versus without retinaculum flexor reconstruction	1	639	2,644	RCT	YES	YES
Li et al.,[42] 2019	Q2	YES	CHINA	Standard incision versus limited incision	2	1,020	2,722	RCT	YES	YES
Li et al,[43] 2016	Q2	YES	CHINA/UNITED STATES	Low frequency laser effectiveness in CTS	4	531	2,112	RCT	YES	NO

Continue....

Table 1. Continuation

Author, Year	Impact factor	Conflict of interest	Country of origin	What comparison?	Number of institutions	Total number of patients	Number of words	Study design	Meta-analysis	Quoted PRISMA?
Lim et al.,[44] 2017	Q1	YES	AUSTRALIA/ SINGAPORE	Mobilization of the median nerve in CTS	2	404	2,676	RCT	NO	YES
Malahias,[45] 2019	Q2	YES	GREECE/ CYPRUS	Platelet rich plasma versus control	2	192	2,636	RCT, CASE CONTROL, PROSPECTIVE CONTROLED TRIAL, CASE CONTROL, CASE REPORT	NO	YES
Marshall et al.,[46] 2007	Q1	YES	CANADA	Corticosteroid injection into the carpal tunnel	1	671	7,052	RCT/QUASI-RCT	YES	NO
Medina McKeon et al.,[47] 2008	Q2	NO	UNITED STATES	CTS nerve slip	1	428	4,284	CT	YES	NO
Muller et al.,[48] 2004	Q1	NO	CANADA	Effects of non-surgical treatment on CTS	2	1,280	5,387	RCT UNTIL AUTHOR'S OPINION	NO	NO
O'Connor et al.,[49] 2003	Q1	YES	CANADA/ AUSTRALIA	Non-surgical treatment in CTS (except steroid injection)	3	884	10,131	RCT/QUASI-RCT	YES	NO
O'Connor et al.,[50] 2012	Q1	YES	AUSTRALIA/ CANADA	Effects of ergonomic positioning or equipment versus no treatment, placebo, non-surgical treatment	3	105	4,654	RCT/QUASI-RCT	YES	NO
Page et al.,[51] 2012	Q1	YES	AUSTRALIA	Orthosis versus no treatment, placebo, other non-surgical intervention	2	1,190	14,163	RCT/QUASI-RCT	YES	NO
Page et al.J,[52] 2012	Q1	YES	AUSTRALIA	Exercise and mobilization versus placebo, no treatment or non-surgical treatment	2	741	20,024	RCT/QUASI-RCT	NO	NO
Page et al.,[53] 2013	Q1	YES	AUSTRALIA	Therapeutic ultrasound versus other treatments for CTS	3	443	14,759	RCT	YES	NO
Piazzini et al.,[54] 2007	Q1	NO	ITALY	Non-surgical treatment in CTS	1	1,556	2,569	RCT	NO	NO
Sanati ka et al.,[55] 2011	Q1	YES	SCOTLAND/ UNITED KINGDOM/ UNITED STATES/IRAN	Standard incision versus limited incision	6	1,512	1,697	RCT	YES	NO
Sayegh et al.,[56] 2014	Q1	YES	UNITED STATES	Open versus endoscopic release	1	1,859	3,505	RCT	YES	YES

Continue....

Table 1. Continuation

Author, Year	Impact factor	Conflict of interest	Country of origin	What comparison?	Number of institutions	Total number of patients	Number of words	Study design	Meta-analysis	Quoted PRISMA?
Scholten et al.,[57] 2007	Q1	YES	NETHERLANDS	Different surgical treatments	1	1,284	4,137	RCT	YES	NO
Shi et al.[58] 2011	Q2	YES	CANADA	Surgical treatment versus non-surgical treatment	1	712	2,948	RCT, CT	YES	NO
Shi et al.,[59] 2018	Q2	YES	CANADA	Surgical intervention versus no surgical intervention	4	1,028	2,800	RCT	YES	YES
Sim et al.,[60] 2011	Q2	YES	SOUTH KOREA/ UNITED KINGDOM	Acupuncture versus other non-surgical treatments	4	442	2,245	RCT	YES	NO
Soltani et al.,[61] 2013	Q1	YES	UNITED STATES	CTS recurrence: open decompression versus flap	1	658	2,990	CASE SERIES: PROSPECTIVE/ RETROSPECTIVE	YES	NO
Thoma et al.,[62] 2004	Q1	NO	CANADA	Open versus endoscopic release	1		2,448	RCT	NO	NO
Vasiliadis et al.,[63] 2014	Q1	YES	GREECE/ SWEDEN/ CANADA/ NETHERLANDS	Endoscopic release versus other surgical intervention in CTS	4	2,586	11,843	RCT/QUASI-RCT	YES	NO
Vasiliadis et al.[64] 2015	Q1	YES	SWITZERLAND/ GREECE/ CANADA/ UNITED KINGDOM/ NETHERLANDS	Open versus endoscopic release	6	2,449	4,754	RCT/QUASI-RCT	YES	YES
Verdugo et al.,[2] 2008	Q1	YES	CHILE	Surgical treatment versus non-surgical treatment	1	198	3,276	RCT/QUASI-RCT	YES	NO
Wade et al.,[65] 2018	Q1	YES	UNITED KINGDOM/ ITALY	Absorbable versus non-absorbable suture	4	255	9,703	RCT/QUASI-RCT	YES	YES
Zuo et al.,[66] 2015	Q2	YES	CHINA	Open versus endoscopic release	1	1,253	3,940	RCT	YES	NO

PRISMA = preferred reporting items for systematic reviews and meta-analyzes; CTS = carpal tunnel syndrome; RCT = randomized controlled trial; CT = controlled trial.

Table 2. Quantitative data

	Average	CI 95%
PRISMA E1	12.67	11.36–13.99
PRISMA E2	14.00	12.94–15.06
PRISMA average	13.34	12.17–14.5
AMSTAR E1	7.17	6.38–7.96
AMSTAR E2	7.21	6.59–7.83
AMSTAR average	7.19	6.51–7.87
Number patients	1326.66	905.74–1747.58
Number words	4872.27	3.867.37–5877.18

CI = confidence interval; E1 = examiner 1; E2 = examiner 2.

impact of the risk of bias on the results. Studies lose points in the AMSTAR score for not explaining the study designs included, not describing the studies in detail, not citing the study funding, not discussing the impact of the risk of bias of the studies on the results, and not explaining the causes of heterogeneity between studies. An ideal systematic review of CTS would explain all of these aspects.

The use of PRISMA and AMSTAR is important for the generation of quality scientific evidence, and allows for the critical evaluation of available publications to date. The dissemination of other

Table 3. Qualitative results of the A measurement tool to assess systematic reviews assessment

	E1		E2		Average E1; E2	
"Very low" quality	26	(47%)	17	(31%)	21.5	(39.1%)
"Low" quality	22	(40%)	25	(45.4%)	23.5	(42.7%)
"Moderate" quality	5	(10%)	12	(21.8%)	8.5	(15.5%)
"High" quality	2	(3%)	1	(1.8%)	1.5	(2.7%)

E1 = Examiner 1; E2 = Examiner 2.

Table 4. Comparison of covariates for PRISMA

	Number of studies (total = 55)	Average	CI	P value
Impact factor	Q1 (n = 34)	14.16	12.64–15.68	0.095
Meta-analysis	Yes (n = 31)	15.61	14.25–16.97	0.008
Study design	RCT (n = 33)	14.47	12.82–16.12	0.103
Conflict of interest	Conflict (n = 46)	13.95	12.69–15.21	0.155
Country of origin	China (n = 6)	14.67	12.96–16.38	0.268
Quote PRISMA	Yes (n = 17)	14.47	12.19–16.75	0.131

CI = confidence interval; PRISMA = preferred reporting items for systematic reviews and meta-analyzes; RCT = randomized controlled trial.

Table 5. Comparison of Covariates for A Measurement Tool to Assess Systematic Reviews

	Number of studies (total = 55)	Average	CI	P value
Impact factor	Q1 (n = 34)	7.55	6.68–8.42	0.372
Meta-analysis	Yes (n = 31)	8.43	7.55–9.31	0.009
Study design	RCT (n = 33)	7.95	6.98–8.92	0.043
Conflict of interest	Conflict (n = 46)	7.57	6.83–8.31	0.173
Country of origin	China (n = 6)	8.21	6.72–9.7	0.16
Quote PRISMA	Yes (n = 17)	7.47	6.04–8.9	0.183

CI = confidence interval; PRISMA = Preferred Reporting Items for Systematic Reviews and Meta-Analyses; RCT = randomized controlled trial.

Table 6. Impact factor X covariates

		Low impact (Non Q1)		High impact (Q1)		Total		P value
		n*	%	n*	%	n*	%	
Quote PRISMA	Yes	10	47.60%	7	20.60%	17	30.90%	0.035
Conflict of interest	Conflict	18	85.70%	28	82.40%	46	83.60%	0.743
Study design	RCT	18	85.70%	31	91.20%	49	89.10%	0.528
N. Institutions	Multicentric	13	61.90%	20	58.80%	33	60.00%	0.821
Meta-analysis	Yes	12	57.10%	19	55.90%	31	56.40%	0.927
Country of origin	China	4	19.00%	2	5.90%	6	10.90%	0.128

*Total number of studies = 55.

PRISMA = Preferred Reporting Items for Systematic Reviews and Meta-Analyses; RCT = randomized controlled trial.

Table 7. Country of origin X covariates

		Chinese studies		Chinese studies		Total		P value
		n*	%	n*	%	n*	%	
Quote PRISMA	Yes	3	50%	14	28.60%	17	30.90%	0.284
Conflict of interest	Conflict	5	83.30%	41	83.70%	46	83.60%	0.983
Study design	RCT	6	100%	43	87.80%	49	89.10%	0.364
N. Institutions	Multicentric	3	50%	30	61.20%	33	60.00%	0.596
Meta-analysis	Yes	6	100%	25	51.00%	31	56.40%	0.022

*Total number of studies = 55.

PRISMA = Preferred Reporting Items for Systematic Reviews and Meta-Analyses; RCT = randomized controlled trial.

Table 8. Intra-observer correlation between the scores for A Measurement Tool to Assess Systematic Reviews and Preferred Reporting Items for Systematic Reviews and Meta-Analyzes

		E1	E2	Average
Spearman	Corr (r)	0.82	0.798	0.829
	P value	< 0.001	< 0.001	< 0.001
ICC	Corr (r)	0.856	0.839	0.857
	P value	< 0.001	< 0.001	< 0.001

ICC = intraclass correlation coefficient; E1 = examiner 1; E2 = examiner 2.

Table 9. Inter-observer correlation between the scores for a PRISMA and AMSTAR

	PRISMA	AMSTAR
Average	-1.33	-0.04
Standard deviation	1.91	1.48
P value	< 0.001	0.856
Regression	< 0.001	0.001

PRISMA = Preferred Reporting Items for Systematic Reviews and Meta-Analyses; AMSTAR = A Measurement Tool to Assess Systematic Reviews.

Table 10. Inter-observer correlation for A Measurement Tool to Assess Systematic Reviews

	Kappa	P value
Original*	0.442	< 0.001
Grouped**	0.641	< 0.001

*Very low, low, moderate, high; **Low, moderate/high.

Table 11. Results of multivariate analysis

	PRISMA		AMSTAR	
	Coef. (B)	P value	Coef. (B)	P value
Constant	4.89	0.03	3.36	0.016
Impact Q1	2.54	0.01	1.06	0.076
Meta-analysis	4.74	< 0.001	2.53	< 0.001
Multicentric	2.2	0.022	1.69	0.005
Conflict of interest	1.41	0.263	1.16	0.138
Non-Chinese studies	0.17	0.911	-0.45	0.633
Quote PRISMA	1.12	0.275	-0.2	0.747
RCT	1.34	0.353	0.26	0.77
ANOVA	< 0.001		< 0.001	
R2	54.40%		49.20%	

PRISMA = Preferred Reporting Items for Systematic Reviews and Meta-Analyses; AMSTAR = A measurement tool to assess systematic reviews; Coef. = coefficient; RCT = randomized controlled trial; ANOVA = analysis of variance.

similar systems allows for the organization and systematization of the main aspects related to the quality and reliability of information sources. This would further improve the refinement of the best currently available evidence for the treatment of carpal tunnel syndrome.

Limitations

The main limitation of this study was that the search for systematic reviews was published in all languages, except Mandarin.

We tried to minimize biases in the selection, application of questionnaires, and data analysis by carrying out our analysis with independent examiners, and any disagreements were concluded with reference to the senior author. Statistical analysis was conducted by an independent statistician with no conflicts of interest.

CONCLUSION

Our results suggest that published systematic reviews on the treatment of CTS are of low quality, and those that contain meta-analyses and include randomized clinical trials are generally of better quality.

The PRISMA and AMSTAR scores are effective tools for formulating and guiding systematic reviews, although AMSTAR performed better. The reproducibility of AMSTAR scores allows for the analysis of future studies on the treatment of CTS, which is useful for the preparation of other high-quality studies.

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Hypertension from the patient's perspective: contributions to the care offered by health professionals and self-care – a qualitative study

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ABSTRACT

BACKGROUND: Hypertension is the most common disease in primary care settings. Only 30% of cases were adequately controlled.

OBJECTIVES: To analyze the knowledge and understanding of patients with hypertension regarding the factors that facilitate and limit adherence to treatment and, based on the results, build specific guidelines on hypertension self-care and control.

DESIGN AND SETTING: This qualitative study was conducted in a primary healthcare setting.

METHODS: Patients with hypertension who were followed at a primary healthcare unit were interviewed through focus groups, and a qualitative interpretation of their statements according to Bardin's content analysis was performed.

RESULTS: Three focus groups were formed (21 participants), from whose analysis emerged 74 core ideas related to the concept of hypertension, causes of increase in blood pressure, clinical consequences of hypertension, and possible patients' contributions to help control blood pressure, arising from eating habits, psychosocial conditions, and lifestyle. Patients tend to accept the concept of "high blood pressure" as an inherent condition of the disease in their lives. Eating habits are strongly related to life history and self-perception of health. The association between high blood pressure and nervousness or stress appears to be strong.

CONCLUSION: The experience of having "pressure problem" is unique for each person. It is necessary to optimize listening, recognizing that, for the patient to understand what hypertension is and its management, there must be understanding and convergence of proposals, adjustments, and changes in a positive and personalized way. As a result of this study, we implemented educational actions in primary healthcare units.

INTRODUCTION

Hypertension, defined as the persistent elevation of systolic blood pressure (BP) to values ≥ 140 mmHg and/or diastolic BP ≥ 90 mmHg, is a chronic disease with a high worldwide prevalence.[1,2] In Brazil, the disease affects 21.4–32.3% of the population, varying according to the survey's methodological criteria.[2,3] Among the risk factors for hypertension development are heredity, age, sex, race, overweight/obesity, excessive sodium consumption, sedentary lifestyle, excessive alcohol consumption, smoking, and socioeconomic factors, such as educational level.[2] Hypertension is directly associated with a higher risk of cardiovascular and renal complications, particularly stroke, myocardial infarction, chronic kidney disease, and other serious complications.[2] There is a slight increase in the mortality rate directly related to hypertension; however, 50% of deaths from cardiovascular disease are associated with hypertension.[2,4]

As the main objective of treatment is to reduce cardiovascular and renal morbidity and mortality associated with hypertension, the use of non-pharmacological and pharmacological treatment is essential in the reduction of BP levels and prevention of hypertension complications.[2] In practice, non-pharmacological treatment mainly involves dietary measures aimed at weight loss and reduction of sodium consumption, regular physical activity, alcohol consumption reduction (when excessive), and smoking cessation. Regarding pharmacological treatment, adherence to medication is essential to achieve BP control.

Although the diagnosis of hypertension is relatively simple and some consider its treatment easy, the high percentage of individuals with undiagnosed hypertension and the number of patients diagnosed with hypertension who continue to have elevated BP express the complexity of monitoring these patients, requiring great attention and effort from the healthcare system, and there is no doubt about the importance of a multidisciplinary approach.[2]

Adherence to a therapeutic plan can be understood as the relationship between the guidance and prescription of the healthcare team and the patient's conduct to follow them. Compliance with the therapeutic plan is a multidimensional process, which involves several circumstances: lack of knowledge about the disease and lack of motivation to comply with the treatment of a chronic disease; the absence of symptoms; unfavorable socioeconomic and educational background; difficulties in the relationship with healthcare services and in scheduling appointments; cost of certain medications and their adverse effects; and other aspects such as cultural and social beliefs and changes in quality of life after treatment initiation.[2,5]

Considering that a patient's relationship with the healthcare team is an important element in the context of chronic diseases, a multidisciplinary approach in the follow-up of patients with hypertension, which focuses on the therapeutic process, is fundamental to the adherence and maintenance of treatment.[6]

In a primary healthcare unit (PHU) in a large city in São Paulo state, a pilot study is underway to evaluate a new systematization of care for the entire population with hypertension and/or diabetes mellitus accompanied by a family healthcare team (approximately 2,600 residents). This includes nursing care and home visits that aim for BP and glycemic control and individual and family guidance.

OBJECTIVES

In the context of this pilot project, medical students working regularly at the PHU dedicated themselves to identifying the factors that facilitate and limit adherence to the treatment of hypertension in this population and understanding, from the patient's perspective, the meaning and repercussions of the disease in their lives, contributing to the follow-up by the healthcare team.

METHODS

This was an exploratory, qualitative, cross-sectional, analytical observational study. Individuals with hypertension belonging to the territory of a PHU with a family health strategy were invited to participate. The selection of participants with hypertension was aleatory among those attending the PHU. All the participants who agreed to participate were included in the study.

The areas of competence related to hypertension self-care were defined through a bibliographic survey in the Virtual Health Library database, considering articles written in Portuguese, English, and Spanish, from 2013 to 2018, using the descriptors "hypertension," "self-care," and "health education," and involved the following topics: general notions about hypertension and its complications, BP self-control, self-care in drug treatment, self-care in the prevention of chronic and acute hypertension complications, and nutritional self-care. From this list of competencies, a script was formulated, which contained questions that guided the focus groups in analyzing patients with hypertension.

Focus groups were formed based on the definition proposed by Morgan: "A research technique that collects data through group interactions when discussing a special topic suggested by the researcher," to understand feelings, beliefs, and participants' behaviors.[7] The focus group discussions were conducted until saturation of alternative answers was achieved and not pre-established. Three focus groups consisted of an average of seven participants per group. The discussions were recorded, transcribed, and analyzed by two authors, aiming to understand the most significant contents, according to the analysis process recommended by Bardin.[8] The units were categorized according to the semantic criteria, establishing thematic categories that were exhaustively reviewed and described below.

The research project and informed consent form were submitted to a research ethics committee, approved on May 8, 2018, and only started after their approval (CAAE 86670318.6.0000.5373).

RESULTS

A total of 21 participants with hypertension were included in the focus group. The participants' characteristics are presented in **Table 1**. The sample of participants and their distribution by age, sex, autodeclared race or skin color, time from diagnosis of hypertension, BP levels, and number of antihypertensive prescriptions were similar to the profiles of those attending the PHU.

The content analysis allowed the classification of the speeches into categories in accordance with the core ideas, which summarized

Table 1. Demographic and clinic characteristics of the participants

Parameter	Mean ± SD	Comments
Age	65.4 ± 13.6 years	> 60 years (70%)
Sex	13 women, 8 men	
Autodeclared race (skin color)	16 whites, 5 blacks	
Time from hypertension diagnosis	14.6 ± 8.7 years	
Systolic blood pressure	154.6 ± 18.3 mmHg	< 140/90 mmHg (33.3%)
Diastolic blood pressure	87.5 ± 11.6 mmHg	
Number of AH prescribed	Median = 2 AH	3 persons 1 AH 12 persons 2 AH 5 persons 3 AH 1 person 4 AH

SD = standard deviation; AH = antihypertensive.

the topic addressed in the response. To analyze these core ideas, summary tables were prepared from the statements listed for each issue raised in the discussions. The different statements of the participants were considered and counted. **Table 2** shows the core ideas based on the frequency of their appearance among the statements.

Regarding the first question, "Does anyone know what hypertension or 'high blood pressure' is?" some representative expressions of the participants' understanding of what hypertension is were as follows: "It is a silent disease, I don't feel anything," which is related to the absence of symptoms; "It must be a blood problem, right doctor? Change the heartbeat"; and "It messes with the circulation," which is related to the core idea of cardiovascular disease.

Table 2. Core ideas expressed during focus group discussion

Regarding the concept of hypertension or high blood pressure	Frequency
1. Cardiovascular diseases	5
2. Asymptomatic	4
3. Heredity	4
4. Unknown	3
5. Lifestyle	3
6. Related to the nervous system	2
7. Blood pressure levels	2
Regarding possible causes of increased blood pressure	**Frequency**
1. Nervousness/stress	17
2. Inadequate food intake	16
3. Salt consumption	10
4. Anxiety	5
5. Hypercholesterolemia/fat consumption	5
6. Consumption of alcoholic beverages and smoking	4
7. White coat hypertension	3
8. Treatment interruption	3
9. Sedentary lifestyle	3
10. Kidney injury	2
11. Weight excess	1
12. Others	4
Regarding consequences of high blood pressure	**Frequency**
1. Circulatory problems	5
2. Stroke/paralysis/dementia	4
3. Nephropathy	4
4. Neck pain	3
5. Myocardial infarction	3
6. Dizziness	3
7. Death	2
Regarding control or prevention of high blood pressure	**Frequency**
1. Healthy eating/salt reduction/water intake	54
2. Medicine treatment	47
3. Physical exercise	16
4. Access to health/information services	14
5. Emotional control	13
6. Self-care	5
7. Faith	4

Regarding the second question, 'What can cause hypertension or high blood pressure?' some examples of how they expressed themselves during the focus groups were as follows: "It's an unwelcome inheritance, it's hereditary," which is related to the heredity of hypertension; "It's what you eat, what you drink, and what you do during your life, right?," which is related to dietary habits and lifestyle; "Pressure is nervous, stuff like that"; "The increase in blood pressure ... has a lot of emotional influence, a lot of," which is related to the core idea of nervousness, stress, and/or the nervous system.

Regarding the third question, "What are the consequences of high blood pressure?" the consequences were mentioned in a similar way to those illustrated in the following examples, which were obtained from their statements: "It can really cause kidney problems"; "Oh, it causes stroke, [hypertension] can cause a heart attack"; and "My mother died suddenly of a heart attack at age 47, from high blood pressure."

In view of the nature of the answers, analyses of the fourth and fifth questions were grouped. The fourth question was "What can you do to control high blood pressure?" and the fifth was "What can you do to prevent high blood pressure?" Some statement on what helps hypertension control were as follows: "to consume little salt, and eliminate nervousness helps a lot"; "that's where I think physical activity comes in, right?"; "oh... exercise, walking, medication..."; "you have to control the salt, which is the main thing, … and control the nerves"; "The only thing I do, my whole life, I've been taking medication for about 18 years, I take it all together, in the morning and at night."

DISCUSSION

Focus group discussion, the method selected for this study, provides the appreciation of the individual within the collective, under the influence of social pressure and the reactions that demand it, being in an intermediate position between pure observation and in-depth interviews.[9]

In brief, the results showed that the participants expressed the concept that hypertension is an asymptomatic disease caused by hereditary and behavioral factors, particularly dietary habits and lifestyle, and is associated with circulatory and renal diseases and complications. This was also evident in their statements regarding the understanding of emotional factors as possible causes of high BP. Regarding the control of hypertension, they valued adherence to adequate eating habits, physical exercise, emotional control, drug treatment, and access to health services. Self-care and faith were rarely mentioned but were present in their statements. Overweight or obesity was mentioned as a possible cause of hypertension only once. Difficulties in accessing the healthcare system or lack of antihypertensive medications did not emerge as problems in hypertension care.

Although the definition, awareness of causes, and recognition of complications of hypertension have been mentioned, these concepts were confused and mixed in their statements. Some participants

provided the definition of "high blood pressure" as a pressure value achieved by assessing it with measuring devices. Others related it to a problem with the heart or blood vessels, while others associated it with lifestyle habits. Some studies have already shown that most patients do not know how to define or wrongly define hypertension.[10-12] Renovato and Dantas claim that there is a "crisis of understanding" about the disease by patients with hypertension.[13] These authors suggest that the absence of symptoms at the time when the healthcare professional imputes him as sick is responsible for the contradiction, while the constant high BP levels throughout the disease follow-up end up convincing them that there is really something wrong, making them move along this gradient of conviction about being carriers of this "hypertension" entity.[13]

In addition to this difficulty in recognizing the problem, there is still semantic disagreement in the discourse between doctors and patients. Fleischer, in her ethnographic study conducted in Guariroba (Federal District) on patients with hypertension, recognized the disparity in meanings between the terms used by doctors and what the patient understands.[14] The nosological category "hypertension" does not exactly match "high blood pressure" in popular vocabulary but the term "pressure problem."[14] This is due to the fact that patients link the moments of uncontrolled BP, which are represented by pressure peaks, to the term "high blood pressure" and understand this phenomenon as transitory, often related to the emotional status, as arising from a moment of stress. Conversely, having the disease "under control," without documented moments of pressure peaks, is better understood by patients as a "pressure problem." This is preceded by the verb "to have," presenting a permanent character, while "high blood pressure" is usually preceded by the verb "to be/*estar*," evidencing its transience.[14]

Our study also showed that, as a group, patients tended to assume the definition of "high blood pressure" as the practical condition that the disease has in the life of each of them and not on a biomedical basis as was expected by the researchers, which allows us to understand that, in the participant's view, the full concept of hypertension did not matter only in terms of meaning for them but in what it would pragmatically reflect, that is, its consequences (stroke, heart attack, kidney problems, circulatory problems, and even death). Moreover, symptoms such as neck pain, dizziness, leg pain, shortness of breath, and tachycardia have been reported, which, from a physician's perspective, will only be present after the complications of hypertension arise.[1,2] It is evident in the speech of the study participants and in the literature that there is a misconception that these reported symptoms represent hypertension itself and not common complications of the advanced stage of the disease, which are preventable with adequate BP control.[10-12]

Participants also mentioned the need for chronic food restriction and drug treatment for the rest of their lives, factors recognized in the literature for influencing quality of life and adherence to treatment.[15,16] Food intake is strongly linked to the history of people's lives, culture, and self-perception of health. Many people have a history of vulnerability or food deprivation at other times in their lives and are negatively associated with restrictions required by their disease at such times, which makes their adherence difficult. The absence of visible signs of the disease in their daily lives makes them question the real need to adopt such habits as well as influence adherence to drug treatment.[17]

In the quest to identify the origin of their health problems, participants recognized factors such as high consumption of salt, fatty foods, alcoholic beverages, and cigarettes; sedentary lifestyle; and heredity as present in the genesis of hypertension. Such factors have already been reported by patients in other studies, and the result was not surprising.[10] However, it is noteworthy that there was only one mention of overweight and obesity as risk factors for hypertension. Although there were several references to inadequate nutrition as a possible cause of the disease, the participants did not relate carbohydrate excess and weight gain as a risk factor for hypertension nor did they recognize the limitation of the consumption of carbohydrates and fat as a way of reducing weight and consequently BP. We were also surprised by the overestimation of the etiological association between hypertension and nervousness, which were mentioned in terms such as "nervous system," "nervous," "nerve," "emotional," "stress," "anxiety," and "frightening." Such a relationship has already been demonstrated in other studies, although it is unclear whether the association made by patients is a cause or a consequence.[10,11,13,17-20] It is assumed that patients perceive the disease as a thermometer of their emotional state, oscillating along with their emotions, even treating the two things as the same entity.[16] The two things are so strongly aggregated in the participants' imagination that they assume as valid the strategy that it is possible to control the disease just by controlling nervousness, even evoking a curative characteristic of hypertension if the emotions that trigger it were controlled.[14,19,21]

Fava et al. and Fleischer discussed in their ethnographic studies how this hypertension–nervousness marriage is taken into account by healthcare professionals who take care of these patients.[14,22] Although there are physiological bases on the contribution of stress in the development of high BP, the hypertension control programs of our healthcare system do not include effective strategies to deal with these factors.[14,22] In fact, in many places of the Unified Health System, it is difficult to adequately discuss and treat mental health disorders, a topic shrouded in taboo, which allows the perpetuation of myths and prejudices when referring to the topic of hypertension.[14]

In addition to controlling the emotional state, patients understand that the modification of lifestyle recognized as causes of high BP is a way of exercising self-care and controlling BP. However, this is a challenge in practice. The chronic nature of the treatment is one of the reasons that leads to the discontinuation of these practices,

causing discouragement, since the practices that need correction are often the same ones that produce a psychologically compensatory effect for the individuals, considered by them as protectors of the stress that they believe to be the cause of the increase in their BP.[15,17] Moreover, the state of social vulnerability that most patients are in makes it difficult to access healthier life practices.[20]

Health professionals have an opportunity to intervene in these groups of people, aiming to spread techniques that are economically viable and easily accessible, so that these people can find qualified scientific information.

Adherence to pharmacological treatment is ambiguous, as it is frequently associated with the occurrence of symptoms, which are often late in this group. In the absence of BP peaks and symptoms, patients with hypertension carry a conception of having been cured, allowing themselves to interrupt the treatment, even with the opposite orientation.[16]

As a result of this study and with the support of medical students who attend the PHU, we are implementing several actions in health units, such as forming support networks via social media that can offer health education, exchanging information, and facilitating the follow-up of patients with hypertension; distributing educational posters and leaflets in PHU with short and direct information; encouraging self-care and self-measurement of BP at home; and establishing simple and direct nutritional guidelines. Some examples of sentences with information and guidelines were communicated:

"Did you know that the best medicine to fight the pressure problem is to lose weight?"

"People with pressure problem don't feel any discomfort, but it can hurt their heart, brain, and kidneys."

"If you have pressure problem, learn how to measure your blood pressure at home with automatic (arm) devices. It is very simple and cheap and helps to control your blood pressure."

"If you have high blood pressure and you take medication to control it, keep taking them, even if you have had alcoholic beverages."

"You can help control your blood pressure. Eats with little salt, lose weight if they are overweight, and perform regular physical exercise (walking is the best)."

Due to the coronavirus disease 2019 pandemic, we should still avoid crowds to prevent disease transmission; however, as soon as sanitary conditions allow, group meetings will be promoted to encourage self-care educational practices for patients with hypertension.

CONCLUSION

The group approach of patients with hypertension allowed us to analyze how the experience of having "pressure problem" is unique for each person. Being personal, it is not possible to imagine an awareness strategy that can reach everyone. It is important to confirm in this study the perception that these patients need professionals who listen to them, seeking to recognize the meanings of their speeches, in contrast to the use of scientific and biomedical jargon, through pre-shaped recipes for a human being impersonal and generalized. For this, it is necessary to listen to these patients, with a high degree of empathy, recognizing that, for the patient to understand what hypertension is and its management, there must be understanding, convergence of proposals, adjustments, and changes in a positive and personalized way.

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Vascular complications in 305 severely ill patients with COVID-19: a cohort study

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ABSTRACT

BACKGROUND: Although an association has been made between coronavirus disease 2019 (COVID-19) and microvascular disease, data on vascular complications (other than venous thromboembolism) are sparse.

OBJECTIVE: To investigate the vascular complications in severely ill patients hospitalized with COVID-19 and their association with all-cause mortality.

DESIGN AND SETTING: This cohort study was conducted at the Universidade Federal de São Paulo, Brazil.

METHODS: All 305 consecutive patients diagnosed with COVID-19 and hospitalized in the intensive care unit (ICU) of a tertiary university hospital from April 2 to July 17, 2021, were included and followed up for 30 days.

RESULTS: Of these, 193 (63.3%) were male, and the mean age was 59.9 years (standard deviation = 14.34). The mortality rate was 56.3% (172 patients), and 72 (23.6%) patients developed at least one vascular complication during the follow-up period. Vascular complications were more prevalent in the non-survivors (28.5%) than in the survivors (17.3%) group and included disseminated intravascular coagulation (DIC, 10.8%), deep vein thrombosis (8.2%), acrocyanosis (7.5%), and necrosis of the extremities (2%). DIC (adjusted odds ratio (aOR) 2.30, 95% confidence interval (CI) 1.01–5.24, P = 0.046) and acrocyanosis (aOR 5.21, 95% CI 1.48–18.27, P = 0.009) were significantly more prevalent in the non-survivors than in the survivors group.

CONCLUSION: Vascular complications in critically ill COVID-19 patients are common (23.6%) and can be closely related to the mortality rate (56.3%) until 30 days after ICU admission. Macrovascular complications have direct implications for mortality, which is the main outcome of the management of COVID-19.

REGISTRATION: RBR-4qjzh7 (https://ensaiosclinicos.gov.br/rg/RBR-4qjzh7).

INTRODUCTION

Coronavirus disease 2019 (COVID-19), caused by severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2), has rapidly grown into a pandemic and affected populations worldwide, challenging public health and healthcare systems.[1] The clinical spectrum of COVID-19 comprises a wide range of clinical manifestations such as mild upper respiratory tract illness, severe pneumonia with respiratory failure, disseminated intravascular coagulation, and even death. At the beginning of the COVID-19 outbreak, the three primary symptoms of the disease were fever, cough, and dyspnea, as well as other less common symptoms, including muscle pain, anorexia, malaise, and headache. However, 2–10% of patients with COVID-19 present with gastrointestinal symptoms such as diarrhea, abdominal pain, and vomiting; therefore, fecal-oral transmission, other than via close contact through respiratory droplets, has been questioned.[2]

During the COVID-19 pandemic, the authors have explored the risk factors related to life-threatening conditions or mortality in severely ill people with COVID-19. Age > 70 years and male sex were first associated with worse prognosis in hospitalized patients with COVID-19 who underwent surgical procedures.[3]

Recently, some studies have discussed other complications of COVID-19, including acute coronary syndrome, arrhythmia, pulmonary hypertension, arterial and venous thrombosis, and coagulopathy, especially in critically ill patients.[4-11] Some publications discuss vascular complications and the hypercoagulability status in severe COVID-19 disease, but the related management is still under discussion.[6,8,11] Although some studies discuss cardiovascular complications mainly during the late phase of COVID-19, there are sparse and conflicting data regarding the vascular complications and the real burden and course of these complications.[12,13]

OBJECTIVE

The aim of this study was to evaluate vascular complications in critically ill patients hospitalized with COVID-19 and investigate their association with all-cause mortality. Second, the association between baseline conditions and vascular complications, invasive mechanical ventilation, vasopressors, and mortality was studied.

METHODS

Ethical approval and registration

The local research ethics commission approved this study (3.966.152) on June 24, 2020, and the methods were prospectively registered (RBR-4qjzh7) at the Rebec portal and the International Clinical Trials Registry Platform (U1111-1252-1318), World Health Organization (WHO). The study was conducted in accordance with the Brazilian Ethical Review System for research involving human beings and conformed to the Declaration of Helsinki of the World Medical Association (June 1964) and subsequent amendments. This study was conducted and reported in accordance with the Strengthening the Reporting of Observational Studies in Epidemiology Statement guidelines for reporting observational studies.[14]

Patients and study design

The researchers enrolled consecutive patients with confirmed COVID-19 who were admitted to the intensive care unit (ICU) of a tertiary hospital between April 2 and July 17, 2021. The clinical outcomes were monitored until August 30, 2021. All patients were included retrospectively and were diagnosed with COVID-19 by RNA detection, following the WHO interim guidance.[15] Although the researchers planned to exclude patients younger than 18 years old and those who died within 24 hours of admission to the ICU, all 305 enrolled patients were included, and none fulfilled the criteria for exclusion. All patients underwent a clinical examination, laboratory tests, and blood gas analysis. Symptoms were evaluated before ICU admission, that is, at hospital admission. All other outcomes are reported at the longest possible time point. At least one additional objective test, such as chest radiography, computed tomography, or duplex ultrasound, was used to confirm the diagnosis. All patients were treated in the ICU, with electrocardiography, non-invasive pressure, and peripheral oxygen saturation continuous motorization, and received prophylactic anticoagulants if there were no contraindications. Thromboprophylaxis was done according to the American Society of Hematology.[16] The use of low molecular weight heparin was preferred for all patients except those with severe renal impairment and, due to the lack of evidence, no patient received the treatment dose for prophylactic purposes.[8,9,11,16]

Outcomes of interest

As primary outcomes, the researchers analyzed the following vascular complications: disseminated intravascular coagulation (DIC), deep vein thrombosis (DVT), acrocyanosis, acute arterial occlusion, rhabdomyolysis, and distal extremity necrosis until 30 days after admission, discharge from the ICU, or death. All diagnoses were made after a specialized physical examination and at least one additional objective laboratory or imaging test. Second, the association between baseline conditions and vascular complications, invasive mechanical ventilation (IMV) requirement, vasopressors, and mortality was studied. All outcomes were monitored until August 30, 2021. The researchers evaluated core outcomes as predefined by the Core Outcome Measures in Effectiveness Trials Initiative for people with COVID-19.[17]

Data collection

Epidemiological, demographic, clinical presentation, laboratory, imaging, and clinical data were extracted from electronic medical records. Two physicians independently checked all imputed data to avoid bias during the data collection and analysis processes. Details of the treatment measures (respiratory support, kidney replacement, and anticoagulant therapy) were also analyzed. Laboratory tests were collected at ICU admission, after 7, 10, 14, and 30 days, and at death, following the ICU routine.

The date of disease onset was defined as the day on which the first symptom or sign was observed. DIC was defined according to the International Society on Thrombosis and Hemostasis (ISTH) in 2001.[18] The duration from disease onset to hospital admission, acute respiratory distress syndrome, and ICU admission were recorded.

Laboratory procedures

The method used for laboratory confirmation of SARS-CoV-2 infection was throat swab real-time reverse transcriptase polymerase chain reaction. Blood cell count, alanine transaminase, aspartate transaminase, renal function, coagulation profile, C-reactive protein, liver function, D-dimer, troponin, and arterial blood gases were also determined. All patients underwent chest radiography or computed tomography. When there was clinical suspicion of DVT, the patient underwent a full bilateral lower limb venous duplex ultrasound scan (11 MHz linear transducer, Logic P6, GE Healthcare, Milwaukee, Wisconsin, United States). In cases of acute arterial occlusion, an additional arterial duplex ultrasound scan of the affected lower limb was performed to confirm clinical suspicion.

Statistical analysis

Categorical variables were described as frequency rates (number of events and %), and continuous variables were described as mean or median values, in addition to standard deviation (SD) or

minimum and maximum ranges when appropriate. For dichotomous variables, researchers calculated the odds ratio (OR), adjusted odds ratio (aOR), and 95% confidence intervals (CIs) by comparing baseline characteristics and outcomes of interest or by comparing different groups of patients. Age > 70 years and sex were used as confounding parameters to calculate the adjusted values. Mean differences (MD) and 95% CIs were used for continuous data and were compared using the t-test. Categorical variables were compared using the Pearson chi-square or Wald chi-square independence test, and multivariate analysis using multinomial logistic nominal regression or Poisson regression. Statistical analysis was based on all cases with valid data for all the variables in the model. Poisson regression models would be used when it was not possible to proceed with analyses using multinomial logistic nominal regression model. However, at the end of our study and after corrections, the Poisson regression model was not used. For adjusted and unadjusted analyses, we used the statistical software IBM SPSS Statistics for Windows (version 20.0, 2011, IBM Corp. Released, Armonk, New York, United States) and Minitab (version 17.1.0, 2013, Minitab Inc., State College, Pennsylvania, United States). In all tests, $P < 0.05$ was defined as statistically significant. IBM SPSS Statistics for Windows (version 20.0, 2011, IBM Corp. Released, Armonk, New York, United States) was used for forest plot graph development.

RESULTS

General characteristics

All 305 included patients were treated in the ICU due to the development of organ dysfunction; 193 (63.3%) were male, and the mean age was 59.94 (SD = 14.34) years. The mean age was higher in non-survivors than in survivors (MD 9.32, 95% CI 6.23–12.42, $P < 0.00001$), but there was no sex-related difference. All patients had at least one previous medical condition, and there was a mean of three comorbidities per patient (mean 3.04 [SD = 1.70]). Comorbidities and addiction were less prevalent in the survivors than in the non-survivors (MD 0.97, 95% CI 0.60–1.34, $P < 0.00001$), and hypertension (69.8%), diabetes (40.7%), chronic kidney disease (34.8%), and smoking (27.5%) were the most common in all samples. However, when adjusted for age and sex, hypertension (aOR 1.78, 95% CI 1.06–2.96, $P = 0.028$) and chronic kidney disease (aOR 1.89, 95% CI 1.14–3.12, $P = 0.013$) were significantly more prevalent in the non-survivors than in the survivors group (**Table 1**). The most common

Table 1. Demographics and baseline characteristics

	General (n = 305)	Survivors (n = 133)	Non-survivors (n = 172)	Difference*			Adjusted difference*		
				MD† | OR	CI (95%)	P value	MD† | OR	CI (95%)	P value
Age, mean years (SD)	59.94 (14.34)	54.68 (13.69)	64.01 (13.53)	9.32†	(6.23; 12.42)	0.000‡	9.32†	(6.23; 12.42)	0.000‡
Female, n (%)	112 (36.7)	46 (34.6)	66 (38.4)	0.85	(0.53; 1.36)	0.496	0.79	(0.49; 1.28)	0.34
Male, n (%)	193 (63.3)	87 (65.4)	106 (61.6)						
Comorbidities									
Mean per Patient, mean (SD)	3.04 (1.70)	2.50 (1.57)	3.46 (1.68)	0.97†	(0.60; 1.34)	0.000‡	0.97†	(0.60; 1.34)	0.000‡
Hypertension, n (%)	213 (69.8)	81 (60.9)	132 (76.7)	2.12	(1.29; 3.48)	0.003‡	1.78	(1.06; 2.96)	0.028‡
Diabetes, n (%)	124 (40.7)	48 (36.1)	76 (44.2)	1.40	(0.88; 2.23)	0.154	1.43	(0.88; 2.30)	0.145
Chronic kidney disease, n (%)	106 (34.8)	37 (27.8)	69 (40.1)	1.74	(1.07; 2.83)	0.026‡	1.89	(1.14; 3.12)	0.013‡
Current smoking, n (%)	84 (27.5)	28 (21.1)	56 (32.6)	1.81	(1.07; 3.06)	0.027‡	1.71	(0.99; 2.95)	0.056
Symptoms									
Mean per Patient, mean (SD)	4.02 (1.85)	4.35 (1.90)	3.78 (1.78)	-0,57†	(-0,99; -0,15)	0.008‡	-0.57†	(-0.99; -0.15)	0.008‡
Dyspnea, n (%)	248 (81.3)	110 (82.7)	138 (80.2)	0.54	(0.30; 0.97)	0.039‡	0.92	(0.50; 1.68)	0.787
Dry cough, n (%)	195 (63.9)	92 (69.2)	103 (59.9)	0.53	(0.33; 0.86)	0.009‡	0.69	(0.42; 1.13)	0.145
Fever, n (%)	155 (50.8)	77 (57.9)	78 (45.3)	0.59	(0.37; 0.93)	0.023‡	0.71	(0.44; 1.15)	0.162
Asthenia, n (%)	118 (38.7)	47 (35.3)	71 (41.3)	0.56	(0.35; 0.90)	0.016‡	1.27	(0.78; 2.06)	0.332
Myalgia, n (%)	81 (26.6)	41 (30.8)	40 (23.3)	0.71	(0.43; 1.19)	0.197	0.72	(0.43; 1.23)	0.229
Hyporexia, n (%)	55 (18.0)	26 (19.5)	29 (16.9)	0.67	(0.37; 1.20)	0.182	0.7	(0.38; 1.29)	0.251
Vomiting, n (%)	40 (13.1)	20 (15.0)	20 (11.6)	0.74	(0.38; 1.45)	0.383	0.79	(0.40; 1.56)	0.497
Headache, n (%)	39 (12.8)	22 (16.5)	17 (9.9)	0.87	(0.45; 1.71)	0.696	0.58	(0.29; 1.17)	0.126
Anosmia, n (%)	37 (12.1)	20 (15.0)	17 (9.9)	0.86	(0.43; 1.71)	0.663	0.64	(0.32; 1.31)	0.223
Abdominal pain, n (%)	31 (10.2)	13 (9.8)	18 (10.5)	0.78	(0.38; 1.59)	0.493	0.92	(0.42; 2.02)	0.835
Chest pain, n (%)	26 (8.5)	17 (12.8)	9 (5.2)	1.34	(0.58; 3.12)	0.491	0.39	(0.16; 0.93)	0.033‡
Sweating, n (%)	5 (1.6)	3 (2.3)	2 (1.2)	1.15	(0.19; 6.97)	0.882	0.63	(0.10; 3.87)	0.619

CI = confidence interval; MD = mean difference; n = number of patients; OR = odds ratio; SD = standard deviation.

*Comparison between surviving and non-surviving patients, †MD, ‡$P < 0.05$ (t-test for non-adjusted and nominal regression multinomial logistics for adjusted (age > 70 years and sex) comparisons).

symptoms were dyspnea (81.3%), cough (63.9%), and fever (50.8%). Although there were more symptoms in survivors than in non-survivors (MD -0.57, 95% CI -0.99 to -0.15, P = 0.008), only chest pain (aOR 0.39, 95% CI 0.16–0.93, P = 0.033) was significantly less incident in the non-survivors group (**Table 1**).

Clinical manifestations

Of the 305 included patients, 172 (56.3%) died by the end of the follow-up on August 30, 2021. The mean hospitalization time of the included patients was 24.68 (SD = 20.98) days, and the mean time in the ICU was 15.14 (SD = 15.88) days. The non-survivors group stayed more time in the ICU (MD 6.41, 95% CI 3.03–9.79, P < 0.0001) and had less time until the first outcome of interest for this study (MD -4.43, 95% CI -8.45 to -0.41, P = 0.032) (**Table 2**).

Seventy-two (23.6%) patients developed at least one vascular complication during the follow-up period. Among all the vascular complications identified, DIC (10.8%), DVT (8.2%), acrocyanosis (7.5%), and necrosis of the extremities (2%) were the most common. DIC (aOR 2.30, 95% CI 1.01–5.24, P = 0.046) and acrocyanosis (OR 5.21, 95% CI, 1.48–18.27; P = 0.009) were significantly more common in the non-survivors than in the survivors group (**Table 2**). DVT, necrosis of the extremities, acute arterial occlusion, and rhabdomyolysis were also more common in the non-survivor group, but the difference was not significant (**Table 2**).

Endovenous vasopressor medicines and IMV were required in 55.1% and 59% of the patients, respectively. Non-survivors had significantly higher IMV requirements than survivors (aOR 5.07, 95% CI 3.03–8.50, P < 0.0001) (**Table 2**).

Investigating the association between baseline characteristics and clinically relevant outcomes, there was more death in patients older than 70 years (aOR 3.31, 95% CI 1.83–5.99, P < 0.0001) and in those who presented with two or more comorbidities (aOR 2.00, 95% CI 1.06–3.78, P = 0.033) (**Figure 1**). Among all assessed baseline risk factors, only the previous use of heparin was associated with a decreased incidence of vascular complications (aOR 0.46, 95% CI 0.22–0.98; P = 0.043) (**Figure 2**). There was a greater need for IMV in patients who were hospitalized for surgical reasons (aOR 3.72, 95% CI 1.05–13.19, P = 0.042) (**Figure 3**). None of the baseline risk factors evaluated (age, sex, comorbidities, reason for hospitalization, use of heparin, and heparin dose used during hospitalization) were associated with any difference in the necessity of vasopressor agents during hospitalization (**Figure 4**).

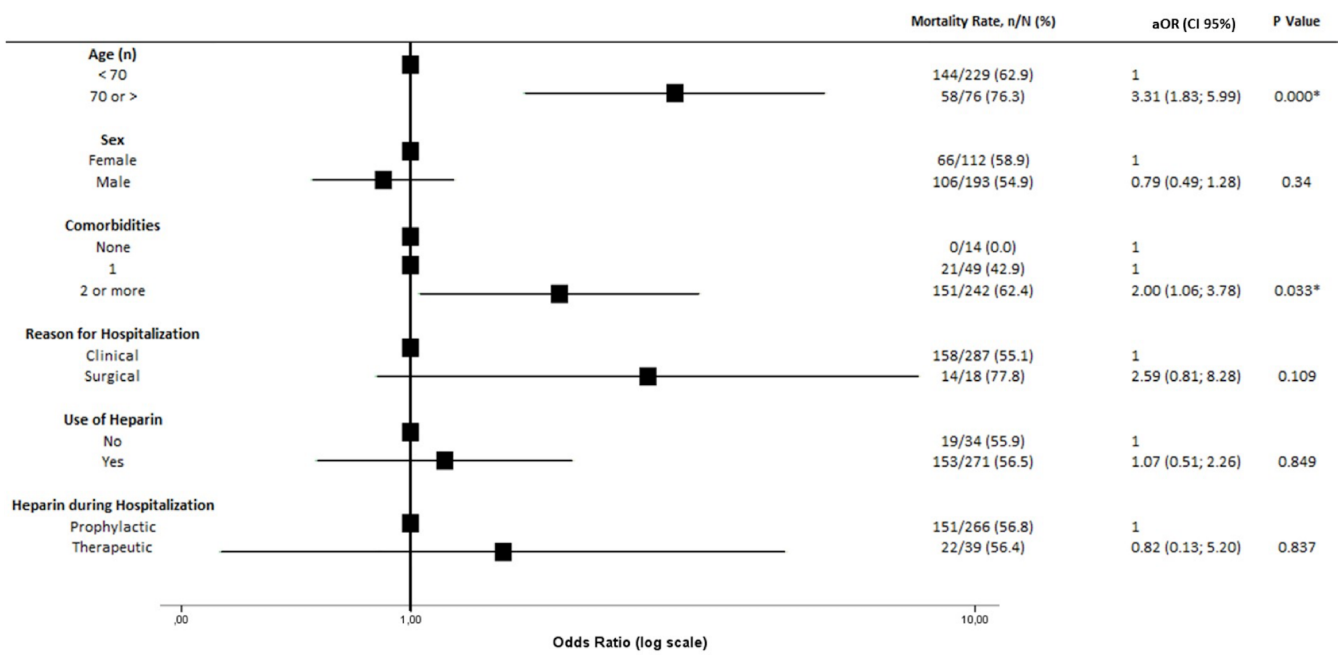
Laboratory findings

Laboratory tests were performed on all patients. See **Appendix 1** for the full local reference range used and **Appendix 2** for the full laboratory testing results. Tests with values outside the local reference range were considered an event of interest, and the results were compared between non-surviving and surviving patients (**Figure 5**). Non-surviving patients presented significantly abnormal values for leukogram, platelets, international normalized ratio, normalized ratio, urea, and creatinine compared with surviving patients in the adjusted analysis (**Appendix 2** and

Table 2. Clinical outcomes

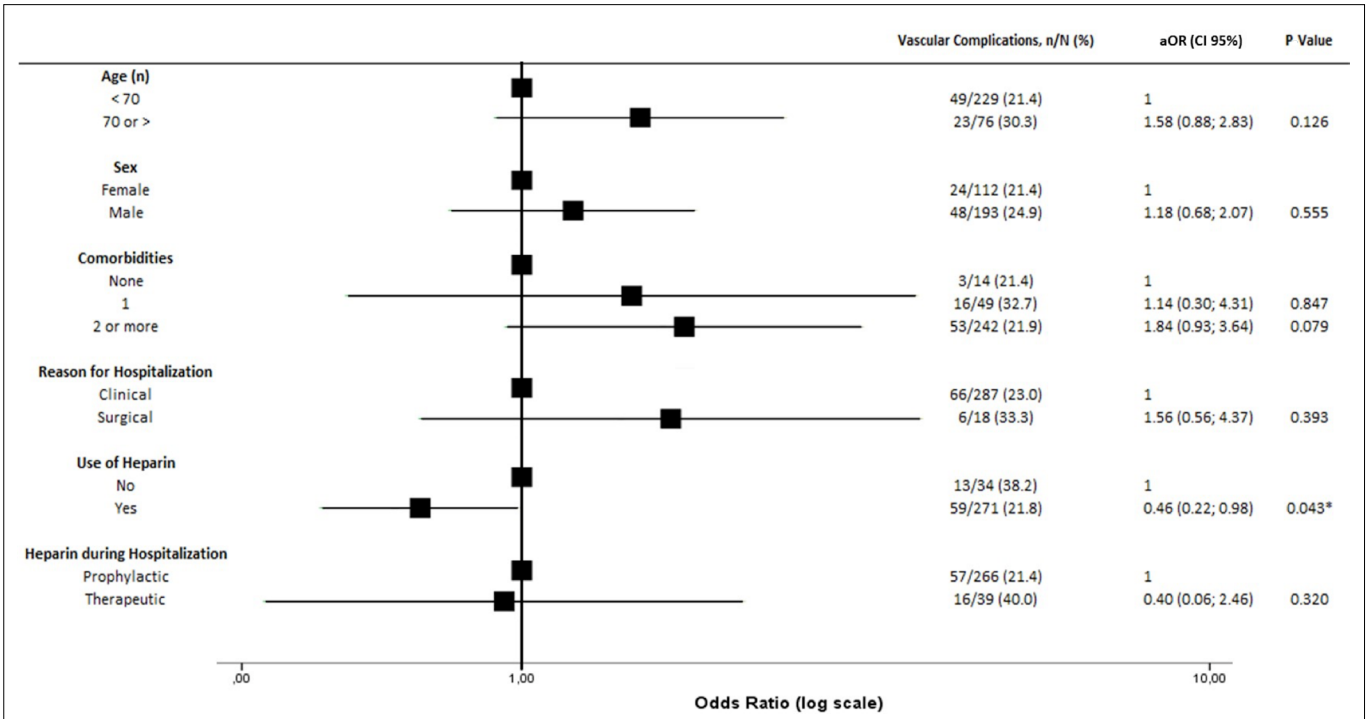
Time mean (days)	General (n = 305)		Survivors (n = 133)		Non-survivors (n = 172)		Difference*			Adjusted difference*		
	Mean	SD	Mean	SD	Mean	SD	MD	CI (95%)	P value	MD	CI (95%)	P value
ICU	15.14	15.88	11.53	12.16	17.94	17.78	6.41	(3.03; 9.79)	0.000†	N/A	N/A	N/A
Hospitalization	24.68	20.98	25.65	18.66	24.05	22.62	-1.60	(-6.26; 3.06)	0.500	N/A	N/A	N/A
ICU time until the outcome	20.01	17.86	22.50	17.48	18.08	17.96	-4.43	(-8.45; -0.41)	0.032†	N/A	N/A	N/A
Symptom onset to mechanical ventilation	8.96	6.68	8.32	4.85	9.24	7.33	0.92	(-0.98; 2.82)	0.342	N/A	N/A	N/A
Outcomes	**General (n = 305)**		**Survivors (n = 133)**		**Non-Survivors (n = 172)**		**Difference***			**Adjusted Difference***		
	n	%	n	%	n	%	OR	CI (95%)	P value	OR	CI (95%)	P value
Disseminated intravascular coagulation, n (%)	33	10.8	11	8.2	24	13.9	2.23	(1.00; 4.98)	0.050†	2.30	(1.01; 5.24)	0.046†
Deep vein thrombosis, n (%)	25	8.2	9	6.8	14	11.6	0.98	(0.43; 2.24)	0.967	0.87	(0.37; 2.04)	0.742
Acrocyanosis, n (%)	23	7.5	3	2.2	20	8.1	5.70	(1.66; 19.62)	0.005†	5.21	(1.48; 18.27)	0.009†
Necrosis of extremities, n (%)	6	2.0	2	1.5	5	2.9	3.95	(0.46; 34.24)	0.212	4.76	(0.54; 42.17)	0.161
Acute arterial occlusion, n (%)	4	1.3	1	0.7	2	1.1	0.77	(0.11; 5.54)	0.796	0.98	(0.14; 7.12)	0.985
Rhabdomyolysis, n (%)	1	0.3	0	0	1	0.6	2.34	(0.09; 57.79)	0.604	N/A	N/A	N/A
Complication free, n (%)	233	76.4	110	82.7	123	71.5	N/A	N/A	N/A	N/A	N/A	N/A
IMV requirement, n (%)	180 (59.0)		52 (39.1)		128 (74.4)		4.53	(2.78; 7.38)	0.000†	5.07	(3.03; 8.50)	0.000†
Vasopressors, n (%)	168 (55.1)		75 (56.4)		93 (54.1)		0.91	(0.58; 1.44)	0.686	0.856	(0.54; 1.37)	0.517

CI = confidence interval; IMV = invasive mechanical ventilation; MD = mean difference; n = number of patients; OR = odds ratio; SD = standard deviation.
*Comparison between surviving and non-surviving patients; †P < 0.05 (t-test for non-adjusted and nominal regression multinomial logistics for adjusted (age > 70 years and sex) comparisons).



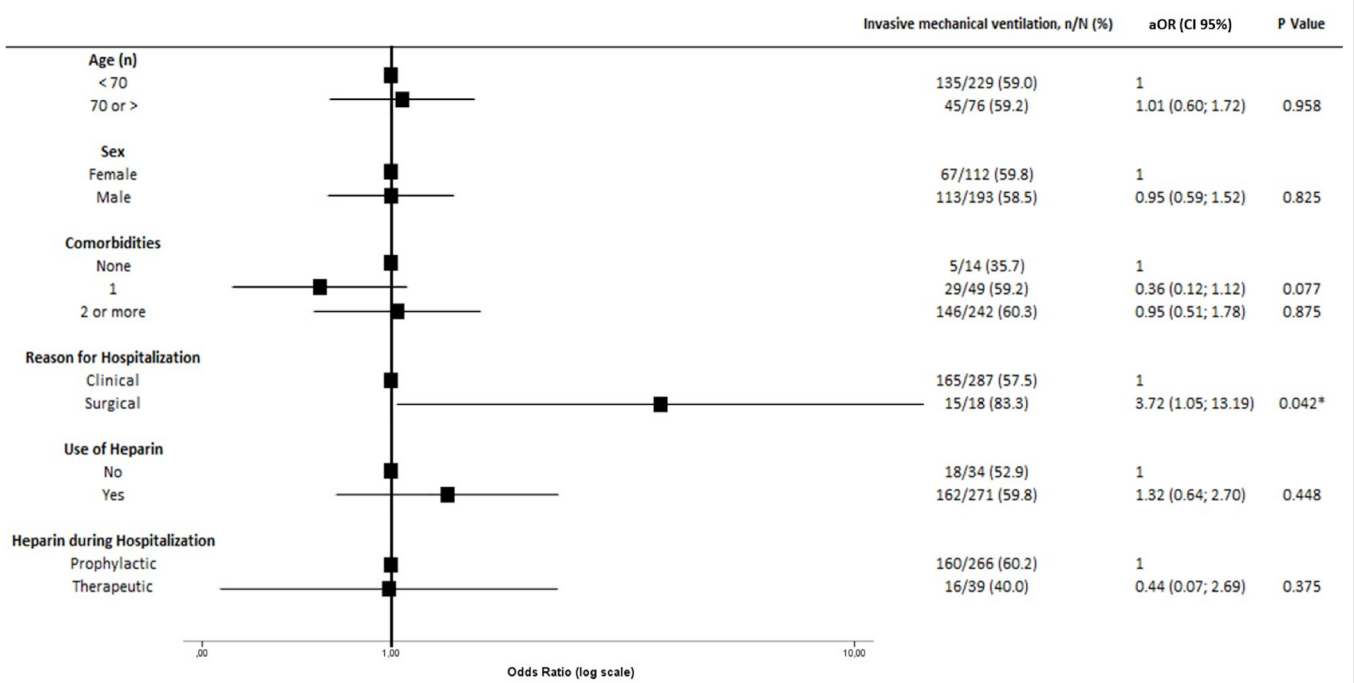
The researchers assumed an OR of 1 for control baseline characteristics.
aOR = adjusted odds ratio; N = total number of patients; n = number of events.
*P < 0.05 (nominal regression multinomial logistics; IBM SPSS Statistics for Windows).

Figure 1. Association between baseline characteristics and all-cause mortality.



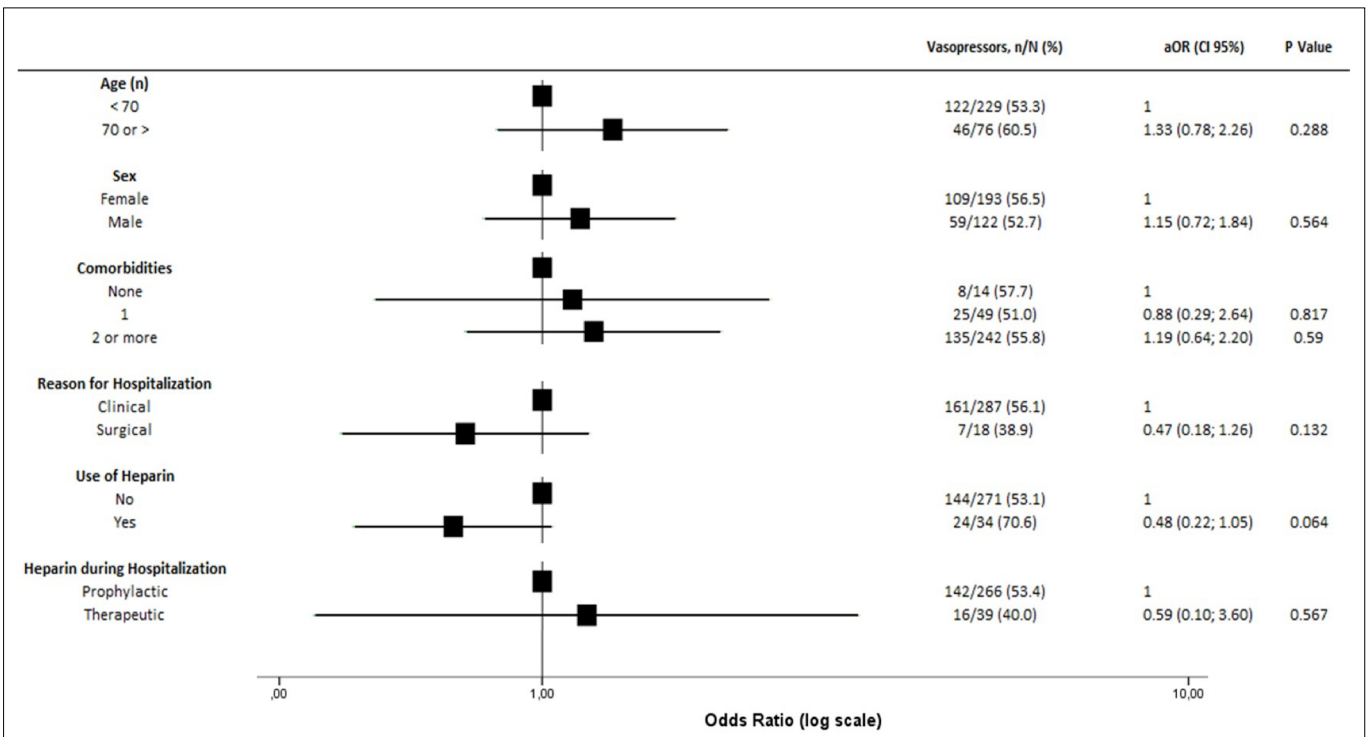
The researchers assumed an OR of 1 for control baseline characteristics.
aOR = adjusted odds ratio; N = total number of patients; n = number of events.
*P < 0.05 (nominal regression multinomial logistics; IBM SPSS Statistics for Windows); †disseminated intravascular coagulation, deep vein thrombosis, acrocyanosis, necrosis of extremities, acute arterial occlusion, and rhabdomyolysis.

Figure 2. Association between baseline characteristics and vascular complications.



The researchers assumed an OR of 1 for control baseline characteristics.
aOR = adjusted odds ratio; N = total number of patients; n = number of events.
*P < 0.05 (nominal regression multinomial logistics; IBM SPSS Statistics for Windows).

Figure 3. Association between baseline characteristics and invasive mechanical ventilation



The researchers assumed an OR of 1 for control baseline characteristics.
aOR = adjusted odds ratio; N = total number of patients; n = number of events.
*P < 0.05 (nominal regression multinomial logistics; IBM SPSS Statistics for Windows).

Figure 4. Association between baseline characteristics and vasopressor necessity

Figure 5). Notably, the baseline D-dimer count was significantly higher in all 305 patients during the study period (**Figure 6).** According to the ISTH diagnostic criteria for DIC, 33 patients (10.8%) matched the grade of overt DIC (≥ 5 points). The criteria were matched in the later stages of COVID-19. In our enrolled patients with DIC, all had a high D-dimer count, that is, more than five times the upper normal limit.

DISCUSSION

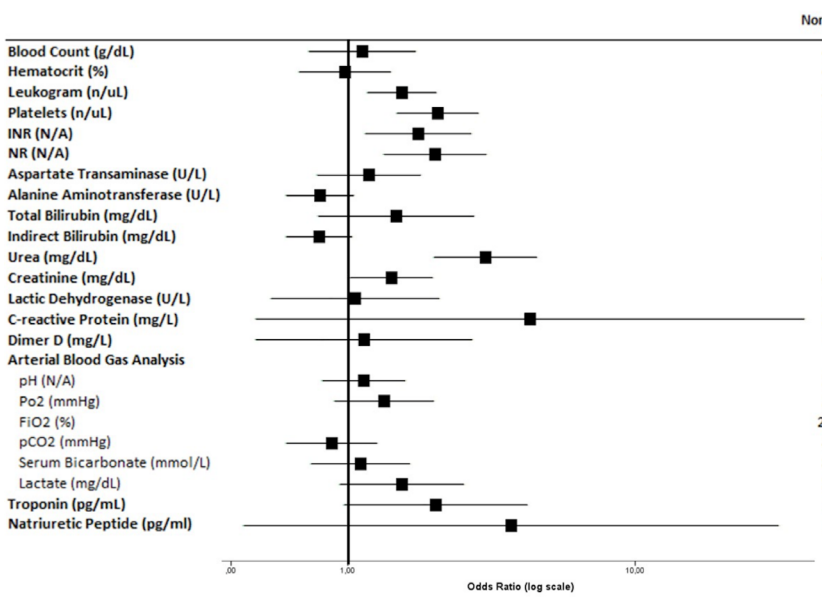
Patients with confirmed COVID-19 are commonly prone to in-hospital mortality and an elevated rate of thromboembolic events, including other vascular complications.[8,9,23] A higher D-dimer level was observed in all patients admitted to the ICU, which suggests an association with the severity of the disease.[5] The incidence of vascular complications were DIC = 10.8%, 8.2%, 7.5%, 2%, 1.3%, and 0.3% up to one month. The risk factors associated with death were age > 70 years and the presence of two or more comorbidities, while the risk factors associated with the necessity of invasive mechanical ventilation were hospitalization for surgical reasons in critically ill patients with COVID-19.

All 305 consecutive severely ill patients with confirmed COVID-19 were followed up for at least 30 days or until death. The majority were male (n = 193, 63.3%) and older adults (mean age 59.94 years [SD = 14.34]). Similarly, SARS-CoV-2 has been reported to infect more males than females.[19]

Of the 305 patients, 142 (79 %) had more than two comorbidities and chronic underlying diseases, including hypertension (69.8%), diabetes (40.7%), chronic kidney disease (34.8%), and smoking (27.5%). Previous studies have indicated hypertension and diabetes as highly prevalent in hospitalized patients with COVID-19, but we introduced chronic kidney disease as another highly incident comorbidity on this site.[20] Our data also confirm the probable association with severe COVID-19 related outcomes such as chronic kidney disease.[20]

Of the 305 included patients, 172 (56.3%) died, and 72 (23.6%) developed at least one vascular complication (DIC, 10.8%; DVT, 8.2%; acrocyanosis, 7.5%; necrosis of extremities, 2%; acute arterial occlusion, 1.3%; and rhabdomyolysis, 0.3%) during the follow-up period. One patient (0.3 %) presented rhabdomyolysis, which is not a frequent complication related to novel coronavirus infection, but has already been described in the literature.[21] Another study reported rates of 6.6% pulmonary embolism and 11.6% other cardiac complications in hospitalized patients with COVID-19.[22] We reported other clinically relevant and highly prevalent vascular complications such as DIC, acrocyanosis, necrosis of extremities, acute arterial occlusion, and rhabdomyolysis. Our symptomatic DVT rate (8.2%) was similar to previous venous thromboembolism (VTE) rates of 11.2% in hospitalized patients, but was less than the rates (31% to 49%) reported for ICU patients.[8,9,23]

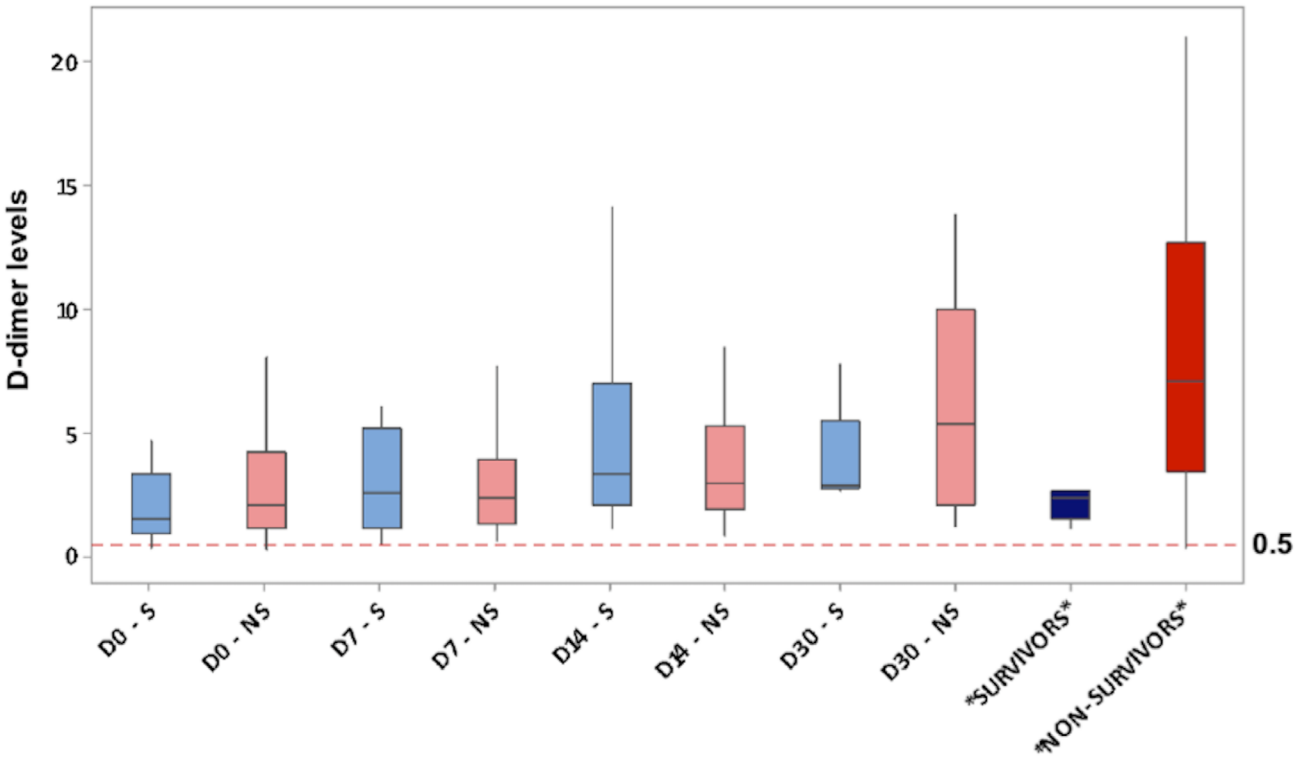
Thromboembolic events have been frequently described in patients with COVID-19, but the actual incidence of these events



	Non-Survivors, n/N (%)	Survivors, n/N (%)	aOR (CI 95%)	P Value
Blood Count (g/dL)	470/559 (84.1)	356/465 (76.6)	1.08 (0.59; 1.99)	0.808
Hematocrit (%)	447/558 (80.1)	335/464 (72.2)	0.89 (0.50; 1.58)	0.693
Leukogram (n/uL)	360/559 (64.4)	184/462 (39.8)	1.73 (1.25; 2.38)	0.001*
Platelets (n/uL)	222/550 (40.4)	98/462 (21.2)	2.37 (1.68; 3.34)	0.000*
INR (N/A)	193/383 (50.4)	51/223 (22.9)	1.96 (1.22; 3.16)	0.005*
NR (N/A)	238/398 (59.8)	70/221 (31.7)	2.29 (1.48; 3.55)	0.000*
Aspartate Transaminase (U/L)	149/230 (64.8)	85/152 (55.9)	1.18 (0.67; 2.08)	0.565
Alanine Aminotransferase (U/L)	122/297 (41.1)	81/185 (43.8)	0.65 (0.39; 1.07)	0.091
Total Bilirubin (mg/dL)	62/286 (21.7)	15/164 (9.1)	1.48 (0.68; 3.23)	0.320
Indirect Bilirubin (mg/dL)	109/287 (38.0)	59/168 (35.1)	0.64 (0.39; 1.05)	0.080
Urea (mg/dL)	474/551 (86.0)	234/450 (52.0)	3.47 (2.34; 5.14)	0.000*
Creatinine (mg/dL)	437/517 (84.5)	261/433 (60.3)	1.55 (1.03; 2.31)	0.034*
Lactic Dehydrogenase (U/L)	143/154 (92.9)	88/99 (88.9)	0.81 (0.27; 2.44)	0.702
C-reactive Protein (mg/L)	283/284 (99.6)	288/290 (99.3)	2.16 (0.16; 29.02)	0.562
Dimer D (mg/L)	179/186 (96.2)	119/123 (96.7)	0.72 (0.16; 3.18)	0.661
Arterial Blood Gas Analysis				
pH (N/A)	250/391 (63.9)	85/157 (54.1)	1.14 (0.72; 1.81)	0.563
Po2 (mmHg)	292/391 (74.7)	120/158 (75.9)	1.41 (0.85; 2.33)	0.179
FiO2 (%)	235/235 (100.0)	106/106 (100.0)	N/A	N/A
pCO2 (mmHg)	330/391 (84.4)	127/159 (79.9)	0.74 (0.39; 1.38)	0.338
Serum Bicarbonate (mmol/L)	324/388 (83.5)	114/155 (73.5)	1.07 (0.61; 1.89)	0.813
Lactate (mg/dL)	215/279 (77.1)	74/129 (57.4)	1.65 (0.91; 2.98)	0.098
Troponin (pg/mL)	143/161 (88.8)	54/89 (60.7)	2.15 (0.96; 4.80)	0.062
Natriuretic Peptide (pg/ml)	28/30 (93.3)	11/13 (84.6)	1.41 (0.08; 24.77)	0.813

FiO2 = fraction of inspired oxygen; INR = international normalized ratio; N = total number of patients; n = number of events; NR = normalized ratio; aOR, adjusted odds ratio; pCO2, partial pressure of carbon dioxide; pO2, partial pressure of oxygen.
*P < 0.05 (t-test).

Figure 5. Laboratory findings and mortality prediction.



D0 = date of admission; D7 = day 7; D14 = day 14; D30 = day 30; NS = non-survivors; S = survivors.
*Values in mg/L.

Figure 6. D-dimer levels* of all patients.

might be underestimated due to underdiagnosis and the low number of imaging tests performed.[24,25] Further studies are necessary to determine the real incidence of these events and to improve the prevention and facilitate the diagnosis and treatment of thromboembolic complications in patients with COVID-19. As there is high certainty evidence against the use of a therapeutic dose of anticoagulation for prophylactic purposes in patients hospitalized with COVID-19, strategies for early VTE diagnosis, mainly in critically ill patients, could be helpful.[8,9,26]

Tang et al. reported a higher D-dimer level and a longer prothrombin time in non-surviving patients when compared to survivors, and a high rate of DIC manifested in the majority of deaths.[5] It is well established that sepsis is one of the most common causes of DIC and that viral infection may develop into sepsis associated with organ dysfunction.[3] However, in our analysis, D-dimer levels were elevated in all patients (mean 4.54, SD = 5.41 mg/L), that is, almost five times the local upper normal limit. Recent studies have associated D-dimer levels with a poor prognosis in people with COVID-19[5]; therefore, it is considered a typical marker related to hypercoagulability and thrombotic events, and it also has the potential to be used as an indicator for prognosis and progression of the disease.[27] We observed DIC in 33 (10.8%) of all included patients and in 24 (15%) of the non-survivors group, differing from the currently available data, which reached 70% DIC occurrence in some samples.[5] It can be explained by the fact that D-dimer levels were not measured daily in the ICU, only on admission. Hence, DIC was diagnosed based on the ISTH criteria in our sample.

The most prevalent symptoms at the onset of the illness were dyspnea (81.3%), cough (63.9%), and fever (50.8%), similar to those reported in other studies.[20] However, other symptoms such as thoracic and abdominal pain, vomiting, and sweating were present in our patients, showing that coronavirus infection can present itself with a wide range of clinical manifestations.

Most patients required IMV (59%) and endovenous vasopressor medication (55.1%) in the ICU. All non-survivors developed acute respiratory failure, underwent oral intubation, and required vasopressor administration. Half of these patients needed hemodialysis as a result of acute kidney injury diagnosed using the Kidney Disease Improving Global Outcomes (KDIGO) clinical practice guidelines.[28] Cheng et al. found a higher in-hospital death rate for patients with kidney abnormalities, showing that acute kidney injury or even chronic renal disease can contribute as a risk factor for a poor prognosis in COVID-19 patients.[29]

Benson et al.[30] emphasized a high mortality rate of 11% after vascular and endovascular procedures (elective or urgent) during the pandemic period, even at lower rates (4%) of confirmed COVID-19 cases. COVIDSurg Collaborative et al.[31] found that 30-day mortality in patients with COVID-19 increased from 7.4% to 40.8% in those with VTE, and Kollias et al.[32] reported that severely ill patients with COVID-19 had high rates of pulmonary embolism (32%) and DVT (27%) despite prophylactic anticoagulation. In our study, the death rate was even higher: 55.1% in those hospitalized for clinical reasons and 77.8% in those hospitalized for surgical reasons. Most deaths also occurred during the first two weeks after admission to the ICU, which demonstrates that the length of stay in the ICU can be long, demanding more resources and meaning a longer time of intubation for these patients.

Our study had some limitations. First, this was a retrospective observational study based on the analysis of medical records. Although laboratory tests were performed for all patients, not all laboratory tests, including D-dimer and fibrinogen, were performed. Hence, their importance in the poor outcomes of these patients could be underestimated. However, establishing the incidence of highly relevant vascular complications is essential for providing better treatment for all patients with COVID-19.

Even more than two years after its outbreak, the COVID-19 pandemic is a global health issue. However, non-transmissible circulatory diseases remain the leading cause of disease burden worldwide.[33] The high prevalence of related risk factors, such as hypertension (69.8%), diabetes (40.7%) and smoking (27.5%), reaffirmed their burden. Additionally, severely ill patients with COVID-19 are often followed by cardio-, cerebral-, and peripheral vascular complications, and clinicians prescribe pharmacological and non-pharmacological interventions to avoid complications such as VTE, acute limb ischemia, amputation, and death.[8,12,22,26] However, there is no consensus regarding the impact of vascular complications on managing severely ill patients with COVID-19. The high prevalence of vascular complications (23.6%) in our study suggests that this impact may also be observed in severely ill patients with COVID-19.

CONCLUSION

The high death rate (56.3%) and the relatively high incidence of all vascular complications (23.6%) demonstrate the need to improve specific diagnostic and prevention strategies to manage COVID-19 complications.

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Appendix 1. Local reference range for laboratory tests

Laboratory tests	Reference range
Blood count (g/dL)	13.5–17.5
Hematocrit (%)	39–50
Leukogram (n/µL)	3,500–10,500
Platelets (n/µL)	150,000–450,000
INR (N/A)	0.8–1.2
NR (N/A)	0.8–1.2
Aspartate transaminase (U/L)	Up to 40
Alanine aminotransferase (U/L)	Up to 41
Total bilirubin (mg/dL)	Up to 1.0
Indirect bilirubin (mg/dL)	0.1–0.6
Urea (mg/dL)	10–50
Creatinine (mg/dL)	0.7–1.2
Lactic dehydrogenase (U/L)	Up to 250
C-reactive protein (mg/L)	Up to 1.0
D-dimer (mg/L)	Up to 0.5
Arterial blood gas analysis	
pH (N/A)	7.35–7.45
pO_2 (mmHg)	80–100
FiO_2 (%)	95–98
pCO_2 (mmHg)	35–45
Serum bicarbonate (mmol/L)	22–26
Lactate (mg/dL)	4.5–14.4
Troponin (pg/mL)	Up to 14
Natriuretic peptide (pg/mL)	125–400

INR = international normalized ratio; NR = normalized ratio; U/L = units/liter; pH = potential of hydrogen; N/A = not available; pO_2 = partial pressure of oxygen; $FiO_{2=}$ fraction of inspired oxygen; $pCO_{2=}$ partial pressure of carbon dioxide.

Appendix 2. Laboratory testing

Laboratory testing	General (N)	Non-survivors	Survivors		Difference*		Adjusted difference*		
		n (%)	n (%)	OR	CI (95%)	P value	OR	CI (95%)	P value
Blood Count (g/dL)	1024	470 (84.1)	356 (76.6)	1.62	(1.18; 2.21)	0.002†	1.08	(0.59; 1.99)	0.808
Hematocrit (%)	1022	447 (80.1)	335 (72.2)	1.55	(1.16; 2.07)	0.003†	0.89	(0.5; 1.58)	0.693
Leukogram (n/uL)	1021	360 (64.4)	184 (39.8)	2.73	(2.12; 3.52)	0.000†	1.73	(1.25; 2.38)	0.001†
Platelets (n/uL)	1012	222 (40.4)	98 (21.2)	2.51	(1.90; 3.33)	0.000†	2.37	(1.68; 3.34)	0.000†
INR (N/A)	606	193 (50.4)	51 (22.9)	3.43	(2.36; 4.97)	0.000†	1.96	(1.22; 3.16)	0.005†
NR (N/A)	619	238 (59.8)	70 (31.7)	3.21	(2.27; 4.54)	0.000†	2.29	(1.48; 3.55)	0.000†
Aspartate Transaminase (U/L)	382	149 (64.8)	85 (55.9)	1.45	(0.95; 2.20)	0.082	1.18	(0.67; 2.08)	0.565
Alanine Aminotransferase (U/L)	482	122 (41.1)	81 (43.8)	0.89	(0.62; 1.30)	0.558	0.65	(0.39; 1.07)	0.091
Total Bilirubin (mg/dL)	450	62 (21.7)	15 (9.1)	2.75	(1.51; 5.01)	0.001†	1.48	(0.68; 3.23)	0.320
Indirect Bilirubin (mg/dL)	455	109 (38.0)	59 (35.1)	1.13	(0.76; 1.68)	0.542	0.64	(0.39; 1.05)	0.080
Urea (mg/dL)	1001	474 (86.0)	234 (52.0)	5.68	(4.19; 7.70)	0.000†	3.47	(2.34; 5.14)	0.000†
Creatinine (mg/dL)	950	437 (84.5)	261 (60.3)	3.60	(2.65; 4.89)	0.000†	1.55	(1.03; 2.31)	0.034†
Lactic Dehydrogenase (U/L)	253	143 (92.9)	88 (88.9)	1.62	(0.68; 3.91)	0.278	0.81	(0.27; 2.44)	0.702
C-reactive Protein (mg/L)	574	283 (99.6)	288 (99.3)	1.96	(0.18; 21.79)	0.582	2.16	(0.16; 29.02)	0.562
Dimer D (mg/L)	309	179 (96.2)	119 (96.7)	0.86	(0.25; 3.00)	0.812	0.72	(0.16; 3.18)	0.661
Arterial Blood Gas Analysis									
pH (N/A)	548	250 (63.9)	85 (54.1)	1.50	(1.03; 2.19)	0.034†	1.14	(0.72; 1.81)	0.563
pO_2 (mmHg)	549	292 (74.7)	120 (75.9)	0.93	(0.61; 1.44)	0.756	1.41	(0.85; 2.33)	0.179
FiO_2 (%)	341	235 (100.0)	106 (100.0)	2.21	(0.04; 112.19)	0.692	N/A	N/A	N/A
pCO_2 (mmHg)	550	330 (84.4)	127 (79.9)	1.36	(0.85; 2.19)	0.200	0.74	(0.39; 1.38)	0.338
Serum Bicarbonate (mmol/L)	543	324 (83.5)	114 (73.5)	1.82	(1.16; 2.84)	0.008†	1.07	(0.61; 1.89)	0.813
Lactate (mg/dL)	408	215 (77.1)	74 (57.4)	2.50	(1.60; 3.90)	0.000†	1.65	(0.91; 2.98)	0.098
Troponin (pg/mL)	250	143 (88.8)	54 (60.7)	5.15	(2.69; 9.85)	0.000†	2.15	(0.96; 4.8)	0.062
Natriuretic Peptide (pg/ml)	43	28 (93.3)	11 (84.6)	2.54	(0.32; 20.38)	0.379	1.41	(0.08; 24.77)	0.813

CI = confidence interval; MD = mean difference; n = number of patients or tests; SD = standard deviation; U/L = units/liter; pH = potential of hydrogen; pO_2 = partial pressure of oxygen; $FiO_{2=}$ fraction of inspired oxygen; $pCO_{2=}$ partial pressure of carbon dioxide.
*Comparison between surviving and non-surviving patients. †$P < 0.05$ (t-test).

Investigation of the relationship between red blood cell distribution width and mortality in patients with hemophagocytic lymphohistiocytosis: a retrospective study

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Red blood cell distribution width.
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Correlation.

ABSTRACT

BACKGROUND: Red blood cell distribution width (RDW) is related to sepsis-related mortality. Hemophagocytic lymphohistiocytosis (HLH) is a syndrome caused by severe infection, tumors, or autoimmunity without a specific diagnosis.

OBJECTIVE: To explore the correlation between RDW and mortality in patients with HLH.

DESIGN AND SETTING: A retrospective study conducted in a hospital in China.

METHODS: A total of 101 inpatients with HLH from January 1, 2017 to December 31, 2021 were divided into non-survivor (n = 52) and survivor (n = 49) groups. A non-parametric test was used to analyze demographic, clinical, and laboratory data between groups. Independent variables with $P < 0.05$ were analyzed using binary logistic regression to screen out mortality-related variables. Selected variables were subjected to multivariate logistic regression analysis, and those with strong correlations were screened. Receiver operating characteristic (ROC) curves of strongly correlated variables and area under curve (AUC) values were obtained.

RESULTS: The APACHE II score, RDW, and platelet (PLT) and fibrinogen (FIB) levels ($P < 0.05$) different significantly. RDW, PLT, FIB were correlated with mortality. The AUC values of RDW, PLT, and FIB were 0.857, 0.797, and 0.726, respectively. RDW was associated with mortality in patients with HLH ($P < 0.01$, cut-off value: 16.9). The sensitivity and specificity of predicting mortality were 97.96% and 96.1%, respectively.

CONCLUSION: Logistic regression analysis showed a correlation between RDW and patients' mortality. Therefore, RDW can be used to predict mortality in patients with HLH.

INTRODUCTION

Hemophagocytic lymphohistiocytosis (HLH) is a high inflammatory response syndrome, wherein uncontrolled immune activation leads to multiple organ failure, with high mortality.[1,2] Impaired immune function, such as that of natural killer (NK) or T cells, is a key factor in the occurrence of HLH.[1,3] Overactivation of macrophages can induce hemophagocytosis and a cytokine storm, resulting in clinical manifestations, such as fever, enlargement of the liver and spleen, and reduction of extracellular cells.[4,5]

The concept of HLH was proposed by two pediatricians, Scott and Robb Smith, in 1939.[6] Therefore, our understanding of HLH was initially concentrated in children, and adult HLH was gradually recognized.[7] Adult HLH in Italy, Sweden, and the United States have an annual incidence rate of 1 per 800,000 people.[8,9] Increasing annual infections, tumors, and autoimmune diseases are the leading causes of secondary adult HLH in China.[10,11]

Red blood cell distribution width (RDW), derived from whole blood count, is a parameter reflecting the volume heterogeneity of red blood cells that can classify anemia.[12,13] Elevated RDW is considered an inflammatory marker that can predict the adverse prognosis of various diseases, including heart failure, acute renal injury, sepsis, and cancer. Platelets play an important role in regulating inflammation and innate immunity.[13,14] They adhere to endothelial cells during acute inflammation, mediating neutrophil chemotaxis, infiltration, and secretion of pro-inflammatory chemokines. Severe infection can lead to a decreased platelet count. Studies[15,16] have shown that platelet count is a predictor of mortality. Adult secondary HLH is associated with rapid progress and high mortality. More biological indicators are needed to predict patients' mortality as they have attracted clinicians' attention and improved patient vitality thus far.

RDW is also considered a novel inflammatory predictor in various conditions including functional bowel conditions,[17] autoimmune diseases,[18] rheumatoid arthritis,[19] degenerative vertebral conditions,[20] malignancy,[21] autoimmune hepatitis,[22] and even coronavirus disease 2019 infection.[23] Moreover, increased RDW has been linked with multiple hospital admissions in patients with chronic conditions.[24] Since RDW and cardiovascular conditions are associated with inflammation, RDW could also be associated with HLH prognosis.

OBJECTIVE

This study aimed to explore the correlation between RDW and mortality in patients with HLH.

METHODS

Ethics committee approval

This study was approved by the ethics committee of Daping Hospital of Army Medical University (Approval No. 2022-11; January 24, 2022). It was performed in accordance with the Helsinki Declaration of 1975, as revised in 2013 (http://www.wma.net/en/20activities/10ethics/10helsinki/).

Patients

This retrospective study was conducted among 105 inpatients with HLH from January 1, 2017 to December 31, 2021. According to the inclusion criteria, of these patients, three who were younger than 18 years and one with recurrence after treatment were excluded. Finally, a total of 101 patients were included in this study (**Figure 1**). These patients were divided into non-survivor (n = 52) and survivor (n = 49) groups.

Inclusion criteria

The patients involved in this study had to comply with the following requirements. First, the patient must be aged over 18 years. Second, the patient must meet the following criteria (HLH-2004 diagnostic criteria):[25] 1) fever ≥ 38.5 °C; 2) splenomegaly; 3) cytopenia that affects at least two peripheral blood samples of three

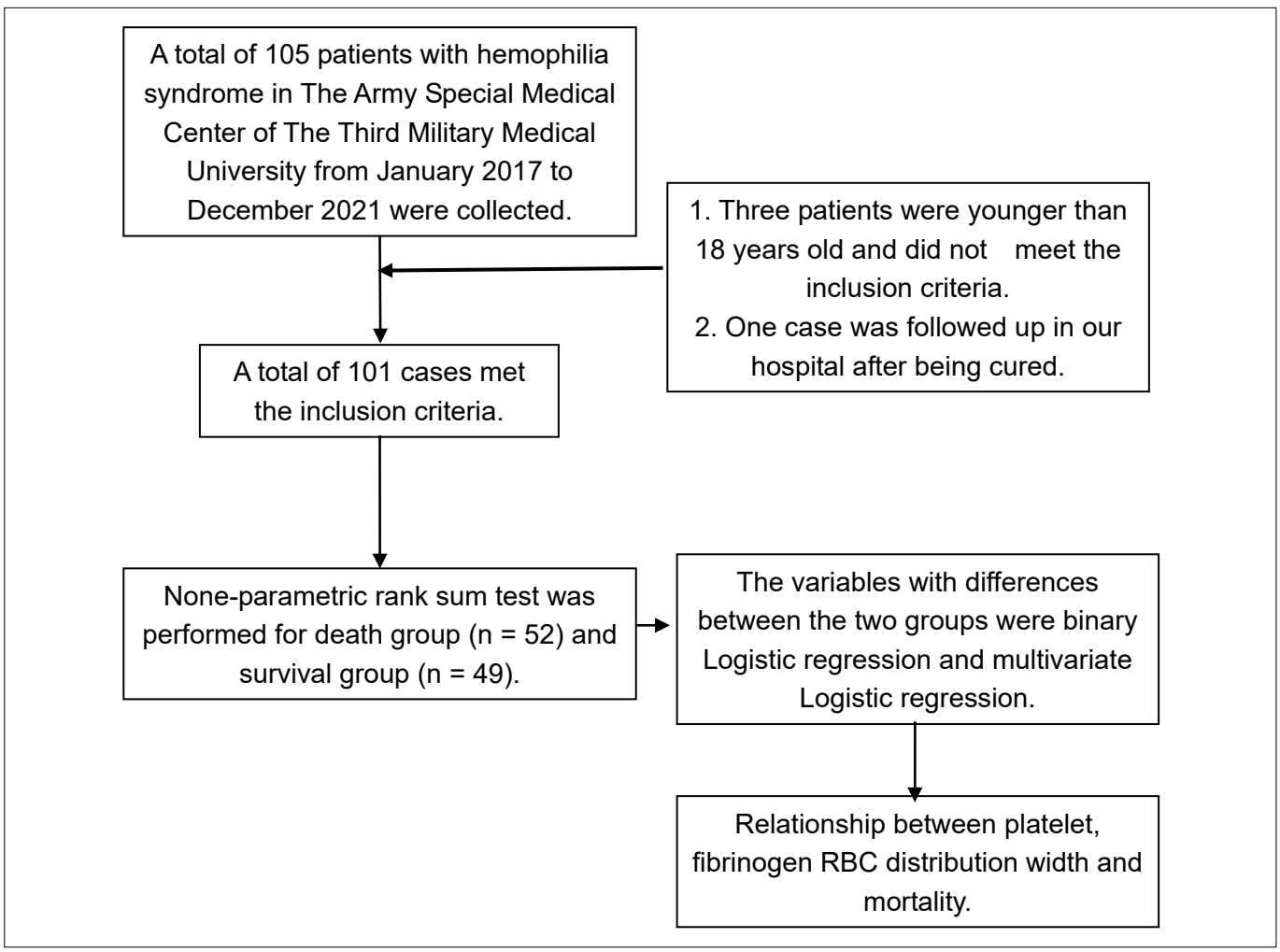


Figure 1. Flow chart for the study selection process.

cell lines (i.e., hemoglobin < 90 g/L, platelet count $<100\times10^9$/L, and neutrophils $<1\times10^9$/L); 4) high serum triglyceride (3 mmol/L) and/or low fibrinogen (FIB ≤ 1.5 g/L) levels; 5) hemophagocytosis of the bone marrow, spleen, or lymph nodes; 6) low or absent NK cell activity; 7) ferritin ≥ 500 μg/L; and 8) soluble CD25 (soluble interleukin-2 [IL-2] receptor) ≥ 2400 U/mL.

Parameter measurement

The non-rank sum test was used to analyze the following parameters of the two groups: patient age, sex, Acute Physiology and Chronic Health Evaluation II (APACHE II) score, APACHE II death risk coefficient, sequential organ failure assessment (SOFA) score, blood routine, coagulation, liver and renal function, interleukin (IL)-2, IL-6, ferritin, bone marrow puncture, immunoglobulin, and hormone use. Moreover, this study also measured whether the liver and kidney were enlarged.

Statistical analysis

In this study, data were analyzed using the STATA statistical software (Corp, College Station, Texas, United States). Kolmogorov–Smirnov test was used to verify whether all data conform to the normal distribution. The measurement data satisfying the normal distribution were represented as means ± standard deviations. The measurement data that did not meet the normal distribution were represented as medians (P25, P75). Categorical variables were expressed as percentages (%). Two groups of data were analyzed using a non-parametric test. The assumption of normality of the variances required for comparison was analyzed with the Kolmogorov–Smirnov test. $P < 0.05$ showed a statistical difference. The variables with statistical differences were used as independent variables and death as the dependent variable for binary and multiple logistic regression analyses ($P < 0.05$ indicated the correlation). Finally, a Cox proportional hazards model was established for the relevant variables to generate a receiver operating characteristic (ROC) curve that can improve the prediction accuracy of RDW and platelet and FIB levels and calculate the area under the curve (AUC).

RESULTS

Comparison of clinical data and laboratory records

In this study, the demographics, clinical data, and laboratory results of patients with HLH in the non-survivor and survivor groups were analyzed and compared (**Table 1**). The results showed no significant difference between non-survivor and survivor groups regarding population data, including age and sex ($P > 0.05$). There were significant differences in most clinical data and laboratory indicators between both groups, including APACHE II and SOFA scores, APACHE II death risk coefficient, levels of leukocytes, hemoglobin, high-sensitivity C-reactive proteins, platelets, IL-6, FIB, D-dimer, albumin, globulin, γ-glutamyl transpeptidase, lactate dehydrogenase, total cholesterol, and blood lactic acid; percentage of neutrophils; lymphocyte count; RDW; international normalized ratio; activated partial thromboplastin time; oxygenation index; length of hospital stay; hormone treatment; and proportion of tumor diseases. Bone marrow puncture results showed that phagocytes and liver size increased (**Table 1**, all $P < 0.05$). However, there was no significant difference between non-survivor and survivor groups in other parameters and data listed in **Table 1** (all $P > 0.05$).

RDW, FIB, and platelets were positively correlated with mortality in patients with HLH

This study analyzed the correlation between RDW and other laboratory parameters (**Table 2**). The results showed a significant positive correlation between RDW and patients' mortality ($P = 0.01$, odds ratio [OR]: 0.97, 95% confidence interval [CI]: 1.31–2.97). FIB ($P = 0.05$, OR: 0.43, 95% CI: 0.18–1.02) and platelets ($P = 0.04$, OR: 0.99, 95% CI: 0.95–1.02) were slightly to moderately correlated with patients' mortality (**Table 2**). After binary and multiple logistic analyses, the results showed no significant difference between other indexes and patients' mortality (**Table 2**, all $P > 0.05$).

AUC analyses of RDW, FIB, and platelets for the predictive ability on mortality in patients with HLH

To clarify the predictive ability of RDW, FIB, and platelets on mortality, ROC curves were drawn and analyzed in this study. The AUC curve of RDW was 0.857 (**Figure 2A**), which was higher than that of FIB (**Figure 2B**, AUC: 0.726) and platelet (**Figure 2C**, AUC: 0.797) levels; however, there were no significant differences.

RDW demonstrated higher sensitivity and specificity for predicting mortality in patients with HLH

In this study, we assigned the cut-off level as 16.9%. Based on the cut-off value, the sensitivity of RDW for predicting patients' mortality was 97.96%, whereas the specificity was 96.1% (**Figure 3**). However, the sensitivity and specificity of FIB were 90.9% and 59.6%, respectively. Therefore, RDW demonstrated higher sensitivity and specificity for predicting mortality in patients with HLH.

DISCUSSION

Adult HLH has received a lot of attention recently, but the current diagnostic criteria have some limitations for clinical patients.[26] Usually, patients with HLH can only be diagnosed in the middle and late stages of the disease; however, the initial stage is the

Table 1. Demographics, clinical data, and laboratory findings of patients with hemophagocytic lymphohistiocytosis (HLH) in the non-survivor and survivor groups

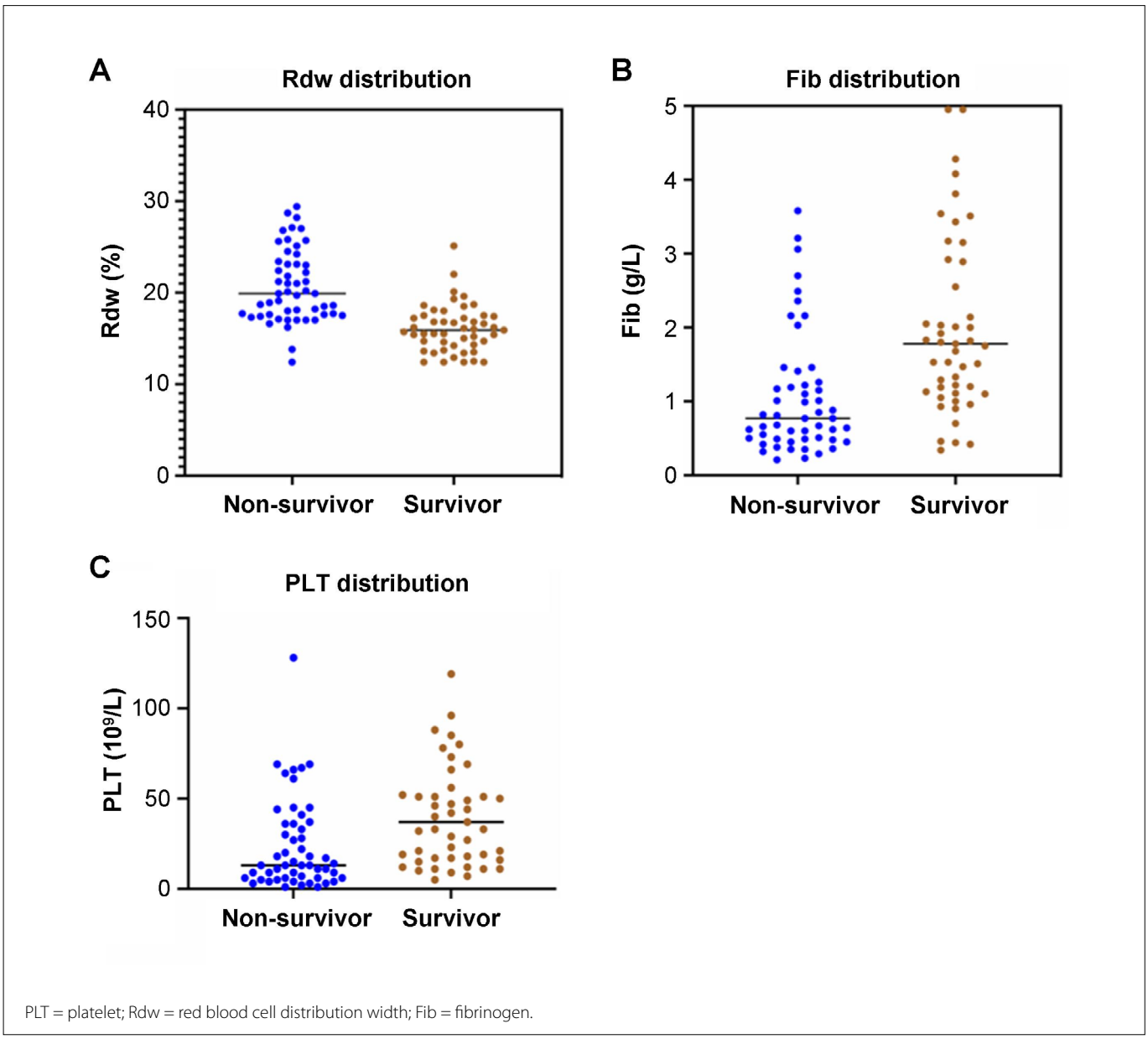
Characters	Non-survivor (n = 52)	Survivor (n = 49)	P value (P < 0.05)
Age (years), Mean (Min, Max)	50.8 (13.0, 89.0)	48.7 (14.0, 75.0)	0.67
Male/Total (%)	38%	42%	0.28
APACHEII SCROE, Mean (Min, Max)	29.4 (15.0, 47.0)	20.9 (8, 31)	< **0.001**
APAHCHEII Dead Rate, Mean (Min, Max)	71.9 (32.6, 97.9)	51.8 (16.8, 88.3)	< **0.001**
SOFA, Mean (Min, Max)	10.6 (3.0, 18.0)	6.8 (2, 14)	< **0.001**
Temperature upon admission, Mean (Min, Max)	39.6 (37.0, 41.2)	39.4 (36.9, 41)	0.314
WBC (10^{12}/L), Mean (Min, Max)	0.9 (0.1, 189.3)	2.7 (0.8, 20.0)	0.05
HB (g/L), Mean (Min, Max)	63 (42, 95)	71 (30, 136)	**0.04**
NEUT (%), Mean (Min, Max)	1.9 (0, 45.2)	1.5 (0, 13.5)	0.38
LY (10^{9}/L), Mean (Min, Max)	0.5 (0, 8.2)	0.4 (0.3,1.2)	**0.04**
CRP (mg/L), Mean (Min, Max)	127.0 (8.3, 294.8)	89.9 (0.5, 255.7)	**0.006**
RDW (%), Mean (Min, Max)	20.6 (12.4, 29.4)	16.0 (12.4, 25.1)	< **0.001**
PLT (10^{12}/L), Mean (Min, Max)	23.7 (1.0, 128.0)	51.5 (5, 365)	< **0.001**
PCT (ng/L), Mean (Min, Max)	9.6 (0.2, 64.5)	3.8 (0.1, 36.3)	0.07
IL-2 (U/mL), Mean (Min, Max)	6,241.1 (48.5, 7500.0)	5,696 (883.0, 7,500.0)	0.33
IL-6 (pg/mL), Mean (Min, Max)	824.5 (1.5, 5000.0)	163.8 (1.5, 1,921.0)	< **0.001**
INR, Mean (Min, Max)	2.0 (0.6, 16)	1.4 (0.7, 11.5)	< **0.001**
FIB (g/L), Mean (Min, Max)	1.1 (0.2, 3.6)	2.2 (0.34, 9.7)	< **0.001**
APTT (s), Mean (Min, Max)	53 (1.4, 240.0)	44.9 (23.6, 240)	**0.01**
DD (μg/L), Mean (Min, Max)	10,308.5 (437.8, 8,6287.0)	4,852.4 (10.6, 48,745)	**0.01**
ALB (g/L), Mean (Min, Max)	22.7 (10.1, 45.6)	24.2 (15, 39.8)	**0.01**
GLOB (g/L), Mean (Min, Max)	22.4 (10.8, 48.0)	25.6 (11.2, 46.8)	**0.01**
AST (U/L), Mean (Min, Max)	671.9 (11.6, 9,315.6)	324.7 (23.6, 2915)	0.87
ALT (U/L), Mean (Min, Max)	545.1 (9.9, 15,876)	234.9 (15.3, 1102.8)	0.26
AKP (U/L), Mean (Min, Max)	297.3 (51.9, 1,091.0)	382.1 (61.9, 1496.2)	0.29
γ-GT (U/L), Mean (Min, Max)	141.4 (21.7, 453.0)	296.1 (11.2, 1320)	**0.04**
LDH (U/L), Mean (Min, Max)	2,415.0 (4.6, 21,205.0)	1,182.8 (78.5, 8,849)	0.05
TB (μmol/L), Mean (Min, Max)	64.5 (4.5, 391.9)	52.5 (6.7, 385)	0.63
DB (μmol/L), Mean (Min, Max)	35.5 (2.0, 336.9)	24.7 (1.5, 231.3)	0.91
IB (μmol/L), Mean (Min, Max)	27.8 (2.9, 160.3)	23.6 (2, 119)	0.93
CHOL (mmol/L), Mean (Min, Max)	3.6 (0, 35.3)	4.8 (1.7, 44.4)	**0.01**
Triglyceride (mmol/L), Mean (Min, Max)	2.9 (0, 16.3)	3.3 (0.8, 9.7)	0.21
Ferritin (ng/mL), Mean (Min, Max)	2,515.7 (307.0, 27,406.0)	1,947.7 (79.5, 7,500)	0.81
Na^+ (mmol/L), Mean (Min, Max)	132.8 (117.0, 184.0)	131.9 (121, 175)	0.18
K^+ (mmol/L), Mean (Min, Max)	3.5 (2.2, 5.7)	3.4 (2.5, 5.8)	0.76
FiO_2 (mmHg), Mean (Min, Max)	168.7 (42.0, 350.0)	256 (80, 402)	< **0.001**
Lac (mmol/L), Mean (Min, Max)	6.5 (1.7, 17.1)	3.4 (1, 15)	< **0.001**
SCR (μmol/L), Mean (Min, Max)	120.6 (16.8, 586.7)	91.2 (25.9, 426.8)	0.13
Length of stay (days), Mean (Min, Max)	11.0 (1.0, 17.0)	15.5 (1.0, 48.0)	**0.03**
Hormone therapy, (%)	53.8%	79.6%	**0.04**
Immunoglobulin shock therapy, (%)	25%	28.6%	0.18
Tumor disease, (%)	58%	32.6%	**0.03**
Phagocytes in bone marrow biopsy, (%)	78.8%	96.0%	0.05
Liver enlargement, (%)	38.4%	57.0%	0.05
Spleen enlargement, (%)	82.6%	85.7%	0.22
Lung Infection, (%)	59.6%	53%	0.32

Min = minimum; Max = maximum; APACHE II = Acute Physiology and Chronic Health Evaluation II; SOFA = Sequential Organ Failure Assessment; WBC = white blood cell; HB = hemoglobin; NEUT = neutrophils; LY = lymphocyte; CRP = C-reactive protein; RDW = red blood cell distribution width; PLT = platelet; PCT = procalcitonin; IL-2 = interleukin 2; IL-6 = interleukin 6; INR = International Normalized Ratio; FIB = fibrinogen; APTT = activated partial thromboplastin time; DD = D-dimer; ALB = albumin; GLOB = globulin; AST = aspartate aminotransferase; ALT = alanine aminotransferase; AKP = alkaline phosphatase; γ-GT = γ-glutamyl transpeptidase; LDH = lactate dehydrogenase; TB = total bilirubin; DB = direct bilirubin; IB = indirect bilirubin; CHOL = cholesterol; Na^+ = sodium ion; K^+ = potassium ion; FiO_2^+ = fraction of inspiration O_2; Lac = lactic acid; SCR = creatinine. The P values in bold font represent significant differences.

Table 2. Correlation analyses between red blood cell distribution width (RDW), fibrinogen and platelets levels, and mortality in patients with hemophagocytic lymphohistiocytosis (HLH)

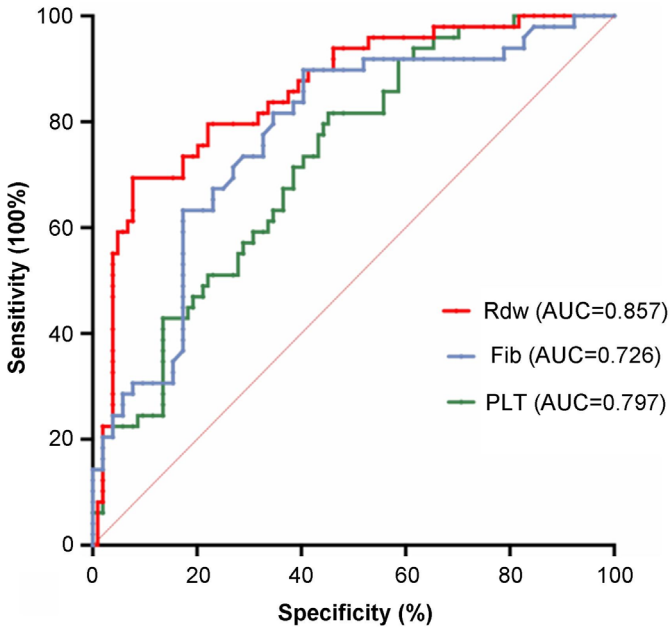
Variables	Survival rate			
	OR crude	P value	OR adjusted crude (95% CI)	P value
Hemoglobin	0.97 (0.95–0.99)	0.03	0.98 (0.93–1.02)	0.34
C-reactive protein	1.01 (1.00–1.01)	0.01	0.99 (0.99–1.00)	0.44
Red cell distribution width	1.61 (1.31–1.97)	0.00	0.97 (1.31–2.97)	**0.01**
Platelet count	0.98 (0.96–0.99)	0.01	0.99 (0.95–1.02)	**0.04**
Fibrinogen	0.38 (0.23–0.63)	0.00	0.43 (0.18–1.02)	0.05
Globulin	0.95 (0.90–1.00)	0.05	1.06 (0.97–1.15)	0.20
γ-glutamyl transpeptidase	0.99 (0.99-1.00)	0.05	0.99 (0.99–1.00)	0.30

CI = confidence interval; OR = odds ratio; RDW = red blood cell distribution width; HLH = hemophagocytic lymphohistiocytosis.
The P values in bold font represent significant differences.



PLT = platelet; Rdw = red blood cell distribution width; Fib = fibrinogen.

Figure 2. Distribution map of red blood cell distribution width and platelet and fibrinogen levels between non-survivor and survivor groups.



PLT = platelet; Rdw = red blood cell distribution width; Fib = fibrinogen; AUC = area under curve.

Figure 3. Receiver operating characteristic curves for the red blood cell distribution width and platelet and fibrinogen levels evaluating the area under the curve and predictive value of mortality in patients with hemophagocytic lymphohistiocytosis.

best treatment period. The RDW is correlated with mortality in patients with sepsis.[12] Previous studies[27,28] have reported that RDW is significantly associated with the prognosis of many diseases, such as cancer, sepsis, and cardiovascular disease. However, there are limited reports[29,30] on the relationship between HLH and RDW. HLH is characterized by an excessive inflammatory response and a cytokine storm. During the inflammatory reaction, proinflammatory cytokines affect the survival of circulating red blood cells, damage the cell membrane of these cells, produce larger and renewed reticulocytes that enter the blood circulation, and increase the distribution width of red blood cells.[31] This is also a pathophysiological foundation for us to clarify the relationship between HLH and RDW. In this study, most adult HLH cases were induced by infection through blood phagocytosis. Therefore, this study explored whether there was a correlation between RDW and mortality in patients with adult HLH. We found that RDW was positively correlated with mortality in patients with HLH and had a high prediction level. Furthermore, the sensitivity of RDW for predicting mortality was 97.96%, and the specificity was 96.1%, providing more auxiliary diagnostic evidence for patients with HLH.

Hormone pulse therapy is a double-edged sword for clinicians. The application of sufficient hormone pulse at the right time is a rescue treatment for patients, but in the case of severe infection, high-dose hormone pulse may lead to the death of patients. More clinical studies are needed to provide a clinical basis for hormone pulse therapy. In this study, we found significant differences in hormone pulse therapy between non-survivor and survivor groups. We also found that the RDW, and platelets and FIB levels had predictive values for mortality in patients with adult HLH. Fardet et al.[6] proposed HScore to predict the possibility of a single patient with HLH so that clinicians can make appropriate treatment decisions as soon as possible. However, HScore is a complex index that needs to be improved and comprehensively evaluated after several laboratory tests. Therefore, faster and more easily available laboratory indexes are needed to assist in the diagnosis of adult HLH.[6,7] The HScore includes the FIB level. This study found that RDW, compared with FIB, demonstrated higher sensitivity and specificity on mortality of patients with HLH (sensitivity: 90.9%, specificity: 59.6%). The sensitivity and specificity of RDW are higher than those of FIB, which has a high predictive value for mortality in adult HLH.

This study had a few limitations. First, this study is a single-center, small sample, cross-sectional retrospective study. Patients with HLH in the survival group were not followed up. Second, IL-2 and ferritin tests in our center have not been analyzed for accuracy. The test results of most patients are greater than a certain value that is not accurate. Therefore, RDW cannot be compared with the predicted values of IL-2 and ferritin.

CONCLUSION

This study collected data from patients with HLH in the hospital and expounded the clinical understanding and treatment perception of HLH from the perspective of the critical care department. This study showed that RDW was associated with mortality in patients with HLH. The cut-off value of RDW was 16.9. The sensitivity and specificity of predicting mortality were 97.96% and 96.1%, respectively. Logistic regression analysis showed a correlation between RDW and mortality. In summary, the RDW can be used as an important index to predict mortality in patients with HLH. The findings of this study suggest that RDW may be suitable as an auxiliary diagnostic method for HLH and an auxiliary means for predicting mortality in adult patients with HLH clinically.

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Efficacy of methimazole before the administration of radioactive iodine in the management of Graves' disease: a systematic review and meta-analysis

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Graves disease.
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Hyperthyroidism.

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Anti-thyroid drugs.
Radioactive iodine.
Hyperthyroidism secondary.

ABSTRACT

BACKGROUND: The efficacy of anti-thyroid drugs in conjunction with radioactive iodine therapy in the management of Graves' disease is still controversial.

OBJECTIVE: To compare the efficacy of pretreatment with methimazole before the administration of radioactive iodine for the treatment of Graves' disease.

DESIGN AND SETTING: A systematic review and meta-analysis was conducted at a teaching/tertiary hospital in Ibadan, Nigeria.

METHODS: A systematic search of the PubMed, Embase, Cochrane Library, and Web of Science databases was performed from inception to December, 2021.

RESULTS: Five studies with 297 participants were included. There was no difference in the risk of persistent hyperthyroidism when radioactive iodine was used in conjunction with methimazole compared with when radioactive iodine was used alone (relative risk: 1.02, 95% confidence interval, CI: 0.62–1.66; $P = 0.95$, $I^2 = 0\%$). Subgroup analysis based on the duration between discontinuation of methimazole and the administration of radioactive iodine showed a lower risk of persistent hyperthyroidism when methimazole was discontinued within 7 days before radioactive iodine use, although this did not reach statistical significance (risk ratio: 0.85, CI: 0.28–2.58).

CONCLUSIONS: The use of methimazole before radioactive iodine administration was not associated with an increased risk of persistent hyperthyroidism. Concerns about medication toxicity and adverse effects should be considered when clinicians make decisions on combination therapies for the treatment of Graves' disease.

PROSPERO REGISTRATION: CRD42020150013, https://www.crd.york.ac.uk/prospero/display_record.php?RecordID=150013.

INTRODUCTION

Graves' disease is an immune system disorder that results in an unregulated and overproduction of thyroid hormones due to circulating antibodies in the blood.[1-3] The antibodies produced bind to the thyrotropin receptor and activate glandular function, resulting in hyperthyroidism.[2] Graves' disease leads to major cardiovascular and psycho-cognitive complications if left untreated, thus contributing to significant morbidity and mortality.[3,4]

As a leading cause of hyperthyroidism worldwide with an incidence of 30 cases per 100,000 persons per year in the United States, it is imperative to understand the pathophysiology and treatment modalities for the management of Graves' disease.[5-7] According to the 2016 American Thyroid Association guidelines for the diagnosis and management of hyperthyroidism and other causes of thyrotoxicosis, patients with overt Graves' hyperthyroidism should be treated with any of the following modalities: radioactive iodine therapy, anti-thyroid drugs, and thyroidectomy.[5]

In the United States, radioactive iodine therapy (RAI) has been the most preferred therapy by physicians, with 59.7% of clinical endocrinologists opting for this as the primary therapy for an uncomplicated case of Graves' disease.[8,9] There has also been an increasing trend toward the use of anti-thyroid drugs (ATD), as this is the preferred first-line treatment for Graves' disease by thyroidologists in Europe, Latin America, and Japan.[5,10-13] However, a network meta-analysis has suggested higher relapse rates with ATDs (52.7%) than with RAI (15%).[3]

Although there is widespread and accepted use of radioactive iodine and anti-thyroid drugs individually, there is no consensus regarding their use in conjunction.[14] It has been noted in the literature that following radioiodine therapy, an acute rise in thyroid hormone levels could occur, thus triggering a clinical exacerbation of symptoms.[15-17] It has also been postulated that anti-thyroid medications such as methimazole could have radioprotective attributes and are thus beneficial for patients receiving radioactive iodine therapy.[18,19] While some authors have explored the use of adjunct anti-thyroid drugs before radioactive iodine therapy,[9,19-26] others prefer the use of anti-thyroid medications continuously during radioactive iodine[14,27] and after radioactive iodine treatment.[28,29]

The varying study designs (retrospective studies, narrative reviews), disease population (toxic multinodular goiter, toxic adenoma), interventions (use of carbimazole and propylthiouracil), and the interval between therapies (use of ATD before, during, or after RAI) in the established literature produce considerable heterogeneity, which makes it difficult to reach a conclusion on the efficacy of anti-thyroid drugs in conjunction with radioactive iodine therapy.

OBJECTIVE

We conducted a systematic review and meta-analysis of randomized controlled trials to evaluate the efficacy of treatment with methimazole before the administration of radioactive iodine compared to the use of radioactive iodine therapy alone for the treatment of Graves' disease.

METHODS

Search strategy

The PubMed, Embase, Cochrane Library, and Web of Science electronic databases were searched for randomized controlled trials comparing adjunctive anti-thyroid drug use with radioactive iodine therapy versus radioactive iodine only in the treatment of Graves' disease, from inception to December, 2021. The search terms included "Hyperthyroidism," "Radioactive iodine," and "Antithyroid drugs". There were no restrictions on language or publication period. The searches were rerun immediately before the final data extraction and analyses, with further studies retrieved for inclusion.

Study identification and selection

The Preferred Reporting Items for Systematic Reviews and Meta-Analyses[30] was used as a guide for the identification and selection of studies (**Figure 1**).Two investigators independently screened and reviewed the titles and/or abstracts retrieved using the search strategy to identify titles that potentially met the inclusion criteria. The full texts of these potentially eligible studies were retrieved and independently assessed for eligibility by the two review team members. Disagreements between the two over the eligibility of the selected studies were resolved through consensus with a third reviewer.

Randomized clinical trials that compared adjunctive anti-thyroid medications with radioactive iodine therapy were deemed eligible for an in-depth review. Subsequently, 20 full-text articles were assessed for eligibility. Randomized clinical trials that evaluated initial treatment with methimazole before the administration of radioactive iodine therapy, regardless of the duration of treatment, were selected for final data extraction. We excluded studies that utilized anti-thyroid medications other than methimazole (such as carbimazole propylthiouracil) and those that administered methimazole either continuously or post-radioiodine therapy. We also excluded studies that incorporated other causes of hyperthyroidism, such as toxic multinodular goiter, because the focus was on Graves' hyperthyroidism. This systematic review was specified in a registered protocol (PROSPERO: CRD42020150013, https://www.crd.york.ac.uk/prospero/display_record.php?RecordID=150013) before data extraction commenced.

Risk of bias assessment

The risk of bias for studies incorporated in the systematic review and meta-analysis was assessed using the Cochrane risk of bias tool for randomized control trials. The studies were assessed for the following domains: random sequence generation, allocation concealment, blinding of participants and personnel, blinding of outcome assessment, incomplete outcome data, selective reporting, and other biases. The studies were further judged as 'low risk,' 'some concerns, 'or' high risk.'

Data extraction and synthesis

The RevMan 5.4 software (The Cochrane Collaboration, Oxford, United Kingdom)was used to perform the meta-analysis. The primary outcome measure was evidence of persistent hyperthyroidism after treatment (methimazole and radioiodine therapy in the experimental arm and radioiodine only in the control arm). The presence of hyperthyroidism after treatment was considered a "treatment failure." Hypothyroid or normal thyroid values following treatment were stratified to be under the same class as "non-hyperthyroid state," and thus considered a treatment success. Thyroid status was determined based on the clinical and laboratory criteria used for each clinical trial. The secondary outcome measure was the duration of discontinuation of adjunctive treatment with methimazole and its effect on the cure rates in patients with Graves' disease.

We employed the random-effects meta-analysis model and inverse variance weighting method. A summary of the intervention effect for each study was provided by calculating the risk ratios and corresponding 95% confidence intervals (CI) for the main

dichotomous variables: hyperthyroidism or non-hyperthyroidism. Heterogeneity was assessed using both the Q test and I-squared statistics. An I^2 value greater than 50% was considered indicative of substantial heterogeneity. Forest plots were generated to evaluate the risk of publication bias.

RESULTS

A total of 378 studies were identified through multiple database searches. Twenty full-text articles were assessed for eligibility, of which five randomized control trials were included in the final qualitative synthesis and meta-analysis. Full-text articles that were excluded were those with a patient population that had hyperthyroidism from other causes (n = 1), used other anti-thyroid medications (n = 9), and those with continuous treatment or treatment with methimazole after radioiodine (n = 5). Only trials that used methimazole as the drug of choice for the initial medical treatment were selected. The follow-up duration varied among the eligible studies; thus, studies were analyzed

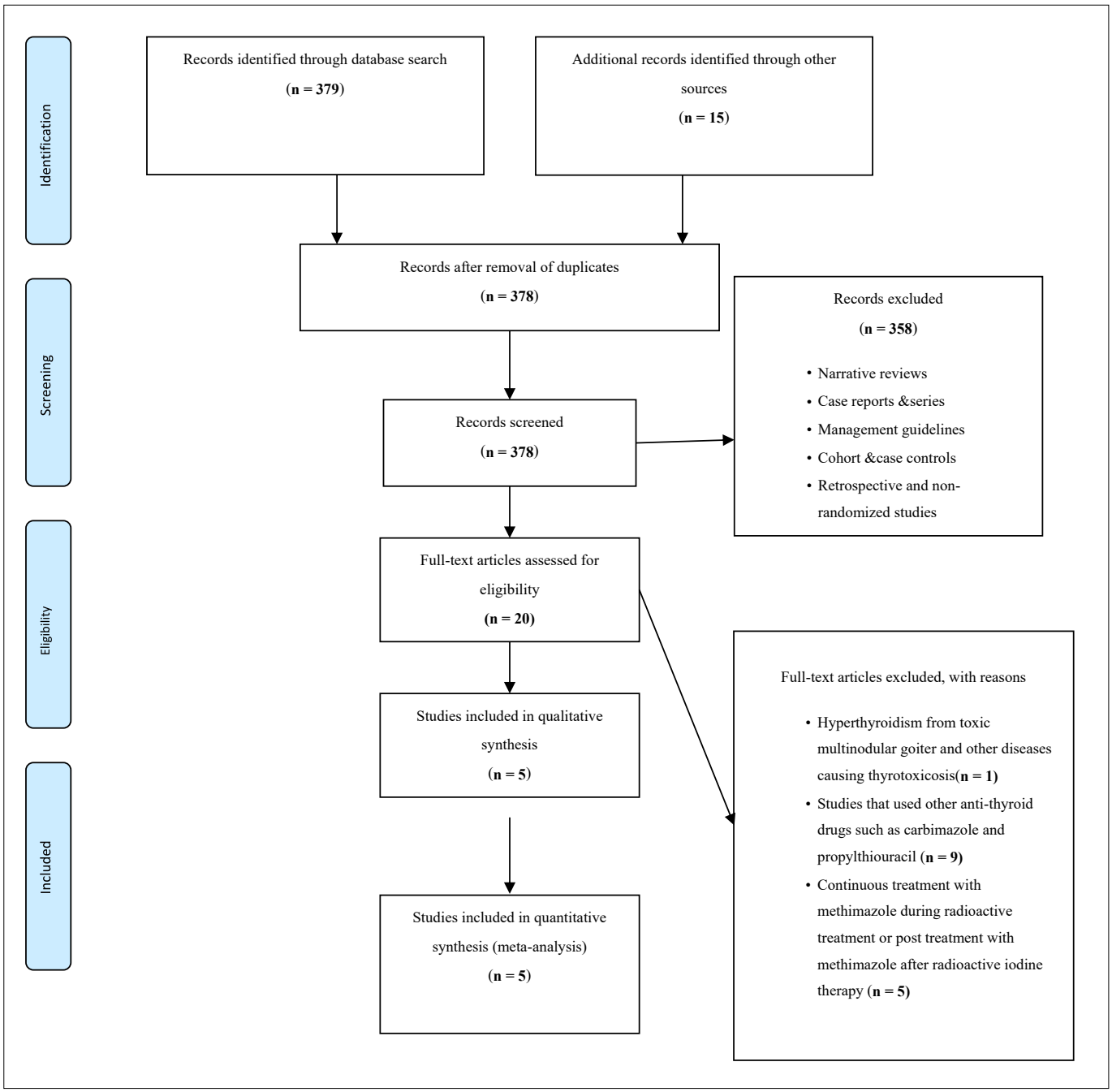

Figure 1. The Preferred Reporting Items for Systematic reviews and Meta-Analyses flow chart for study selection.

independently based on the duration of follow-up and evaluation of thyroid status at each visit. This was done to limit heterogeneity and incorporate all values into the final data synthesis. In the final meta-analysis, 289 patients who received methimazole before radioactive treatment were randomized to the treatment arm, while 335 were assigned to the control arm and received radioactive iodine therapy only.

Study characteristics

The clinical trials included in this study were conducted in Brazil (n = 2), Slovenia (n = 1), and the United States of America (n = 2). All included studies were randomized trials, with the patient population being adults with Graves' disease. The follow-up duration ranged from 14 days to one year (**Table 1**).

Minimal heterogeneity was found in the trials regarding the diagnostic criteria for hyperthyroidism. All studies utilized clinical assessments, suppressed thyroid stimulating hormone levels, thyroid hormone levels, 24-hour radioactive iodine uptake, and antibody levels to diagnose patients. Based on Cochrane's tool to assess the risk of bias, there was no study with a high risk of bias (**Table 2**). One study had a low risk of bias, while others had concerns regarding the randomization process and selection of reported data (**Figure 2**).

Outcome analysis

Using a random effects model for the meta-analysis, pretreatment with methimazole in conjunction with radioactive iodine therapy alone was not associated with an increased risk of persistent hyperthyroidism at follow-up in patients with Graves' disease (relative risk, RR:1.02, 95% CI: 0.62–1.66; P = 0.95). Heterogeneity among the treatment effects was low (I2 = 0%). The funnel plot displayed an asymmetric distribution (Egger's t-test = 1.31, P = 0.238) (**Figure 3**).

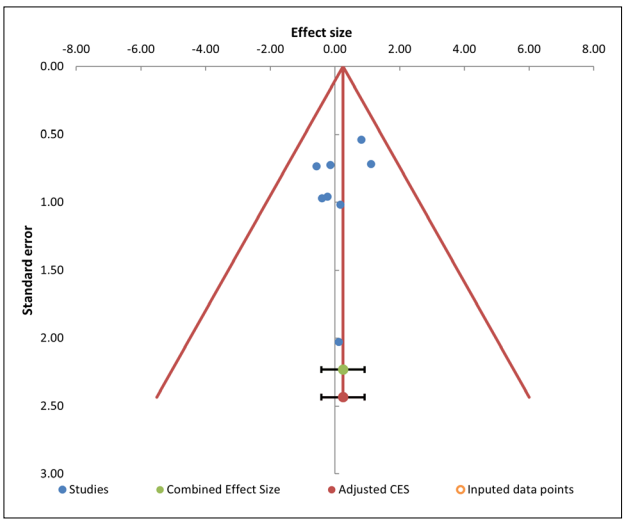

Figure 2. Funnel plot of publication bias in selected studies.

Table 1. Baseline characteristics of participants in included trials

Study	Country	Age RAI+MMZ	Age RAI	Sex RAI+MMZ (M/F)	Sex RAI (M/F)	No. assigned to RAI+MMZ	No. assigned to R AI	Duration of MMZ discontinuation (days)	FT4 RAI+MMZ (pmol/L)	FT4 RAI (pmol/L)	Follow up (months)
Andrade et al.[20]	Brazil	37.6	34.5	2/25	4/24	23	28	4	61.78 ± 5.15	59.20 ± 5.92	1
Andrade et al.[22]	Brazil	37.4	35.1	2/27	4/28	29	32	4	59.20 ± 27.00	57.90 ± 21.90	12
Braga et al.[21]	United States	43.0	35.0	6/10	0/18	16	18	6	44.30 ± 21.00	66.80 ± 35.70	8
Burch et al.[23]	United States	42.0	36.0	7/14	2/19	21	21	6	80.00 ± 45.00	52.00 ± 40.00	0.5
Pirnat et al.[24]	Slovenia	43.5	46.8	8/42	8/51	50	59	7	20.40 ± 9.10	38.00 ± 17.80	1,3,6,&12

RAI = radioactive iodine; MMZ = methimazole; FT4 = free tyrosine.

Table 2. Risk of bias assessment of included studies

Unique ID	Experimental	Comparator	Randomization process	Deviations from intended interventions	Missing outcome data	Measurement of the outcome	Selection of the reported result	Overall
Andrade et al.[22]	RAI+MMZ	RAI	+	+	+	+	?	+
Braga et al.[21]	RAI+MMZ	RAI	?	+	+	?	?	?
Andrade et al.[20]	RAI+MMZ	RAI	+	+	+	+	?	?
Burch et al.[23]	RAI+MMZ	RAI	+	?	+	+	+	?
Pirnat et al.[24]	RAI+MMZ	RAI	?	?	+	?	?	?

+ = Low risk; ? = Some concerns.

RAI = radioactive iodine; MMZ = methimazole.

A subgroup was created based on the interval between the discontinuation of methimazole and radioactive iodine therapy. Subsequently, a subgroup analysis was performed, which revealed an RR of 1.52 (CI: 0.28–8.18) for studies with a 4-day duration of discontinuation of methimazole before radioactive therapy, while an RR of 1.38 (CI: 0.27–7.16) and 0.85 (CI: 0.28–2.58) was calculated for studies with 6 days and 7 days' intervals between discontinuation of anti-thyroid drugs and radioactive treatment, respectively. The combined effect size for subgroup analysis was 1.38 (CI: 1.07–1.79) (**Table 3**).

DISCUSSION

Our meta-analysis showed no difference between the risk of persistent hyperthyroidism when radioactive iodine was used in conjunction with methimazole and when radioactive iodine was used alone (RR: 1.02, 95% CI: 0.62–1.66; P = 0.95, I^2 = 0%). Subgroup analysis based on the duration between discontinuation of methimazole and the administration of radioactive iodine showed a lower risk of persistent hyperthyroidism when methimazole was discontinued within 7 days before radioactive iodine use, although this did not reach statistical significance (RR: 0.85, CI: 0.28–2.58)

Over the years, there have been debates on the use of anti-thyroid drugs in conjunction with radioactive iodine therapy for the management of hyperthyroidism in Graves' disease, with the increasing popularity of adjunctive anti-thyroid medications with radioactive iodine therapy.[5] To the best of our knowledge, this is the first meta-analysis to evaluate the efficacy of treatment with methimazole before the administration of radioactive iodine therapy inpatients with Graves' disease.

In our study, we focused on the risk of persistent hyperthyroidism (treatment failure) following adjunctive treatment for Graves' disease; our analysis showed that the risk was not significant and was only 1.02 times higher in patients treated with methimazole

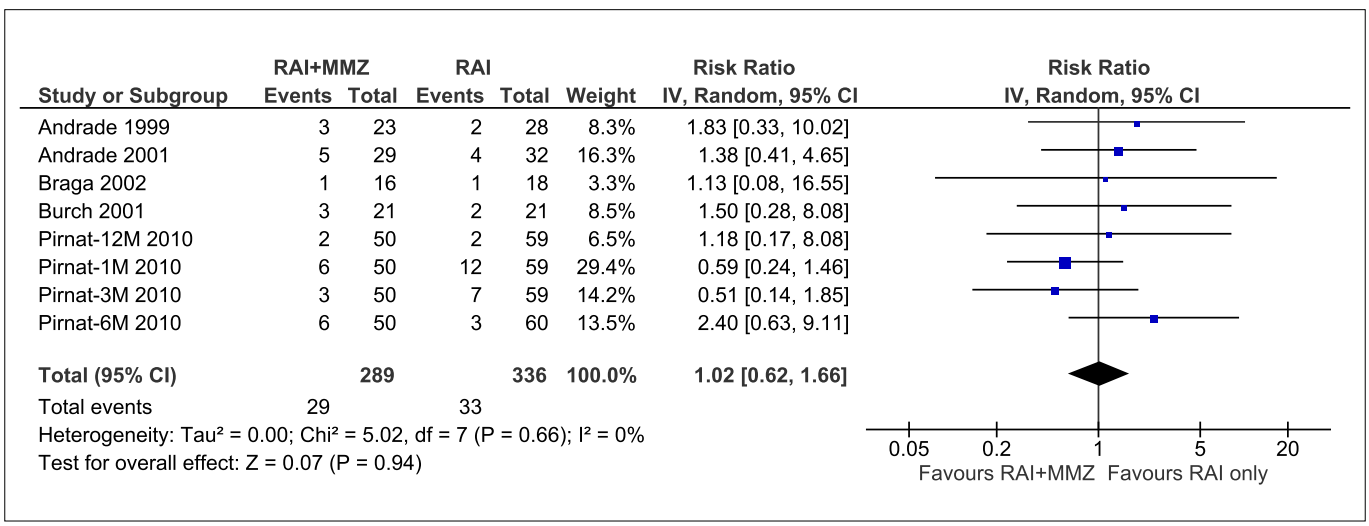

Figure 3. Forest plot of comparison: radioactive iodine + methimazole versus radioactive iodine only; outcome: persistent hyperthyroidism.

Table 3. Subgroup analysis based on interval between discontinuation of methimazole and initiation of radioactive iodine

	Study name / Subgroup name	Risk ratio	CI lower limit	CI upper limit	Weight	Q	p_Q	I^2
1	Andrade et al.[22]	1.38	0.40	4.77	66.25%			
2	Andrade et al.[20]	1.83	0.32	10.45	33.75%			
3	**4 days**	**1.52**	**0.28**	**8.18**	**45.01%**	**0.07**	**0.793**	**0.00%**
4	Braga et al.[21]	1.13	0.07	18.34	28.17%			
5	Burch et al.[23]	1.50	0.26	8.50	71.83%			
6	**6 days**	**1.38**	**0.27**	**7.16**	**46.69%**	**0.03**	**0.859**	**0.00%**
7	Pirnat et al.[24] (12 months)	1.18	0.17	8.25	11.87%			
8	Pirnat et al.[24] (6 months)	2.36	0.61	9.09	22.70%			
9	Pirnat et al.[24] (3 months)	0.51	0.14	1.88	23.73%			
10	Pirnat et al.[24] (1 month)	0.59	0.24	1.47	41.71%			
11	**7 days**	**0.85**	**0.28**	**2.58**	**8.30%**	**3.59**	**0.309**	**16.46%**
12	**Combined effect size**	**1.38**	**1.07**	**1.79**		**4.96**	**0.665**	**0.00%**

CI = confidence interval.

before radioactive iodine as compared with those who received radio-iodine therapy alone.

A similar meta-analysis done by Walter et al.[31] on a per protocol basis revealed a summary RR of 1.34 (0.96–1.88; P = 0.09) for treatment failure with adjunctive anti-thyroid drugs compared with the control. This study differs from ours in that the authors evaluated the combined effect of adjunctive anti-thyroid drugs administered before and after radioactive iodine. In addition, some studies included in this meta-analysis had patient populations other than those with Graves' disease.

While some studies concluded that treatment with anti-thyroid drugs during the peri-therapeutic period in patients treated with ^{131}I reduced the effectiveness of radioiodine, thus leading to higher treatment failure rates,[18,32-37] we can argue that the flawed methodology and selection bias of some observational studies could have imposed some limitations.

Crooks et al.[37] opined that methimazole has radioprotectant properties even if discontinued 6 days before administration of radioactive iodine and that the single dose RAI treatment failure rate was significantly higher in the group pretreated with methimazole (71%) than in those receiving RAI alone (25%). This correlates with the study by Connell et al.[19] which reported a higher incidence of persistent hyperthyroidism in the group administered adjunct treatment with carbimazole 46% versus 16% (P < 0.05). One year after treatment, a similar proportion of each group had persistent thyrotoxicosis (23% in the pretreated group versus 21% in the non-pretreated group).

In a retrospective study by Tuttle et al.,[32] pretreatment with propylthiouracil was also associated with higher treatment failure rates. Persistent hyperthyroidism was observed in 4% of patients (2/48) treated with only RAI and in 34% of patients (13/38) receiving RAI after pretreatment with propylthiouracil (P = 0.003). Patients were treated with propylthiouracil for a mean of 151 ± 32 days.[32] Another retrospective study conducted by the authors on a later date showed that discontinuation of the anti-thyroid drug at least a week before radioactive iodine was associated with higher failure rates.[33] The effects of propylthiouracil and methimazole/carbimazole may not be directly comparable, making it difficult to extrapolate findings from different sources that utilize varying anti-thyroid medications for adjunctive treatment.

Sabri et al.[26] conducted a prospective randomized clinical trial that showed significantly greater success in the group without carbimazole during radioactive therapy(93% versus 49%, respectively). Stepwise logistic regression demonstrated that the failure was related to the administration of carbimazole during ^{131}I therapy (P < 0.005) and the absorbed dose of radioiodine (P < 0.025). It is interesting to note that in this study, simultaneous administration of the anti-thyroid drug was the decisive factor for successful radioactive iodine therapy, as16 patients who discontinued ATD 1-3 days before radioiodine therapy showed a 94% success rate. Thus, the authors recommended that, if clinically feasible, ATDs should be discontinued at least a day before the initiation of radioiodine treatment.

This is in tandem with the study by Bonnema et al.[14] which assessed cure rates in a group receiving continuous methimazole therapy during and 4 weeks after radioactive iodine therapy versus a group that discontinued methimazole 8 days before radioiodine therapy. Patients receiving continuous methimazole had a lower cure rate (44%) than those who discontinued methimazole 8 days before radioactive iodine therapy (61%). Pirnat et al.[24] also reported similar lower cure rates in patients who were continuously administered methimazole until radioiodine application.

Some studies have advocated adjunctive treatment with ATDs in conjunction with radioactive iodine. Kung et al.[38] studied the use of a block replacement regimen of methimazole plus L-thyroxine on the result of radioactive iodine therapy and determined that persistent hyperthyroidism was found in 38.7% of the patients pretreated with methimazole plus L-thyroxine versus 44.5% of those who were administered radioactive iodine only. In addition, the time to achieve euthyroidism was earlier with adjunctive treatment (two versus eight weeks).[38]

Similar effectiveness and cure rates were observed in patients pretreated with methimazole compared to non-pretreated patients in two of the studies included in our meta-analysis.[21,24] However, Burch et al.[23] had the opinion that most patients with Graves' disease should not be pretreated with anti-thyroid drugs before receiving radioiodine, as pretreatment with methimazole results in a rapid increase in thyroid hormone levels upon discontinuation of these medications in preparation for radioiodine therapy. This was also supported by an earlier clinical trial by Andradeet al.[20]which observed that interruption of anti-thyroid drugs caused a short-term increase in serum thyroid hormone levels in patients with Graves' hyperthyroidism receiving radioactive iodine therapy. One year later, the pretreated group and those who received radioactive iodine therapy alone were similar in terms of persistent hyperthyroidism (15.6% in the radioactive iodine group versus 13.8% in the adjunctive methimazole group).

The 2016 American Thyroid Association guidelines state that pretreatment with methimazole before radioactive iodine therapy for Graves' disease should be considered in patients at increased risk of complications due to worsening hyperthyroidism, and methimazole should be discontinued 2-3 days before radioactive iodine therapy.[5] The subgroup analysis performed in our study with regard to the interval between stopping ATD and RAI therapy showed a lower risk ratio with increasing duration of discontinuation of ATD. The risk ratio was 1.52 (0.28–8.18) for a 4-day interval, 1.38 (0.27–7.16) for a 6-day interval, and 0.85 (0.28–2.58) for a 7-day

interval between discontinuation of methimazole and administration of radioiodine. This implies that the risk of persistent hyperthyroidism is reduced by 15% if pretreatment with methimazole is administered 7 days before radioiodine therapy, although the observation was not considered statistically significant.

Publication bias was minimal, as the funnel plot displayed an asymmetric distribution (Egger's t-test = 1.31, P = 0.238). There are significant side-effect profiles of ATDs, with 13% of patients developing an adverse reaction, as shown in a network meta-analysis conducted by Sundareshet al.[39] Liver injury and elevated transaminases (worse with propylthiouracil), and dermatologic reactions are common adverse effects.[3,40] Therefore, the choice of therapy in Graves' disease is influenced by many factors and must be tailored to each patient's characteristics and needs.[41,42] Pretreatment may be considered in patients who require rapid biochemical control and are at increased risk of thyrotoxic complications.[43]

Limitations and recommendations

The narrow eligibility criteria of our systematic review resulted in a small sample size and limited number of studies included in the final synthesis. This might have reduced the power of the study and accounted for the statistical insignificance of the results obtained. The limited number of randomized controlled trials motivates the essence of conducting well-designed RCTs with a homogenous disease population (Graves' disease) and a larger sample size to expand the evidence needed to make informed decisions. The last randomized study reported on this subject was conducted by Pirnat et al.[24] over nine years ago.

The only anti-thyroid drug considered in the included trials for our systematic review was methimazole. This might limit the translation of our findings with regard to other anti-thyroid medications, such as carbimazole (a precursor of methimazole) and propylthiouracil. Overall, our study showed minimal statistical heterogeneity ($I^2 = 0\%$) for the main outcome measure. We also included a uniform sample population with Graves' disease only and ATD (methimazole) utilized. However, the dose of radioactive iodine utilized (fixed or adapted dose)and the varying duration of follow-up for the different studies included could be imminent sources of heterogeneity. Future systematic reviews with a subgroup analysis evaluating the varying duration of follow-up as it pertains to persistent hyperthyroidism should be conducted.

CONCLUSION

This study shows that treating patients with an anti-thyroid medication(methimazole)before utilizing radioactive iodine has the same treatment failure risk as using radioactive iodine therapy alone. The use of methimazole before radioactive iodine administration was not associated with an increased risk of persistent hyperthyroidism.

Although the treatment failure risks were similar between the two groups, only the subgroup that discontinued methimazole seven days before the use of radioactive iodine had a lower risk of persistent hyperthyroidism. Concerns about medication toxicity and adverse effects should be considered when clinicians make decisions on combining therapies for the treatment of Graves' disease.

Key implications

- Clinicians who schedule radioactive iodine therapy for Graves' disease treatment may not need to administer an initial methimazole use to patients, except in cases of increased risk of thyrotoxic complications, such as liver injury and dermatological reactions, which are associated with methimazole use.
- Research institutions should conduct randomized controlled trials with larger patient cohorts on treatment options for Graves' disease to obtain statistically significant results that aid clinical decisions and improve patient outcomes.

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Prevalence and predisposing factors for fatigue in patients with chronic renal disease undergoing hemodialysis: a cross-sectional study

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ABSTRACT

BACKGROUND: Patients with chronic renal disease and undergoing hemodialysis are at a high risk for developing several complications. Fatigue is a common, troubling symptom that affects such patients and can contribute to unfavorable outcomes and high mortality.

OBJECTIVE: This cross-sectional study aimed to evaluate the prevalence of fatigue in Brazilian patients with chronic kidney disease undergoing hemodialysis and determine the predisposing factors for fatigue.

DESIGN AND SETTING: An observational, cross-sectional, descriptive study was conducted in two renal replacement therapy centers in the Greater ABC region of São Paulo.

METHODS: This study included 95 patients undergoing dialysis who were consecutively treated at two Brazilian renal replacement therapy centers between September 2019 and February 2020. The Chalder questionnaire was used to evaluate fatigue. Clinical, sociodemographic, and laboratory data of the patients were recorded, and the Short Form 36 Health Survey, Pittsburgh Sleep Quality Index, and Beck Depression Inventory were administered.

RESULTS: The prevalence of fatigue in patients undergoing hemodialysis was 51.6%. Fatigue was independently associated with lower quality of life in terms of physical and general health. Patients with fatigue had a higher incidence of depression (65.9% vs. 34.1%, P = 0.001) and worse sleep quality (59.1% vs. 49.9%; P = 0.027) than those without fatigue.

CONCLUSION: Prevalence of fatigue is high in patients undergoing hemodialysis and is directly related to physical and general health.

INTRODUCTION

Patients with chronic renal disease undergoing hemodialysis are at a higher risk of developing several complications, including infection, cardiovascular and bone disease, and metabolic changes.[1,2] The prevalence of chronic kidney disease is exponentially increasing in Brazil, with 596 patients per million undergoing dialysis and an annual gross mortality rate of 18.2%.[3]

Patients undergoing renal replacement therapy present with varying levels of disease severity that compromise their quality of life and affect their physical and psychological health. Dialysis-induced changes include physical, self-care, and social activity limitations, intense body pain, frequent episodes of fatigue, and poor self-assessment of physical health. Mental changes include psychological distress, emotional problems related to the social impact of treatment, and poor mental health assessment.[4]

A meta-analysis of patients undergoing hemodialysis showed that physical and emotional symptoms were also associated with depressive symptoms.[1] Furthermore, patients with signs of depression report fatigue.[1] Thus, it is believed that fatigue and depression or mood disorders may share the same pathogenic pathway.[5] Sleeping disorders are frequently associated with fatigue as well.[5,6]

The definition of fatigue remains unclear and is often characterized by an increased feeling of weakness, tiredness, and lack of energy. Furthermore, it is described as a physical and mental experience.[7,8]

Several multifaceted and multidimensional factors affect fatigue in patients with chronic renal disease undergoing hemodialysis.[7] Although it is a prevalent symptom in patients undergoing dialysis, fatigue has been poorly studied in Brazilian patients.

OBJECTIVE

This cross-sectional study aimed to assess the prevalence of fatigue in patients with chronic kidney disease undergoing renal replacement therapy in the form of hemodialysis at two dialysis centers in the ABC Paulista region. This study also examined the predisposing factors for fatigue in the study population.

METHODS

This observational, cross-sectional, descriptive study analyzed the prevalence of and predisposing factors for fatigue in patients with chronic kidney disease undergoing hemodialysis. The study was conducted at two renal replacement therapy centers in the Greater ABC region of São Paulo. One of the centers was located at a high-complexity hospital treating patients from the Unified Health System; the other was located in a center treating patients from the private sector.

Patients with stage 5 chronic kidney disease who were undergoing hemodialysis were eligible to participate in the study. The exclusion criteria were as follows: peritoneal dialysis, age < 21 years, dialysis for < 12 months, psychiatric disorders with cognitive deterioration, active infectious or autoimmune disease, liver failure, and metastatic malignant neoplasms.

The study protocol was approved by our institution's ethics committees for research on humans under the CAAE number 24471419.7.0000.0082 (Decision number: 3.705.408) on November 14, 2019. The study was conducted in accordance with the Declaration of Helsinki. All participants provided written informed consents before any study-related procedures were performed.

The patients' demographic characteristics (age, sex, race, marital status, education, and income) were collected directly from clinical databases and records. Clinical data, including the cause of chronic kidney disease, existing comorbidities, medications being used, treatment complications, and duration of dialysis, were collected from the patients' medical records. The patients' laboratory parameters, including the serum hemoglobin, albumin, urea, parathyroid hormone, ferritin, calcium , phosphorus, and potassium levels and dialysis adequacy were also collected from the system.

Patients were evaluated during a single consultation and instructed to complete the following surveys: Chalder Fatigue Questionnaire, 36-Item Short Form Survey (SF-36), Beck Depression Inventory II (BDI-II), and Pittsburgh Sleep Quality Index (PSQI).

The Chalder Fatigue Scale is a self-administered questionnaire used to measure the extent and severity of fatigue in both clinical and non-clinical epidemiological populations. This scale consists of 11 items which are answered on a 4-point scale ranging from asymptomatic to maximum symptomology ("better than usual," "no worse than usual," "worse than usual," and "much worse than usual"). The total score ranges from 0 to 33 and spans two dimensions: physical and psychological fatigue.[9]

The SF-36 questionnaire consists of the following eight multi-item scales: physical functioning, body pain, mental health, general health, vitality, role limitation due to emotional problems, role limitations due to physical health, and social functioning. The scores range from 0 to 100, where 0 corresponds to bad health and 100 corresponds to good health.[10]

BDI-II is a self-administered scale used worldwide to detect depressive symptoms. This questionnaire consists of 21 statements about depression ranked on an ordinal scale from 0 to 3, resulting in a total score ranging from 0 to 63.[11]

The PSQI is a self-evaluation tool developed by Buysse that assesses sleep quality. It consists of 18 items, and the total score ranges from 0 to 21. A score ≤ 7 indicates good sleep quality; a score > 7 indicates poor sleep quality. This questionnaire has been widely used to measure sleep quality in different groups of patients, including those with kidney and intestinal diseases, asthma, and cancer.[12]

In both institutions, dialysis was performed in three shifts per day; each session lasted for four hours with a half hour in between for reorganizing the rooms. Dialysis sessions started at 06:00 and ended at 19:00. Questionnaires were administered by an investigator and a nurse responsible for each dialysis, who had been duly trained for this study.

Statistical analysis

Qualitative variables are described using absolute and relative frequencies, whereas, quantitative variables are presented as summary measures (mean, standard deviation, median, minimum, and maximum).[13]

The prevalence of fatigue was analyzed according to each qualitative characteristic, using absolute and relative frequencies. Chi-square or likelihood ratio tests were used to evaluate the association between the characteristics and presence of fatigue. Quantitative characteristics were described in terms of their association with fatigue and compared using Student's t- or Mann-Whitney U-tests.[13]

Odds ratios (OR) were calculated with unadjusted 95% confidence intervals (CI). A binary logistic regression model was used to identify the presence or absence of fatigue for each of the evaluated characteristics. The model included descriptive sex and age characteristics with a P value < 0.20 and the probability for fatigue. A backward stepwise regression selection method was used, with the input and output criteria of the final model at 5%.[14]

All statistical analyses were performed using the Statistical Package for Social Sciences (SPSS) for Windows (version 20.0; IBM, Armonk, New York, United States). Clinical significance was set at $P < 0.05$.

RESULTS

A total of 155 patients were registered at two hemodialysis clinics in the Greater ABC region of São Paulo. Of these, 60 patients were excluded for the following reasons: cognitive deterioration (4), diagnosis of liver failure (1), withdrawal of consent (5), refusal to participate (7), dialysis for <12 months (30), hospitalization (6), diagnosis of an active infection (3), and diagnosis of cancer (4). The remaining eligible 95 patients, who were diagnosed with chronic kidney disease and were undergoing hemodialysis were included in the study (**Figure 1**). After obtaining patient consent, relevant data were extracted from their medical records, including from physician and nursing notes and diagnostic tests. The medical records of the 95 eligible patients were complete and kept updated because these patients underwent monthly routine examinations and medical consultations to obtain information necessary for determining treatment plan.

The demographic characteristics of the participants are presented in **Table 1**. There were 53 (55.8%) female and 42 (44.2%) male patients with a mean age of 56.4 ± 14.3 years. Most patients had a low educational level and economic status (78.9% were unemployed and only 10.6% had an income four times above the national/regional/local minimum wage). The main reported comorbidities were hypertension (40%) and diabetes (33.7%); most of the patients led a sedentary lifestyle (78.9%).

The laboratory examination results of the patients' samples were predominantly within the normal range expected for the population studied.[15] There were no significant differences in the laboratory values between patients with or without fatigue.

All the patients in our study had a low quality of life, depressive symptoms (34.7%), and a high prevalence of sleep disorders (69.5%). Among the 95 enrolled patients undergoing hemodialysis, the prevalence of fatigue was 51.6% (**Table 2**). Although depression was more frequently seen in women in our study, there was no significant difference in the incidence of depression in either sex (P = 0.392) (data not shown).

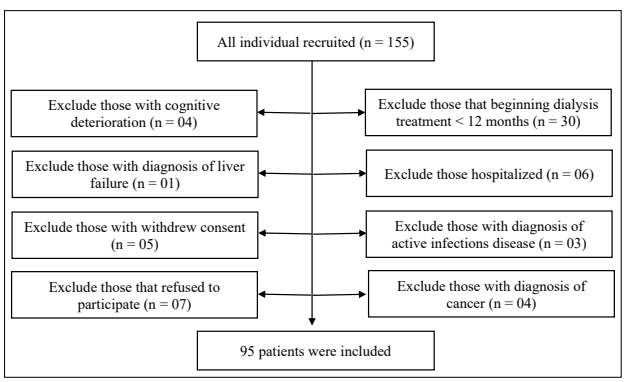

Figure 1. Flow chart depicting the inclusion and exclusion of the study population.

Table 1. Demographic characteristics and clinical variables (n = 95)

Variables	Number of patients (%)
Sex	
Male	42 (44.2)
Female	53 (55.8)
Age, years	
Mean ± SD	56.4 ± 14.3
Median (min.; max.)	57 (24; 87)
Marital status	
Unmarried	29 (30.5)
Married	49 (51.6)
Divorced	8 (8.4)
Widowed	9 (9.5)
Race	
White	49 (51.6)
Black	22 (23.2)
Other	24 (25.3)
Religion	
Catholic	45 (47.4)
Evangelical	26 (27.4)
Others	24 (25.3)
Education	
Illiterate	8 (8.4)
Elementary school	45 (47.4)
High school	32 (33.7)
University	10 (10.5)
Employment status	
Not employed	75 (78.9)
Being employed	20 (21.1)
Household number	
Mean ± SD	2.89 ± 1.46
Median (min.; max.)	2 (1; 7)
Family income	
Up to 2 times minimum wage	46 (48.4)
2–4 times minimum wage	39 (41.1)
4–10 times minimum wage	9 (9.5)
10–20 times minimum wage	1 (1.1)
Etiology of kidney disease	
Hypertensive nephrosclerosis	28 (29.5)
Diabetic nephropathy	35 (36.8)
Chronic glomerulonephritis	3 (3.2)
Other	29 (30.5)
Comorbidity	
None	13 (13.7)
Diabetes mellitus	32 (33.7)
Hypertension	38 (40)
Other	12 (12.6)
Regular exercise	
No	75 (78.9)
Yes	20 (21.1)
Hospitalization	
No	38 (40)
Yes	57 (60)
Time on dialysis, years	
Mean ± SD	3.94 ± 4.04
Median (min.; max.)	3 (0.3; 24)

SD = standard deviation; min = minimum; max = maximum.

Table 2. Responses to the Quality of life questionnaire

Variable	Description
Functional capacity	
Mean ± SD	48.7 ± 32.1
Median (min.; max.)	50 (0; 100)
Physical health	
Mean ± SD	33.2 ± 40.2
Median (min.; max.)	25 (0; 100)
Pain	
Mean ± SD	57.4 ± 29.8
Median (min.; max.)	51 (0; 100)
General health	
Mean ± SD	46.1 ± 20.7
Median (min.; max.)	47 (5; 100)
Vitality	
Mean ± SD	52.1 ± 23.3
Median (min.; max.)	50 (5; 100)
Social aspect	
Mean ± SD	65.9 ± 27.8
Median (min.; max.)	62.5 (0; 100)
Emotional aspect	
Mean ± SD	47.7 ± 42
Median (min.; max.)	33.3 (0; 100)
Mental health	
Mean ± SD	64.3 ± 23
Median (min.; max.)	68 (12; 100)
BDI-II, n (%)	
Normal	41 (43.2)
Mild disorder	21 (22.1)
Onset of clinical depression	14 (14.7)
Moderate depression	14 (14.7)
Severe depression	4 (4.2)
Extreme depression	1 (1.1)
PSQI, n (%)	
Bad	66 (69.5)
Good	29 (30.5)
Fatigue, n (%)	
No	46 (48.4)
Yes	49 (51.6)

BDI-II = Beck Depression Inventory II; PSQI = Pittsburg Sleep Quality Index; SD = standard deviation; min = minimum; max = maximum; n = number of observations.

Binary analysis revealed that fatigue was not significantly associated with demographic or clinical characteristics when analyzed in isolation ($P > 0.05$) (**Table 3**). However, quality of life domains were significantly lower in patients with fatigue than in those without fatigue ($P < 0.05$). Additionally, the prevalence of depression ($P = 0.001$) and poor sleep quality ($P = 0.027$) were significantly higher among patients with fatigue than in those without fatigue (**Table 4**).

In the final adjusted model, regardless of the other evaluated characteristics, the domains of physical and general health in the joint quality of life significantly influenced the presence of fatigue in patients with chronic kidney disease undergoing hemodialysis ($P < 0.05$). The probability of being fatigued decreased by 2% for each percentage of increase in the patient's physical health. The probability of being fatigued decreased by 3% for each additional percentage of increase in the patient's general health.

DISCUSSION

Fatigue has a high prevalence among patients with chronic kidney disease worldwide, with several unfavorable outcomes. Fatigue is considered to be an independent risk factor for increased mortality in such patients.[16] Although studies on this subject are scarce in Brazil, our findings suggest that the observed high prevalence of fatigue is comparable to the current scientific evidence.[17,18] There was no statistical difference in the presence of fatigue between the sexes; this result is in contrast to previous studies that suggest that fatigue is more prevalent in females.[19] Demographic characteristics can be predictors of fatigue;[20] in our study population, low socioeconomic level, age, and comorbidities did not significantly influence the presence of fatigue. Most of the affected patients led a sedentary lifestyle; studies suggest that regular physical exercise that has been adapted to the clinical conditions contribute to the reduction in fatigue and improvement in quality of life.[21,22]

Fatigue may be related to objective laboratory data. Univariate analysis has shown that fatigue is associated with changes in the serum parathyroid hormone, iron, urea, calcium, albumin, and hemoglobin levels; a multivariate analysis detected a relationship between fatigue and serum parathyroid hormone.[7] Resistance to erythropoietin, independent of the degree of anemia and level of transferrin saturation, is associated with factors related to fatigue.[23] Clinical indicators are objective and reflect a combination of several symptoms; one symptom alone cannot significantly influence serum and biochemical indicators.[7] In addition, patients undergoing hemodialysis are monitored by nephrologists who encounter frequent clinical changes, which may influence the correlation with symptoms. In this study, there was no statistically significant difference in the laboratory results between the patients with and without fatigue, which may have been due to the immediate treatment of the biochemical changes. The fact that patients with chronic kidney disease have varying symptoms may reflect a multidimensional issue, which has been suggested in previous clinical studies.[24]

Up to 50% of patients undergoing hemodialysis have some degree of depression that impacts the quality of life, decreases

Table 3. Laboratory results of patients based on the presence of fatigue and the bivariate analysis results

Variable	Fatigue		OR	95% CI		P
	No	Yes		Lower	Upper	
Kt/V			0.831	0.333	2.074	0.696**
Mean ± SD	1.49 ± 0.5	1.45 ± 0.39				
Median (min.; max.)	1.6 (0.08; 2.68)	1.5 (0.75; 2.8)				
Kt/V, n (%)						0.087
Major 1.2	38 (53.5)	33 (46.5)	1.00			
Minor 1.2	8 (33.3)	16 (66.7)	2.30	0.87	6.07	
Hemoglobin			0.896	0.737	1.090	0.271**
Mean ± SD	11.6 ± 1.8	11.1 ± 2.4				
Median (min.; max.)	11.6 (5.1; 14.4)	11.3 (2.6; 15.3)				
Albumin			1.023	0.344	3.044	0.967**
Mean ± SD	3.99 ± 0.32	3.99 ± 0.42				
Median (min.; max.)	4 (3; 4.7)	4.03 (2.2; 4.98)				
Urea pre-dialysis			0.996	0.985	1.008	0.537**
Mean ± SD	156.8 ± 38	152.3 ± 33.5				
Median (min.; max.)	158.5 (94; 264)	149.4 (93.2; 226)				
Urea post-dialysis			1.002	0.982	1.023	0.840**
Mean ± SD	51.3 ± 21.7	52.1 ± 18.1				
Median (min.; max.)	48.4 (4.2; 134)	47.6 (26.6; 103)				
Parathormone			1.000	0.998	1.002	0.571[c]
Mean ± SD	299.7 ± 206.2	293.6 ± 267.8				
Median (min.; max.)	257.8 (22.4; 759.4)	212.9 (33.4; 1620.9)				
Ferritin			0.999	0.997	1.000	0.110**
Mean ± SD	349.3 ± 307.6	263.3 ± 201.1				
Median (min.; max.)	258.6 (28.7; 1431.6)	200.2 (34.9; 792.8)				
Calcium			0.727	0.413	1.280	0.270**
Mean ± SD	8.7 ± 0.7	8.6 ± 0.7				
Median (min.; max.)	8.7 (7; 11)	8.5 (7.3; 10.8)				
Phosphorus			0.851	0.665	1.090	0.201**
Mean ± SD	5.38 ± 1.77	4.94 ± 1.6				
Median (min.; max.)	4.85 (1.8; 10.2)	5 (1.6; 9.6)				
Potassium			0.899	0.532	1.520	0.695**
Mean ± SD	4.85 ± 0.77	4.79 ± 0.78				
Median (min.; max.)	4.8 (3.5; 6.4)	4.61 (3.1; 7)				

Chi-square test (χ^2); **Student's t-test; [c]Mann-Whitney test.
SD = standard deviation; min = minimum; max = maximum; OR = odds ratio; CI = confidence interval.

the adherence to treatment, and increases the rate of suicide and mortality.[25] Tryptophan metabolites, the precursors of serotonin and melatonin, are increased in patients undergoing dialysis and may be associated with depression and fatigue.[26] Considering that there is a causal relationship between fatigue and depression, the finding of increased fatigue in patients undergoing dialysis suggests the need for further investigation and potential diagnosis of depression. Various types of fatigue, such as physical, mental, and emotional, have been described as precursors of depression; furthermore, fatigue has been reported in 22–49% of patients treated with antidepressants and in depression remission.[27] However, bivariate analyses indicate that

Table 4. Questionnaire responses according to the presence of fatigue and the bivariate analysis results

Variable	Fatigue		OR	CI (95%)		P
	No	Yes		Lower	Higher	
Functional capacity			0.970	0.956	0.985	**< 0.001**[c]
Mean ± SD	62.7 ± 30.2	35.5 ± 28.2				
Median (min.; max.)	70 (0; 100)	30 (0; 100)				
Physical health			0.976	0.964	0.988	**< 0.001**[c]
Mean ± SD	51.1 ± 43.4	16.3 ± 28.2				
Median (min.; max.)	50 (0; 100)	0 (0; 100)				
Pain			0.976	0.961	0.991	**0.001**[c]
Mean ± SD	67.5 ± 25.8	47.9 ± 30.3				
Median (min.; max.)	62 (0; 100)	41 (0; 100)				
General health			0.960	0.937	0.983	**< 0.001**[c]
Mean ± SD	54 ± 21.5	38.8 ± 17.1				
Median (min.; max.)	57 (5; 100)	42 (5; 77)				
Vitality			0.961	0.940	0.982	**< 0.001**[c]
Mean ± SD	61.7 ± 22.6	43.1 ± 20.2				
Median (min.; max.)	62.5 (15; 100)	45 (5; 80)				
Social aspect			0.964	0.947	0.982	**< 0.001**[c]
Mean ± SD	78.3 ± 23.9	54.3 ± 26.3				
Median (min.; max.)	87.5 (12.5; 100)	50 (0; 100)				
Emotional aspect			0.980	0.970	0.991	**< 0.001**[c]
Mean ± SD	64.5 ± 41.8	32 ± 36				
Median (min.; max.)	100 (0; 100)	33.3 (0; 100)				
Mental health			0.969	0.950	0.989	**0.002**[c]
Mean ± SD	72.1 ± 19.8	57.1 ± 23.5				
Median (min.; max.)	76 (24; 100)	60 (12; 100)				
BDI-II, n (%)			1.823	1.260	2.637	**0.001**[c]
Normal	27 (65.9)	14 (34.1)				
Mild disorder	11 (52.4)	10 (47.6)				
Onset of clinical depression	3 (21.4)	11 (78.6)				
Moderate depression	4 (28.6)	10 (71.4)				
Severe depression	1 (25)	3 (75)				
Extreme depression	0 (0)	1 (100)				
PSQI, n (%)						**0.027**
Bad	27 (49.9)	39 (59.1)	1.00			
Good	19 (65.5)	10 (34.5)	0.36	0.15	0.91	

Chi-square test (χ^2); [c]Mann-Whitney test.

BDI-II = Beck Depression Inventory II; PSQI = Pittsburgh Sleep Quality Index; SD = standard deviation; min = minimum; max = maximum; OR = odds ratio; CI = confidence interval.

depression is causally correlated with an impact on all fatigue types.[28] Depression was found to be more prevalent in patients with fatigue in our study.

In patients undergoing hemodialysis, sleep disorders predispose them to complications in general health, mental health, and physical capacity and fatigue. The most prevalent etiologies of sleep

disorders include psychological factors, such as stress, anxiety, and depression, metabolic changes, pain, dietary restrictions, dyspnea, fatigue, cramps, and hypocapnia secondary to metabolic acidosis.[29] Sleep alterations affect 40–83% of patients undergoing dialysis,[29-31] and their association with restless leg syndrome increases the risk of death[30]. The treatment of restless leg syndrome reportedly leads to an improvement in fatigue-related symptoms.[30] Patients with chronic kidney disease undergoing hemodialysis have increased tryptophan catabolism, an essential amino acid that increases serotonin production in the central nervous system. A subsequent decrease in the serum concentration of tryptophan could be related to changes in the sleep quality and fatigue.[6,26] A study demonstrated that non-pharmacological treatments that decreased anxiety were associated with a reduction in fatigue and improvement in sleep quality.[31] Additionally, a meta-analysis showed that performing aerobic exercises during dialysis sessions and acupuncture sessions can improve the sleep quality and decrease the reliance on drugs for the treatment of sleep disorders;[32] performing aerobic exercises before the dialysis session could also have similar benefits.[33] Our study established a significant association between sleep disorders and fatigue, suggesting that the treatment of these disorders could decrease the prevalence of fatigue and improve the quality of life.

The quality of life in patients undergoing hemodialysis influences their prognosis and mortality rate. Thus, diagnosing sleep disorders and fatigue is as an integral part of the treatment.[34,4] Our results were comparable to that of a study where the quality of life was inversely related to fatigue and depression. Additionally, married patients whose treatments were financially supported experienced a better quality of life.[34] Our study confirmed this inverse relationship, especially in the domains of physical and general health. Physical exercise programs performed during the intradialytic period reportedly have a positive impact on the patient's quality of life, depression, and fatigue.[35]

Our study had several limitations. Due to the observational nature of this study, we could not infer a cause-and-effect relationship among the observed variables, that is, between the occurrence of fatigue and depression or sleep disorders. Therefore, caution should be exercised when applying these results to patients undergoing hemodialysis in daily practice. Further prospective studies are needed to determine the etiology of fatigue and assess its prognostic role in patients with chronic kidney disease undergoing hemodialysis.

CONCLUSION

Fatigue is common among patients undergoing hemodialysis and is associated with depression and sleep disturbances. Clinicians should proactively investigate signs of fatigue to avoid its impact on the quality of life in patients with end-stage kidney disease.

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Is *Helicobacter pylori* infection associated with non-alcoholic fatty liver disease in individuals undergoing bariatric surgery? Cross-sectional study

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ABSTRACT

BACKGROUND: A possible direct link between nonalcoholic fatty liver disease (NAFLD) and *Helicobacter pylori* (*H. pylori*) infection has recently emerged.

OBJECTIVE: This study aimed to analyze associations between the presence of histologically demonstrated NAFLD aspects with *H. pylori* infection in individuals with obesity undergoing bariatric surgery.

DESIGN AND SETTING: An observational analytical cross-sectional study was conducted based on data collected from the medical records of individuals undergoing bariatric surgery at a tertiary university hospital in 2019.

METHODS: NAFLD was assessed through histological examination of wedge liver biopsies collected during the proceedings. *H. pylori* infection was analyzed through the association of the urease test and histological examination performed in biopsies routinely collected during preoperative esophagogastroduodenoscopy.

RESULTS: Of the 88 participants, 85% were female, and the average age was 39.1 ± 8.4 years. *H. pylori* infection was present in 61.4% of the patients. The mean body mass index was 36.6 ± 3.4 kg/m^2. The most prevalent histopathological aspects of NAFLD were macrovesicular steatosis (92%), hepatocellular ballooning (92%), lobular inflammation (93.2%), portal inflammation (96.6%), and fibrosis (93.2%). No histopathological aspect of NAFLD was found to be significantly associated with *H. pylori* infection.

CONCLUSION: In this study population, *H. pylori* infection was not significantly associated with the histopathological aspects of NAFLD in individuals with obesity undergoing bariatric surgery.

INTRODUCTION

The association between non-alcoholic fatty liver disease (NAFLD) and extrahepatic conditions has been increasingly reported in recent years, and its correlation has been described with conditions such as obesity, metabolic syndrome, diabetes, sarcopenia, heart disease, and chronic kidney disease. Furthermore, a possible direct link between NAFLD and *Helicobacter pylori* (*H. pylori*)infection has emerged. The mechanisms of this association, however, remain unclear and seem to be associated with low-grade inflammation underlying chronic infection by this bacterium and its connection with insulin resistance and imbalances in lipid metabolism.[1,2]Meta-analyses carried out by Mantovani et al.[3] and Wei et al.[4] suggested a significantly increased risk of NAFLD among *H. pylori* carriers. Nonetheless, these reviews included studies that assessed NAFLD using heterogeneous diagnostic methods, primarily imaging techniques.

This study aimed to analyze the association between the presence of histologically demonstrated NAFLD and *H. pylori* infection in individuals with obesity undergoing bariatric surgery (BS).

METHODS

Study design

An observational, analytical, cross-sectional study was conducted based on data collected from medical records of individuals undergoing BS at a tertiary university hospital in 2019. The study protocol was evaluated and approved by the local institutional review board under opinion 4.677.470 (CAAE: 45210321.8.0000.5404; date: April 28, 2021). All the participants provided informed consent.

Study population

This study included individuals aged 18 to 70 years, of any sex, who underwent Roux-en-Y gastric bypass(RYGB) according to the National Institutes of Health criteria. Exclusion criteria were history of other liver diseases, cholestatic diseases and viral hepatitis, belonging to vulnerable groups (underaged or with severe mental or intellectual impairment), recent or current use of alcohol, illicit drugs or hepatotoxic medications, and incomplete medical records.

Of the101 individuals who underwent RYGB, 88 were selected for the study; 13 individuals were excluded for viral hepatitis (n = 2), hepatotoxic medications (n = 3), previous cholestasis (n = 1), and incomplete medical records (n = 7).

Demographic, anthropometric, clinical, and biochemical data

Data regarding age, sex, body mass index (BMI), and presence of hypertension and type 2 diabetes were collected. The following laboratory parameters were analyzed in this study: fasting glucose (mg/dL), aspartate aminotransferase (AST, IU/L), and alanine aminotransferase (ALT, IU/L).

NAFLD assessment

NAFLD was assessed through histological examination of wedge liver biopsies collected during the procedure. The main NAFLD features were classified into following categories:1) macrovesicular steatosis; 2) microvesicular steatosis; 3) hepatocellular ballooning; 4) lobular inflammation; 5) portal inflammation); and6) fibrosis. These aspects were classified as absent or present according to the classification system proposed by Brunt et al.[5] (Reviewer #1; Comment #2) Biopsies were systematically performed in all bariatric operations at this facility as part of routine care. The histopathological examination was performed by the same pathology team.

Helicobacter pylori infection assessment

H. pylori infection was analyzed by means of a urease test and histological examination with Giemsa stain was performed on biopsies that were routinely collected during preoperative esophagogastroduodenoscopy. *H. pylori* infection was classified as present or absent.

H. pylori infection status was correlated with the presence and severity of NAFLD aspects above cited.

Statistical analysis

To compare proportions, the chi-square test or Fisher's exact test was used, when necessary. The Mann–Whitney test was used to compare continuous variables. The significance level was set at 5% ($P < 0.05$). Analyses were performed using the SAS System for Windows (Statistical Analysis System, version 9.2; SAS Institute Inc., 2002-2008, Cary, North Carolina, United States).

RESULTS

Demographic, anthropometric, and clinical data

Ofthe88 participants, 85% were female, and the average age was 39.1 ± 8.4 years. *H. pylori* infection was present in 61.4% of the patients. The mean BMI was 36.6 ± 3.4 kg/m^2. Hypertension was present in 40.9% of patients, and 22.7% presented with diabetes. There were no significant differences between these variables in individuals with or without *H. pylori* infection.

Biochemical variables

The mean AST levels were 22.4 ± 8 IU/L and ALT levels were 27.4 ± 14.7 IU/L. The average fasting glucose was 88.9 ± 20.1 mg/dL. There were no significant differences in biochemical variables between individuals with or without *H. pylori* infection.

Histopathological features

The most prevalent histopathological aspects of NAFLD were macrovesicular steatosis (92%), hepatocellular ballooning (92%), lobular inflammation (93.2%), portal inflammation (96.6%), and fibrosis (93.2%). No histopathological aspect of NAFLD was significantly associated with *H. pylori* infection.

Complete comparisons between individuals with and without *H. pylori* infection are shown in **Table 1**.

Table 1. Comparison of demographic, anthropometric, clinical, biochemical, and NAFLD-related histopathological aspects between individuals with or without *H. pylori* infection

	H. pylori infection	No *H. pylori* infection	P value
N	54 (61.4%)	34 (38.6%)	NA
Age (years)	39.1 ± 11	39.4 ± 8.1	0.9
Gender	Female: 48 (88.9%) Male: 6 (11.1%)	Female: 27 (79.4%) Male: 7 (20.6%)	0.2
BMI (kg/m^2)	37.8 ± 6.4	36.5 ± 0.6	0.8
Hypertension	20 (44.4%)	16 (47.1%)	0.4
Type 2 diabetes	9 (16.7%)	11 (32.4%)	0.1
AST (IU/L)	22.6 ± 8.4	22.2 ± 7.4	0.8
ALT (IU/L)	28.1 ± 16.5	26.4 ± 11.8	0.6
Fasting glucose (mg/dL)	90.1 ± 19.1	87.1 ± 21.6	0.5
Macrovesicular steatosis	49 (90.7%)	32 (94.1%)	0.6
Microvesicular steatosis	19 (35.2%)	11 (32.4%)	0.8
Hepatocellular ballooning	50 (92.6%)	31 (91.2%)	0.8
Lobular inflammation	48 (88.9%)	34 (100%)	0.1
Portal inflammation	52 (96.3%)	33 (97.1%)	0.8
Fibrosis	50 (92.6%)	32 (94.1%)	0.8

H. pylori = *Helicobacter pylori*; NAFLD = non-alcoholic fatty liver disease; N = number of individuals; NA = not applicable; BMI = body mass index; AST = aspartate aminotransferase; ALT = alanine aminotransferase.

DISCUSSION

In the current study, the occurrence of both *H. pylori* infection and NAFLD was considerably high in individuals undergoing BS. These findings are comparable to those of the previous studies. There were no significant associations between *H. pylori* infection and anthropometric, clinical, biochemical, or histopathological aspects in the current population sample. The study population mainly comprised women (85%) aged between 30 and 50 years, which is common in BS. Fuchs et al.[6] analyzed the sex gap in BS in the United States through a multicenter database comprising 190,705 individuals who underwent BS between 1998 and 2010 and found a similar 4:1 proportion, despite an almost 1:1 proportion of obesity between males and females. The authors attributed this gap to several factors, highlighting a slightly greater eligibility for BS among women alongside some degree of sociocultural pressure regarding weight loss within this gender group and a lower willingness to seek medical care among men. Furthermore, this study pointed out that the gender gap is more prominent in lower-income populations.

H. pylori infection has been suggested to play a role in the pathogenesis of insulin resistance by several mechanisms, mostly through increased levels of pro-inflammatory cytokines, eicosanoids, acute phase proteins, reactive oxygen species production, and changes in serum cytokines.[7-10] Recent studies have shown that *H. pylori* also plays a potential role in systemic chronic inflammation by increasing intestinal permeability.[11-13] These mechanisms are also reported to be directly related to the development of NAFLD.[1,14-16]

Some high-quality studies have reported this association. A large cross-sectional study carried out by Jiang et al.[17] with 4,081 individuals identified a positive correlation between NAFLD diagnosed by ultrasound and *H. pylori* infection evaluated through urease breath test, mostly among females and individuals with dyslipidemia. Ina large prospective cohort study that included 17,028 participants initially free of NAFLD, Kim et al.[18] demonstrated that *H. pylori* infection was independently associated with the incidence of *"de novo"* NAFLD. These findings were reinforced by the meta-analyses by Mantovani et al.[3] and Wei et al.[4]

Nevertheless, the currently available literature is far from consensus on the existence of this positive association between *H. pylori* and NAFLD, with other methodologically appropriate studies demonstrating opposite findings. In large studies carried out in Japan by Okushin et al.[19] and in China by Fan et al.[20] with 13,737 and 21,456 participants, respectively, *H. pylori* was not an isolated risk factor for NAFLD. A study carried out by Baeg et al.[21] that identified *H. pylori* infection as a variable significantly correlated with metabolic risk factors, including high BMI, blood pressure, triglycerides, and low HDL, failed to demonstrate an independent association between *H. pylori* and NAFLD. Furthermore, a prospective study by Jamali et al.[22] showed that *H. pylori* eradication per se does not affect liver fat content and lipid profile in dyspeptic patients with NAFLD.

Considering that most population studies included samples of individuals with heterogeneous BMI status, this also raises the question of whether this putative association could be more or less likely to be identified among individuals with or without obesity. Lecube et al.[23] analyzed a population of 416 individuals with both obesity and NASH and concluded that in patients with morbid obesity, *H. pylori* infection does not seem to be associated with abnormal carbohydrate metabolism and suggested that the low-grade inflammation that accompanies obesity seemingly mitigated the diabetogenic effect of *H. pylori*. In contrast, Doulberis et al.,[24] investigating the metabolic burden of *H. pylori* infection in 64 morbidly obese individuals, observed that *H. pylori* infection was independently associated with insulin resistance, NASH, and liver fibrosis. Thus, even in this setting, the answer seems far from a consensus.

The current study has some limitations that should be considered. Its cross-sectional design did not provide insights into causal or consequential links. Since it included individuals undergoing BS, there was a tendency towards a very homogeneous population in relation to BMI status. Furthermore, this population has a high prevalence of NAFLD. Prospective studies enrolling individuals without obesity could clarify this issue. Considering that most previous studies were carried out in Asia and the current study was performed in a population of highly multi-ethnic heritage in South America, ethnicity may also play a role in the conflicting results. On the other hand, this study has the clear strength of analyzing NAFLD through the best possible method, that is, histopathological examination, which provided a detailed evaluation that imaging methods are unable to equally provide and, thus, adds more accurate information to the currently available evidence on this relevant topic.

CONCLUSION

In the studied population, *H. pylori* infection was not significantly associated with either histopathological or biochemical variables of NAFLD in obese individuals undergoing BS.

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The Brazilian Portuguese version of the Pregnancy Mobility Index: Cross-cultural adaptation and psychometric evaluation – a validation study

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Health, women's.

ABSTRACT

BACKGROUND: The Pregnancy Mobility Index (PMI) was developed to assess mobility in pregnant women in the Netherlands. At present, no similar questionnaire is available in Brazil.

OBJECTIVE: The present study aimed to translate, cross-culturally adapt, and evaluate the psychometric properties of a Brazilian PMI.

DESIGN AND SETTING: The present study was a validation study conducted at the Universidade Federal do Paraná and a public maternity ward in Curitiba, Brazil.

METHODS: Text translation and cross-cultural adaptation followed international guidelines. Construct validity, internal consistency, and inter- and intra-rater reliability tests included 97 women. The Pelvic Girdle Questionnaire, Multidimensional Pain Evaluation Scale, Schober's test, and lumbar spine range of motion assessment were administered on the first day. Intra-rater reliability (n = 19) was measured after 15 days. Exploratory factor analysis was performed, and the correlation matrix was analyzed using Pearson's coefficient.

RESULTS: Pregnant women (88%) understood the cultural adaptation process. The internal consistency was high (Cronbach's alpha > 0.90), construct validity was moderate, with significant correlation between lumbar spine range of motion (r = 0.283–0.369) and Schober's test (r = -0.314), and high correlation between the Multidimensional Pain Evaluation Scale (r = -0.650 and -0.499) and Pelvic Girdle Questionnaire (r = -0.737). Intra- and inter-rater reliabilities were excellent (intraclass correlation coefficient = 0.932 and 0.990, respectively).

CONCLUSION: The Brazilian version of the PMI was successfully translated with excellent reliability and moderate-to-high construct validity. It is an important tool for assessing mobility in pregnant women.

CLINICAL TRIAL: RBR-789tps (Validation study), https://ensaiosclinicos.gov.br/rg/RBR-789tps.

INTRODUCTION

The anatomical and physiological changes that occur during pregnancy frequently increase musculoskeletal disorders. Symptoms frequently related to pregnancy are largely due to ligamentous laxity and joint hypermobility, which are associated with hormonal changes and weight gain. This, in turn, increases mechanical stress. Additionally, pregnant women have a displaced center of gravity, which is associated with hyperlordosis that contributes to the mechanical strain on the sacroiliac and back joints.[1,2] Low back and pelvic girdle pain are the most frequent complaints during pregnancy, and both negatively affect mobility and functionality, contributing to physical disability that can affect work performance and day-to-day activities.[3,4]

Although there are several questionnaires that evaluate disability and loss of mobility caused by back pain in the general population, none are specific to pregnant individuals.[3,4] Pregnancy-related back pain differs from that in the general population, and has distinctive mobility patterns and expectations.[4] A questionnaire is a tool that transforms subjective information into objective and measurable data. In this way, it is possible to demonstrate the patient's evolution to them in a clearer and more understandable way. The advantage of using questionnaires is that they are self-reported by the patient or the healthcare worker, in research or the clinical setting. In clinical practice, questionnaires can become a facilitator for medical records, assisting the healthcare professional in understanding the patient's needs and, later, in the execution of the treatment plan.[5]

In Brazil, there is only one questionnaire available with which to assess the interference of lumbopelvic pain in sexual activity, sleep quality, and day-to-day activities during pregnancy.[3] As of yet, there is no questionnaire that assesses the mobility of pregnant women which has been validated for the Brazilian population;[3,4] however, the Pregnancy Mobility Index (PMI) could fill this gap, as it was developed to specifically assess this variable.[4] The PMI, composed of 24 questions which aim to assess the effects of low back and pelvic pain during and after pregnancy on day-to-day activities, is considered a reliable and valid instrument when applied to the Dutch population. The PMI can also assess the effects of pain interventions and help understand normal levels of mobility during pregnancy.[4]

OBJECTIVE

The aim of the present study was to provide a cross-cultural adaptation and psychometric evaluation of a Brazilian Portuguese version of the PMI.

METHODS

The present validation study, performed using the Consensus-Based Standards for the Selection of Health Measurement Instruments (COSMIN) guidelines,[6] was approved by the ethics committee at the Universidade Federal do Paraná (UFPR) (Number:2.399.033; CAAE 78877417.8.0000.0096; approved in 2017) and registered in the Brazilian Registry of Clinical Trials as a validation study (RBR-789tps - https://ensaiosclinicos.gov.br/rg/RBR-789tps). The present study was conducted in Curitiba, Brazil, at the Victor Ferreira do Amaral Hospital and Maternity Ward, and at the Prevention and Rehabilitation in Physical Therapy Department of the UFPR. All individuals provided written informed consent prior to participating in the study.

To begin, we requested authorization for the translation and validation of a Brazilian Portuguese version of the PMI. The Dutch and English versions of the PMI were utilized for the preparation of the Brazilian version.[4,7] The process of translation, back translation, and cross-cultural adaptation rigorously followed the Guidelines for the Process of Cross-Cultural Adaptation of Self-Report Measures.[8]

Four bilingual translators, all native speakers of Brazilian Portuguese, translated the instrument; two were healthcare professionals (T1D and T1E), while the other two had no healthcare experience (T2D and T2E). The translations were discussed by the translators and the authors of the present study, and the first version of the translated PMI was created (T-12D and T-12E). This version was translated back to English and Dutch by four native speakers, none of whom were healthcare professionals or had prior knowledge of the original version of the PMI (BT1D, BT2D, BT1E, and BT2E). To reach a consensus, a committee of experts reviewed a document containing the translations, back-translations, original versions, and a report prepared by the research team, including each item of the instrument, alternative answers, and instructions. The committee's decisions were aimed at ensuring semantic, idiomatic, experimental, and conceptual equivalence between the versions. The pre-final version was administered to 30 eligible participants to evaluate for any difficulties in item comprehension.

In order to verify the comprehension of the instrument by the participants, we followed the steps described in a previous study.[9] Pregnant women were questioned about the comprehension of each item, and answers were based on a scale that ranged from 0–5. Additionally, participants were instructed to answer three open-ended questions. The research team calculated the percentage of understanding, and the committee verified that all recommended steps had been followed. The final version of the Brazilian Portuguese PMI was created.

The Brazilian Portuguese PMI has 22 questions using the following 3 subscales (**Appendix**): daily mobility in the home; household activities; and mobility outdoors. Each question regarding the limitations of the lumbopelvic region in performing the activities was scored on 4-point Likert scale (0 = no difficulty; 1 = little difficulty; 2 = very difficult; and 3 = impossible to perform without help). Additionally, it was also possible to choose "not applicable" as an answer (this item, when checked, was not used to calculate the final score).

After the translation and cross-cultural adaptation, validity and reliability were assessed at a public maternity hospital. Primiparous and multiparous pregnant women at a gestational age > 20 weeks, without cognitive deficits, and who were native Brazilian Portuguese readers were included. Women were excluded if they had a high-risk pregnancy (twins, triplets, or more pregnancies and/or with diabetes, hypertension, measles, rubella, and/or a urinary tract infection), had psychiatric and/or neurological disorders, and/or were unable to perform the tests.

Sociodemographic data were collected during the first interview, including age, gestational age, ethnic characteristics (Caucasian, African, Asian, multiple ethnicities), marital status (single, married, divorced), level of education (primary incomplete/complete, secondary complete, college complete), occupational status (employed, homemaker), lifestyle (smoking habits, alcohol consumption, physical activity), and presence of low back pain before and during pregnancy. After the researchers collected the data, the Brazilian Portuguese PMI was administered three times (at the beginning of the interview, after 30 minutes, and after 15 days), per the guidelines provided by the COSMIN initiative.[10]

The participants were asked to answer the Brazilian Portuguese PMI multiple times – first at the beginning of the interview (Examiner 1) and again after 30 minutes (Examiner 2). In the same interview, lumbopelvic incapacity was evaluated using the

Pelvic Girdle Questionnaire (PGQ),[11] pain intensity was evaluated using the Multidimensional Pain Evaluation Scale,[12] and lumbar spine range of motion was evaluated using the modified Schober's test[13] and fleximetry.[14]

In the second interview, which was arranged on average 15 days after the first interview, the PMI was completed again, by 19 pregnant women who had already answered the PMI at the first assessment, via a posting by Examiner 1 on a mobile instant messaging service. The participants did not receive any interventions or treatment for low back or pelvic pain during the study period.

In the present study, we made changes in the following: 1) the way the questions were described (statement); 2) we added an answer option ("not applicable") to the questions; and 3) we added a scoring formula to the questionnaire, which guarantees a consistent calculation of the final score. Semantic and cultural adaptations provided the greatest comprehension of the questionnaire.

The final score was calculated by adding the score obtained for each question, multiplying by 100, and dividing by the number of questions scored multiplied by 3. The final scores ranged from 0–100, where 0 equaled 'normal performance' and 100 indicated 'maximum disability', and consisted of the mobility index of the pregnant woman, as formulated below.

$$Mobility\ index = \frac{[100 - (sum\ of\ the\ scores\ obtained) \times 100]}{number\ of\ questions\ scored \times 3}$$

Statistical analysis

Descriptive statistics (mean and standard deviation for continuous data, and frequency and percentages for categorical data) were analyzed to characterize the participants. All analyses were performed using a 95% confidence interval (CI). The intraclass correlation coefficient (ICC) and Bland-Altman method[15,16] were utilized to evaluate the inter- and intra-rater reliability and concordance of the PMI, respectively. ICCs were interpreted as follows: poor (< 0.4); fair (0.4–< 0.6); good (0.6–< 0.75); and excellent (≥ 0.75).[15] The factor analysis followed the main component analysis with Varimax rotation. To analyze the internal consistency, a standardized Cronbach's alpha coefficient was utilized. The Pearson coefficient was utilized to evaluate the construct validity of the PMI between other instruments and tests (PGQ, Multidimensional Pain Evaluation Scale, Schober's test, and lumbar spine range of motion), and the coefficients were interpreted as follows, based on the magnitude scale proposed by Hopkins:[17] trivial (< 0.1); small (0.1–0.29); moderate (0.30–0.49); large (0.50–0.69); very large (0.70–0.90); and nearly perfect (> 0.90). Statistical analyses were performed using the Statistical Package for the Social Sciences (SPSS) software, version 22 (IBM, SPSS Inc., Chicago, IL, United States), and the significance level was set at $P < 0.05$.

The sample size was determined according to guidance from Terwee et al.,[18] which suggested a ratio of ≥ 4–10 participants for each instrument containing 24 questions. A total of 106 pregnant women participated in the present study, although 9 were excluded because they were either high-risk (n = 6) or failed to complete the proposed tests (n = 3). The final validation sample included a total of 97 pregnant women.

RESULTS

Some discrepancies between the original version and those analyzed by the committee were observed during the translation and back-translation processes. These discrepancies were resolved using strategies such as word addition, omission, or substitutions to search for semantic, conceptual, idiomatic, and experimental equivalence. Using these strategies, it was possible to generate equivalent expressions in Brazilian Portuguese. All modifications were performed prior to pretesting. The cross-cultural adaptation involved 30 women, and high comprehension (88%) of all items of the pre-final version was observed, which indicated no further need for revisions.

The validation phase included a total of 97 pregnant women. The mean age was 26.8 ± 6.2 years, and the intensity of the low back pain was considered light before pregnancy and advanced-to-moderate during pregnancy. The results are shown in **Table 1**.

The reliability and concordance results of the intra- and inter-rater reliability tests, which are shown in **Table 2**, indicated high intra- and inter-rater reliability (ICC = 0.93 and 0.99, respectively). The paired-samples Student's t-test did not show significant differences in the average test-retest scores for intra-examiner reliability ($P = 0.722$), although it was different ($P = 0.000$) from inter-examiner reliability. Bland-Altman plots (**Figures 1A-B**), however, revealed a mean error in the difference between the intra- (1.00, standard deviation, SD = 12.06, 95% CI = -24.63–22.63) and inter-examiner reliability (1.85, SD = 4.32, 95% CI = -10.35–6.60) close to zero. The P-value of the regression analysis showed that the slope of the curve did not deviate from zero (intra-examiner reliability, $P = 0.412$; inter-examiner reliability, $P = 0.741$). Therefore, these results represent 95% agreement between the test and retest scores.

The suitability of the scale was evaluated using factor analysis. The Kaiser-Meyer-Olkin value vas was 0.857, and the Bartlett sphericity test ($\chi 2 = 1232.79$; d.g. [degrees of freedom]: 210; $P < 0.000$) indicated that the data was adequate for conducting the factorial analysis.

The factor analysis included 22 questions from the original PMI; however, questions 17 ("traveling by train") and 19 ("traveling by bicycle") were removed because they did not apply to the study population. The Brazilian Portuguese version of the PMI extracted three components, as did the original PMI. After the removal of an item that presented an unsatisfactory factorial load

Table 1. Characteristics (frequency and percentage) of the study sample (n = 97)

Continuous characteristics	Mean	SD
Age (years)	26.8	6.2
Gestational age (weeks)	31.7	6.2
Low back pain intensity (points)		
Before pregnancy	1.6	2.7
During pregnancy	5.7	2.4
Categorical characteristics	**n**	**%**
Ethnic		
Caucasian	59	60.8
Mixed ethnicity	21	21.6
African	13	13.4
Asian	4	4.1
Marital status		
Married	52	53.6
Single	39	40.2
Divorced	6	6.2
Educational level		
Primary incomplete	7	7.2
Primary complete	12	12.4
Secondary complete	56	57.8
College complete	22	22.7
Occupational status		
Housewife	25	25.8
Administrative assistant	23	23.7
Businesswoman	13	13.4
Student	11	11.3
Healthcare professional	9	9.3
Maid	8	8.2
Saleswoman	6	6.2
Teacher	2	2.1
Lifestyle		
Smoking habits	6	6.2
Alcohol consumption	0	0
Physical activity practice	12	12.4
Presence of low back pain		
Before pregnancy	30	30.9
During pregnancy	92	94.8
Only during pregnancy	62	64.8

SD = standard deviation; n = number.

(Item 4), the three components showed a delimitated factorial distribution, each with at least four questions, presenting self-values > 1 (**Table 3**). A cut-off value of 0.40 was applied for the factor loadings, both in relation to the proximity of the items in the analysis and adherence to the theory. These factors corresponded to the subscales for daily mobility in the house (eigenvalue = 5.503), household activities (eigenvalue = 4.757), and mobility outdoors (eigenvalue = 4.691), which explained 71.20% of the variance. The model presents limitations related to cross-loading, which was < 0.20 for questions 7, 13, 14, and 18. The maintenance of the model's structure was chosen because of the higher loads in the question origin factor and the expected correlation between the scale factors. These results indicate the reliability of the PMI, meaning that the Brazilian Portuguese version of the questionnaire was able to accurately evaluate mobility during pregnancy. Furthermore, each subscale had high internal consistency (0.933, 0.911, and 0.907 for the first, second, and third components, respectively), with Cronbach's alpha above the recommended value.[18]

The PMI construct validity was established through Pearson's coefficient with gestational age and tests (PGQ, Multidimensional Pain Evaluation Scale, Schober's test, and lumbar spine range of motion) which ranged between -0.737 and 0.369. The results are presented in **Table 4**.

DISCUSSION

The main findings of the present study are related to the translation and cross-cultural adaptation of the Brazilian Portuguese version of the PMI. The results of the present study indicate that the Brazilian Portuguese PMI is reliable, consistent, and can discriminate between regular and irregular mobility.

The translation, validity, and reliability process should be rigorously followed, as the assessment tools must be precise, objective, and of high quality.[8,18] The present study carefully followed guidelines specifying how to perform a psychometric evaluation of a questionnaire,[19] based on suggestions regarding the use of guidelines for the cross-cultural adaptation of patient-reported outcome measurements.[8]

Other studies reinforce the importance of ensuring the equivalence of the items of the translated questionnaire with descriptors of the original and translated instrument.[8,18] This equivalence,

Table 2. Results of reliability and concordance of intra- and inter-rater test (n = 96)

	ICC		Bland-Altman			95% LoA	
	ICC	95% CI	$\overline{d}$	95% CI of $\overline{d}$	SD of $\overline{d}$		
Intra-examiner	0.93	0.78; 0.97	-1.00	-6.81; 4.81	12.06	-24.63	22.63
Inter-examiner	0.99	0.97; 0.99	1.85*	0.98; 2.72	4.32	-10.35	6.60

ICC, intraclass correlation coefficient; CI, confidence interval; LoA, limits of agreement; $\overline{d}$ = bias, the difference between the two measures; SD, standard deviation; SD of $\overline{d}$, standard deviation mean difference; *P < 0.05, paired sample *t*-test.

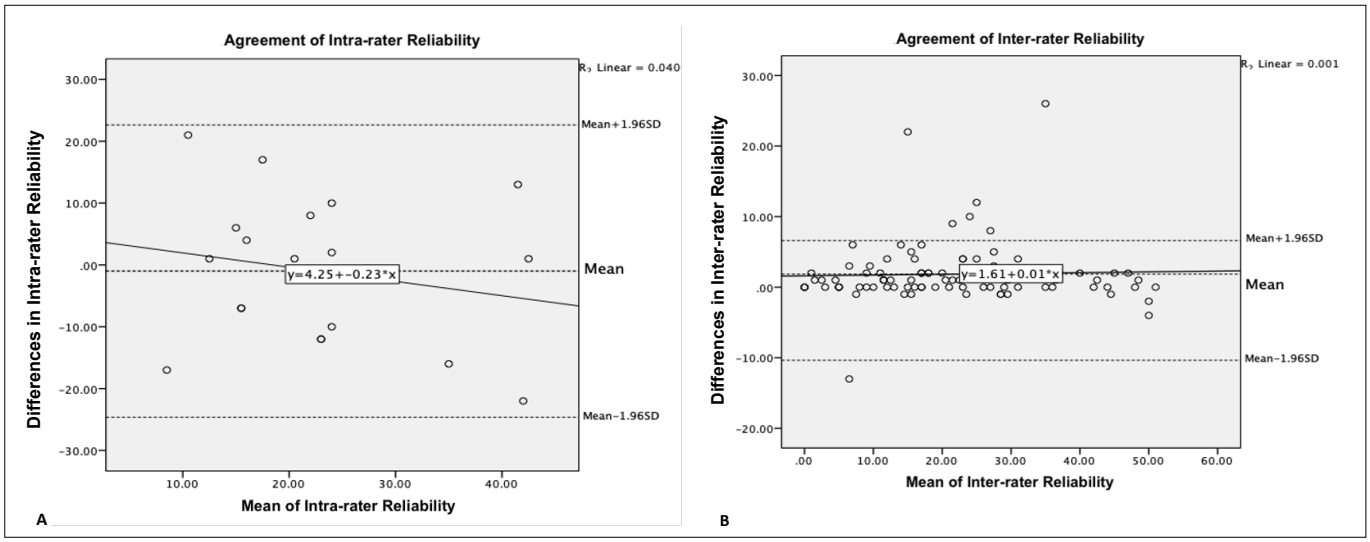

Figure 1A-B. Bland-Altman Intra- and Inter-rater Reliability graphic.

Table 3. Factor and principal component analysis with Varimax rotation

	Component 1[a]	Component 2[b]	Component 3[c]
Question 1		0.725	
Question 2		0.882	
Question 3		0.882	
Question 5		0.735	
Question 6		0.812	
Question 7	0.496	0.665	
Question 8	0.760	0.423	
Question 9	0.708		
Question 10	0.704		
Question 11	0.814		
Question 12	0.849		
Question 13	0.605		0.471
Question 14	0.687		0.494
Question 15	0.745		0.439
Question 16			0.579
Question 18		0.476	0.549
Question 20			0.615
Question 21			0.795
Question 22			0.825
Eigenvalues	5.503	4.757	4.691
Variance explained (%)	26.21	22.65	22.34
Cronbach's alpha coefficient	0.933	0.911	0.907

[a]Daily mobility in the house; [b]Household activities; [c]Mobility outdoors.

Table 4. Pregnancy Mobility Index construct validity between other variables, instruments, and tests

Variables and tests	Pearson's coefficient
Gestational age	-0.173[a]
Low back pain intensity	
Before pregnancy	0.027
During pregnancy	-0.591[b]
Pelvic Girdle Questionnaire	-0.737[b]
Schober's test	-0.314[b]
Lumbar spine range of motion	
Flexion	0.325[b]
Extension	0.283[b]
Right lateral flexion	0.347[b]
Left lateral flexion	0.369[b]
Right rotation	0.161
Left rotation	0.162
Multidimensional Pain Evaluation Scale	
Acute pain intensity	-0.650[b]
Chronic pain intensity	-0.499[b]

[a]$P < 0.05$; [b]$P < 0.01$.

however, is not only due to the direct and literal translation of the questionnaire, but also the necessary adjustment of each question of the instrument, to ensure that each measurement objective is preserved in a new culture.[8,18]

During the process of converting the PMI questionnaire to a Brazilian Portuguese version, it was necessary to remove three items from the original questionnaire. The first question (Question 4) was excluded using principal component analysis. The other two items (Questions 17 and 19) were excluded because they did not

provide sufficient relevant answers for the analysis. In Brazilian culture, is it not common to travel by bicycle or train, unlike in other countries such as the Netherlands. Therefore, the Brazilian Portuguese version of the PMI included only 21 questions, compared to 24 in the original version.

The results of the present study showed a high internal consistency (Cronbach's alpha > 0.90) for the Brazilian Portuguese PMI, indicating that the items of the instrument correlate with both the other items and the final score. This metric, therefore, shows an aspect related to reliability.[18,19] Reliability was considered excellent for the intra- and inter-rater assessments (> 0.75), indicating that a set of PMI questions can evaluate pregnancy mobility, with similar results when the same respondents are assessed on different occasions without undergoing any change in health.[10]

Interestingly, the data showed that there was a reduction in the mean score (21.30) as measured by Examiner 2 after 30 min, compared to Examiner 1 (23.17, mean difference 1.85, P = 0.000). The reduction in mobility could be justified by the fact that pregnant women underwent clinical tests to evaluate mobility and range of motion (Schober's test and fleximetry), demonstrating that they would be able to perform the clinical tests, contrary to their previous judgment as expressed in the PMI questions. In contrast, no systematic measurement error (P = 0.722) was found during the intra-rater reliability assessment performed 15 d after the first evaluation. One possible justification for this result may be related to the fact that pregnant women may have returned for their follow-up while retaining their initial perception of mobility, considering that the 3rd administration of the questionnaire did not precede mobility and range of motion tests. Despite these findings, the Bland-Altman agreement analysis revealed that there were no systematic and/or random errors in the PMI scores attributed to true changes in mobility, as seen in **Figures 1A-B**, ensuring the reproducibility and concordance of the PMI.

The analysis of the construct validity between the Brazilian Portuguese PMI and other assessments (PGQ,[3] Multidimensional Pain Evaluation Scale,[12] Schober's test,[13] and lumbar spine range of motion[14]) indicated high and moderate correlations, proving the effectiveness of the Brazilian Portuguese PMI in evaluating mobility. During pregnancy, women undergo several physiological changes that impair mobility, which are usually enhanced by the presence of pain,[3,20-22] justifying the greater correlation of the PMI with instruments that measure pain and reinforce the instrument's quality of construct validity.

Pain is one of the predictors of mobility limitations during pregnancy, especially low back and/or lumbopelvic pain.[21] Previous studies[21,23] have identified that women at advanced gestational ages have a higher rate of low back pain (visual analog scale = 7, moderate-to-intense) and, consequently, greater mobility limitation in day-to-day activities. These limitations can subsequently affect the emotional state of pregnant woman.[23] Corroborating these findings, the pregnant women assessed in the present study had more intense lower back pain in the third trimester of pregnancy than the first or second. The greatest degree of limitation, however, occurs in the second trimester, as previously demonstrated by Bakker et al.[23]

Data analysis revealed a high prevalence of lower back pain during pregnancy, and it is widely known that pain and discomfort have a significant impact on the daily, domestic, and work activities of pregnant women.[21,22] Moreover, health education during pregnancy is an important tool to avoid inadequate movements in daily activities, and can be useful to prevent complaints about increased levels of pain.[24] The PMI proved to be a tool that could help health professionals identify inadequate movements, considering that the instrument individually points out the difficulty of movement execution. In a prospective cohort study,[23] 223 pregnant women in the Netherlands were followed from the 12th to 36th week of gestation, and the results supported the use of PMI to evaluate physical factors that can help in the prevention of significant pain.

One limitation of the present study is the high educational level of the sample population, which does not correspond to the profile of pregnant women from public hospitals in Brazil,[25] highlighting the importance of replicating this instrument for various regions of the country. Patient profiles may be related to the location of the hospitals, which tend to be in the neighborhoods in the city with the highest Human Development Index ([HDI] 0.956) in the city. All participants in the present study, however, completed the questionnaire by themselves without receiving help from the interviewer, which may confirm the clear and simple description of the questionnaire, ensuring that all women, regardless of their educational level, were able to use this questionnaire. Another limitation of the present study is the absence of a relevant evaluation of women during the postpartum period, which is included in the original version of the PMI.[3] Nonetheless, the main objective of the present study was to include pregnant women in the sample population. Therefore, we recommend that future studies should investigate the psychometric properties of the Brazilian Portuguese version of the PMI in the postpartum population. One strength of the present study is that the PMI presented high internal consistency and reliability, corroborating the original version. These results showed that the Brazilian Portuguese version of the PMI is adequate for detecting changes in mobility related to low back and pelvic pain in pregnant women. Additionally, the questionnaire may be utilized during research and clinical practice to assist and promote health education among pregnant Brazilian women.

CONCLUSION

The Brazilian Portuguese PMI has been shown to be a reliable and valid questionnaire for use during pregnancy to evaluate and assist pregnant women in Brazil. The translation, cross-cultural adaptation, and psychometric evaluation of the Brazilian Portuguese PMI were successfully completed, and will contribute to health professionals' clinical decisions, as the PMI is an important tool to assess the mobility of pregnant women in Brazil.

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Appendix. Pregnancy Mobility Index – Brazilian Portuguese version.

Por favor, assinale com um "X" a opção mais adequada para cada item/atividades do quadro abaixo, relacionada a alguma queixa ou limitação em sua pelve e/ou coluna lombar.

Todos os itens/atividades têm pontuação de 0-3, conforme:

0 - Nenhuma dificuldade ou esforço para a realização da atividade;

1 - Um pouco de dificuldade ou esforço para a realização da atividade;

2 - Muita dificuldade ou esforço para a realização da atividade;

3 - É impossível realizar a atividade sem ajuda de outros

Caso nenhuma das opções satisfaça a sua resposta e/ou você não realiza a atividade questionada, você deve assinalar como "não se aplica".

Nenhum dos itens/atividades pode ficar sem resposta.

Você vivencia alguma queixa ou limitação em sua pelve e/ou coluna lombar realizando as seguintes atividades?	**Nenhuma (0)**	**Um pouco (1)**	**Bastante (2)**	**Precisa de ajuda (3)**	**Não se aplica**
Na movimentação diária em casa					
1. Levantando-se de uma cadeira					
2. Levantando-se de um sofá					
3. Levantando-se da cama					
4. Colocando os sapatos					
5. Virando-se na cama					
6. Levantando-se do chão					
Realizando atividades domésticas?					
7. Limpando com o aspirador de pó/vassoura/esfregão					
8. Lavando roupas					
9. Colocando roupas para secar					
10. Na posição ajoelhada					
11. Na posição agachada					
12. Na posição em pé					
13. Levantando 5 kg					
14. Levantando 10 kg					
15. Subindo ou descendo escadas					
Atividades fora de casa:					
16. Viajando de carro					
17. Viajando de ônibus					
18. Caminhando 50 metros					
19. Caminhando 200 metros					
20. Caminhando 500 metros					
21.Caminhando em uma superfície irregular					

Cálculo: *as questões marcadas em 'não se aplica', não serão consideradas para o cálculo de incapacidade, devendo ser anuladas. A pontuação final varia de 0 a 100 pontos, em que 0 indica "capacidade normal" e 100 indica "máxima incapacidade".*

$$\textit{Índice de mobilidade} = \frac{[100 - (\textit{ pontuação obtida }) \times 100]}{\textit{número de questões pontuadas} \times 3}$$

Chromosomal abnormalities detected by karyotyping among patients with secondary amenorrhea: a retrospective study

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Karyotype.
Chromosomal abnormalities.
Short stature.

ABSTRACT

BACKGROUND: Chromosomal abnormalities (CAs) have been described in patients with secondary amenorrhea (SA). However, studies on this association are scarce.

OBJECTIVES: To evaluate the frequency and types of CAs detected by karyotyping in patients with SA.

DESIGN AND SETTING: This retrospective study was performed in a reference clinical genetic service in South Brazil.

METHODS: Data were obtained from the medical records of patients with SA who were evaluated between 1975 and 2022. Fisher's bicaudate exact test and Student's t-test were used, and $P < 0.05$ was considered significant.

RESULTS: Among 43 patients with SA, 14 (32.6%) had CAs, namely del (Xq) (n = 3), 45,X (n = 2), 46,X,r(X-)/45,X (n = 2), 46,XX/45,X (n = 1), 46,X,i(q10)/45,X (n = 1), 47,XXX (n = 1), 46,XX/47,XXX (n = 1), 46,XX/47,XX-,+mar (n = 1), 45,XX,trob(13;14)(q10;q10)/46,XXX,trob(13;14)(q10;q10) (n = 1), and 46,XX,t(2;21)(q23;q11.2) (n = 1). Additional findings were observed mostly among patients with CA compared with those without CA ($P = 0.0021$). No difference in the mean age was observed between the patients with SA with or without CAs ($P = 0.268025$).

CONCLUSIONS: CAs are common among patients with SA, especially those with short stature and additional findings. They are predominantly structural, involve the X chromosome in a mosaic, and are compatible with the Turner syndrome. Patients with SA, even if isolated, may have CAs, particularly del (Xq) and triple X.

INTRODUCTION

Amenorrhea is a symptom, not a proper condition, characterized by an alteration in the menstrual cycle that affects 2%–5% of women of childbearing age.[1,2] Secondary amenorrhea (SA) corresponds to most amenorrhea cases and affects 3%–4% of women of childbearing age. It is defined by the cessation of menstruation for a minimum period of 3 months in patients with previously regular cycles or 6 consecutive months in women who have had at least one previous menstruation.[1,3] The diagnostic evaluation of patients with SA begins with assessing patient history, followed by conducting physical examination, laboratory tests, and imaging.[4,5] Although karyotyping is not routinely performed, it can be an important test.

Considering hormones, SA can be classified as having a central (hypothalamic–hypophyseal) or peripheric (ovarian) origin.[1,6] Hypothalamic disorders are some of the most common causes of amenorrhea, including SA.[7] SA might also have a peripheric origin because of a primary ovarian insufficiency that occurs after menarche and before the age of 40 years.[8]

Several factors can be related to SA, including genetics, the environment, and the interactions between them. Among genetic causes, chromosome abnormalities (CAs),[1,6] which are generally identified by cytogenetic tests (e.g. karyotyping) are observed. Most CAs are chromosome X-related, similar to the Turner syndrome (TS).[6,9]

Thus, determining the cause of SA is essential for the appropriate management and treatment of patients.[5] However, studies on SA and CAs are few, and most of them are case reports or case series.[9-11]

OBJECTIVE

This study aimed to evaluate the frequency and types of CAs detected by karyotyping in a sample of patients with SA, attempting to correlate these CAs with other clinical features observed in such patients.

METHODS

This retrospective study was performed in the Department of Genetics in the southern region of Brazil. The sample comprised patients with SA who were examined between 1975 and 2022. Clinical data and information on karyotypes were gathered from the medical records and clinical protocols of the patients. All the patients underwent a GTG-banding karyotype test in the same laboratory, following the modified technique of Yunis.[12]

The variables present in the clinical protocol were age at first evaluation, medical specialty from which the patients were referred, family history of amenorrhea, age at menarche and cessation of menstruation, period between age of menarche and cessation of menstruation, anthropometric measurements, data of physical examination, presence or absence of other comorbidities, syndromic appearance, and results of hormone levels, imaging exams, and karyotype.

Anthropometric measures were evaluated according to the Growth Charts of the Centers for Disease Control and Prevention.[13] The patients were also classified as either syndromic or non-non-syndromic by a single clinical geneticist. Additionally, the patients were divided into those with hypogonadotropic hypogonadism or hypergonadotropic hypogonadism.[6] The CAs identified were described according to the International System for Human Cytogenetic Nomenclature 2016.[14] Furthermore, they were classified into numeric or structural and with or without mosaicism.

For data analysis, Fisher's exact test (https://www.socscistatistics.com/tests/fisher/default2.aspx) and Student's T-test (https://www.socscistatistics.com/tests/studentttest/default.aspx) were used to compare frequencies and means, respectively. Significance was set at $P < 0.05$. The study was approved by the Ethics Committees of the Federal University of Health Sciences of Porto Alegre (UFCSPA) CAAE: 09909712.3.3001.5345 on January 12, 2018, and of Presidente Vargas Mother and Child Hospital (HMIPV) CAAE: 09909712.3.1001.5329 on October 10, 2017.

RESULTS

The sample comprised 43 patients, with age at first evaluation ranging from 17 to 47 years (mean, 28.8). Most of the patients were referred from the Department of Gynecology (61%), followed by the Department of Endocrinology (36%) and the Department of Neurology (3%). The age at menarche was 9–18 years (mean, 13.1), and the age at menstruation cessation was 11–34 years (mean, 21.5). The period between menarche and cessation of menstruation was 1–21 years (mean, 8.2).

A family history of amenorrhea was noted in 17.2% of the patients. Regarding physical appearance, 10 patients (23.3%) had additional clinical features other than SA, and 9.3% were considered syndromic. The main findings were short stature (17.6%), intellectual deficit (9.3%), hypothyroidism (5.6%), congenital heart disease (3.7%), and hearing loss (2.8%). Regarding hormonal profiles, 93.3% of the patients had hypergonadotropic hypogonadism, whereas 6.7% had hypogonadotropic hypogonadism.

CAs were identified in 14 patients (32.6%), and the number of analyzed cells was 15–100 (average, 38.7). Structural anomalies involving the X chromosome (64.3%) were the predominant CAs (**Table 1**). Numeric CAs were observed in 35.7% of the patients, and mosaicism was noted in seven patients (50%). Six patients (14%) were diagnosed with TS, and 3 (7%) had triple X syndrome.

When comparing the groups with and without CAs, those with CAs only had more additional findings ($P = 0.0021$). We did not identify significant differences in mean age at the first evaluation ($P = 0.9612$), mean age of SA ($P = 0.2680$), periods between age at menarche and cessation of menstruation ($P = 0.4285$), hormonal profile ($P = 1.0000$), or syndromic aspect ($P = 0.5855$) (**Table 2**) between the two groups. The mean age of SA in patients with TS was 17.2 years old (range, 15–24 years), and the normal karyotype was 22.5 (ranging, 11–34 years). No significant difference in the mean values was observed between the two groups ($P = 0.1617$). The frequency of CAs was 30.7% among the patients with hypergonadotropic hypogonadism and 33.3% among those with hypogonadotropic hypogonadism.

DISCUSSION

SA may have multiple causes. Genetic causes include single gene alterations and CAs.[1,6] CAs have been associated with SA in 3.8% to 44% of the cases; this variation occurs most likely because of the different forms of selection of individuals in each study, as well as the varying sample sizes.[6] In our study, a frequency of 32.6% was recorded. This elevated index may be related to the place where the patients were evaluated, which was the Department of Clinical Genetics (patients with SA were commonly evaluated in other departments, especially in the Department of Gynecology and Endocrinology, from which almost all the patients in our sample were referred from). Therefore, they were selected before the clinical genetics evaluation.

CAs described in association with SA can be numeric or structural, and they can occur in an isolated form or involve more than one cellular lineage.[6,9] Furthermore, these patients generally exhibit a wide range of phenotypic abnormalities, other clinical features, and hormonal profiles.[15]

In the literature, CAs associated with SA have been described to mainly affect the X chromosome,[9] a finding that accords with that of our study reporting that among patients with CAs, 85.7% had abnormalities involving the X chromosome. In our sample, the main alteration involving the X chromosome was the deletion of

parts of its long arm, which corresponded to 21.4% of the CA cases. Proper functioning of the gonads depends on the integrity of both X chromosomes.[9] A region of great importance related to normal ovary development and functioning is localized at the long arm of the X chromosome and ranging from Xq13.3 to Xq27.[16] Thus, deletions involving the long arm of this chromosome, as observed in three of our patients, can result in ovarian failure. Thus, considering that these patients often have primary amenorrhea or SA but without a short stature or other features of TS,[17] as observed in our patients with Xq deletions, is crucial.

Additionally, loci located in the long arm of the X chromosome (named POF1 and POF2) are associated with premature ovarian failure and infertility. Locus POF1 involves the segment between Xq26 to Xqter, while locus POF2 involves the segment between Xq13.3 to Xq22.[10,11,16] Locus POF1 and locus POF2 are clinically associated with ovarian failure in patients aged 24–29 years old and in those aged 16–21 years old, respectively.[18] In our sample, the two patients presenting deletions involving POF1 (regions q22q28 and q24q28) were diagnosed with ovarian failure at 27 and 28 years old, respectively. Meanwhile, the patient with the deletion involving the POF2 (region q13q26) was diagnosed with ovarian failure at 15 years old. As previously mentioned, these findings are consistent with those in the literature.[11,18]

The genes placed in the POF1 and POF2 loci of X chromosome are as follows: *CHM* (Xq21.1) (OMIM *300390), *POF1B* (Xq21.1) (OMIM *300603), *DACH2* (Xq21.3) (OMIM *300608), *DIAPH2* (Xq22) (OMIM *300108), *NXF5* (Xq22.1) (OMIM *300319), *COL4A6* (Xq22.3) (OMIM *303631), *PGRMC1* (Xq24)

Table 1. Chromosomal findings observed among the patients with secondary amenorrhea

Karyotypic findings	Number of patients (%)	Patients with syndromic aspect (%)	Patients with additional findings (%)
Normal (46.XX)	29 (67.4)	2 (50)	3 (30)
Abnormal	14 (32.6)	2 (50)	7 (70)
46,X,del(Xq)	3 (7)	–	–
q13q26	1 (2.3)	–	–
q22q28	1 (2.3)	–	–
q24q28	1 (2.3)	–	–
45,X	2 (4.7)	–	2 (20)
mos 45,X/46,X,r(X)	2 (4.7)	–	2 (20)
mos 45,X[28]/46,X,r(X)[7]	1 (2.3)	–	1 (10)
mos 45,X[36]/46,X,r(X)[6]	1 (2.3)	–	1 (10)
mos 45,X/46,XX	1 (2.3)	–	–
mos 45,X[3]/46,XX[50]	1 (2.3)	–	–
mos 45,X/46,X,i(q10)	1 (2.3)	–	1 (10)
mos 45,X[2]/46,X,i(q10)[48]	1 (2.3)	–	1 (10)
47,XXX	1 (2.3)	–	–
mos 47,XXX/46,XX	1 (2.3)	–	–
mos 47,XXX[95]/46,XX[2]	1(2.3)	–	–
mos 46,XXX,der(13;14)(q10;q10)/45,XX,der(13;14)(q10;q10)	1 (2.3)	1 (25)	1 (10)
mos 46,XXX,der(13;14)(q10;q10)[15]/45,XX,der(13;14)(q10;q10)[72]	1 (2.3)	1 (25)	1 (10)
mos 47,XX,+mar/46,XX	1 (2.3)	–	–
mos 47,XX,+mar[37]/46,XX[4]	1 (2.3)	–	–
46,XX,t(2;21)(q23;q11.2)	1 (2.3)	1 (25)	1 (10)
Total	**43 (100)**	**4 (100)**	**10 (100)**

Table 2. Clinical and laboratory findings verified among the patients with normal karyotype and chromosomal abnormalities

Clinical features	Normal karyotype	Chromosomal abnormalities	P
Age at first evaluation (years)	28.8 (17–47)	28.9 (19–42)	0.9612
Mean age of secondary amenorrhea (years)	22.5 (11–34)	19.7 (12–18)	0.2680
Period between age of menarche and cessation of menstruation (years)	9 (1–21)	6.9 (1–15)	0.4285
Hormonal profile			
Hypergonadotropic hypogonadism (%)	27 (93,1)	13 (93)	1.0000
Hypogonadotropic hypogonadism (%)	2 (6.9)	1 (7)	
Syndromic appearance (%)	2 (6.9)	2 (14.3)	0.5855
Additional findings (%)	2 (6.9)	7 (50)	0.0021
Total	**29 (67.4)**	**14 (32.6)**	

(OMIM *300435), *XPNPEP2* (Xq25) (OMIM *300145), *FMR1* (Xq27.3) (OMIM *309550), and *FMR2* (Xq28) (OMIM *300806).[19-26] However, despite the description of all these candidate genes, the cause of premature ovarian failure remains unknown in most cases.[27,28]

In our study, 14% of the patients had TS, a condition characterized by total or partial absence of the X chromosome. As observed in our sample, it can present as different chromosomal constitutions.[17] It occurs in approximately 1 in 2,500–5,000 women and is commonly diagnosed later, on average at the age of 15 years.[29] Patients with this syndrome may have typical clinical characteristics that include cardiac, skeletal, and endocrine abnormalities, including hypothyroidism and short stature.[17,30] However, this clinical spectrum ranges from a typical appearance to a presentation without clinical characteristics or minimal findings.[30] These characteristics and clinical variability were also observed in our sample, in which the most consistent finding was short stature, which was present in all the patients. Moreover, of the patients with short stature in our sample, 71.4% were diagnosed with TS, and this finding was associated with the presence of the syndrome. Thus, a short stature in TS is due to the haploinsufficiency of the *SHOX* gene, which is located on the short arm of the X chromosome.[31]

Post-pubertal patients with TS commonly present with hypergonadotropic hypogonadism due to ovarian dysgenesis that leads to premature ovarian failure. Therefore, most patients experience pubertal delay and primary amenorrhea. However, SA has also been observed, especially when associated with mosaicism.[17,30] This was also observed in our sample, in which 66.7% of the patients with TS presented with mosaicism. Moreover, previous studies have demonstrated that one third of patients with TS present with spontaneous thelarche, which also occurs more often in patients with mosaicism.[32] Regular menstrual cycles occur in approximately 6% of these patients.[33] Hence, TS might be only diagnosed later in life.[17] In our sample, the patients with TS were diagnosed at approximately 26.2 years old. Their low age of ovarian failure, ranging from 15 to 21 years (mean: 17.2 years), is an important finding to highlight.

As previously mentioned, the chromosome constitution of patients with TS is variable.[17] with total monosomy of X (45,X) being the main alteration and representing 40%–50% of all cases.[17,29] These patients generally have more phenotypic abnormalities, such as a short stature[34] and premature ovarian failure leading to primary amenorrhea or SA[35] in which the streak ovaries commonly lack follicles. However, the clinical spectrum can be variable.[17,29] In our sample, 2 of the 6 patients with TS had a 45,X constitution. Short stature was the only additional finding in both patients, and cessation of menstrual cycles occurred at 15 and 16 years of age in the two patients.

TS may also be caused by short-arm monosomy of the X chromosome.[17] In our sample, 3 of 6 patients with TS had this chromosome particularity. Two of them had the ring form of the X chromosome [r(X)] and mosaicism (with an associated 45,X lineage). The ring form of the X chromosome occurs because of the deletion of parts of its short and long arms, along with their posterior fusion. This constitution is related to atypical and severe cases of TS, including intellectual deficiency. This may occur because of *XIST* changes, which are the main genes responsible for controlling X chromosome inactivation. Therefore, modifications involving this region cause a greater expression of chromosomal material, leading to a higher frequency of abnormalities, including atypical abnormalities, such as microcephaly, agenesis of the corpus callosum, and seizures. The size of the ring X chromosome lacking *XIST* and, therefore, unable to become inactivated, correlates with phenotype severity in some cases. By contrast, patients with large rings that undergo selective X-chromosome inactivation are frequently associated with a more normal phenotype.[36]

Most patients with ring X chromosomes are infertile, as are other patients with TS. The gonads comprise striae with no follicular development. However, some patients are fertile and may transmit the ring X-chromosome to their progeny. In these rare cases, the ring is commonly large, with breakpoints on the short arm at bands p13 and p22. On the long arm, the breakpoints are at band q24 or q27.[36] In our study, patients with ring X chromosome did not present atypical clinical features (possibly due to mosaicism with the associated 45,X lineage). One patient presented with hypothyroidism; however, as mentioned previously, this is a common finding in TS. The age of menstrual cycle cessation was low, as observed in patients with a 45,X constitution, and ranged from 15 to 16 years. This premature age of SA might be influenced by the 45,X lineage present in association with the ring X chromosome lineage that was observed in both patients.

Approximately 20%–30% of patients with TS are carriers of an isochromosome of the X chromosome long arm.[17] This finding was observed in one patient in our sample in association with a 45,X lineage. Patients with isochromosomes commonly present with clinical features similar to those of patients with a 45,X constitution. However, they have a higher frequency of dysgenetic gonads, primary amenorrhea, SA, short stature, and major anomalies, such as congenital heart defects and renal malformations. Autoimmune diseases, such as Hashimoto thyroiditis, are also common in these cases.[37] The patient with an X long arm isochromosome in our sample had a short stature without any associated malformations or autoimmune diseases. Her menstrual cycle was interrupted at 24 years of age, which is an age older than that commonly described among patients with TS.

As previously mentioned, TS may occur in a mosaicistic constitution. The most common constitution is associated with a normal cellular lineage,[17] as detected in one patient in our sample. This constitution is observed in 15% to 25% of TS cases.[17] These patients commonly present with a higher stature, a lower frequency of major abnormalities, and, most commonly, SA, when compared to those with a 45,X karyotype. Menarche has been described in approximately 2%–5% of cases. These findings may be attributable to the presence of a normal cell lineage.[9]

Triple X syndrome is characterized by an extra X chromosome resulting from the nondisjunction of sexual chromosomes during the first meiotic division, and it occurs in 1 in every 1,000 women. This alteration is highly related to advanced maternal age. The phenotype observed in each individual with triple X might vary, and only approximately 10% of the cases are diagnosed.[38] Although sexual development and ovarian function are normal in most of these patients, ovarian dysfunction may manifest as premature menopause, SA, or oligomenorrhea.[13,39] The first report of triple X syndrome involving a 35-year-old woman with SA was by Jacobs et al.[40] In our study, one patient had triple X syndrome and hypergonadotropic hypogonadism due to premature ovarian failure. SA was her only finding, and her menstrual cycle was interrupted at 19 years of age.

Although more rarely (10% of cases), triple X might also occur in mosaicism.[41] Temoçin et al.[42] have reported that 1 in every 9 patients (11.1%) with SA has 46,XX/47,XXX mosaicism. Additionally, a study by Ayed et al.[43] has revealed that in a sample of 40 patients with SA due to premature ovarian failure, 5 patients (12.5%) had CAs, and 2 (40%) had triple X in mosaic (1 with 45,X/47,XXX constitution and 1 with 46,XX/47,XXX constitution; 5% of all the patients had premature ovarian failure. In our sample, 2 patients with triple X mosaicism were identified. The first was mosaicism with a normal lineage. The patient was not syndromic and had premature ovarian failure. Her menstrual cycle was interrupted at 19 years of age. Interestingly, 1 patient with triple X mosaicism had a balanced Robertsonian translocation between chromosomes 13 and 14. Clinically, she had an important intellectual deficit, behavioral disorder (with aggressive episodes), short stature, obesity, and hypothyroidism, in addition to SA due to hypogonadotropic hypogonadism. In this case, the occurrence of triple X syndrome related to maternal uniparental disomy of chromosome 14 due to the translocation between chromosomes 13 and 14 in both lineages cannot be disregarded. Interestingly, Bertini et al.[44] have described a patient with similar clinical findings and uniparental maternal disomy of chromosome 14, which was also associated with Robertsonian translocation between chromosomes 13 and 14.

Chromosome markers comprise a few structurally abnormal chromosomes of unknown origin. One patient with mosaicism involving one normal cellular lineage with a supernumerary marker chromosome (47,XX+mar) was observed in our sample. In these cases, the use of molecular cytogenetic techniques, such as fluorescent *in situ* hybridization, is recommended to determine the marker chromosome origin.[17] However, our patient did not undergo this test since she was evaluated 20 years ago. As for her clinical condition, she did not have a syndromic appearance, and SA was the only finding.

Interestingly, one patient in our sample had an apparently balanced *de novo* translocation involving chromosomes 2 and 21 with normal parental karyotypes. The patient had an intellectual deficit associated with SA. First, no genes associated with her clinical condition were located at translocation breakpoints in the literature. Additionally, at the time of evaluation, molecular cytogenetic techniques were still unavailable.

The frequency of mosaicism identified in our study (50%) and that described in the literature (40%–100%) are both high.[6,42,43,45] It should also be recalled that most patients with TS presenting with SA have a mosaic constitution.[17,30] Hence, among the cases of SA, the number of analyzed cells in karyotypic evaluation should be higher, targeting the detection of potential mosaicism (this is in agreement with the higher cell count that is routinely performed in mosaicism suspicion, that is, in general, 100).[46]

CONCLUSION

As CAs are common among patients with SA, cytogenetic analysis by karyotyping is important, especially in patients with short stature and additional findings. The main types of CAs observed were structural, involving the X chromosome, and compatible with a TS diagnosis. Several CAs occurred in the mosaic. This finding is also commonly reported in previous studies, which have suggested that patients with SA should be evaluated by karyotyping with more cells counted as a precaution.

However, the absence of additional findings other than SA did not exclude karyotype indication. This is because a significant number of patients, even those with CAs, may have SA as an isolated finding, especially in patients with the Xq deletion and triple X syndrome (with or without mosaicism). In our sample, we did not observe a difference in SA age between patients with and without CAs. However, we cannot rule out the influence of the small sample size on this result.

Therefore, the diagnosis of CAs, especially when performed in the early stages, is possible and important for better management of patients with SA.

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Minimally invasive interventions for biopsy of malignancy-suspected pulmonary nodules: a systematic review and meta-analysis

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ABSTRACT

BACKGROUND: Imaging tests are important for diagnosis during the management of pulmonary nodules; however, biopsy is required to confirm the malignancy.

OBJECTIVES: To compare the effects of different techniques used for the biopsy of a pulmonary nodule.

DESIGN AND SETTING: Systematic review and meta-analysis were conducted using Cochrane methodology in São Paulo, São Paulo, Brazil.

METHODS: We conducted a systematic review of randomized controlled trials (RCTs) on minimally invasive techniques, including tomography-guided percutaneous biopsy (PERCUT), transbronchial biopsies with fluoroscopy (FLUOR), endobronchial ultrasound (EBUSR), and electromagnetic navigation (NAVIG). The primary outcomes were diagnostic yield, major adverse events, and need for another approach.

RESULTS: Seven RCTs were included (913 participants; 39.2% female, mean age: 59.28 years). Little to no increase was observed in PERCUT over FLUOR (P = 0.84), PERCUT over EBUSR (P = 0.32), and EBUSR over NAVIG (P = 0.17), whereas a slight increase was observed in NAVIG over FLUOR (P = 0.17); however, the evidence was uncertain. EBUSR may increase the diagnostic yield over FLUOR (P = 0.34). PERCUT showed little to no increase in all bronchoscopic techniques, with uncertain evidence (P = 0.02).

CONCLUSION: No biopsy method is definitively superior to others. The preferred approach must consider availability, accessibility, and cost, as safety and diagnostic yield do not differ. Further RCTs planned, conducted, and reported with methodological rigor and transparency are needed, and additional studies should assess cost and the correlation between nodule size and location, as well as their association with biopsy results.

SYSTEMATIC REVIEW REGISTRATION: PROSPERO database, CRD42018092367 -https://www.crd.york.ac.uk/PROSPERO/display_record.php?RecordID=92367.

INTRODUCTION

Lung cancer is the leading cause of cancer-related deaths worldwide.[1,2] Imaging tests are important for the diagnostic suspicion and risk evaluation of pulmonary nodules; however, biopsy is needed to confirm the malignancy.[1,2] The technique of choice should have the highest accuracy, good diagnostic yield, and acceptable complication rate.

The minimally invasive techniques currently used include transthoracic approaches, such as percutaneous computed tomography-guided biopsy (PERCUT), and transbronchial approaches performed by bronchoscopy, such as fluoroscopy-guided transbronchial biopsies (FLUOR), transbronchial biopsies guided by endobronchial radial probes (EBUSR), and transbronchial biopsies guided by electromagnetic navigation (NAVIG).[3-7]

Mapping the literature on the comparative effects of different techniques is essential to better inform the clinicians for handling pulmonary nodules. With this evidence, better decisions can be made by incorporating the aspects of availability and affordability.

OBJECTIVES

To identify, critically evaluate, and synthesize evidence regarding the effects of different minimally invasive techniques for the biopsy of malignancy-suspected pulmonary nodules. We aimed to highlight the benefits and harms of these techniques in comparison with each other according to the results of randomized controlled trials (RCTs).

METHODS

We conducted a systematic review following the recommendations of the Cochrane Handbook for Systematic Reviews of Interventions[8] and reported them in accordance with the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) Statement.[9] The protocol was prospectively registered in PROSPERO database (CRD42018092367, https://www.crd.york.ac.uk/PROSPERO/display_record.php?RecordID=92367) and no changes were made from the protocol since then.

Types of studies

Only RCTs were eligible for inclusion. We included studies regardless of their status (full text or abstract), date, and language of publication.

Types of participants

Adults with malignancy-suspected peripheral pulmonary nodules, defined as those > 8 mm and < 30 mm, with characteristics such as spiculation, pleural retraction, and growing size.[2]

Types of interventions and comparators

- PERCUT;
- FLUOR;
- EBUSR;
- NAVIG.

RCTs comparing different sizes of bronchoscopes, nodule localization techniques, or a combination of two or more techniques were not considered.

Outcomes of interest

The following primary outcomes were considered:

- Diagnostic yield was measured as the proportion of biopsies that defined the histological diagnosis of pulmonary nodules.
- Major adverse events were measured as the frequency of participants who experienced at least one major complication event, such as pneumothorax and hemothorax (symptomatic and/or requiring drainage), and death.
- The need for another technique, measured as the frequency of participants requiring further biopsy.

The following secondary outcomes were considered:

- Non-serious adverse events were measured as the frequency of at least one non-serious event, including pain.
- Time of procedure, measured in hours.
- All time points of outcome measurement were considered.

Search strategy

Comprehensive searches were performed in the following electronic databases or sources: CINAHL (Cumulative Index to Nursing and Allied Health Literature), Cochrane Library (via Wiley), Embase (via Elsevier), LILACS (Latin American and Caribbean Health Sciences Literature, via BVS), and MEDLINE (Medical Literature Analysis and Retrieval System Online, via PubMed). Additional searches were conducted on two clinical trial registry platforms: Clinicaltrials.gov and the WHO International Clinical Trials Registry Platform [ICTRP]) and OpenGrey (https://opengrey.eu). Manual searches were performed by screening the reference lists of included studies. All databases were searched from their inception until May 17, 2021. The search strategy is described in **Supplementary material 1** - https://drive.google.com/drive/folders/1lSHRxvUWz_Vr-cWqj3v3UFS4Nl3Z4-6K.

Study selection and data extraction

The study selection was performed in two phases. First, the titles and abstracts identified through the search strategy were evaluated by pre-selecting potentially eligible studies. Second, the full text was assessed to confirm the eligibility. The selection process was carried out using the Rayyan platform (https://www.rayyan.ai/)[10] independently by two reviewers, and a third reviewer resolved any disagreements. The full selection process is detailed in the PRISMA flow diagram.

Data extraction was independently performed by two reviewers using the data extraction form, and a third reviewer resolved the disagreements.

Risk of bias assessment

To evaluate the risk of bias, seven domains of the Cochrane Risk of Bias (RoB) tool were used (sequence generation, allocation concealment, blinding of participants and personnel, blinding of outcome assessors, incomplete data, selective reporting, and other bias), which were classified as high, low, or unclear.[8] Two authors independently conducted the evaluation, and a third author resolved the disagreements. The third, fourth, and fifth domains were assessed at the outcome level.

Data analyses

Quantitative data synthesis was performed on the results of these clinically and methodologically homogeneous studies through meta-analyses with random effect models, using the Review Manager 5.4.1 (RevMan 5.4.1) software (The Cochrane Collaboration, London, England, 2020).[8] Relative risk (RR) and mean difference (MD) were used to estimate the effect size of dichotomous and continuous variables, respectively. A 95% confidence interval (CI) was used for all the estimates. When

quantitative data synthesis was not possible, the results were reported narratively, considering whenever available, effect size estimates (including RR, absolute risk difference, odds ratio, and number needed to treat [NNT]) and their respective measures of confidence and variance (dispersion measures, CI, and P values).

Inconsistency (statistical heterogeneity) was evaluated by visual inspection of forest plots, and chi-square tests; $P > 0.10$ was considered indicative of statistical heterogeneity. Additionally, I^2 tests were used to measure the extent of inconsistency ($I^2 > 50\%$ was considered to indicate significant inconsistency).[9] We explored the reasons for heterogeneity by conducting subgroup and sensitivity analyses. When necessary, the authors were contacted to obtain missing data on the outcomes of interest.

Additional analyses

For subgroup analyses, different anatomical regions of the nodules (central or peripheral) were explored, as different diagnostic yields were expected for each technique. Bronchoscopy methods tended to present better results in central lesions, and the transthoracic approach tended to present better yields in peripheral lesions. Sensitivity analyses were performed according to the risk of bias of the included studies (low risk versus high/unclear risk), considering the high/unclear risk of bias in at least one domain of the Cochrane RoB tool.

Evidence certainty

The Grading of Recommendations, Assessment, Development and Evaluations (GRADE)[12] approach was used to assess the certainty of the body of evidence (high, moderate, low, or very low) for all comparisons. The certainty of evidence was downgraded owing to methodological limitations, inconsistencies, indirectness, imprecision, and publication bias. We developed a summary of the findings table using an online software (GRADEpro Guideline Development Tool [Software]. McMaster University, Ontario, Canada, 2022).

RESULTS

The search strategy retrieved 7,625 references. After removing 903 duplicates, 6,722 references were screened by title and abstract (first phase), of which 6,702 references were eliminated because they did not fulfill the eligibility criteria and 20 references were pre-selected for the second phase. After full-text reading, 11 RTCs were included: seven completed RCTs[6, 11, 13-17] and four ongoing RCTs.[18-21] The list of the nine excluded studies[22-30] and reasons for exclusion are presented in **Supplementary material 2** - https://drive.google.com/drive/folders/1lSHRxvUWz_Vr-cWqj3v3UFS4Nl3Z4-6K. A flowchart of the study selection process is shown in **Figure 1**.

Characteristics of included studies

Seven completed RCTs included in this study were published from 1998 to 2018, which included a total of 913 participants (39.2% female, n = 357) with a mean age of 59.28 years.[6,11,13-17] All the participants had pulmonary nodules up to 3 cm on chest computed tomography without a definitive diagnosis. All RCTs reported a diagnostic yield and were considered to yield a positive biopsy when there were benign or malignant findings in the anatomopathological results. If the result was non-specific, the biopsy was considered negative and a comparison technique was performed sequentially. The main characteristics of the RCTs are shown in **Table 1**. Ongoing RCTs are detailed in **Supplementary material 3** - https://drive.google.com/drive/folders/1lSHRxvUWz_Vr-cWqj3v3UFS4Nl3Z4-6K.

Risk of bias

The risk of bias of the RCTs, as assessed using the Cochrane RoB tool, is summarized in **Figure 2**. The reasons for each judgement

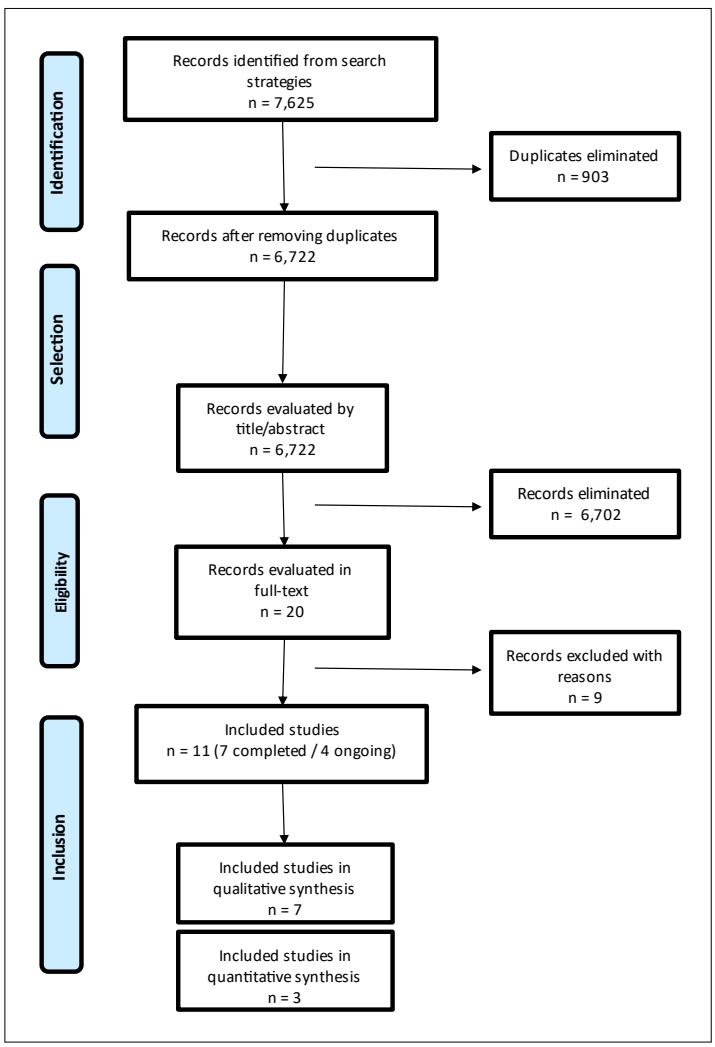


Figure 1. Study selection flowchart.

Table 1. Main study characteristics

	Population	Study type	Intervention (versus control group)	Participants	Controls	Diagnostic yield	Major complications
Asano et al.[13]	Adults with suspected pulmonary nodules	RCT	NAVIG versus FLUOR	167	167	67.1% versus 59,9%	2.39% versus 1.79%
Eberhardt et al.[11]	Adults with suspected pulmonary nodules	RCT	NAVIG versus EBUSR	39	39	59% versus 69.23%	5% versus 5%
Gupta et al.[14]	Adults with suspected pulmonary nodules	RCT	EBUSR versus PERCUT	25	25	72% versus 84%	48% versus 36%
Paone et al.[15]	Adults with suspected pulmonary nodules	RCT	EBUSR versus FLUOR	87	119	75.8% versus 52.1%	0% versus 8.4%
Shankar et al.[16]	Adults with suspected pulmonary nodules	RCT	PERCUT versus FLUOR	16	18	78% versus 75%	0% versus 0%
Steinfort et al.[17]	Adults with suspected pulmonary nodules	RCT	EBUSR versus PERCUT	32	19	78.12% versus 81.25%	3% versus 20%
Wang et al.[5]	Adults with suspected pulmonary nodules	RCT	EBUSR versus PERCUT	80	80	65% versus 85%	6.25% versus 25%

RCT = randomized controlled trial; NAVIG = electromagnetic navigation transbronchial biopsy; FLUOR = fluoroscopy-guided transbronchial biopsy; EBUSR = endobronchial ultrasound with radial probe transbronchial biopsy; PERCUT = tomography-guided percutaneous biopsy.

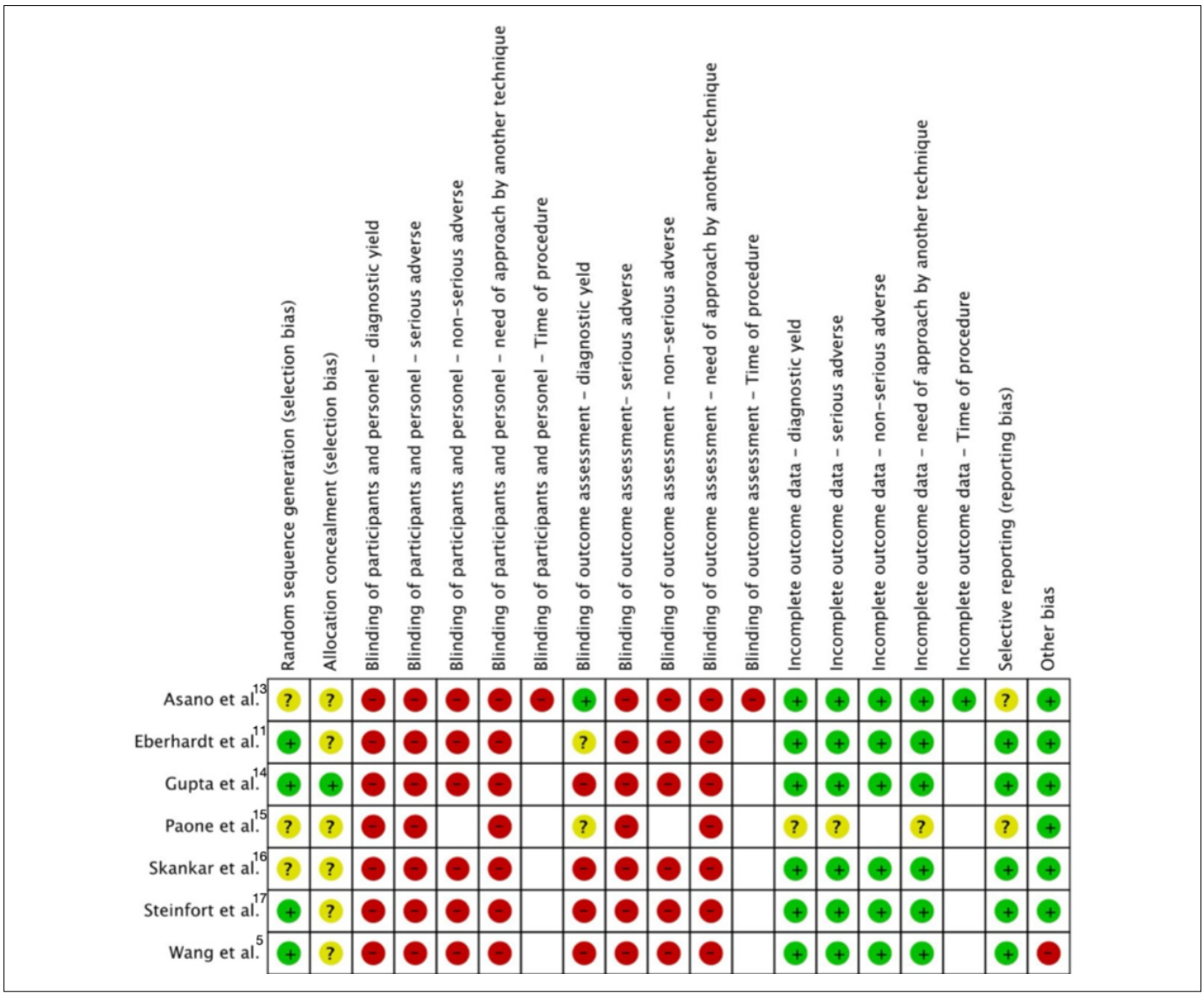


Figure 2. Risk of bias assessment. Summary of the risk of bias in the randomized controlled trials included for each domain.

are in **Supplementary material 4** - https://drive.google.com/drive/folders/1lSHRxvUWz_Vr-cWqj3v3UFS4Nl3Z4-6K. All the RCTs presented at least one domain that was judged to have a high risk of bias.

Effects of interventions

Comparison 1: PERCUT versus FLUOR

One RCT assessed this comparison[11] and the following results were found:

- Diagnostic yield: There was no difference between PERCUT and FLUOR; however, the CI was wide (RR, 1.04; 95% CI, 0.71 to 1.51), and the effect estimate was imprecise (P = 0.84; 34 participants; one RCT; very low evidence certainty) (**Supplementary material 5** - https://drive.google.com/drive/folders/1lSHRxvUWz_Vr-cWqj3v3UFS4Nl3Z4-6K).
- Need for another technique: There was no difference between FLUOR and PERCUT; however, the CI for effect estimate was wide (RR, 0.22; 95% CI, 0.03 to 1.79) and the effect estimate was imprecise (P = 0.15; 34 participants; one RCT; very low evidence certainty).

Major adverse events: No adverse events were reported in either group.

Non-serious adverse events: Two non-serious adverse events were reported in the PERCUT group and none in the FLUOR group (RR, 4.47; 95% CI, 0.23 to 86.7; 34 participants; one RCT; very low evidence certainty). In both cases, the patient had small-volume pneumothorax that was not observed during the conservative treatment, and no further intervention was necessary. There was little to no increase in safety in FLUOR compared with PERCUT; however, the effect estimate was imprecise (P = 0.32).

Comparison 2: PERCUT versus EBUSR

Three RCTs assessed this comparison[5,15,16] and the following results were found:

- Diagnostic yield: There was no difference between PERCUT and EBUSR; however, the CI for the effect estimate was wide (RR, 1.16; 95% CI, 0.86 to 1.57; I^2 = 52%) and the effect estimate was imprecise (P = 0.32; 258 participants; three RCTs; very low evidence certainty) (**Figure 3**, **Supplementary material 6** - https://drive.google.com/drive/folders/1lSHRxvUWz_Vr-cWqj3v3UFS4Nl3Z4-6K).
- Need for another technique: There was no difference between EBUSR and PERCUT; however, the CI for effect estimate was wide (RR, 0.74; 95% CI, 0.31 to 1.77; I^2 = 60%), and the effect estimate was imprecise (P = 0.51; 258 participants; three RCTs; very low evidence certainty).

Major adverse events: There were no differences between PERCUT and EBUSR. The CI for the effect estimate was wide (RR, 2.13; 95% CI, 0.51 to 8.99; I^2 = 81%), and the effect estimate was imprecise (P = 0.30; 258 participants; three RCTs; very low evidence certainty).

- Non-serious adverse events: PERCUT may result in a higher risk of non-serious adverse events, with a slight increase in the estimate (P = 0.02; 258 participants; three RCTs; low evidence certainty).

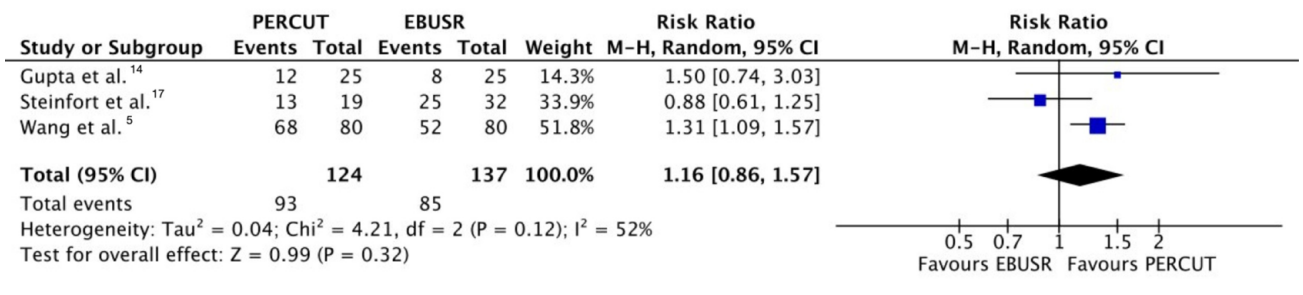
Comparison 3: FLUOR versus EBUSR

One RCT assessed this comparison[14] and following results were found:

Diagnostic yield: FLUOR may result in a reduction in diagnostic yield (RR, 0.69; 95% CI, 0.56 to 0.85; 206 participants; one RCT; low evidence certainty; P ≤ 0.05) (**Figure 4**, **Supplementary material 7** - https://drive.google.com/drive/folders/1lSHRxvUWz_Vr-cWqj3v3UFS4Nl3Z4-6K).

- Need for another technique was higher in the FLUOR group (RR, 1.98; 95% CI, 1.31 to 3.01; 206 participants; one RCT; very low evidence certainty; P ≤ 0.05).

Major adverse events: There was an increase in the risk of major adverse events with FLUOR; however, the CI for the effect



PERCUT = tomography-guided percutaneous biopsy; EBUSR = endobronchial ultrasound with radial probe transbronchial biopsy; CI = confidence interval.

Figure 3. Comparison between PERCUT (CT-guided percutaneous biopsy) and EBUSR (radial probe endobronchial ultrasound-guided transbronchial biopsy) in relation to the diagnostic yield of each procedure.

estimate was wide (RR, 15.40; 95% CI, 0.91 to 259.31; 206 participants; one RCT; low evidence certainty; P ≤ 0.05).

Non-serious adverse events: No such events occurred in either group.

Comparison 4: FLUOR versus NAVIG

One RCT assessed this comparison[16] and following results were found:

Diagnostic yield: There was a slight increase in NAVIG compared to FLUOR (RR, 0.89; 95% CI, 0.76 to 1.05; 334 participants; one RCT; low evidence certainty; P = 0.17) (**Supplementary material 8** - https://drive.google.com/drive/folders/1lSHRxvUWz_Vr-cWqj3v3UFS4Nl3Z4-6K).

Need for another technique: There was a slight increase in NAVIG compared to FLUOR; however, the effect estimate was imprecise (RR, 1.22; 95% CI, 0.92 to 1.62; 334 participants; one RCT; very low evidence certainty; P = 0.17).

Major adverse events: There was a slight increase in NAVIG compared to FLUOR, the CI for effect estimate was wide (RR, 0.75; 95% CI, 0.17 to 3.34), and the effect estimate was imprecise (P = 0.70; 334 participants; one RCT; low evidence certainty).

Non-serious adverse events: There were no non-serious adverse events.

- Procedure time (in minutes): No difference was observed between the interventions (MD = -3.00; 95% CI, 45.90 to 39.90; 334 participants; one RCT; low evidence certainty; P = 0.89).

Comparison 5: NAVIG versus EBUSR

One RCT assessed this comparison[17] and following results were found:

- Diagnostic yield: There was no difference between EBUSR and NAVIG; however, the CI was wide (RR, 1.17; 95% CI, 0.84 to 1.64), and the effect estimate imprecise (P = 0.34; 78 participants; one RCT; very low evidence certainty) (**Supplementary material 9** - https://drive.google.com/drive/folders/1lSHRxvUWz_Vr-cWqj3v3UFS4Nl3Z4-6K).
- Need for another technique: There was no difference between EBUSR and NAVIG; however, the CI for the effect estimate was wide (RR, 0.75; 95% CI, 0.41 to 1.37), and imprecise (P = 0.34; 78 participants; one RCT; very low evidence certainty).

Major adverse events: Two patients in each group developed pneumothorax and underwent pleural drainage. No significant difference was observed (RR, 1.00; 95% CI, 0.15 to 6.75; 78 participants; RCT; very low evidence certainty; P = 1.00).

Non-serious adverse events: None were reported in any group.

Subgroup analysis (considering the location of the nodule: peripheral versus central), sensitivity analysis (considering the risk of bias: low versus high/unclear), and publication were not conducted because of the scarcity of available data assessed or reported by the included RCTs and the low number of RCTs included in a unique meta-analysis (less than ten).

Post-hoc analysis

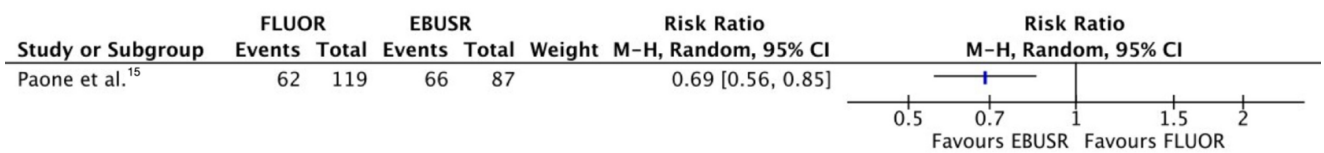
In clinical practice, we believe it would be interesting to have an additional comparison of PERCUT versus any other bronchoscopic technique for diagnostic yield. There was no difference between PERCUT and bronchoscopic techniques; however, the CI for the effect estimate was wide and the effect estimate was imprecise (RR, 1.14; 95% CI, 0.92 to 1.42; four RCTs; 295 participants; P = 0.02) (**Supplementary material 11** - https://drive.google.com/drive/folders/1lSHRxvUWz_Vr-cWqj3v3UFS4Nl3Z4-6K).

Analysis of the certainty of evidence

The GRADE methodology was used to assess the certainty of evidence.[19] Overall, the certainty of evidence was considered low or very low due to methodological limitations, indirect evidence, small sample size, and a wide CI. A summary of the certainty of evidence analysis is presented in **Supplementary material 10** - https://drive.google.com/drive/folders/1lSHRxvUWz_Vr-cWqj3v3UFS4Nl3Z4-6K.

DISCUSSION

The choice of the method or invasive diagnosis of pulmonary nodules depends on many factors, including nodule size, localization, method availability, cost, and professional expertise. This systematic review was designed to help make this choice; however, it is difficult to compare the four different types of interventions indirectly. It is also worth noting that some of the rarely known and unavailable techniques were compared. The simplest technique evaluated was FLUOR, which requires only a common



FLUOR = fluoroscopy-guided transbronchial biopsy; EBUSR = endobronchial ultrasound with radial probe transbronchial biopsy; CI = confidence interval.

Figure 4. Comparison between PERCUT (CT-guided percutaneous biopsy) and bronchoscopic techniques, in relation to the diagnostic yield of each procedure.

fluoroscopy device and a trained specialist. Other procedures, such as PERCUT, EBUSR, and NAVIG, require more expensive and less available materials and technology. EBUSR is a complex procedure that is performed at few centers in emerging countries. NAVIG is unavailable in Brazil and its use is far from being a current reality in many countries. Considering the rational use of resources in the health system, data from this and future related studies may help in defining which methods to carry on with realistic availability, rational use of resources, and investment in the future.

To our knowledge, no systematic review has evaluated comparisons of different lung nodule biopsy methods. There are reviews considering specific comparisons carried out under different methodologies, with different study designs and combined techniques.[6,7] Ali et al.[6] analyzed 25 prospective and 32 retrospective studies from a total of 7,872 lesions biopsied. The diagnostic yield for the R-EBUS group (described as EBUSR in this review) was 70.6% (95% CI, 68–73.1) and was significantly higher in malignant nodules greater than or equal to 2 cm and with a patent bronchus sign on tomography. This was a large review, with many studies included; however, the certainty of evidence was lost with the inclusion of retrospective studies, which comprised the majority of included studies. Furthermore, the conclusion that patients undergoing PERCUT have higher complication rates (up to 23%) versus 2.8% for EBUSR, should be considered as having low certainty as most of the studies used this analysis were retrospective and not masked. However, Gupta et al.,[14] a study included in our review, showed 20% pneumothorax in PERCUT, confirming the rate suggested by Ali et al.[6] This high rate may be the result of the small number of participants in the study. Gupta et al.[14] also showed that the diagnostic yield for nodules located in the right superior lobe was significantly lower in EBUSR.

McGuire et al.[7] analyzed 41 prospective and retrospective studies of 2,988 involved nodules (2,102 biopsied by EBUSR and 886 biopsied by NAVIG). The methods had a complication rate of less than 2% and were considered good options for diagnosing peripheral nodules. However, the review was conducted considering a large proportion of retrospective studies, which reduced the certainty of the evidence and increased the risk of bias. Additionally, other biopsy methods were not considered.

Our search was more comprehensive and sensitive (beyond the MeSH term, we used text words and a list of synonyms for each term) with no restrictions on date, language, or status of the publication. We assessed the certainty of the evidence using the GRADE approach, which was not used in the aforementioned reviews.

The limitations of our study were primarily related to the poor methodological quality of the included RCTs. In general, the included RCTs had a high risk of bias, small sample sizes, and clinical heterogeneity. As we considered any technique, different comparisons were assessed by the included RCTs using the same technique, which made it difficult to define the best method. Further RCTs, planned, conducted, and reported with methodological rigor and transparency are needed on this issue, and additional studies should provide information about the nodule size and location and their relation to the biopsy results.

Although the techniques described in this study have been used in clinical practice, we did not find sufficient evidence to determine the preferred technique. Until more robust evidence can better support therapeutic decisions, the available evidence suggests the following:

- In the choice between PERCUT and FLUOR, there seems to be no difference between the methods regarding diagnostic yield (P = 0.84); however, PERCUT required fewer approaches using another technique (P = 0.15), and FLUOR was safer (P = 0.32). However, this benefit might not be clinically relevant.

PERCUT appears to be more advantageous than EBUSR in terms of diagnostic yield (P = 0.32) and safety for serious (P = 0.30) and non-serious (P = 0.02) adverse events. EBUSR may have a lower need for another technique (P = 0.51). However, whether this difference is clinically relevant remains unclear.

- Between FLUOR and EBUSR, EBUSR has an advantage regarding diagnostic yield, safety for serious adverse events, and a lower need for another technique ($P \leq 0.05$).

No differences were observed between PERCUT and NAVIG regarding safety (P = 0.70); however, there was an advantage for NAVIG regarding diagnostic yield (P = 0.17) and a lower need for an approach using another technique (P = 0.17). There was no difference in the procedure time between the FLUOR and NAVIG groups (P = 0.89).

- Between NAVIG and EBUSR, EBUSR appears to be advantageous regarding diagnostic yield (P = 0.34) and a lower need for the use of another technique (P = 0.34), but there was no difference regarding safety (P = 1.00). However, whether this difference is clinically relevant remains unclear.

The most recommended technique is unclear, but PERCUT and NAVIG stand out as favored techniques in most RCTs. In direct comparison, PERCUT has an advantage, although not significant because of the wide CI (P = 0.02).

A cost analysis was not performed, as only clinical trials were included. Study designs that evaluate cost-utility, effectiveness, and benefit would better assess these data. A study that evaluated the cost-effectiveness of PERCUT versus NAVIG in the United Kingdom in 2020 showed that NAVIG may be more cost-effective than PERCUT in some subgroups; however, there is no general definition of one method in relation to another, particularly if the cost of implementing NAVIG is considered.[31]

The procedures had similar risks of complications and no significant difference; however, there was still a difference. It is up to the physician to discuss each method and present the possible risks and benefits of a shared decision on the method, respecting the ethics and opinions of patients and families.

CONCLUSION

This systematic review did not identify high-certainty evidence to support the choice of one method of lung nodule biopsy over others. In this scenario of uncertainty, until the results of new studies are published, the preferred choice of biopsy method must consider availability and accessibility. Potential risks and benefits must be presented to patients for a shared decision.

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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.

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

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

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

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

Figures and tables

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

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

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

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

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

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

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