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Rise of palliative care in cardiology

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Cardiovascular diseases (CVDs) are among the most prevalent and widespread diseases worldwide, regardless of gender, age, ethnicity, or social class, and are the leading cause of death, especially in older age groups.[1,2] Cardiology has developed exponentially over the last few decades, with scientific and technological advances improving disease control and increasing longevity. Therefore, a gradually increasing number of patients should be living with CVD.

Death remains the great villain that must be fought by healthcare professionals. Research and interventions focus on the search for alternatives that increase lifespan.[2] However, another key aspect of health is quality of life (QoL). The QoL cannot be ignored but often takes a backseat to other priorities.[2,3]

CVDs bring about symptoms that negatively impact QoL, especially in the more advanced stages of these diseases.[1,4-6] They cause functional loss and disability, absence from work and recreational activities, and increased stress on caregivers. In addition, CVDs increase direct and indirect expenses, in the self-perpetuating cycle from individual to public health.[2]

Palliative care (PC) is a way of approaching patients (children and adults) that aims to improve QoL in situations of life-threatening illnesses. These are contexts that experience physical, psycho-emotional, socio-cultural, and spiritual suffering, resulting from the disease itself or the treatments to which they are subjected. PC actions must be multidisciplinary and extend to family members and others involved, who are also exposed to suffering and need support.[1-6]

The indication of PC does not depend on disease type (cancer or not), stage (early stage or terminal), course (acute or chronic), or treatment goal (whether curative treatment is proposed or not).[2,4] PC is not only a philosophy but also an active practice rooted in the principles of patient-centered medicine, with personalized care focused on human well-being, comfort, and dignity. Biography and personal values are crucial for planning health-promotion actions and are as important as disease aspects.[3,5]

By such definitions, CP should be an integral part of cardiology routines. However, this is not the case in practice.[1] In comparison with cancer patients, patients with CVD 1) are less likely to receive PC throughout the disease course, 2) receive PC late, close to death, 3) are less often referred to hospices (inpatient units focused on providing care for symptom management, as well as promoting comfort and dignity at the end of life), and 4) usually remain in hospices for a shorter time, when they are admitted, until they die, highlighting the late recognition of PC needs and corresponding actions, as shown by several studies.[1-4,6,7]

This late recognition occurs even though CVDs account for more deaths than cancer and are considered equivalent in terms of symptoms and suffering experienced in the terminal stage.[1,4,6,7] Heart failure (HF) is the main disease model in which PC has been studied and applied in cardiology. However, there is also evidence of its benefits in coronary and valvular diseases, arrhythmias, peripheral vascular disease, and congenital heart disease.[1,8] Despite these benefits, various barriers to the introduction of PC to cardiology clinical practice are often induced by ignorance and prejudice.[1-4,6,7]

PC is often erroneously conflated with care exclusively for cancer patients and misperceived as end-of-life care or other practices linked to limiting/withdrawing life-sustaining care.[2,4,7] The PC specialist is more often than not wrongly associated with the figure of the Grim Reaper, who suspends life-prolonging treatment.[6] Providing PC does not preclude continuing

disease-modifying therapies,[4] as feared by many, who ignore its true meaning. These misconceptions make it difficult for patients, families, and healthcare professionals to engage in discussions on PC.

PC is commonly associated with death, which remains a taboo in contemporary society.[1,2,6] However, PC supports life. It enables patients to live better, even if they have a serious illness. Therefore, PC misperceptions result in the loss of valuable opportunities to improve the symptoms of patients, mitigate their suffering, and meet the needs of family members/caregivers.[4,7]

Notwithstanding these difficulties in introducing PC in cardiology, specialist societies have increasingly advocated for a culture change.[1,2,4,5] Nonetheless, some publications still contextualize PC only when all disease-modifying treatment options have been exhausted or failed.

The 2021 guideline from the Brazilian Society of Cardiology (*Sociedade Brasileira de Cardiologia* – SBC) made progress in the country by addressing pertinent topics in PC for patients with HF. For example, this guideline highlights the importance of empowering professionals with skills to recognize patients' needs and to develop palliative strategies.[8] However, PC remains reserved for patients who are not candidates for a heart transplant or an implantable ventricular assist device (VAD). This recommendation is not in line with the World Health Organization (WHO) guidelines.

According to the WHO, PC should be provided early in the disease course[2,4] to improve its implementation. Conversely, a Manichean and exclusionary view reinforces the error that PC should only be introduced in the context of refractoriness and end of life.[2,6] As argued by Kavalieratos, "Crisp demarcations between curative and palliative modalities reflect an unnecessary dichotomy that defers focusing on quality of life improvement until disease futility has been established (i.e., hospice)."[6]

The unpredictability of the disease course and prognosis is underscored by experts as one of the explanations for difficulties in introducing PC. Consequently, professionals wait for the worst-case scenario or unequivocal signs of therapeutic failure and near death.[2,6] This argument is easily refuted because the trigger for starting PC is not the prognosis but the symptoms and suffering, regardless of disease stage.[2,4]

By contrast, an increasing number of scientific studies and institutions are associating early PC with standard cardiology therapies, reaping the benefits resulting from the synergism between these two strategies. In addition, combined with heart transplantation and VADs, PC has proved effective in helping patients and families with their suffering, communication, and care planning.[4,7]

The Palliative Care in Heart Failure (PAL-HF) Randomized, Controlled Clinical Trial[9] was a landmark study in the history of PC in cardiology that prospectively compared two groups of patients with HF. In both groups, the patients received the usual cardiological treatment, but in one of the groups, the patients were jointly monitored by the PC team. After 6 months, those who received PC showed improved QoL, depression, anxiety, and well-being, without significant differences in mortality. These findings are unsurprising because PC aims at providing additional care and facilitating the disease process by alleviating difficulties along the way, without anticipating or postponing death.

Integrating PC into cardiology makes sense and can be achieved through different models.[1,3,4] Most CVDs have no cure[5] and are controlled with medications, procedures, and surgeries, but the patient usually has to live with such conditions until death. Inevitably, sooner or later, they present demands met by PC.[6]

Properly managing an underlying disease, whether hemodynamically or by controlling risk factors, improves clinical compensation, thereby minimizing symptoms and enhancing comfort and QoL. Good cardiology practices provide the supported need to enable patients to achieve goals shared by PC.[5] Unquestionably, cardiologists already follow these principles in their essence, providing patients with the first opportunity to access PC.

PC is already welcomed in cardiology. Most surgical and interventional procedures performed in congenital heart diseases are palliative and referred to as such by specialists.[10] Perhaps they intend to use the word as a synonym for "non-curative;" regardless, the meaning is correct because patients can improve their symptoms and QoL through these interventions, the main goal of PC. Case in point, in adults, this rationale applies to valve replacements or coronary revascularizations, which do not cure but achieve palliative goals of improving symptoms and QoL.

However, simply practicing good cardiology is not enough. Patients and families have needs that require taking additional actions, especially regarding aspects often neglected in conventional medicine, such as physical symptoms and psychosocial and spiritual approaches, dimensions inherent to PC.[1,2,4,5,7]

Communication plays a key role in the physician–patient–family relationship and is one of the pillars of PC. However, communication has failed in cardiology. A study published in the *European Journal of Heart Failure*, in 2023, flagged this problem by revealing that 70.4% of patients with HF would like to receive more information about the disease and its consequences; 74.5%, about prognosis; and 76.6%, about treatments.[11]

The study also showed a dissociation between the patients' and the cardiologists' care goals. While 70% of patients expect that HF treatment will enable a life with more quality, independence, and function, as well as with fewer symptoms, for health professionals, such goals are the third treatment priority, behind prolonging life and reducing hospitalizations.

Another study showed a significant disparity between what cardiologists deem appropriate end-of-life care (such as not introducing or suspending treatments) and what is actually practiced

in the last 72 hours of life.[12] The findings highlighted an inadequate ability to predict futile treatments, which can be harmful to patients, and a nonrational consumption of healthcare resources. The authors suggest that the lack of professional training is the cause, especially on ethical, legal, and communication issues.

Cardiologists, in particular, report discomfort when addressing PC and death. Justified by their lack of confidence, education, or personal beliefs, they inevitably end up ignoring patients' needs and delaying necessary communications regarding advance care planning.[2]

Especially in urgent situations, interventions tend to focus on solving immediate problems, often in an "automatic" or "generalized" approach. Reactive, more than planned, without adequate deliberation, these interventions can lead to a dissociation between the patient's real expectations and personal preferences, yielding harmful outcomes.[3,4] The healthcare professional must have a long-term perspective, projecting consequences and anticipating problems, especially in delicate situations, such as those experienced in the terminal stage of the disease.

Aligning the treatment plan with the patient's care goals, based on values, is one of the guiding principles of PC.[3,4] This alignment makes it possible to adapt diagnostic and therapeutic interventions, individualizing technical knowledge to the personal and biographical aspects of each person.[5,11] Especially at the end of life, care must prevent suffering from being merely postponed stubbornly or uselessly, which ultimately leads to the abominable practice of dysthanasia.

Even though PC is an undeniable, universal right of patients, several barriers to PC must be overcome. Increasing access to PC requires educating both healthcare professionals and the lay population.[3,6] At present, cardiology is not yet a specialty eligible as a prerequisite for PC in Brazil, which delays the recognition of this need by the society of specialists.

Inevitably, PC is increasingly found in cardiology practice, becoming essential. PC has never stopped being part of cardiology because PC is the essence of caring, practicing medicine to help others, who are sick and suffering. However, it is now emerging as a powerful, structured, and targeted approach to meet evolving demands and bridging the gaps of "so-called" traditional medicine, strengthening its position as a necessary, integrated, and nonelective strategy. The needs are evident, and the reasons are explained, but cardiology must be involved in PC.

As stated by Hippocrates: "*there are no diseases but sick people*;" the physician's goals should be "*to cure sometimes, to relieve often, and to comfort always*."

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Is ankle taping effective to limit the ankle dorsiflexion in a single-training session? An observational study in semi-professional basketball players

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ABSTRACT

BACKGROUND: Ankle taping (AT) is effective in preventing ankle sprain injuries in most common sports and is employed in rehabilitation and prevention sports.

OBJECTIVE: This study aimed to investigate the effectiveness of AT to restricting excessive frontal plane ankle movements in semi-professional basketball players throughout the training session.

DESIGN AND SETTING: A cross-sectional study was performed at the Universidad Europea de Madrid.

METHODS: Forty male and female semi-professional basketball players were divided into two groups. The ankle dorsiflexion range of motion (ROM) and interlimb asymmetries in a weight-bearing lunge position were evaluated at four time points: 1) with no tape, 2) before practice, at 30 min of practice, and 3) immediately after practice.

RESULTS: In male basketball players, no differences were observed in the right and left ankles between the baseline and 30 min and between baseline and 90 min of assessment. In female athletes, significant differences were reported between baseline and pre-training assessments for the right ankle and also significant differences between baseline and 90 min in both ankles.

CONCLUSIONS: Ankle taping effectively decreased the ankle dorsiflexion ROM in male and female basketball players immediately after application. However, ROM restriction was very low after 30 and 90 min, as assessed in a single basketball practice. Therefore, the classic taping method should be revised to develop new prophylactic approaches, such as the implementation of semi-rigid bracing techniques or the addition of active stripes during training or game pauses.

INTRODUCTION

It is known that ankle taping (AT) is effective in preventing ankle sprain injuries in the most common sports (e.g., basketball and soccer). Current research suggests that prophylactic approaches, such as taping or bracing, are effective in protecting the ligaments and soft tissues in maximal stress situations.[1] AT is employed in the rehabilitation and prevention context, both in sports and non-sports populations. However, players who practice jumping and repeated landings commonly use AT as a prophylactic method to restrict the ankle range of motion (ROM).[2] Additionally, it is associated with competition or training moments with the aim of reducing the incidence of ankle sprains. Several factors were described in individuals who use AT approaches, for example, Karlsson and Adreasson described a decrease of the peroneus muscle contraction time evaluated with electromyography.[3] The effectiveness of AT to decrease the average inversion velocity, maximum inversion velocity, and time to maximum inversion velocity have been analyzed; however, no differences were observed between individuals with and without pre-wrap pads.[4] Regarding the effect of AT in rugby players, taping of the ankle joint was effective in decreasing the inversion ROM.[5] Moreover, Callaghan et al. showed a limited ankle eversion-inversion ROM in individuals with AT in the non-weight bearing position.[6] A systematic review developed by Kerkhoffs et al.[7] supports the fact that the AT and elastic bandage were considered effective to reduce the ankle dorsiflexion ROM. Similarly, Kemler et al.[8] carried out a systematic review showing the benefits of elastic bandages and AT in individuals with ankle sprain episodes. Taping applications have been widely extended, and several athletes learn the taping technique. For example, Smyth et al. assessed AT with and without

self-application and reported the benefits on the proprioception aspect.[9] However, several authors reported non-desired effects on the lower limb biomechanics and sports tasks. In this context, McCaw et al. and Riemann et al. reported a decrease in the jump performance time to reach forces in the landing phase.[10,11] Skin disturbances, such as erythema or irritation have also been reported in subjects who have to perform AT repeatedly.[7]

Currently, the ankle sprain has been reported as the most common injury in sports.[12] This condition shows an incidence ratio of 3.85 per 1,000 participants in basketball players, with the landing phase being the main cause of injury.[13] Therefore, biomedical staff have focused on over-plantar flexion biomechanics that occur during running or landing considering the ankle joint position as one of the main injuries in basketball players.[14]

Current research reported that AT is effective in preventing and reducing the incidence and severity of ankle sprains in basketball players during practice or games. Romero et al.[15] in previous research showed that AT was effective in basketball players at the beginning of practice; however, at the end of practice, the taping effect for ROM restriction was very low. Thus, the aim of the present study was to investigate the effectiveness of AT for ankle joint ROM restriction in semi-professional basketball players throughout a training session. Thus, we assessed the ankle dorsiflexion ROM in a weight-bearing lunge position at four time-points: 1) with no tape, 2) before practice, at 30-min after practice, and 3) immediately after practice. Based on previous research and our clinical experience, we hypothesized that taping had lost the initial effectiveness for restricting the ankle ROM in the first 30 min of the training session, substantially decreasing the joint restriction, which was the second part of the session in which there was a high injury risk for basketball players.

OBJECTIVE

The aim of the present study was to investigate the effectiveness of AT in restricting excessive frontal plane ankle movements in semi-professional basketball players throughout the training session.

METHODS

A cross-sectional observational study was conducted in January 2022 following the Strengthening the Reporting of Observational Studies in Epidemiology (STROBE) guidelines.[16]

Ethical statement

This study was approved by the Research and Ethics Committee of the Universidad Europea de Madrid (CIPI/19/157; December 10, 2021). Before participating in the study, the players were fully informed about the protocol, and written informed consent was obtained from their parents. The Declaration of Helsinki was adhered to throughout this study.

Participants

A total sample of 40 semi-professional basketball players were enrolled in the present study and divided into two groups: group A composed by 20 male basketball players (20.00±6.00 years) and group B composed by 20 female basketball players. (24.00±3.50 years). Both ankle joints of all players were taped, usually as prescribed by a specialized medical doctor. The players recruited for the study belonged to male and female basketball teams that played in the third Spanish basketball division. Semi-professional individuals followed a training schedule of 2 h per day, 4 days per week, and played one to two matches in a week.[17] The subjects were excluded if they underwent a physical therapy treatment program, suffered any musculoskeletal condition in the last six weeks, had skin allergies, and any history of lower limb surgery, did not complete all the training sessions, or had other foot orthoses.[15]

Taping procedure

All taping procedures were developed by the same therapist with two years of experience in sports taping methods[18] according to the Sport Medicine protocols.[19] Before the taping procedure, both ankles were covered by a pre-wrap in order to avoid skin disturbances for repetitive daily use.[20] Following the procedure described by Williams et al., two strips were applied around the leg, 10 cm above the tibialis malleoli with a 38-mm self-adhesive tape with the foot placed in a neutral position.[18] Subsequently, two strips were placed from the medial to the lateral side of the ankle. Finally, the classic "figure sixes" for the subtalar joint were initially placed onto the medial anchor through the plantar surface of the foot to attach back onto the medial anchor. To complete the AT procedure, all free endings and spaces were not covered with tape. All procedures were performed with a classic rigid tape, employed in all Spanish basketball male and female divisions as a prophylactic method for ankle injury prevention.

Basketball training sessions

All training sessions comprised a 90 min technical session and were structured into three stages: warm-up (15 min), tactical skills (15 min), and game situations (60 min).

Outcome measurements

All ankle ROM assessments were performed using the Dorsiflex application (v.2.0; Balsalobre-Fernández, 2017, Madrid, Spain) installed on an iPhone 8 (iOS 12.1; Apple Inc., Cupertino, California, United States). The Dorsiflex application is considered a reliable and valid mobile app for the assessment of the ankle ROM and asymmetries between legs in the weight-bearing position.[21] To check the ankle ROM, the iPhone was located at the tibial anterior tuberosity to evaluate the ankle between the tibia

and the ground in the weight-bearing position. This procedure was developed for each subject for both legs, and the Dorsiflex application also reported an asymmetry index between the legs. The assessments were performed in four periods: 1) baseline, before the practice without bandaging; 2) pre-training, immediately after the baseline measurement; 3) at 30 min of practice; and (4) immediately after the end of the training session.

Statistics

SPSS v.23 (IBM SPSS Statistics for MacOS, New York, NY, USA) was used for the statistical analysis. First, the Shapiro–Wilk test was used to check the normality assumption. For each group, a one-way analysis of variance (ANOVA) and Bonferroni's correction were employed to assess the significant differences between the four time points (baseline, pre-training, 30 min of training, and post-training) and check for multiple comparisons. In addition, the effect size was calculated using a partial Eta^2 coefficient.

To evaluate the differences between groups, the Student's *t*-test and Mann–Whitney U test were used for parametric and non-parametric data for the sociodemographic groups, respectively. To evaluate the effects of time and time versus group on the dependent variables, a two-way ANOVA analysis was performed for repeated measures. The Greenhouse–Geisser correction was also applied when the Mauchly test rejected sphericity. In addition, a Bonferroni post–hoc analysis was used for multiple comparisons, and the effect size was calculated using the Eta^2 coefficient. Thorough the study, the level of significance was set at $P < 0.05$, with an β error of 0.05, 95% confidence interval [CI]), and the desired power of 80% (β error of 0.2).

RESULTS

Considering **Table 1** and as expected, due to sex characteristics, height and weight differences were reported between the groups (**Table 1**). In male basketball players, significant differences were observed in the asymmetry variable ($f = 5.510$; $P = 0.002$ [0.186]), and no differences were observed between the right and left ankles. In the female group, significant differences were reported for the right [$f = 6.925$; $P = 0.001$] and left ankles [$f = 5.373$, $P = 0.002$] (**Table 2**). Post-hoc Bonferroni analyses showed significant differences between the baseline and pre-training assessments for male players and between baseline and 30-min assessments. In addition, for the female group, Bonferroni corrections showed significant differences for the right ankle between pre-training and post-training and between baseline and pre-training evaluations. The left ankle showed significant differences between pre-training and post-training assessments (**Figure 2**).

A statistical analysis evaluating the comparison of ankle taping between male and female basketball players did not report significant differences in the time and interaction (time vs. group) for any variable. Bonferroni corrections for the interaction between groups reported differences in the right ankle at baseline, pre-training, pre-training-30-minute training, and pre-training-post-training. For the left ankle, post-training, pre-training 30-minute training, and pre-training-post-training. The asymmetric variable showed significant differences between the baseline and the rest of the variables (**Table 3**).

Table 1. Sociodemographic data of the sample

Data	Men (n = 20)	Women (n = 20)	Total sample (n = 40)	P value
Age, years	20.00 ± 6.00†	24.00 ± 3.50*	24.00 ± 6.00†	0.127††
Height, m	1.87 ± 0.10†	1.72 ± 0.08†	1.80 ± 0.17†	0.001††
Weight, kg	82.00 ± 6.75†	71.25 ± 9.64*	77.00 ± 15.00*	0.001**
BMI (kg/m²)	22.61 ± 1.63*	21.93 ± 2.53*	23.80 ± 2.11†	0.569††

*Mean ± standard deviation was applied; **The Student T-test was performed for independent samples; †Median ± interquartile range was used; ††The Mann–Whitney U test was performed.

DISCUSSION

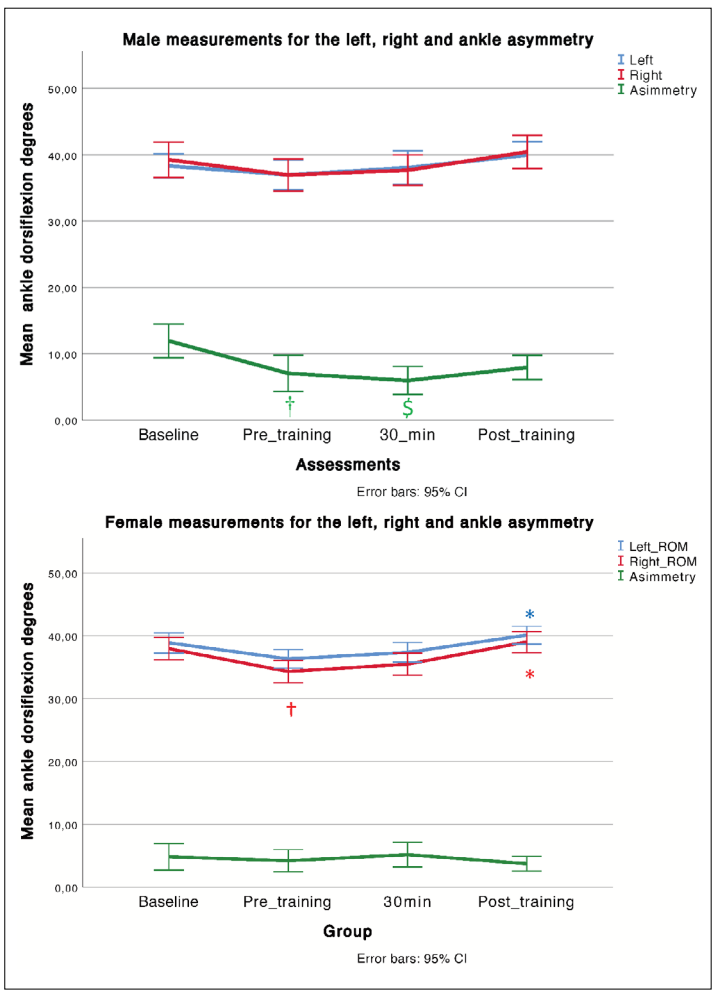
The present study compared the ankle taping procedure on ankle mobility in four practice moments in which it seeks to achieve an ankle ROM limitation in order to prevent ankle and foot injuries (or re-injuries) in basketball players.[2] The main findings of the present study suggest that during the first 30 min of practice, ankle taping did not present differences with the baseline in both male and female basketball players. Thus, based on these results, it might be understood that in a typical practice session of 90 min or even in a basketball game of duration of over 120 min, the taping effectiveness represents approximately 25% of the time making this function and is effective in limiting the ankle joint movement. In addition, pro- and semi-professional basketball teams spent approximately 30 to 45 min of warm-up time based on stretching and neuromuscular performance exercises.[22] These routines were composed of several exercises that involve the ankle joint, such as jumps, calf stretching, or ankle mobility exercises.[23] Therefore, based on the findings of the present study, the authors suggest that even before the start of a basketball game, ankle taping may decrease the effectiveness of ankle ROM restriction.

Regarding a complete training session or full game, prior research showed that ankle taping decreased the ankle dorsiflexion ROM in U18 basketball players; however, at the end of the training session, the ankle ROM limitation was very low, with the last 30 min of a session or a game being the moment of highest injury (or re-injury) risk in a basketball player.[15] At the same line, the findings of this study report no differences between the

Table 2. One-way analysis of variance for the ankle range of motion and asymmetry variables

Group	Baseline	Pre-training	30-min training	Post-training	Time f; P (Eta²)
Male					
Right ankle	39.27 ± 5.49	36.96 ± 5.07	37.68 ± 4.77	40.45 ± 5.16	f = 1.779; P = 0.159 (0.006)
Left ankle	38.33 ± 3.75	36.98 ± 4.07	38.08 ± 5.22	39.95 ± 4.20	f = 1.406; P = 0.248 (0.005)
Asymmetry	11.96 ± 5.30	7.06 ± 5.69	5.98 ± 4.37	7.95 ± 3.74	f = 5.510; P = 0.002 (0.186)
Female					
Right ankle	37.95 ± 3.78	34.30 ± 3.15	35.48 ± 3.66	39.02 ± 3.68	f = 6.925; P = 0.001 (0214)
Left ankle	38.87 ± 3.43	36.32 ± 3.15	37.02 ± 5.71	40.10 ± 3.11	f = 5.373; P = 0.002 (0.174)
Asymmetry	4.84 ± 4.47	4.20 ± 5.10	5.17 ± 4.50	5.20 ± 5.68	f = 0.585; P = 0.627 (0.002)

Values are mean ± standard deviation unless otherwise indicated.



Figures 1 and 2. * Significant differences between pre-training and post-training assessments; †, significant differences between the baseline and pre-training assessments; $ significant differences between the baseline and 30-min.

Table 3. Two-way analysis of variance (ANOVA) and Bonferroni correction values for the intra-subject effects of the total sample

	Two-way ANOVA values	Time versus Group
	Time f; P (Eta²)	f; P (Eta²)
Right ankle	f = 56.809; P = 0.001 (0.606)	f = 1.925; P = 0.130 (0.049)
Left ankle	f = 28.318; P = 0.001 (0.434)	f = 1.196; P = 0.315 (0.031)
Asymmetry	f = 8.633; P = 0.001 (0.189)	f = 7.899; P = 0.002 (0.176)

Bonferroni correction values			
Measure	**Right ankle P value**	**Left ankle P value**	**Asymmetry P value**
Baseline			
Pre-training	0.001	0.001	0.014
30-minute training	0.001	0.467	0.005
Post-training	0.009	0.001	0.001
Pre-training			
30-minute training	0.001	0.001	1.000
Post-training	0.001	0.001	1.000

baseline and the end of the training session. In fact, a slight increase in ankle dorsiflexion ROM was observed. These results could be explained by the decrease in ankle taping added to repeatedly performing high-intensity actions, such as jumps, sprinting, change of direction, or landings, which force the ankle joint to maximum dorsiflexion ranges throughout the training session.[24] Domínguez-Díez et al.[25] reported that these actions require the implementation of intense accelerations and decelerations, with high impact force peaks, which are directly related to joint overload, increasing the injury risk. Consequently, proper prophylactic approaches are necessary to protect the health and development of players. Several authors have researched other ankle joint restriction approaches as alternatives to rigid tapes, such as semi-rigid bracing methods. For example, Gross et al.[26] reported that semi-rigid ankle braces are warranted to reduce initial and recurrent ankle sprain injuries in athletes without affecting their functional parameters. Janssen et al. evaluated the effectiveness of combined bracing and neuromuscular training with respect to an isolated bracing approach on the recurrence of ankle sprain injuries in 384 athletes. They reported that the bracing approach was superior to the neuromuscular training in reducing the incidence, but not for the severity of self-reported ankle injury risk.[27] Authors of the present study

argued that these semi-rigid bracing techniques might be more effective throughout time (e.g. a single training session or a game) that a classic taping on the ankle ROM restriction due to the plastic and semi-rigid materials could not be deformed. Regarding the adverse effects on performance, several authors have observed that the type of ankle stabilizer can influence lower limb kinematics, ground reaction forces, and muscular activity contraction. For example, Theodorakos et al.[28] showed that a semi-rigid ankle brace altered the ankle kinematics owing to the ankle joint ROM restriction. Considering the ground reaction forces, Cordova et al.[20] showed that external ankle support reduces ankle and knee joint displacement, which influences the space-time features of the ground reaction forces during drop landings.

Regarding the ankle ROM asymmetry, the results of the present study reported asymmetric differences when taping was performed. Moreno-Pérez et al.[29] showed an increased ankle dorsiflexion ROM after a soccer match for the dominant ankle; however, a decrease at 48 h post-match in both ankles was observed. Moreover, similar values were reported with an increase in the ankle dorsiflexion ROM post-match with respect to the pre-match and a decrease 48 h post-game in both ankles in semi-professional basketball players.[30] The asymmetry differences in response to the ankle taping procedure could be explained by the restriction of the muscular and ligament structures that surround the ankle joint and by proprioception mechanisms.[31]

Another important aspect to consider was the human resources and taping-time costs, not just for a single practice or game, but during a complete basketball season. A classic taping procedure takes over 3 to 5 min per ankle joint and is approximately three times more expensive than bracing.[32] However, a semi-rigid bracing ankle approach could be self-dressed barely in 1–2 min without any need for a physiotherapist. Therefore, all these aspects should be considered when planning basketball sessions for medical staff.

A full assessment of ankle and foot structures and features is considered essential for complete athlete exploration, such as the degree of ankle stiffness or structural conditions, such as functional hallux limitus.[33,34]

Clinical applications

Based on the current literature and findings of the present study, the classic ankle taping method may be useful for decreasing the ankle dorsiflexion ROM in both male and female basketball players to prevent ankle injury. However, the duration of the efficacy was still questioned due to the present results, which did not show differences between the baseline with no taping and at 30 min evaluation and the end of the practice. Therefore, the "dynamic effectiveness" of the classic taping method should be revised to develop new prophylactic approaches, taking into account the ankle ROM restriction effectiveness, human resources, and the time required to develop full ankle taping. For example, the implementation of semi-rigid bracing techniques or the addition of active stripes in the training or game pauses, being the first option the most appropriate assumed strategy.

Limitations and future studies

This study has a few limitations. First, only one training session was conducted for each group. Second, the height and weight variables were significantly different between the groups.

Additional research is needed to assess the newly available brace approaches and their influence on ankle sprain injury prevention and functional performance. In addition, future studies should compare the effectiveness of classic ankle taping and semi-rigid bracing on ankle sprain injury rates and whether it affects the biomechanics of players. Several authors support ankle bracing as an ankle sprain injury prevention method owing to the restriction of sagittal plane movements. However, future studies are needed to assess whether these prophylactic approaches may have negative effects on the ankle and knee joints. Future research should explore other biomechanical and psychological features, such as asymmetrical values with the idiomatic side or psychological effects of the ankle taping procedure.

CONCLUSIONS

Ankle taping effectively decreased the ankle dorsiflexion ROM immediately after application in both male and female basketball players. However, ROM restriction was very low after 30 and 90 min, as assessed in a single basketball practice. Therefore, the classic taping method should be revised to develop new prophylactic approaches, such as the implementation of semi-rigid bracing techniques or the addition of active stripes during training or game pauses.

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Correlation analysis of cardiopulmonary exercise test indices and conditions of overweight patients with obstructive sleep apnea: a retrospective study

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KEY WORDS (MeSH terms):
Sleep apnea, obstructive.
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AUTHORS' KEY WORDS:
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Condition.

ABSTRACT

BACKGROUND: The cardiopulmonary function of patients with obstructive sleep apnea (OSA) is significantly lower than that of patients with simple snoring and is significantly related to the severity of OSA. Currently, only a few studies have been conducted on cardiopulmonary exercise testing in overweight patients with OSA.

OBJECTIVE: To analyze the correlation between cardiopulmonary exercise test (CPET) indices and the condition of overweight patients with OSA.

DESIGN AND SETTING: Retrospective study in Guangdong Provincial Hospital of Chinese Medicine.

METHODS: This study included 73 hospitalized overweight patients. The patients were divided into no, mild, moderate, and severe OSA groups. Differences in the CPET indices among the four groups were compared. The correlation between the CPET indices and conditions was analyzed.

RESULTS: No, mild, moderate, and severe OSA groups had 18 men and 5 women, 11 men and 3 women, 12 men and 2 women, and 21 men and 1 woman, respectively ($P > 0.05$). No significant difference was observed in resting pulmonary function among the four groups ($P > 0.05$). In the CPET, the anaerobic threshold, maximum oxygen uptake, and oxygen pulse were significantly lower in the severe OSA group than those in the normal OSA group ($P < 0.05$). Moreover, CPET indices negatively correlated with the apnea-hypopnea index.

CONCLUSION: Changes in CPET indices occurred earlier than changes in resting pulmonary function in patients with OSA. CPET might be a potential method for evaluating the severity of OSA combined with overweight status.

INTRODUCTION

Obstructive sleep apnea (OSA) is sleep-disordered breathing involving respiratory, cardiovascular, neurological, digestive, endocrine, and other systemic systems.[1] It refers to the repeated complete or partial obstruction of the upper airway during sleep, which causes frequent apnea or reduced ventilation, leading to intermittent hypoxemia, hypercapnia, and sleep structure disorders.[2] The main clinical manifestations of OSA are snoring with apnea and daytime sleepiness, which can cause damage to multiple organ functions.[3] Epidemiological surveys show that the prevalence in the middle-aged population and men is 2% and 4%, respectively.[4] The prevalence of OSA increases with age.[5]

It is reported that the prevalence of OSA in patients with body mass index (BMI) exceeding 30 kg/m^2 and metabolic syndrome is 40% and 60%, respectively.[6,7] All of the basic research, epidemiological, and clinical data show that obesity is one of the most important risk factors for OSA, and the incidence rate of OSA is strongly correlated with overweight.[8] OSA is an independent risk factor for metabolic syndrome, which can be complicated by diabetes, obesity, hyperlipidemia, and other diseases.[9] Previous studies have confirmed that the cardiopulmonary function of patients with OSA is significantly lower than that of patients with simple snoring and is significantly related to the severity of OSA.[10] However, there are few studies on cardiopulmonary exercise tests (CPETs) of patients with overweight or obesity combined with OSA.

OBJECTIVE

This study aimed to explore the correlation between CPET indices and the condition of overweight patients with OSA.

METHODS

Subjects

This retrospective study was approved by the Ethics Committee of Guangdong Provincial Hospital of Chinese Medicine (Data: December 20, 2019; Approval number: BF2019-216-01) All the participants provided written informed consent. From January 1, 2018, to December 31, 2019, 73 overweight patients hospitalized at the Guangdong Provincial Hospital of Chinese Medicine were included. The inclusion criteria were as follows: (1) patients met the diagnostic criteria of the guidelines for the diagnosis and treatment of OSA hypopnea syndrome (Basic Edition);[11] (2) patients who were older than 18 years; (3) patients with BMI ≥ 24 kg/m^2; (4) patients who underwent CPET to establish exercise-training protocols. The exclusion criteria were as follows: (1) patients who had chronic obstructive pulmonary disease or bronchial asthma; (2) patients who had malignant tumors; (3) patients who had immune system and acute and chronic infectious diseases; (4) patients with hypertension, diabetes, hyperlipidemia, and other basic diseases; (5) patients with severe upper respiratory tract obstruction; (6) patients accompanied by other diseases affecting cardiopulmonary function; and (7) patients who received regular treatment for OSA (such as continuous positive airway pressure [CPAP]).

Diagnostic criteria

The diagnostic criteria for overweight were as per the health industry standard of the People's Republic of China – Determination of adult weight formulated in 2013, 18.5 ≤ BMI < 24 kg/m^2, normal; 24 ≤ BMI < 28 kg/m^2, overweight; and BMI ≥ 28 kg/m^2, obese.[12] The diagnostic criteria of OSA were in accordance with the guidelines for the diagnosis and treatment of OSA hypopnea syndrome (basic level version),[11] mainly based on the medical history, signs, and polysomnography (PSG) results. OSA can be diagnosed if there are typical symptoms, such as night sleep snoring with apnea, Epworth Sleepiness Scale (ESS) score ≥ 9, stenosis and obstruction of any part of the upper airway, and apnea-hypopnea index (AHI) ≥ 5 times/h. For those whose daytime sleepiness is not obvious (ESS score < 9), OSA can be diagnosed if there is an AHI of > 5 times/h, cognitive impairment, hypertension, coronary heart disease, cerebrovascular disease, diabetes, or insomnia. According to the AHI, the severity classification is divided into mild (5 ≤ AHI < 15 times/h), moderate (15 ≤ AHI < 30 times/h), and severe (AHI ≥ 30 times/h).

Grouping and general data collection

Based on the AHI, patients were divided into no (n = 23), mild (n = 14), moderate (n = 14), and severe (n = 22) OSA groups. The sex, age, height, and weight of patients were also recorded. The ESS was used to assess excessive daytime sleepiness.

Sleep breathing monitoring

On the day of the examination, patients were forbidden from drinking coffee or strong tea. On the night of the examination, patients were forbidden from consuming sedatives and sleeping AIDS. An Anbolan M2 sleep-breathing monitor (Anbolan (Beijing) Medical Equipment Co. Ltd., Beijing, China) was used to detect breathing. Oronasal airflow, chest and abdominal movements, finger oxygen saturation, snoring, and pulse rate were recorded. During the monitoring period, the signal was kept in good condition, and the monitoring time throughout the night shall be ≥ 7 h. A report was generated after a review by a sleep-monitoring technician and a sleep professional physician. Detection indicators included the apnea-hypopnea index (AHI, times/h), minimum blood oxygen saturation (%), average blood oxygen saturation (%), percentage of sleep time with blood oxygen saturation < 90% of the total sleep time (TS90%), and oxygen reduction index (times/h).

Cardiopulmonary exercise test

First, resting pulmonary function was tested. The percentage of forced expiratory volume in the predicted value in the first second (FEV1%), percentage of forced expiratory volume in the predicted value (FVC%), one-second rate ((FEV1/FVC) %), percentage of maximum mid-expiratory flow in the predicted value, and percentage of maximum ventilation in the predicted value in a minute (MVV%) were recorded. The determination was repeated three times, the error value between the two replicates was less than 5%, and the highest value was used for analysis.

After resting for 10 min, a CPET was performed with an increasing exercise load plan. The exercise started with zero load, and the load was gradually increased after 3 min. The power load plan increased by 10-25 W/min. The speed of the bicycle was 60 rpm, and the pedaling time was controlled within 8-12 min. The power load was stopped when there was significant fatigue, shortness of breath, leg fatigue or discomfort, inability to maintain a stable speed, or significant changes in the electrocardiogram. In addition, 0 W power was used to relax for 5 min (i.e., the recovery period), and the exercise test was ended.

Endpoint

Various parameters were recorded, including the anaerobic threshold (AT, L/min), the percentage of anaerobic threshold in the predicted value (AT/Ref, %), the percentage of maximum oxygen uptake in the predicted value (O_2 max/PRED, %), respiratory exchange rate (RER), oxygen pulse (O_2 pulse, ml/beat), the percentage of oxygen pulse in the predicted value (O_2 pulse), maximum respiratory times (f-ergo max, times/min), respiratory reserve (BR, %), and carbon dioxide ventilation equivalent ($EQCO_2$).

Statistical analysis

SPSS software (version 25.0; International Business Machines Corp., Armonk, New York, United States) was used for the statistical analysis. If the measurement data met the normal distribution, the means ± standard deviation was used for the description; if the measurement data did not meet the normal distribution, the median (interquartile range) was used for the description. Count data are presented as percentages (%). When the quantitative data met the normal distribution and homogeneity of variance criteria, a one-way analysis of variance was used for multigroup comparisons, and the Student-Newman-Keuls (SNK) test was used for pairwise comparisons. When the quantitative data did not meet the normal distribution or homogeneity of variance criteria, the rank sum test was used for multigroup comparisons and the SNK test was used for pairwise comparisons. The chi-square test was used to compare multiple groups of count data. The Pearson product-moment correlation was used to analyze the correlation between exercise cardiopulmonary function and AHI in patients with OSA. $P < 0.05$ indicated that the difference was statistically significant.

RESULTS

Comparison of general information

The no, mild, moderate, and severe OSA groups comprised 18 men and 5 women, 11 men and 3 women, 12 men and 2 women, and 21 men and 1 woman, respectively ($P > 0.05$). The age in the no, mild, moderate, and severe OSA groups were 50.00 ± 11.236, 51.00 ± 8.218, 54.00 ± 12.134, and 47.64 ± 6.268, respectively ($P > 0.05$). No significant differences were observed in the proportion of men and women, age, BMI, or other general characteristics among the four groups ($P > 0.05$, **Table 1**).

Comparison of sleep monitoring and pulmonary functions

Sleep monitoring showed that the ESS, oxygen reduction index, minimum oxygen saturation, average oxygen saturation, TS90%, and MVV were significantly different among the four groups ($P < 0.001$ or $P < 0.05$). Moreover, significant differences were observed in the minimum oxygen saturation, mean oxygen saturation, and TS90% between the severe OSA group and the other three groups ($P < 0.05$). Similarly, significant differences were noticed in the minimum and average oxygen saturations between the moderate and no OSA groups ($P < 0.05$, **Table 2**).

Comparison of exercise cardiopulmonary test indexes

Differences were observed in O_2max/PRED%, AT/Ref%, and O_2pulse% among the four groups ($P < 0.05$). Specifically, O_2max/PRED%, AT/Ref%, and O_2pulse% were significantly different between the overweight and severe OSA groups ($P < 0.05$). However, no marked differences were noticed in O_2max/PRED%, AT/Ref%, or O_2pulse% between the other two groups ($P > 0.05$; **Table 3**).

Correlation analysis between AHI and exercise cardiopulmonary test indexes

The severity of OSA is generally expressed by the AHI. Pearson correlation analysis showed that OSA severity was negatively correlated with AT, AT/Ref%, O_2max/PRED, and O_2 pulse ($P < 0.05$). However, OSA severity of OSA was not correlated with RER or $EQCO_2$ ($P > 0.05$, **Table 4**).

DISCUSSION

In the present study, we revealed that changes in CPET indices occurred earlier than changes in resting pulmonary function in patients with OSA. CPET might be a potential method for evaluating the severity of OSA combined with overweight status.

OSA is a chronic disease with multiple system damage.[13] The clinical manifestations of mild or early OSA are often hidden.[14] When it develops from moderate to severe, it causes irreversible damage to the body, thus losing the best opportunity for treatment.[15,16] Therefore, it is of positive clinical significance to accurately assess the severity of patients with OSA. PSG or sleep outside center monitoring (OCST) is the gold standard for the diagnosis of OSA.[17,18] The AHI measured using PSG or OCST is the most important indicator for evaluating the degree of obstruction. However, studies have found that AHI does not truly reflect the severity of the condition.[19] For example, for patients with mild to moderate OSA, even if the AHI level is the same, the severity of hypoxemia and arousal can be quite different.[20] Moreover, the

Table 1. Comparison of general information for groups

Groups	Cases	Gender		Age (years old)	BMI
		Male	Female		
no OSA group	23	18	5	50.00 ± 11.24	27.70 ± 2.43
Mild OSA group	14	11	3	51.00 ± 8.22	26.85 ± 2.88
Moderate OSA group	14	12	2	54.00 ± 12.13	27.30 ± 4.51
Severe OSA group	22	21	1	47.64 ± 6.27	28.55 ± 4.43
χ^2 or F			$\chi^2 = 3.152$	$F = 1.278$	$\chi^2 = 4.122$
P		0.369		0.289	0.249

OSA = obstructive sleep apnea; BMI = body mass index.

results of a 2008 study on the cardiovascular endpoint events of sleep apnea (Sleep Apnea Cardiovascular Endpoints study) showed that for patients with OSA and cardiovascular disease, after CPAP treatment, although the AHI index of the patients can be reduced and hypoxia can be improved, it does not affect the cardiovascular risk.[21] It is suggested that a single AHI cannot be used as a predictor of cardiovascular events in patients with OSA.

The CPET mainly relies on exercise stress and comprehensively detects changes in oxygen uptake and carbon dioxide emissions in the heart and lungs under different loads and electrocardiograms. CPET helps to reflect the degree of exercise restriction.[22] The potential of cardiopulmonary function can be evaluated by CPET.[23] Moreover, it can formulate individualized intensity exercise programs to meet the needs of patients with different needs for disease rehabilitation.[24] As a noninvasive, safe, and simple detection method,[25] CPET has not been popularized in China, and the evaluation value of various indicators for OSA has not been fully agreed upon.

Although some studies have shown that AHI, the most important index reflecting disease severity, may not necessarily correlate with the degree of nocturnal hypoxia and the lethargy scale score.[26] In this study, according to the comparison of symptoms, hypoxia, and other indicators among the four groups, symptoms and hypoxia were more serious with an increase in AHI.

Table 4. Correlation analysis between AHI and exercise cardiopulmonary test indexes.

Items	AHI	
	Correlation coefficient (r)	P values
AT, l/min	-0.273	0.019*
O_2max/PRED%	-0.251	0.032*
AT/Ref%	-0.295	0.011*
RER	-0.015	0.899
O_2 pulse ml/beat	-0.119	0.318
O_2 pulse%	-0.301	0.01*
$EQCO_2$	-0.171	0.148

*P < 0.05.
AHI = apnea-hypopnea index; AT = anaerobic threshold; RER = respiratory exchange rate; 0_2 = oxygen; BR% = respiratory reserve; $EQCO_2$ = carbon dioxide ventilation equivalent.

Table 2. Comparison of polysomnography and pulmonary functions

Items	no OSA group	Mild OSA group	Moderate OSA group	Severe OSA group	χ^2 or F	P values
ESS	1.0 (0.00, 2.00)	5.5 (3.00, 7.25)	9.0 (6.75, 11.25)	11.0 (9.00, 16.00)	53.642	< 0.001*
ORI (times/h)	2.90 (1.10, 4.10)	10.60 (6.65, 15.45)	25.35 (20.85, 28)	44.15 (35.33, 68.3)	63.721	< 0.001*
MOS (%)	89.0 (85.00, 90.00)	86.0 (79.00, 87.25)	80.0 (78.50, 84.00)[d]	69.5 (61.25, 76.00)[abc]	46.577	< 0.001*
AOS (%)	95.40 (94.20, 96.40)	94.70 (93.78, 95.80)	93.50 (92.98, 95.03)[d]	91.25 (88.78, 93.43)[abc]	34.949	< 0.001*
TS90 (%)	0.05 (0.00, 0.20)	0.75 (0.18, 2.15)	4.10 (2.25, 8.45)	23.75 (11.13, 47.40)[abc]	54.958	< 0.001*
FEV1 (%)	84.70 ± 16.85	80.43 ± 18.79	91.14 ± 14.49	81.27 ± 12.72	1.446	0.237
FEV1/FVC (%)	83.87 ± 9.27	85.07 ± 9.45	85.21 ± 7.43	84.77 ± 8.22	0.094	0.963
FVC (%)	89.0 (70.00, 94.00)	82.5 (62.50, 92.25)	85.5 (78.25, 94.00)	81.0 (71.00, 91.00)	1.965	0.580
MMEF (%)	84.39 ± 26.03	76.29 ± 24.34	85.93 ± 23.71	79.14 ± 22.90	0.545	0.653
MVV (%)	106.57 ± 18.61	94.86 ± 26.90	109.21 ± 22.53	90.41 ± 20.50	3.242	0.027**

*P < 0.05; [a]P < 0.05, compared with no OSA group; [b]P < 0.05, compared with mild OSA group; [c]P < 0.05, compared with moderate OSA group; [d]P < 0.05, compared with no OSA group; **P < 0.05, there was no significant difference between the four groups by Student–Newman–Keuls method.
OSA = obstructive sleep apnea; ESS = Epworth Sleepiness Scale; ORI = oxygen reduction index; MOS = minimum oxygen saturation; AOS = average oxygen saturation (%); TS90 = < 90% in total sleep time; FEV1 = forced expiratory volume in the predicted value in the first second; FVC = forced expiratory volume in the predicted value; MMEF = maximum mid expiratory flow; MVV = maximum ventilation in the predicted value in a minute.

Table 3. Comparison of cardiopulmonary exercise test indexes

Items	no OSA group	Mild OSA group	Moderate OSA group	Severe OSA group	χ^2 or F	P values
AT, l/min	16.10 (11.60, 20.70)	12.10 (9.88, 16.83)	13.15 (10.90, 19.30)	12.25 (10.15, 14.15)	7.655	0.054
O_2max/pred%	88.65 ± 13.52	75.57 ± 17.32	78.14 ± 15.63	72.41 ± 21.06[a]	3.685	0.016*
AT/Ref%	60.70 ± 316.43	47.21 ± 16.58	51.71 ± 18.41	44.13 ± 10.38[a]	4.823	0.004*
RER	1.24 ± 0.19	1.18 ± 0.15	1.17 ± 0.16	1.20 ± 0.11	0.848	0.472
O_2 pulse ml/beat	10.80 (8.40, 13.70)	9.05 (8.08, 9.95)	9.95 (7.40, 12.70)	9.10 (7.75, 10.83)	3.754	0.289
O_2 pulse%	80.95 ± 12.69	75.14 ± 17.25	74.07 ± 15.81	66.77 ± 18.92[a]	2.879	0.042*
F-ergo (max time/min)	34.95 ± 6.98	32.14 ± 4.85	31.35 ± 5.72	31.81 ± 5.49	1.541	0.211
BR%	47.56 ± 12.68	55.00 ± 13.92	58.93 ± 11.85	49.54 ± 14.41	2.589	0.060
$EQCO_2$	26 (23.00, 27.00)	25 (23.00, 27.25)	25 (23.50, 26.00)	25 (22.00, 26.25)	1.240	0.743

*P < 0.05; [a]P < 0.05, compared with no OSA group.
OSA = obstructive sleep apnea; AT = anaerobic threshold; RER = respiratory exchange rate; 0_2 = oxygen; BR% = respiratory reserve; $EQCO_2$ = carbon dioxide ventilation equivalent.

For example, there were significant differences in the oxygen reduction index and ESS scores between the groups. There were marked differences in the minimum oxygen saturation, average oxygen saturation, and TS90% between the severe OSA group and the other three groups. These results showed that AHI had a good correlation with the sleepiness scale score and hypoxemia, which may be related to the fact that the patients were overweight. This suggests that in overweight and OSA patients, the symptoms and degree of hypoxia become increasingly serious with the progression of the disease.[27] There was no significant difference in resting static pulmonary function among the four groups, indicating that resting static pulmonary function has limitations in evaluating OSA severity. There were significant differences in MVV among the four groups, but there was no significant difference among the four groups using the SNK method, which is consistent with previous literature reports.[28] The contradiction may be related to the small sample size.

In the CPET, the anaerobic threshold, maximum oxygen uptake, and oxygen pulse in the severe OSA group were significantly lower than those in the no OSA group and negatively correlated with AHI. This suggests that the anaerobic threshold, maximum oxygen uptake, and oxygen pulse decreased with disease aggravation, especially in the severe OSA group. The anaerobic threshold refers to the maximum oxygen uptake value when a patient's aerobic function does not require the supplementary function of anaerobic metabolism during exercise. This was the highest oxygen uptake observed in the absence of lactic acidosis. It represents the ability of the circulatory system to transport oxygen and reflects a patient's cardiac function. The maximum oxygen-carrying capacity reflects the blood pumping limit of the heart and the oxygen uptake capacity of sports tissues.[29] Oxygen pulse reflects the level of cardiac output and cardiac reserve capacity and is a main index of cardiopulmonary function under maximum load.[30] The above results suggest that the changes in cardiopulmonary exercise test indexes in overweight OSA patients occur earlier than resting static pulmonary functions. CPET can be used as an auxiliary method to evaluate the severity of OSA in overweight patients.

Furthermore, there is poor compliance with the traditional treatment of OSA, such as noninvasive positive pressure ventilation.[31] The CPET is used to understand the cardiopulmonary function of overweight patients with OSA. Early intervention for patients with a downward trend in cardiopulmonary exercise indicators can prevent disease progression. In this study, there were no significant differences in CPET indices between the mild OSA, moderate OSA, and no OSA groups. Moreover, there were no significant differences in respiratory reserve and carbon dioxide ventilation equivalents among the four groups. This may be due to small sample sizes.

CONCLUSION

In conclusion, the CPET may be a potential method for assessing the severity of OSA and overweight status. It provides clinical evidence for formulating exercise prescriptions and early weight loss interventions, which is of great significance in preventing disease exacerbation and improving prognosis.

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Knowledge and attitudes of rural healthcare providers regarding domestic violence against women: a systematic review

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KEY WORDS (MeSH terms):
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Females victims.

ABSTRACT

BACKGROUND: Specific types of violence such as intimate partner sexual violence and intimate partner homicide occur more frequently in rural areas.

OBJECTIVE: This study aimed to systematically review the literature on the knowledge and attitudes of rural healthcare providers regarding cases of domestic violence against women.

DESIGN AND SETTING: Systematic review developed at Universidade Federal de Uberlândia.

METHODS: We conducted an electronic search of six databases, which only included observational studies, regardless of the year, language, or country of publication, except for studies that used secondary data and were exclusively qualitative. Two reviewers performed the selection, data extraction, and risk of bias assessment using a specific Joanna Briggs Institute tool.

RESULTS: Six studies met the inclusion criteria. All the studies had a low risk of bias. Approximately 38% of these professionals identified injuries caused by violence in patients. When asked about knowing the correct attitude to take in cases of confirmed violence, between 12% and 64% of rural healthcare providers answered positively; most of them would refer to specialized institutions and promote victim empowerment and counseling. The number of professionals with an educational background in the field ranged from 16% to 98%.

CONCLUSIONS: The evident disparity across studies shows that some professionals have suboptimal knowledge and require training to adopt the correct attitude when identifying female victims of domestic violence in clinical practice.

SYSTEMATIC REVIEW REGISTRATION: This systematic review was registered in the Open Science Framework Database under the registration http://doi.org/10.17605/OSF.IO/B7Q6S.

INTRODUCTION

According to the Rural Health Information Hub,[1] violence is exacerbated in rural areas, and social support for victims is not always available. The reasons behind this phenomenon include country-specific cultural differences, the education level of victims and perpetrators, and their socioeconomic status.[2] Over the last decade, scientific literature on the topic has been scarce,[3,4] especially if compared to studies in urban areas. Violence persists as official institutions and the scientific community overlook this scenario. The more vulnerable individuals are the predominant victims, such as children and women. All types of violence can grow exponentially if they occur in silence, such as in a domestic environment among intimate partners. The authors have highlighted that violence caused by an intimate partner might be the leading global cause of homicide of women.[5] In this scenario, violence rates increase primarily because this is an underreported condition susceptible to the fear of retaliation.[6]

Specific types of violence are more frequent in rural areas, such as intimate partner sexual violence and intimate partner homicide.[7] The different types of violence may lead to profound physical and psychological adverse effects on women, namely depression, anxiety, sleeping and eating disorders, panic attacks, and reduction of the quality of life as a consequence of sexually transmitted diseases, injuries, and trauma.[8] For at least 25 years, healthcare providers have been promoted as vital components in the process of detecting, registering, and reporting cases of

violence against women.[9] Recent studies, however, have demonstrated that these professionals need more knowledge and training to identify and manage cases of violence against women.[10,11] A systematic literature review among oral healthcare providers, for instance, revealed that less than 24% knew how to identify signs of domestic violence against women[11]. Nurses and midwives, however, seem to have a better understanding of the signs of domestic violence.[12] The justification of subsequent research on the topic relies on the gap of scientific evidence among healthcare providers in rural areas.

By understanding the reality of rural healthcare providers and their knowledge and attitudes toward domestic violence against women, protective strategies for patients could be designed and incorporated into the routine of health services.

OBJECTIVE

This systematic literature review compiled and analyzed evidence to understand the level of knowledge and attitudes of rural healthcare providers related to cases of domestic violence against women. To this end, the following question will be answered: "What are the knowledge and attitudes of rural healthcare providers regarding domestic violence against women?".

METHODS

Protocol and registration

The protocol was reported in accordance with the Preferred Reporting Items for Systematic Review and Meta-Analysis Protocols (PRISMA-P)[13] and registered in the Open Science Framework database (https://doi.org/10.17605/OSF.IO/B7Q6S). This systematic review was conducted according to the PRISMA[14] and was conducted according to the Joanna Briggs Institute (JBI) Manual.[15]

Research Question and Eligibility Criteria

The research question "What are the knowledge and attitudes of rural healthcare providers regarding domestic violence against women?" was structured with the following PICo[14] framework: Population (P)—rural healthcare providers (doctors and nurses), Interest (I)—educational background, management, perception, knowledge level and attitude regarding cases of domestic violence against women, and Context (Co)—domestic violence against women in the rural area. The systematic review included only observational cross-sectional, cohorts, and case-control studies. No restriction of language and year of publication was applied. The exclusion criteria consisted of studies that used secondary data, such as epidemiological investigations from existing databases, surveys with questionnaires that did not include specific questions regarding violence against women in rural areas, and exclusively qualitative studies.

Sources of information, search, and selection of studies

An electronic search was performed using MedLine/PubMed, Scopus, LILACS, SciELO, Embase, and Web of Science databases. Google Scholar, OpenGrey, and OATD were used to retrieve grey literature. Medical Subject Headings (MeSH), Health Sciences Descriptors, and Embase Subject Headings were used in their inherent databases. Synonyms and alternative terms were added to enhance the search strategy. The combination of terms was accomplished with the Boolean operators AND and OR (**Table 1**). The search was conducted in December 2021. The detected files were imported into EndNote Web (Thomson Reuters, Toronto, Canada) to remove automated duplicates. Grey literature was listed in Microsoft Word (Microsoft™ Ltd., Washington, USA) to manually remove duplicates. Prior to selecting the studies, training sessions were conducted between the two reviewers. In this phase, eligibility criteria were discussed and applied to 20% of the sample. The reviewers were considered able to proceed to the analysis of the total sample only when their agreement was ≥ 0.81 (Kappa).

The Rayyan Qatar Computing Research Institute (Doha, Qatar) was used for the study selection. Initially, selection was performed based only on the titles. Next, abstracts were read and selected based on eligibility criteria. Studies that did not have abstracts were kept for the subsequent phase. In this phase, full texts were read and selected and those that were excluded were registered separately with their respective reasons. If the full texts were not available via institutional access, an international bibliographic network was activated (COMUT/IBICT). Corresponding authors were contacted via e-mail as a last resort to collect full texts. All search and selection steps were performed in pairs by independent reviewers and supervised by a third researcher.

Data collection

Prior to data extraction, a training session was conducted following the same strategy that was applied to study selection. The reviewers extracted the following data: study identifying information (authors, year of publication, and country of the study), sample characteristics (number of participants, their sex, and time of experience), characteristics of data collection (e.g. questionnaire or interviews), and the main outcomes of the study (number of rural healthcare providers with educational background on the topic, number of professionals that screen patients for signs of violence, number of professionals that state to have knowledge to identify signs and manage situations of violence against women, and the attitude of these professionals when violence is detected), which constitute the most relevant information to interpret the conclusions of the systematic review. In the case of doubt during the data extraction process, the corresponding authors were contacted up to three times via e-mail.

Table 1. Strategies for database search

Database	Search Strategy (December, 2021)
Main Databases	
Embase http://www.embase.com	#**1** 'perception'/exp OR 'perception' OR 'management'/exp OR 'management' OR 'sensation'/exp OR 'sensation' OR 'diagnosis'/exp OR 'diagnosis' OR 'knowledge'/exp OR 'knowledge' OR 'attitude'/exp OR 'attitude' OR 'attention'/exp OR 'attention' #**2** 'domestic violence'/exp OR 'domestic violence' OR 'partner violence'/exp OR 'partner violence' #**3** 'women health' OR 'female'/exp OR 'female' #**4** 'health service'/exp OR 'health service' OR 'medical profession'/exp OR 'medical profession' **#1 AND #2 AND #3 AND #4**
LILACS https://lilacs.bvsalud.org/	#**1** (MH: perception OR MH: attitude OR MH: management OR MH: sensation OR MH: diagnosis OR MH: knowledge OR MH: attention) #**2** (MH: "domestic violence" OR "intrafamily violence" OR MH: "Intimate Partner Violence" OR MH: "Spouse Abuse") #**3** (MH: "Women" OR MH: "Women's Health Services" OR MH: female) #**4** (MH: "health personnel" OR "healthcare" OR MH: "Health Occupations" OR "healthcare provider") **#1 AND #2 AND #3 AND #4**
PubMed http://www.ncbi.nlm.nih.gov/pubmed	#**1** (perception [MeSH Terms] OR attitude [MeSH Terms] OR management [MeSH Terms] OR sensation [MeSH Terms] OR diagnosis [MeSH Terms] OR knowledge [MeSH Terms] OR attention [MeSH Terms]) #**2** ("domestic violence" [MeSH Terms] OR "intrafamily violence" [tw] OR "Intimate Partner Violence" [MeSH Terms] OR "Spouse Abuse" [MeSH Terms]) #**3** ("Women" [MeSH Terms] OR "Women's Health Services" [MeSH Terms] OR female [MeSH Terms]) #**4** ("health personnel" [MeSH Terms] OR "healthcare" [tw] OR "Health Occupations" [MeSH Terms] OR "healthcare provider" [tw]) **#1 AND #2 AND #3 AND #4**
SciELO https://scielo.org/	#**1** ("domestic violence" OR "intrafamily violence" OR "Intimate Partner Violence" OR "Spouse Abuse") #**2** ("health personnel" OR "healthcare" OR "Health Occupations" OR "healthcare provider") **#1 AND #2**
Scopus http://www.scopus.com/	#**1** TITLE-ABS-KEY (perception OR attitude OR management OR sensation OR diagnosis OR knowledge OR attention) #**2** TITLE-ABS-KEY "domestic violence" OR "intrafamily violence" OR "Intimate Partner Violence" OR "Spouse Abuse" #**3** TITLE-ABS-KEY "Women" OR "Women's Health Services" OR female #**4** TITLE-ABS-KEY "health personnel" OR "healthcare" OR "Health Occupations" OR "healthcare provider" **#1 AND #2 AND #3 AND #4**
Web of Science http://apps.webofknowledge.com/	#**1** TS=(perception OR attitude OR management OR sensation OR diagnosis OR knowledge OR attention) #**2** TS=("domestic violence" OR "intrafamily violence" OR "Intimate Partner Violence" OR "Spouse Abuse") #**3** TS=(Women OR "Women's Health Services" OR female) #**4** TS=("health personnel" OR healthcare OR "Health Occupations" OR "healthcare provider") **#1 AND #2 AND #3 AND #4**
Grey Literature	
OpenGrey http://www.opengrey.eu/	((violence OR "domestic violence" OR "intrafamily violence" OR "intimate partner violence" OR "spouse abuse") AND (female OR "women's health services" OR women)
Open Access Theses and Dissertations (OATD) https://oatd.org/	(perception OR attitude OR management OR sensation OR diagnosis OR knowledge OR attention) AND (violence OR "domestic violence" OR "intrafamily violence" OR "intimate partner violence" OR "spouse abuse") AND (female OR "women\'s health services" OR women) AND ("Health personnel" OR "health care providers" OR "health care occupations" OR "health care")
Google Scholar https://scholar.google.com.br/	allintitle: (perception OR attitude OR management OR sensation OR diagnosis OR knowledge OR attention) AND (violence OR "domestic violence" OR "intrafamily violence" OR "intimate partner violence" OR "spouse abuse") AND (female OR "women's health services"

Assessment of the risk of bias

The risk of bias was assessed using the JBI Critical Appraisal Checklist for Analytical Cross-Sectional Studies.[15] As recommended by PRISMA,[14] two reviewers independently analyzed each eligible study to assess the risk of bias. The studies were categorized based on their percentage of positive answers for the JBI questions regarding the risk of bias.[11] High risk of bias is when the positive answers are 49% or less. Moderate risk of bias is between 50–69% of positive answers, whereas low risk of bias is when the positive answers represent 70% or more.

Synthesis of results

Data collection was performed in the eligible studies, and the results were presented as a narrative/descriptive synthesis. The absolute (n) and relative (%) values of the participants' answers in each study were collected. The data quantified rural healthcare providers' educational background, management, perception, knowledge level (e.g. participation in lectures, guided orientations and discussion meetings about the theme) and attitude (e.g. any mention of professional action due to verification of signs of violence against women, regarding cases domestic violence against women).

RESULTS

Study selection

During the first phase of study selection, 11,375 entries were identified. After removing duplicates, 3,442 entries were retained to assess titles and abstracts. After reading the titles, 3,155 entries were excluded because they did not relate to the topic. Of the 287 entries remaining for abstract reading, 259 were excluded. The remaining 28 articles were selected for full-text analysis, and 22 articles were excluded. Finally, six studies[18–23] were included in the qualitative analysis (**Figure 1**).

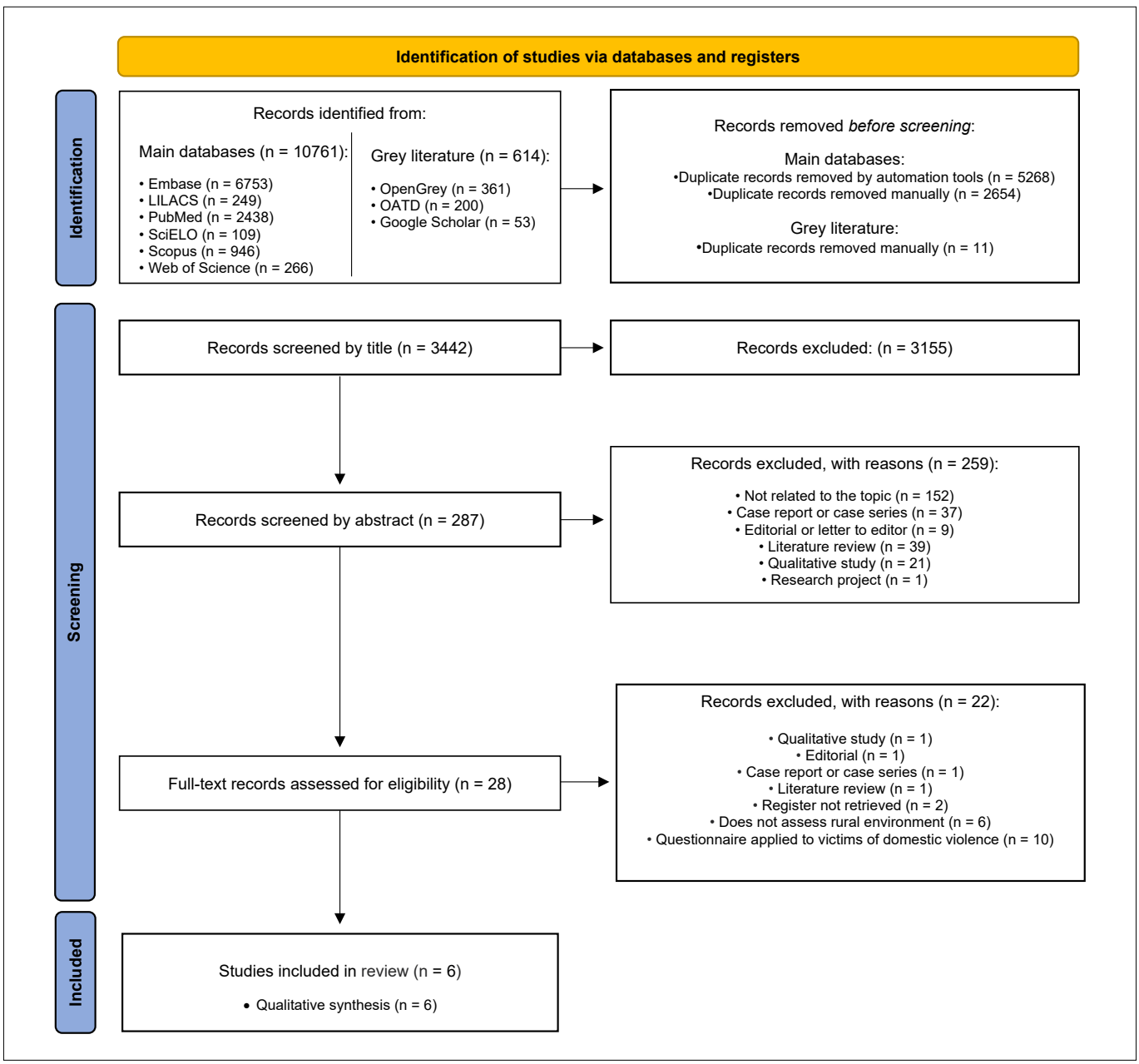

Figure 1. Flowchart depicting the study selection process (Preferred Reporting Items for Systematic Reviews and Meta-Analyses flow diagram).

Study characteristics

The studies were published between 1998 and 2018 and performed in two different countries: four in the United States[20–23] and two in Australia.[18,19] All studies consisted of surveys with self-applicable questionnaires. The answers were quantified using Likert[18,20,22,23] and adapted scales.[19,21] All studies investigated domestic violence against intimate female partners.

Among the studies that reported the number of rural healthcare providers, 893 participants were included (705 were female). Two studies investigated the specificity of the participants[21,22] and included family health, primary care, medical emergencies, obstetrics, and pediatrics (**Table 2**).

Assessment of the risk of bias of studies

All six studies were classified as having a low risk of bias. Question 1, referring to the eligibility criteria used for sampling, was not answered in five studies.[18–21,23] This question is relevant because it enables sample standardization and reduces the risk of bias. Questions 5 and 6 were not applicable because they referred to experimental studies on exposure or interventions. All remaining questions had positive answers in all studies (**Table 3**).

Results of individual studies

Four studies[18–20,23] provided the percentage of professionals who knew how to identify signs of domestic violence. Five studies[18,20–23] investigated whether rural healthcare providers had any educational background on violence during their academic careers. Four studies[18,20,22,23] asked whether professionals screened their patients for signs of violence in clinical practice (**Table 4**).

Bates and Brown[18] performed a cross-sectional study on physicians and nurses. When asked what kind of injury would raise suspicion of violence, they answered contusion (82%), fractures (58%), and abrasion (38%) and pointed out specific regions of the body, such as injuries to the face (77%). Although only 16% had an educational background on the topic, 38% answered that they would be able to identify signs of domestic violence. Most professionals (90%) agreed that dedicated training would benefit their performance. McCosker et al.[19] applied a questionnaire before and after a training course on domestic violence and observed a significant change in the knowledge of healthcare providers. A similar strategy focused on training was used by Gadomski et al.[20] in their eligible study. The authors assessed the knowledge, behavior, and attitudes of professionals and observed improvements in their

Table 2. Summary of the main characteristics of the eligible studies

Author, year and country	Sample (♂ / ♀)	Health professionals	Experience of professionals (mean in years)	Place of service	Assessment tool
Bates and Brown, 1998[18] Australia	16 / 95	Doctors and nurses	nr	Community hospitals	Likert questionnaire
McCosker et al., 1999[19] Australia	1 / 46	Nurses	nr	Clinics	Adapted questionnaire
Gadomski et al., 2001[20] United States	84 / 296	nr	16	Community hospitals and clinics	Likert questionnaire
Bender, 2016[21] United States	63 / 71	Doctors and nurses	12.2	Clinics	Adapted questionnaire
Rous and Kurth, 2016[22] United States	13 / 75	Doctors and nurses	nr	Primary care centers	Likert questionnaire
Durham-Pressley et al., 2018[23] United States	4 / 122 2 preferred not to inform	Nurses	18.5	Health systems hospitals	Likert questionnaire

nr = not reported in the study.

Table 3. Risk of bias assessed by the Joanna Briggs Institute Critical Appraisal Tools for use in JBI Critical Appraisal Checklist for Analytical Cross-Sectional Studies

Authors	Q1	Q2	Q3	Q4	Q5	Q6	Q7	Q8	% Yes	Risk
Bates and Brown[18]	U	√	√	√	NA	NA	√	√	83.3	Low
McCosker et al.[19]	U	√	√	√	NA	NA	√	√	83.3	Low
Gadomski et al.[20]	--	√	√	√	NA	NA	√	√	83.3	Low
Bender[21]	U	√	√	√	NA	NA	√	√	83.3	Low
Rous and Kurth[22]	√	√	√	√	NA	NA	√	√	100	Low
Durham-Pressley et al.[23]	U	√	√	√	NA	NA	√	√	83.3	Low

Q1 = Were the criteria for inclusion in the sample clearly defined?; Q2 = Were the study subjects and the setting described in detail?; Q3 = Was the exposure measured in a valid and reliable way?; Q4 = Were objective, standard criteria used for measurement of the condition?; Q5 = Were confounding factors identified?; Q6 = Were strategies to deal with confounding factors stated?; Q7 = Were the outcomes measured in a valid and reliable way?; Q8 = Was appropriate statistical analysis used?; √ = Yes; -- = No; NA = Not Applicable; U = Unclear.

knowledge of their role as agents to identify violence. The authors also observed that after the training course, healthcare providers were more aware of the importance of referring patients to specialized institutions. When Bender[21] asked participants about their attitude toward suspicious cases of domestic violence, 16% answered that they would not take any action. The authors observed that the number of hours dedicated to training would increase the likelihood of screening patients for intimate partner violence. Roush and Kurth[22] observed that most participants had good knowledge and judicious attitudes regarding the identification and management of domestic violence against women. Finally, Durham-Pressley et al.[23] observed that most professionals (60.9%) had not identified a single case of violence in the last year. Their reported attitude, however, was predominantly correct (63.9%) (**Table 5**).

DISCUSSION

Violence against women in the rural environment is a multifactorial problem.[2] Socioeconomic status seems to have an important part in this equation.[24] Authors have shown subcategories of women who are even more vulnerable to violence in the rural environment, such as the elderly and the unemployed.[25] More specifically, these women present a major risk of poverty, and their lack of financial independence makes them susceptible to recurrent intimate partner violence.[25] This is a sole example of the vast casuistics often overlooked about women who live in rural areas. This study contributes evidence-based findings to the scarce scientific literature on this topic.

Healthcare providers normally conduct physical examinations of their patients; thus, it is possible to detect signs of violence

Table 4. Summary of the main results of eligible studies

Authors	Question	Knowledge of reporting requirements (%)	Screen for injuries (%)	Perception of physical indicators (%)	Educational background (%)
Bates and Brown[18]	Health professionals received some training in domestic violence	--	--	--	16
	Under real conditions, health professionals expected that they would be able to recognize victims	--	--	38	--
	Aware of some services to which women could be referred (police or women's refuge)	12	--	--	--
	Examine alone only when suspecting that the cause of injury was different from what the patient said	--	50	--	--
McCosker et al.[19]	Correctly know the definition of violence against women	--	--	--	25
Gadomski et al.[20]	Had received some past training relative to domestic violence	--	--	--	38
	Had identified a victim in the preceding year	--	39	--	--
Bender[21]	Ask all new patients or all patients periodically about the possibility of abuse and domestic violence	--	49	--	--
	Knowledge of community resources for occasional screening	--	--	--	36
Roush and Kurth[22]	Can recognize victims of intimate partner violence by the way they behave	--	97	--	--
	Know how to ask about the possibility of intimate partner violence and what to do	--	--	--	98
Durham-Pressley et al.[23]	Have sufficient knowledge about familiar violence	--	--	--	38
	Know how to refer patients positive for family violence	64	--	--	--

Table 5. Summary of the main results related to attitudes of health professionals of eligible studies

Authors	Referral the victims to specialized agencies (%)	Patient counseling about options (%)	Encourage the victims to leave the violent situation (%)	Confront the victim when she does not admit violence (%)	No action, even identifying cases of violence (%)
Bates and Brown[18]	98	--	67	79	--
McCosker et al.[19]	93	--	--	--	--
Gadomski et al.[20]	46	39	--	--	--
Bender[21]	--	39	--	--	16
Roush and Kurth[22]	48	--	57	--	--
Durham-Pressley et al.[23]	64	--	--	--	--

through visual inspection. Early studies in the field noticed that contusions, fractures, and abrasions appeared as the most expected signs of physical violence against women when they asked the rural healthcare providers.[18] Interestingly, most professionals would expect these signs more commonly on the faces of their female patients.[18] The perception of rural healthcare providers, in this case, was correct and later confirmed by Brink.[26] These findings raise particular insights, especially regarding the access of healthcare providers to specific anatomic regions of the body. For instance, faces are examined routinely by dentists, speech therapists, otolaryngologists, and ophthalmologists. However, most professionals were not specifically trained to detect violence against women. In a previous systematic review, oral healthcare providers showed an evident lack of educational background on the topic.[11] It could be speculated, for example, that healthcare providers would receive specialized training in postgraduate studies. It must be noted, however, that the professionals who work in rural areas are not always specialized and have possibly trained for general practice and primary healthcare exclusively.

This systematic review shows that most rural healthcare providers have expressed their interest in specialized training to properly identify and manage cases of violence against women since 1998.[18] Recent studies in developed countries, such as Australia, have shown that training on the topic of intimate partner violence remains poorly embedded in paramedical undergraduate programs.[27] When it comes to the specific field of nursery, other authors showed that most training courses are part of an existing program and are not provided as a sole course.[28] These studies point out a call for a change in the way that training is planned and provided. The positive effects of training were subsequently confirmed by the eligible studies in this systematic review.[19,20] Most healthcare providers sampled in previous studies were general practitioners;[11] thus, the strategies developed to implement training must be compatible with their routines, especially in rural areas. During distance training sessions, itinerary training courses conducted throughout the countryside could reach these professionals more easily and be beneficial in transforming their practices. Among the benefits of training sessions is the increased knowledge of how to refer patients with confirmed exposure to violence.[20] Notably, specific countries impose reports of patients experiencing violence. In Brazil, the Codes of Medical and Dental Ethics, for example, enable the breach of secrecy if justified by the Law. Federal Law n. 10.778/2003 establishes the mandatory report of female patients who are victims of violence and treated in any public or private healthcare institution in the country—including the rural area. In addition to the Brazilian legislation, healthcare providers must expect a transitional scenario of violence against women created by immigrants, especially from neighbors countries in South America. Some immigrants settle in less-expensive cities, such as those in rural areas. Authors have demonstrated that this special group of victims is often marginalized and under-researched;[29] hence, violence could be even more underreported. They are in the Brazilian territory; thus, reporting suspected cases of violence against women remains mandatory and could shed light on this vulnerable population.

However, reporting remains a persistent issue for healthcare providers. This systematic review shows that the available data are contradictory. On the one hand, recent studies show that most of the professionals (nearly 60%) would undertake the correct attitude and refer the patients to specialized institutions that shelter victims of domestic violence.[22,23] On the other hand, a considerable amount (16%) of rural healthcare providers would remain silent.[21] The word "Most," in these studies, must be carefully interpreted. Despite the majority of correct attitudes among rural healthcare providers in some of the eligible studies, a significant percentage (40%) of professionals still lack knowledge about how to protect female victims of violence. Again, this seems to be a matter of continuing education and preparing for the future. An additional contribution to this scenario would be strategies to increase the victims' awareness as well as provide them with solutions to self-report domestic violence in a safe environment. The State of São Paulo, in Brazil, for example, had strategies that directly bridged victims and police. In specific, the Police Department developed a "help button" in a smartphone freeware app. Women are invited to register their personal data and activate the button with a single click to provide the police with a GPS signal that reports not only their location but also the situation of imminent violence. Of course, this solution may not uniformly reach rural women. Hence, a call for tailor-made solutions for these women is necessary, and this systematic review is a compilation of evidence to justify strategies with science.

The limitations inherent to this systematic review include the general methodological heterogeneity between eligible articles, which reflects the random approach of authors to design and apply questionnaires. Future studies could focus on developing and validating questionnaires to enable a more standardized research practice and eventually the application of meta-analyses. Additionally, all the eligible studies were only observational and reduced the level of evidence of this systematic review compared to, for instance, reviews of experimental randomized control trials. Overcoming this limitation, however, might be challenging as observational studies might be the most common approach to studying violence against women, while experimental models are not suitable.

CONCLUSIONS

The screened methodological designs differed considerably among the articles, but, in general, a low risk of bias was

detected. Health professionals attending to patients in the rural environment showed restrictions in their knowledge of violence against women, possibly because of a lack of training in the field. Educational training strategies are required for identifying and reporting violence against women in this particular area.

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The Brazilian version of the High-Activity Arthroplasty Score: cross-cultural adaptation

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Arthroplasty, Replacement, Knee.
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Exercise.

ABSTRACT

BACKGROUND: The High Activity Arthroplasty Score (HAAS) is a self-administered questionnaire, developed in British English, that reliably and validly measures the levels of sports activities in patients following hip and knee arthroplasty surgery.

OBJECTIVE: To cross-culturally adapt the HAAS to Brazilian Portuguese language.

DESIGN AND SETTING: A cross-sectional study was conducted at a public university hospital in Brazil.

METHODS: The Brazilian version of the HAAS was created through a six-step process: translation, synthesis, committee review, pretesting, back-translation, and submission to developers. The translation step was conducted by two independent bilingual translators, both native speakers of Brazilian Portuguese. The back-translation was performed by an independent translator, a native speaker of British English. To ensure the questionnaire's comprehensibility, 46 volunteers (51% men; average age 34-63) participated in the pre-testing step.

RESULTS: The cross-cultural adaptation process necessitated modifications to certain terms and expressions to achieve cultural equivalence with the original HAAS.

CONCLUSION: The HAAS has been translated from English into Brazilian Portuguese and culturally adapted for Brazil. The validation process for HAAS-Brazil is currently underway.

INTRODUCTION

The functional outcome of hip and knee arthroplasty can be evaluated using health-related quality of life instruments, such as questionnaires and scales. Current literature provides instruments that primarily assess pain as the main symptom, thereby presenting a limiting factor in the performance of low-demand daily activities (DA).[1-3]

The focus on pain and DAs presents a challenge in identifying individuals who exhibit no pain limitation during low-demand activities, including DAs, but experience limitations during more strenuous activities, such as sports.[4] Current instruments fall short in assessing significant functional differences, such as walking on uneven terrain, running, climbing stairs, and gauging the level of physical or sports performance.[4]

In response to these dilemmas, Talbot et al. developed and validated the High-Activity Arthroplasty Score (HAAS).[4] This tool is designed to assess a patient's functional ability by incorporating a broader spectrum of physical and sporting activities, in addition to the traditional focus on painful symptoms. The HAAS is a self-administered questionnaire divided into four domains: i) *Walking;* ii) *Running;* iii) *Stair Climbing;* and iv) *Activity Level.* Each domain is designed to assess the patient's maximum capacity, resulting in a score that ranges from 0 to 18. Higher scores indicate superior patient function. The HAAS was originally developed in British English, and no cultural adaptation for Brazilian Portuguese is currently available.

OBJECTIVE

The objective of this study was to adapt the HAAS cross-culturally from British English to Brazilian Portuguese. We hypothesized that the adaptation to Brazilian Portuguese and its subsequent application in Brazil would be both feasible and acceptable.

METHODS

Type of study

This is a cross-sectional, quanti-qualitative study focused on the cross-cultural adaptation of a questionnaire. The primary data was collected between September 2021 and August 2022.

The ethics committee of Hospital Universitário Pedro Ernesto, affiliated with Universidade do Estado do Rio de Janeiro (UERJ), granted approval for this study on August 30, 2021 (approval number 50529321.3.0000.5259). All participants provided their informed consent. Dr. Simon Talbot, the primary author of the HAAS, granted permission for its cross-cultural adaptation into Brazilian Portuguese on December 28, 2020.

Cross-cultural adaptation

To adapt the HAAS, we adhered to the guidelines suggested by Beaton et al.[5] with further considerations by Borsa, Damasio, and Bandeira.[6] The procedure encompasses six steps: translation, synthesis, review by committee, pretesting, back-translation, and submission of documentation to the developers (**Figure 1**).

Step 1: Translation

The HAAS was initially translated from English to Brazilian Portuguese by two independent translators, both native speakers of Brazilian Portuguese and fluent in English. This process resulted in two distinct Brazilian Portuguese blind translations: T_1 and T_2.

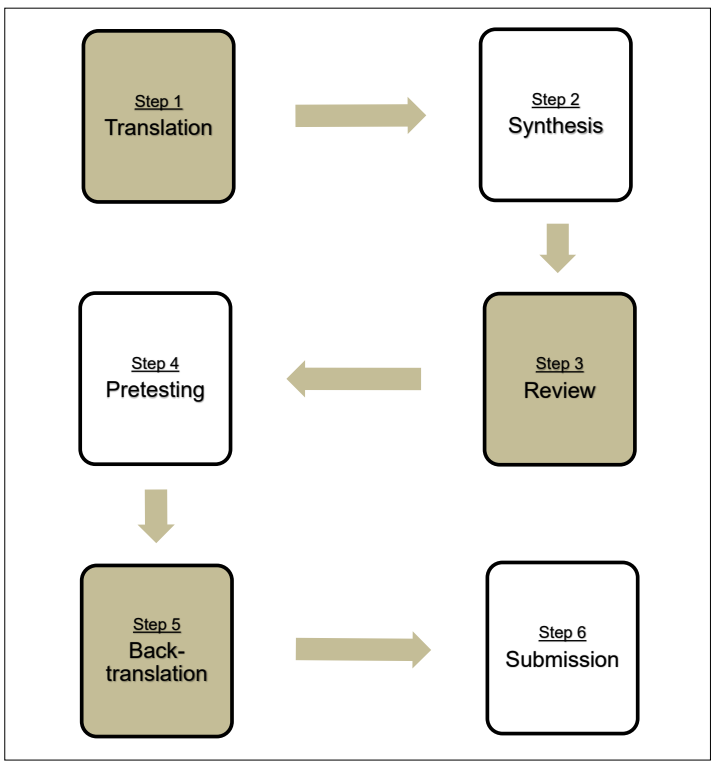


Figure 1. Six steps of cross-cultural adaptation: translation, synthesis, review by committee, pretesting, back-translation, and submission of documentation to the developers.

Step 2: Synthesis

Two native Brazilian Portuguese speakers, residing in Brazil, synthesized T_1 and T_2 into the Brazilian Portuguese language. A reconciled version, $T_{1,2}$, was created, and the entire process was duly documented.

Step 3: Review by a committee

A multidisciplinary committee was formed to review $T_{1,2}$, comprising experts in the construct under evaluation and cross-cultural adaptation studies. This committee included one physiotherapist, two orthopedists, and two physical educators. Additionally, one committee member held a degree in Language, specializing in translation and communication.

The aim of this step was to assess the semantic, idiomatic, cultural, and conceptual equivalences between the original version and $T_{1,2}$, thereby identifying necessary adaptations. Consequently, a pretesting version (V_1) was produced. The adaptation process was guided by the Coefficient Content Validity (CCV) proposed by Hernandez-Nieto.[7]

Step 4: Pretesting

The objective of this step was to determine whether volunteers found the V_1 items, instructions, and response scale comprehensible. The Three-Step Test-Interview (TSTI) employing a 5-item Likert Scale was utilized to evaluate the questionnaire's adaptation.[8,9] The sample size was established using the saturation criteria technique.[10]

The results of the pretesting were analyzed through a qualitative assessment, taking into account suggestions for improved adaptation and comprehension from the volunteers. This process led to the creation of a final version (V_f).

Step 5: Back-translation

Back-translation can be utilized to assess whether the conceptual equivalence between the synthesized and revised V_f and the original instrument has been preserved. This process facilitates the evaluation of the culturally adapted instrument by its developers.[6]

The back-translation was conducted blindly by a native British English speaker who is fluent in Portuguese but lacks technical knowledge of the study's subject matter. The entire process was meticulously documented in writing.

Step 6: Submission of documentation to the developers

The aim of this step was to present the Brazilian version of HAAS to the original developers.

RESULTS

Step 1 produced two independent translations: T_1 and T_2 (**Box 1**).

The synthesis of T_1 and T_2 produced $T_{1,2}$ (**Box 2**), that was evaluated and reviewed by the multidisciplinary committee on the third step.

The main modifications proposed by the committee are listed in **Table 1** and **Table 2**.

The qualitative analysis undertaken by the multidisciplinary committee of specialists was guided by the CCV.[7] Items in which CCV was below 0.8 were modified by the committee prior to pre-testing. Grammar, typing, and formatting errors were revised as part of this step. As a result, a version (V_1) for pre-test was produced (**Box 3**).

V_1 was applied to 46 volunteers (51% men) with a mean age of 36-63 years old (min 19, max 69) in a heterogeneous sample regarding scholarity and income, according to data compiled in **Table 3**.

Among volunteers, 73.33% were engaged in physical activities (PA) (**Graphic 1**).

The occupations of the volunteers were as follows: students (31.11%); medical doctors (13.3%); general service assistants (13%); technical administrators (11.11%); cooks/kitchen assistants (6.66%); and other professions including professors, lawyers, security professionals, physiotherapists, laboratory technicians, marketing analysts, and retired individuals or those without an occupation (each comprising less than 5%).

Box 1. Step 1: Independent Translations (T1 e T2)

T1	T2
Escore de artroplastia e atividade física de alta demanda	Pontuação de Artroplastia de Alta Atividade
Selecione seu maior nível funcional em cada uma das quatro categorias	Selecione seu nível de função mais alta em cada uma das quatro categorias
1 Andando (máx. 5 pontos)	1 Caminhada (máx. 5 pontos)
5 em superfície irregular > 1 hora	5 em ladeira/terreno em subida por mais de 1 hora
4 sem limite em superfície plana, com dificuldade em superfície irregular	4 em terreno plano sem dificuldade, mas em terreno acidentado com dificuldade
3 sem limite em superfície plana, incapaz de andar em superfície irregular	3 em terreno plano sem dificuldade, mas não consigo caminhar em terreno acidentado
2 pelo menos 30 minutos em superfície plana	2 em terreno plano por pelo menos 30 minutos
1 curtas distâncias sem auxílio (até 20 metros)	1 em distâncias curtas sem ajuda (até 20 metros)
0 utilizando dispositivos de auxílio para andar curtas distâncias ou pior	0 usando dispositivos de apoio para distâncias curtas ou não consigo caminhar
2 Correndo (máx. 4 pontos)	2 Corrida (máx. 4 pontos)
4 mais que 5km	4 Corro mais de 5km
3 trotar até 5km	3 Corro devagar até 5km
2 correr facilmente na rua	2 Corro facilmente para atravessar a rua
1 correr alguns passos para evitar trânsito, se necessário	1 Corro poucos passos para evitar o tráfego ao atravessar a rua, se necessário
0 não consegue correr	0 Não consigo correr
3 Subindo escadas (máx. 3 pontos)	3 Subir escadas (máx. 3 pontos)
3 subir dois degraus por vez	3 Subo 2 degraus de cada vez
2 subir sem apoio no corrimão	2 Subo sem apoio de corrimão
1 subir com apoio no corrimão ou bengala/muleta	1 Subo com apoio de corrimão ou bengala
0 não consegue subir escadas	0 Não consigo subir escadas
4 Nível de atividade (máx. 6 pontos)	4 Nível de atividade (máx. 6 pontos)
6 esportes competitivos. Ex.: tênis individual, correr > 10km, andar de bicicleta >80km	6 Esportes competitivos, ex.: tênis simples, corrida > 10km, ciclismo >80km
5 esportes sociais. Ex.: tênis em dupla, esquiar, trotar < 10km, exercícios aeróbicos de alto impacto	5 Esportes sociais, ex.: tênis de dupla, corrida <10km, aeróbica de alto impacto
4 atividades recreacionais vigorosas. Ex.: montanhismo, exercícios aeróbicos de baixo impacto, jardinagem pesada, trabalho braçal / rural	4 Atividades recreativas vigorosas, ex.: caminhada em trilhas, aeróbica de baixo impacto, jardinagem pesada ou trabalho manual/agricultura
3 atividades recreacionais moderadas. Ex.: golfe, jardinagem leve, atividades de trabalho leve	3 Atividades recreativas moderadas, ex.: golfe, jardinagem leve, atividades leve no trabalho
2 atividades recreacionais leves. Ex.: caminhadas leves, bocha	2 Atividades recreativas leves, ex.: caminhadas curtas, boliche,
1 atividades ao ar livre apenas quando necessário. Ex.: caminhar distâncias curtas para fazer compras	1 Apenas atividades ao ar livre obrigatórias, ex.: caminhar uma curta distância para fazer compras
0 restrito ao lar sem necessidade de auxílio	0 Recluso em casa sem assistência
(máx. 18 pontos)	(máx. 18 pontos)

Box 2. Step 2: Synthesis of translations (T1,2)

Pontuação (Escore) de Artroplastia de Alta Atividade
Selecione o seu maior nível funcional em cada uma das quatro categorias.
1 Caminhada (máx. 5 pontos)
5 Em terreno irregular por mais de 1 hora
4 Sem limitação em terreno plano, mas com dificuldade em terreno irregular
3 Sem limitação em terreno plano, mas não consigo andar em terreno irregular
2 Pelo menos 30 minutos em terreno plano
1 Em curtas distâncias sem ajuda (até 20 metros)
0 Usando apoio para caminhar curtas distâncias ou uma condição pior

2 Corrida (máx. 4 pontos)
4 Corro mais de 5km
3 Corro devagar (trote) até 5km
2 Correr facilmente para atravessar a rua
1 Corro poucos passos para desviar dos carros ao atravessar a rua, se necessário
0 Não consigo correr

3 Subir escadas (máx. 3 pontos)
3 Subo 2 degraus de cada vez
2 Subo sem apoiar no corrimão
1 Subo apoiando no corrimão ou na bengala/muleta
0 Não consigo subir escadas

4 Nível de atividade física (máx. 6 pontos)
6 Esportes competitivos.
Exemplos: tênis simples (individual), corrida maior que 10km, ciclismo maior que 80km
5 Esportes sociais.
Exemplos: tênis de dupla, esqui, corrida menor que 10km, exercícios aeróbicos de alto impacto
4 Atividades recreativas vigorosas.
Exemplos: montanhismo (caminhada em trilhas), exercícios aeróbicos de baixo impacto, jardinagem pesada, trabalho braçal/rural
3 Atividades recreativas moderadas.
Exemplos: golfe, jardinagem leve, atividades leves de trabalho
2 Atividades recreativas leves.
Exemplos: caminhadas curtas, bocha/boliche
1 Atividades ao ar livre apenas quando necessário.
Exemplos: caminhar distâncias curtas para fazer compras
0 Recluso em cada (realiza apenas tarefas do lar) sem necessidade de ajuda

(máx. 18 pontos)

Table 1. Main modifications proposed by the committee

Original	Adapted
Competitive sports	*Esportes de alto rendimento com ênfase na competição*
Social sports	*Esportes sociais sem ênfase na competição*
Vigorous recreational activities	*Atividades físicas vigorosas*
Moderate recreational activities	*Atividades físicas moderadas*
Light recreational activities	*Atividades físicas leves*
Select	*Marque um X ou circule*
> 1 hour	*por mais de 1 hora*
e.g.	*exemplos:*

Minimal modifications were proposed for the final version (V_f), which was subsequently represented to the committee. Modifications are highlighted in **Box 4**.

Following consultation with experts, no additional pre-testing was required. The V_f was then back translated (**Box 5**) and shared with the developers for their review.[6] They expressed satisfaction with the results and did not propose any further modifications. Thus, the V_f was the final translation of the HAAS, i.e., the HAAS-Brazil.

DISCUSSION

The functional outcomes of hip and knee arthroplasty can be evaluated using health-related quality of life questionnaires and scales. However, the instruments currently available in the literature are biased by pain and DA limitation.[1-3] Consequently, HAAS was developed and validated to assess the functional outcomes of hip and knee arthroplasty surgery in patients who do not experience significant pain or limitations in low-demand activities.[4]

Table 2. Main modifications proposed about sports and physical activities

Original examples	Adapted examples	
Singles tennis/doubles tennis	*Futebol*	
Running	*Vôlei*	*Faxina pesada*
Cycling	*Basquete*	*Trilha moderada*
Jog/jogging	*Handebol*	*Faxina leve*
Skiing	*Natação*	*Hidroginástica*
High impact aerobics	*Tênis*	*Dança de salão*
Low impact aerobics	*Corrida*	*Pilates*
Hill-walking	*Ciclismo*	*Trilha leve*
Heavy gardening	*Surfe*	*Bocha/boliche*
Manual work/farming	*Skate*	*Hidroterapia*
Golf	*Crossfit*	*Exercícios fisioterápicos para*
Light gardening	*Dança vigorosa*	*fortalecimento muscular*
Light working activities	*Exercício aeróbico vigoroso (bicicleta ergométrica, spinning, elíptico, esteira)*	
Lawn bowls		

Box 3. Step 3: Pre-test version (V1) of HAAS

High Activity Arthroplasty Score - Brazil
Selecione o seu maior nível funcional em cada uma das quatro categorias.
1 Caminhando (máx. 5 pontos)
5 Caminho em terreno irregular por mais de 1 hora
4 Caminho sem limitação em terreno plano, mas com dificuldade em terreno irregular
3 Caminho sem limitação em terreno plano, mas não consigo caminhar em terreno irregular
2 Caminho pelo menos 30 minutos em terreno plano
1 Caminho curtas distâncias sem ajuda (até 20 metros)
0 Caminho curtas distâncias usando ou não consigo caminhar

2 Correndo (máx. 4 pontos)
4 Corro mais de 5km
3 Corro devagar até 5km
2 Corro facilmente para atravessar a rua
1 Corro poucos passos para atravessar uma rua, se necessário
0 Não consigo correr

3 Subindo escadas (máx. 3 pontos)
3 Subo 2 degraus de cada vez
2 Subo sem apoiar no corrimão
1 Subo apoiando no corrimão ou na bengala/muleta
0 Não consigo subir escadas

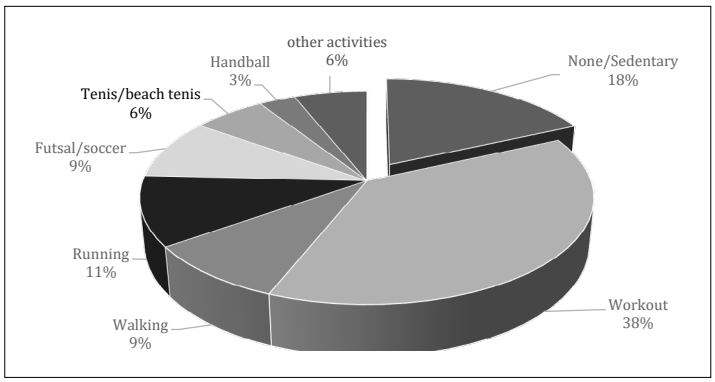
4 Nível de atividade física (máx. 6 pontos)
6 Pratico esportes de alto rendimento com ênfase na competição
Exemplos: futebol, vôlei, basquete, natação, tênis, corrida, ciclismo, surfe, skate etc.
5 Pratico esportes socialmente sem ênfase na competição
Exemplos: futebol, vôlei, basquete, natação, tênis, corrida, ciclismo, surfe, skate etc.
4 Pratico atividades físicas vigorosas
Exemplos: trilha vigorosa, dança vigorosa, exercício aeróbico vigoroso (bicicleta ergométrica, spinning, elíptico, esteira), faxina pesada etc.
3 Pratico atividades físicas moderadas
Exemplos: trilha moderada, faxina leve, hidroginástica, dança de salão, pilates etc.
2 Pratico atividades físicas leves
Exemplos: trilha leve, bocha/boliche, hidroterapia, exercícios fisioterápicos para fortalecimento muscular
1 Pratico atividades ao ar livre apenas quando necessário.
Exemplos: caminhar distâncias curtas para fazer compras
0 Estou recluso em cada (realizo apenas tarefas do lar) sem necessidade de ajuda

(máx. 18 pontos)

Table 3. Descriptive data of pre-test volunteers

Scholarity	Sex	Age mean (min-max)	Income	Skin Color*	BMI (w/h²) mean (min-max)	Comorbidity n (%)	Physical Activity n (%)	HAAS mean (min-max)	Time for filling mean
Middle School or less (n = 10)		42.5 (26-69)	<3 basic salaries (n = 7)		28.6 (24.69-36.8)	3 (30%)	3 (30%)	11 (6-16)	0:04:33
	M (n = 5)	40.2 (26-56)	66% 1-3 basic salaries (n = 3)	**W** 1 **B** 3 **P** 1	29.65 (24.69-38.8)	0	2	12 (6-16)	0:04:28
	F (n = 5)	44.8 (26-69)	75% under 1 basic salary (n = 4)	**W** 0 **B** 5 **P** 0	27.56 (25.32-32)	3	1	10 (7-14)	0:04:38
Complete High School (n = 16)		27.0 (19-56)	<6 basic salaries (n=15)		24.27 (20.94-29.39)	5 (33%)	14 (93.33%)	14.93 (8-18)	0:02:28
	M (n = 8)	25.12 (19-40)	50% no income (n=8)	**W** 3 **B** 1 **P** 4	24.29 (20.94-29.39)	3	8	15.62 (14-18)	0:01:44
	F (n = 8)	28.87 (20-56)	62% <1 basic salary	**W** 3 **B** 3 **P** 2	24.25 (21.64-27.34)	2	6	14.25 (8-17)	0:03:13
College Graduated (n = 20)		36.8 (23-65)	10% >15 basic salaries (n = 19)		26.74 (18.56-32.74)	9 (45%)	16 (80%)	14.05 (8-18)	0:02:22
	M (n = 10)	38.5 (23-65)	22.2% >15 basic salaries (n = 9)	**W** 7 **B** 0 **P** 3	28.04 (22.22-32.74)	4	7	13.8 (8-18)	0:02:49
	F (n = 10)	35.1 (25-59)	40% 3-6 basic salaries (n = 10)	**W** 5 **B** 1 **P** 4	25.43 (18.56-31.80)	5	9	14.3 (8-18)	0:01:56

*Skin color options according to *Instituto Brasileiro de Geografia e Estatística (IBGE)*'s statistics collection (Fonte: IBGE, Diretoria de Pesquisas, Coordenação de Trabalho e Rendimento, Pesquisa Nacional por Amostra de Domicílios Contínua 2012-2019);
BMI = body mass index; HAAS = high activity arthroplasty score; F = female; M = male; W = white; B = black; P = pardo; w = weight; h = height.



Graphic 1. Physical activity practice and sedentary lifestyle among volunteers.

Borsa et al.[6] observed that the translation stage inherently initiates the adaptation process. This is because the subjective act of seeking words that accurately convey the intended content and construct inherently involves a degree of adaptation that a literal translation would not capture. Our understanding of translation, informed by a review of the literature, is that it is a component of the cross-cultural adaptation process. Consequently, the terminology used in the title of this paper reflects this concept.[6]

The initial phase of this study aimed at the cross-cultural adaptation of HAAS to Brazilian Portuguese, during which two translations (T_1 and T_2) of the original HAAS questionnaire were generated. Guillemin et al.[11] and Beaton et al.[5] both propose a minimum of two independent translations of the questionnaire or scale into the target language in their methodologies. The translators ideally should be bilingual, with the target language as their native language, to ensure an enhanced ability to discern the nuances and peculiarities of everyday communication within the target language.[5,6,11] This approach enables the production of comparable translations, thereby facilitating a more effective evaluation of discrepancies and ambiguities. Furthermore, it is acknowledged that the selected translators should have varied profiles: one with a more technical understanding of the construct in question, and the other, a practitioner with a stronger emphasis on language, even if not necessarily proficient in the essence of the construct.[6]

Therefore, one of the translators who contributed to this work was an orthopedist with prior involvement in cross-cultural

Box 4. Step 4: Final version (V_f) of HAAS with highlighted alterations

High Activity Arthroplasty Score - Brazil
Marque um X ou circule o seu maior nível funcional em cada uma das quatro categorias.
1 Caminhando (máx. 5 pontos)
5 Caminho em terreno irregular por mais de 1 hora
4 Caminho sem limitação em terreno plano, mas com dificuldade em terreno irregular
3 Caminho sem limitação em terreno plano, mas não consigo caminhar em terreno irregular
2 Caminho pelo menos 30 minutos em terreno plano
1 Caminho curtas distâncias sem ajuda (até 20 metros)
0 Caminho curtas distâncias usando ou não consigo caminhar

2 Correndo (máx. 4 pontos)
4 Corro mais de 5km
3 Corro devagar até 5km
2 Corro facilmente para atravessar a rua
1 Corro poucos passos para atravessar uma rua, se necessário
0 Não consigo correr

3 Subindo escadas (máx. 3 pontos)
3 Subo 2 degraus de cada vez
2 Subo sem apoiar no corrimão
1 Subo apoiando no corrimão ou na bengala/muleta
0 Não consigo subir escadas

4 Nível de atividade física (máx. 6 pontos)
6 Pratico esportes de alto rendimento com ênfase na competição
Exemplos: futebol, vôlei, basquete, **handebol**, natação, tênis, corrida, ciclismo, surfe, skate, **crossfit**, **lutas** etc.
5 Pratico esportes socialmente sem ênfase na competição
Exemplos: futebol, vôlei, basquete, **handebol**, natação, tênis, corrida, ciclismo, surfe, skate, **crossfit**, **lutas** etc.
4 Pratico atividades físicas vigorosas
Exemplos: **faxina pesada**, **jardinagem pesada/roçado/obras domésticas**, **musculação vigorosa**, **trilha vigorosa**, dança vigorosa, exercício aeróbico vigoroso (bicicleta ergométrica, spinning, elíptico, esteira), etc.
3 Pratico atividades físicas moderadas
Exemplos: **faxina leve**, **jardinagem leve/pequenos reparos domésticos**, **musculação moderada**, trilha moderada, hidroginástica, dança de salão, pilates etc.
2 Pratico atividades físicas leves
Exemplos: **exercícios fisioterápicos para fortalecimento muscular**, **hidroterapia**, trilha leve, bocha/boliche etc.
1 Pratico atividades ao ar livre apenas quando necessário.
Exemplos: caminhar distâncias curtas para fazer compras
0 Estou recluso em cada (realizo apenas tarefas do lar) sem necessidade de ajuda

(máx. 18 pontos)

adaptation projects, which aimed at developing an adaptation that emphasized clinical equivalence. The second translator was a language professional with a degree in Languages and specialization in translation and communication. This ensured a translation that accurately mirrored the language used by the population, often highlighting ambiguous or excessively broad interpretations within the original questionnaire.

The second step involved merging the two translations into a single synthesized version ($T_{1,2}$). Borsa et al.[6] identified two potential complications at this stage: (1) a highly complex translation that may be challenging for the target population to understand, or (2) a somewhat simplistic translation that diminishes the content of the item. The research team noted that the original questionnaire's concise, simplified, and objective format could potentially confuse the target population in Brazil. This observation was considered and subsequently presented to the multidisciplinary committee of experts for further deliberation in the subsequent step.

In the third step, $T_{1,2}$ was submitted for review to a multidisciplinary committee of specialists. This committee evaluated the structure, layout, instructions, scope, and appropriateness of the expressions within the items of the instrument, identifying any potential semantic, idiomatic, conceptual, linguistic, and contextual discrepancies between the original HAAS version and $T_{1,2}$. This process led to several proposed structural modifications aimed at enhancing comprehension across individuals of diverse professions, educational backgrounds, income levels, and physical activity involvement.

Box 5. Step 5: Backtranslation of HAAS-Brazil

High Activity Arthroplasty Score – Brazil
Mark with an (X) your highest level of function in each of these four categories.

1 Walking (max. 5 points)
5 Walk on uneven surfaces for a period of more than 1 hour
4 Walk unrestricted on level surfaces but have trouble on uneven ground
3 Walk unrestricted on flat, level surfaces, but unable to walk on uneven ground
2 Walk for a period of at least 30 minutes on level surfaces
1 Walk short distances of up to 20 meters without requiring assistance
0 Walk short distances with assistance, or unable to walk at all

2 Running (max. 4 points)
4 Run distances more than 5 km
3 Run slowly up to distances of 5 km
2 Run easily to cross a street or intersection
1 Run a few steps to cross a street
0 No facility whatsoever to run

3 Climbing Stairs (max. 3 points)
3 Climb 2 steps at a time
2 Climb steps unassisted without handrail support
1 Climb steps but require handrail or other support, i.e., cane/crutch
0 No facility whatsoever to climb stairs

4 Level of physical activity (max. 6 points)
6 Practice high-performance sports at competition level
E.g., football, volleyball, basketball, handball, swimming, tennis, running, cycling, surfing, skateboarding, crossfit, wrestling, etc.
5 Practice sports on a social basis but not at competition level
E.g., football, volleyball, basketball, handball, swimming, tennis, running, cycling, surfing, skateboarding, crossfit, wrestling, etc.
4 Practice vigorous physical activity
E.g., demanding house cleaning, strenuous gardening/mowing, vigorous weight training, vigorous hiking, energetic dancing, vigorous aerobic exercise, gym workouts: bike, spinning, elliptical, treadmill
3 Practice moderate physical activity
E.g., light housekeeping, light gardening, moderate weight training, moderate hiking, water aerobics, ballroom dancing, pilates, etc.
2 Practice only light physical activity
E.g., physical therapy exercise for muscle strengthening, hydrotherapy, light hiking, bocce/bowling, etc.
1 Participate in outdoor activities only when necessary
E.g., walking short distances to the supermarket
0 I am a recluse who only performs household chores with no assistance required

(max. 18 points)

The practice and definitions of PA are influenced by the historical context of concept formation, which can that vary based on the cultural context in which they are applied.[12,13] Upon acknowledging that the primary objective of the original questionnaire is to assess both motor skill-related PA and sports practice as a skill, the committee suggested conceptual reframing based on available Brazilian sports literature.[12,13] This designated a clear line of difference and hierarchy between organized/systematic sports practice and the practice of physical activities of various intensity within the domain (4) *Nível de atividade física*. Examples: "*Competitive sports*" for "*esportes de alto rendimento com ênfase na competição*" and "s*ocial sports*" for "e*sportes sociais sem ênfase na competição*" (**Table 1**).

The committee opted to distinguish between sports practice and PA according to energy expenditure and expected motor skill within each degree of participation. This differentiation acknowledges that there is a conceptual and practical distinction between these two modalities within the questionnaire structure. Examples: "*vigorous recreational activities*" for "*atividades físicas vigorosas*," "*moderate recreational activities*" for "*atividades físicas moderadas*," and "*light recreational activities*" for "*atividades físicas leves*" (**Table 1**). Expert consensus agreed that there was a need for modification and inclusion of examples based on the culture of the target population; removal of sports such as skiing and the inclusion of more popular sports in Brazil like surfing and soccer.

In relation to the language itself, experts proposed the full use of comparative adjectives, as well as the occurrence of abbreviations present in the original questionnaire. The questionnaire now incorporates clearer and more explanatory commands to assist the target audience in completing it accurately. Examples: "*select*" for "*marque um X ou circule*," "*>1 hour*" for "*por mais de 1 hora*," and "*e.g.*" for "*exemplos*" (**Table 1**). The proposed changes to $T_{1,2}$ by the multidisciplinary committee of specialists, who then produced V_1 for the pre-test step, were adhered to by the quantitative criterion of the CCV.[7]

Borsa et al.[6] recommended conducting the pre-test with the target population, whereas the typical approach, as suggested by Guillemin et al.[11] and Beaton et al.[5], involves using healthy volunteers for this stage. Cross-cultural adaptation proponents have historically advocated for conducting pre-tests beyond the scope of the target population. [1-3,14] Given these perspectives, the decision was made to conduct the pre-test with volunteers.

Traditional empirical methodology suggests a minimum sample size of 30 to 40 volunteers for the pre-test. In this study, volunteers were consecutively selected using the saturation sampling technique. Saturation sampling, a qualitative research method, involves halting the inclusion of new participants when the data starts to show redundancy and is deemed irrelevant for further data collection by the research team.

In this study, we applied saturation sampling, which resulted in a heterogeneous group that aptly represented the Brazilian population's diversity in terms of age, education, and socio-cultural aspects. This approach adhered to the classic methodology proposed by Guillemin et al.[11] and Beaton et al.[5] Following the saturation sampling technique,[10] the recruitment of new volunteers ceased when no substantial or additional contributions were discernible within the data. This cessation point was reached with a total of 46 volunteers. We incorporated the TSTI with a 5-item Likert scale into the pre-test to assess the cultural adaptation of the questionnaire.[9]

Following the initial pre-test, the researchers incorporated several modifications suggested by the volunteers and resubmitted the revised version to the expert committee. A subsequent pre-test was deemed unnecessary as no significant conceptual or structural changes were proposed.[6] Within the TSTI methodology, the active pursuit of critique frequently elicited suggestions that had not been questioned during the examiner's passive assessment of topics. However, on certain occasions, these suggestions, when offered as solutions, risked misrepresenting the intent of a self-administered, objective, and generic questionnaire designed to evaluate the construct of interest.

The fifth step involved a back-translation, a role that has been somewhat debated within the cross-cultural adaptation process.[6] The objective was not to achieve a literal equivalence between an adapted version and original versions but rather to maintain conceptual equivalence.[6] Despite the debate, we acknowledge that back-translation is an effective tool for communicating and presenting the adapted instrument to the original developers. Consequently, we conducted back-translation as the fifth step, as recommended by Borsa et al.[6] This approach contrasts with the classical methodology of Beaton et al.[5], which positions this step after the synthesis.

The back-translation step was successfully completed, and the results were presented to the developers. They expressed satisfaction with the outcomes and did not suggest any additional recommendations. This marked the conclusion of the sixth and final step in the cross-cultural adaptation process of HAAS into Portuguese, culminating in the creation of HAAS-Brazil.

A notable limitation of this study is the execution of the pre-test, which relied on a sample from a single urban center within Brazil. It is important to acknowledge that Brazil, being a continental country, encompasses numerous regional linguistic and cultural differences. To mitigate this limitation, we attempted to assemble a diverse sample of volunteers, considering variables such as education and financial income.

CONCLUSION

The HAAS was translated into Brazilian Portuguese and adapted to the cultural context of Brazil. Our hypothesis that this adaptation is feasible and acceptable in Brazil has been largely corroborated. However, we acknowledge that the validation of the HAAS in Brazil is still ongoing.

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Improving breastfeeding among adolescent mothers: a prospective cohort

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ABSTRACT

BACKGROUND: Exclusive breastfeeding is recommended for the first six months, and mother's age impact early weaning. Educational support and relevant information can increase breastfeeding rates.

OBJECTIVE: To determine whether antenatal education enhances the maintenance, intention, and confidence in breastfeeding among adolescents.

DESIGN AND SETTING: A prospective cohort study involving primiparous adolescents who gave birth at the Woman's Hospital (CAISM), Universidade Estadual de Campinas, Brazil.

METHODS: Adolescent mothers were categorized into two groups based on the location of prenatal care: those at the Woman's Hospital (WH) who received antenatal education, and at the Primary Care (PC) who did not receive antenatal education. All adolescents received breastfeeding orientation during their postpartum hospital stay. The groups were compared using the Student's t-test, Mann–Whitney U test, and chi-squared test. Log-binomial models were used to compare the groups at different time intervals.

RESULTS: The study included 132 adolescents: 59 in the WH group and 73 in the PC group. Six months postpartum, adolescents in the WH group demonstrated higher engagement in breastfeeding ($P < 0.005$) and exclusive breastfeeding ($P = 0.04$) than PC group. PC group showed greater lack of confidence in breastfeeding ($P = 0.02$) and felt less prepared ($P = 0.01$). Notably, all WH adolescents reported a stronger desire to breastfeed after antenatal education.

CONCLUSION: Antenatal education significantly improves the maintenance, intention, and confidence of breastfeeding among adolescents. This education approach can be implemented across all healthcare levels and should be made accessible to all women throughout the pregnancy and postpartum period.

INTRODUCTION

Breastfeeding, due to its protective benefits for the mother and its role in promoting optimal child development, is advocated as the sole form of neonatal nourishment during the initial 6 months of life. It is recommended to continue until the child reaches 2 years of age and beyond.[1] Breastfeeding women are less likely to develop breast and ovarian cancer, type 2 diabetes, postnatal depression, and osteoporosis.[2,3] Additionally, infants nourished with human milk exhibit enhanced protection against infections, asthma, leukemia, and sudden infant death syndrome.[3] Neonatal breastfeeding also has a long-term effect on reducing the prevalence of obesity, heart disease, and diabetes.[3,4] Regrettably, the global breastfeeding rate falls short of the ideal benchmark. Only 42.0% of infants worldwide are exclusively breastfed during their first 6 months postpartum.[5] Alarmingly, breastfeeding rates decline in correlation with income or education status, particularly in low- and middle-income countries.[3]

The age of a mother significantly contributes to the low rates of breastfeeding, with the challenges of motherhood being particularly amplified during adolescence. When compared to women aged 20–29 (36.4%) and those over 30 (45.0%), adolescent mothers are the least likely to exclusively breastfeed their newborns in the first 6 months, with rates falling below 25.0%. Social and cultural norms predominantly influence the decisions of adolescent mothers not to breastfeed.[5,6]

Data on exclusive breastfeeding rates among adolescent mothers is limited. Studies from Brazil have noted a steady decrease in exclusive breastfeeding during the first 6 months postpartum among this demographic. The authors propose that maternal age is not the sole factor linked to early cessation of breastfeeding, suggesting that teenage motherhood possesses distinct attributes.[7] Adolescents often encounter conflicting situations during this period, potentially leading to feelings of psychological incapacity. Given that pregnancy itself is a vulnerable situation,

the state of motherhood can induce feelings of insecurity, anxiety, and fear. These emotional changes may jeopardize breastfeeding practices, causing these young mothers to breastfeed their children for a shorter duration than recommended by the WHO. Furthermore, they may lack understanding or information about the importance of breastfeeding for their child's development.[7]

A woman's understanding of the significance and management of breastfeeding is a crucial factor associated with early weaning. A study involving 297 women demonstrated that knowledge about breastfeeding influenced the choice of child-feeding method (breast milk and/or infant formula) and the duration of breastfeeding.[8] Furthermore, a study on breastfeeding self-efficacy among teenage mothers revealed that 56.90% exhibited a high level of self-efficacy, 35% showed a moderate level, and 8.10% had a low level. These results suggest that adolescents with high breastfeeding self-efficacy tend to breastfeed exclusively for a longer period.[9] Family members, prenatal care professionals, and the media serve as the primary sources of breastfeeding information for teenage mothers.[7] Consequently, it is crucial for healthcare professionals to offer additional support to teenagers during the postpartum period, fostering a more enjoyable and lasting breastfeeding experience.[9]

Despite the existence of laws advocating for breastfeeding and the presence of an extensive and intricate network of milk banks, Brazil continues to exhibit a low rate of exclusive breastfeeding among infants aged 6 months or less (36.6%). This rate falls short of the Global Nutrition Target 2025, which is set at 50.0%. Notably, the mother's age plays a crucial role in early weaning.[10-12]

The global teenage pregnancy rate is estimated at 46 births per 1,000 girls, constituting a significant public health concern, particularly in low and middle-income countries.[13] Various interventions, either standalone or combined, have been employed to enhance the initiation or prolongation of breastfeeding among mothers. These interventions encompass social, physical, and educational support, the latter offering women vital information about breastfeeding.[4]

The primary objective of this study was to compare the 6-month postpartum breastfeeding rates between adolescents who received antenatal breastfeeding education and those who did not. The secondary objectives were to examine the impact of antenatal education on a mother's confidence in breastfeeding and her intention to exclusively breastfeed.

METHODS

Design

We conducted a prospective cohort study involving primiparous adolescents at the Woman's Hospital, University of Campinas, Campinas, Brazil. This hospital is a referral center for high-risk obstetrics, offering specialized antenatal care for pregnant teenagers through an interdisciplinary, multi-professional team.

Characteristics of the sample

All primiparous adolescents aged 19 or under who delivered a single, live infant at the Women's Hospital were chosen for the study. Their medical records were examined to divide the adolescents into two categories: those who received prenatal care at the Women's Hospital and those whose pregnancies were overseen at primary healthcare facilities. After this initial categorization, all adolescents were queried about whether they received breastfeeding guidance during prenatal care, as the study's objective was to comprehend the impact of antenatal education on breastfeeding. Subsequently, adolescents were invited to participate in the study and were divided into two groups:

- Adolescents who received prenatal care and breastfeeding guidance at the Woman's Hospital;
- Adolescents who received prenatal care in primary healthcare facilities but did not receive guidance on breastfeeding.

The study excluded adolescents who received prenatal care at the Woman's Hospital without obtaining breastfeeding guidance, as well as those whose pregnancies were managed in primary healthcare facilities but did receive breastfeeding instruction.

The exclusion criteria encompassed primiparous adolescents with newborns diagnosed with malformations and/or requiring intensive care, those diagnosed with human immunodeficiency virus, those prescribed medication incompatible with breastfeeding, those with psychiatric disorders, and those with hearing or cognitive deficiencies.

Antenatal education

Since 2003, the Woman's Hospital has held accreditation from the Baby Friendly Hospital Initiative (BFHI).[14] In line with BFHI's recommendations, trained nursing staff provide group orientation on breastfeeding to all pregnant women receiving antenatal care. Additionally, the Woman's Hospital consistently offers breastfeeding orientation and support throughout labor and the postpartum hospital stay. To uphold the ten steps to successful breastfeeding and ensure consistent quality, all healthcare professionals involved in promoting and supporting breastfeeding undergo BFHI training and certification. This guarantees that all accredited healthcare facilities maintain the same high standards.[14]

The outpatient clinic routinely offers an open antenatal education group for pregnant teenagers, focusing on various themes related to adolescent pregnancy. This group provides a secure environment and aims to empower these young women through educational interventions. Topics covered include sexual and reproductive rights, contraception, mental health, newborn care, health awareness, and gender issues. The group convenes twice weekly, during both antenatal and postpartum care periods for adolescents.

Data collection

The adolescents were categorized into two groups based on their antenatal care location. The Woman's Hospital (WH) group consisted of adolescents who received pregnancy monitoring at the hospital, thus having access to antenatal education programs. The Primary Care (PC) group comprised adolescents monitored in primary healthcare facilities. Data collection from each participant occurred at three intervals: within 1–3 days post-childbirth (during the postpartum hospital stay), 40–60 days post-childbirth (during the 1st postpartum care visit), and 6 months post-childbirth.

The initial time point takes place in the rooming-in setting, a designated area for accommodating the mother-baby dyad during the postpartum hospital stay. This setting is staffed by a multi-professional team available 24 hours a day to assist women and newborns without perinatal or delivery complications. Consequently, dyads with a contraindication to breastfeeding, such as severe prematurity, are not allocated to the rooming-in setting.

Data about breastfeeding intent and confidence were gathered during the postpartum hospital stay. At the initial postpartum care visit, participants completed a questionnaire regarding breastfeeding maintenance, the newborn support network at home, and pacifier use. Six months post-childbirth, a follow-up phone interview was conducted with the adolescent mothers, during which they were once again asked about breastfeeding maintenance.

The authors designed a questionnaire to assess participants' confidence in breastfeeding, posing the following closed-ended questions: "During pregnancy, were you prepared to breastfeed your child?" and "Upon first holding your child to breastfeed, did you know how to proceed?" To gauge participants' intent to breastfeed, the question asked was: "Did your participation in the WH influence your decision to breastfeed your child?"

The secondary outcomes included: the primary subjects remembered by WH adolescents from the antenatal education (e.g., "Can you recall the topics discussed during the antenatal education?"); the source of breastfeeding information during pregnancy among PC adolescents; the influence of a mother's primary support network; and the utilization of a baby pacifier.

During the postpartum hospitalization, sociodemographic, obstetric, and perinatal outcomes were gathered from both the medical record and the prenatal card.

Sample size

The study's sample size was determined with the aim of comparing exclusive breastfeeding rates 6 months postpartum. However, comparisons were also made during the initial postpartum visit and across two distinct periods within each group, resulting in four comparison groups. The sample size calculation was based on the methodology for a Pearson's Chi-square test,[15] with a significance level of 1.25%, a test power of 80.0%, and an assumed effect size of 0.30, which is considered a medium effect size.[16] Consequently, a minimum of 124 participants was required for the study.

Statistical methods

Descriptive analysis was conducted using the mean and standard deviation for numerical variables, and percentage and n for categorical variables. Bivariate analyses, including Student's t-test, Mann–Whitney, and chi-squared tests, were utilized to compare the groups. Log-binomial models were also calculated to compare the groups across different periods when breastfeeding rates were observed. The level of significance was set at 5%. Stata 17 version 14.0 for Windows (64 bit) (StataCorp, College Station, United States) was the statistical software employed. To ensure data accuracy, double-typing was executed using Microsoft Excel software for Windows (Microsoft, Redmond, United States).

Ethics

The Ethics and Research Committee of UNICAMP approved this study on July 20, 2017 (CAAE: 69198417.4.0000.5404; number: 2.180.783, date: July 20, 2017). All participants under the age of 18, after reading, understanding, and having their queries addressed, signed an informed consent form, which was countersigned by their legal representative. Participants aged 18 years and older provided their signatures on the consent form. The study procedures strictly adhered to the STROBE guidelines.[17]

RESULTS

Between August 2018 and February 2019, 132 adolescents were included in the study, with a mean age of 16.7 (± 1.2) years (**Table 1**).

Following the distribution, 59 adolescents were allocated to the WH group, while 73 were assigned to the PC group (**Figure 1**). In the WH group, 11.9% (7) of the girls failed to attend the initial postpartum visit, compared to 16.4% (12) in the PC group (P = 0.46). Six months post-childbirth, 36.5% (19) of the adolescents in the WH group and 31.1% (19) in the PC group did not respond to the telephone call (P = 0.54).

Of the WH participants, six (15.8%) reported feeling unprepared to breastfeed their children, compared to 21 (43.7%) of the PC participants (P = 0.01). Furthermore, 12 (31.6%) of the WH participants and 29 (56.8%) of the PC participants were unsure about how to breastfeed when they held their newborns for the first time (P = 0.02).

At the first postpartum care visit, 74 (65.5%) of all adolescents were breastfeeding their children, 50 (44.2%) of them exclusively. At 6 months following childbirth, 60 (80%) of all adolescents were breastfeeding their children, 31 (41.6%) of them exclusively.

Table 1. Sociodemographic and anthropometric characteristics, number of antenatal care visits, and perinatal outcomes of adolescent mothers (n = 132)

	Woman's Hospital (n = 59)		Primary Care (n = 73)		P value
	Mean	Standard deviation	Mean	Standard deviation	
Age (years)	16.2	1.3	16.9	1.12	0.01[b]
Number of antenatal care visits	10.6	2.7	9.2	2.2	0.03[b]
BMI before pregnancy	22.7	5.3	23.4	5.5	0.63[b]
Gestational weight gain	10.6	6.7	12.1	6.9	0.27[b]
Newborn weight (g)	3127.7	367.6	3009.9	404.8	0.16[a]
	n	%	n	%	P value
White skin color	25	64.1	26	53.1	0.58[c]
With partner	30	81.1	32	68.1	0.18[c]
Student	26	70.2	26	53.1	0.11[c]
Compatible age-degrees	27	77.1	37	77.1	0.99[c]
Gestational age < 37 (weeks)	1	1.8	7	10.3	0.07[c]
Vaginal delivery	26	70.3	38	79.2	0.35[c]
Newborn weight < 2.500g	4	6.9	5	7.1	< 0.99[c]

[a] Student's t-test; [b] Mann–Whitney test; [c] Chi-squared test.

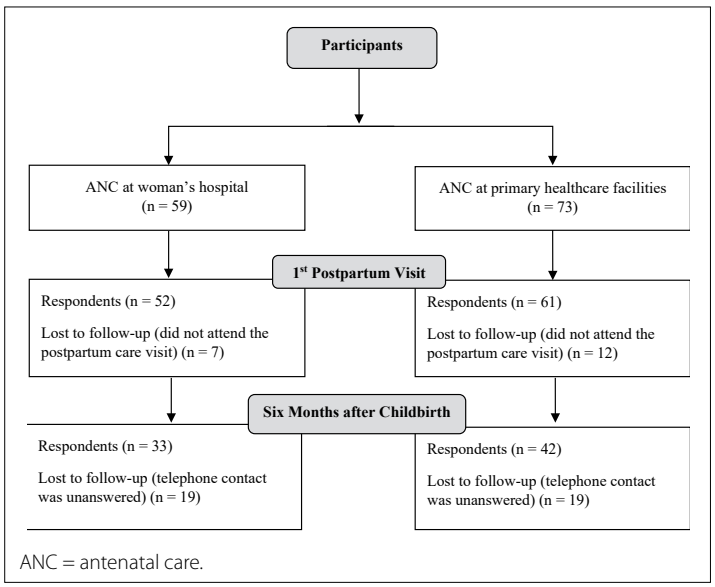

Figure 1. Flowchart of participants' progress through the points of the cohort.

The rates of breastfeeding by group and over time are described in **Table 2** and **Table 3**, respectively.

All WH participants indicated that participating in antenatal education increased their intent to breastfeed their children. Recollection of the topics covered during the antenatal education resulted in the following: the advantages of breastfeeding (n = 41; 71.9%); the importance of breastfeeding in the first hour of a child's life (n = 29; 50.9%); and how to take care of one's breasts during breastfeeding (n = 24; 42.1%).

Among PC participants, 47 (64.4%) did not receive information about breastfeeding during pregnancy and described only having received such information during their postpartum hospitalization at the Woman's Hospital. The main sources of breastfeeding information for adolescents with PC were healthcare professionals (n = 12; 16.4%), family members (n = 11; 15.1%), and the internet (n = 10; 13.7%).

The adolescents consistently identified their primary support network across both groups: their partner (if present) and their mother. The use of a baby pacifier was noted in 15 (39.5%) of the WH participants and 32 (62.7%) of the PC participants (P = 0.03).

DISCUSSION

This research demonstrates that antenatal education positively impacts adolescents' ability to sustain breastfeeding for the first 6 months post-childbirth. It also positively affects a mother's intention to breastfeed. In general, adolescent mothers reported feeling more prepared to breastfeed after participating in antenatal education.

The observed rate of exclusive breastfeeding at 6 months postpartum (41.6%) exceeded the rate reported in the literature for teenagers.[6,18] However, this rate falls short of the global rate (42%) [5] and is significantly lower than the Global Nutrition Targets 2025 (50%).[10] In our study, adolescents from WH breastfed for a longer duration than those from PC, regardless of exclusivity. Other studies that explored the impact of education and support provided to breastfeeding mothers have also noted a positive effect of antenatal education on breastfeeding, not just among adolescents but also in the adult female population.[3,4,18,19] Moreover, research has shown that breastfeeding education can positively influence breastfeeding practices even when offered solely during the postpartum hospital stay and/or the breastfeeding period.[4,20,21] In our study, all adolescents, both from WH and PC, received breastfeeding education during their postpartum hospital stay. This could account for the higher breastfeeding rate achieved in comparison to the rates reported in the literature.[6,20]

Table 2. Univariate logistic regression on maintenance of breastfeeding among primiparous adolescents according to the place where antenatal care was given (n = 132)

	Woman's Hospital		Primary Care		OR	95% CI[a]	P value
	n/total	%	n/total	%			
Breastfeeding							
Postpartum care visit	38/52	97.4	36/33	70.6	1.38	1.15–1.66	> 0.001
Six months after delivery	32/61	82.5	28/42	54.9	1.49	1.12–1.99	0.006
Exclusive Breastfeeding							
Postpartum care visit	26/52	66.6	24/33	47.1	1.42	0.98–2.04	0.062
Six months after delivery	18/61	46.1	13/42	25.5	1.81	1.01–3.23	0.044x

OR = Odds ratio; CI = confidence interval; [a]95%CI OR = 95% confidence interval for odds ratio.

Table 3. Univariate logistic regression on the maintenance of breastfeeding over time among primiparous adolescents (n = 132)

	Postpartum care visit		Six months after delivery		OR	95% CI[a]	P value
	n/total	%	n/total	%			
Breastfeeding							
Woman's Hospital	38/52	97.4	32/33	82.0	0.84	0.72-0.99	0.034
Primary Care	36/61	70.6	28/42	54.9	0.78	0.65-0.93	0.005
Exclusive Breastfeeding							
Woman's Hospital	26/52	66.7	18/33	46.1	0.69	0.54-0.89	0.005
Primary Care	24/61	47.1	13/42	25.5	0.54	0.36-0.81	0.003

OR = Odds ratio; CI = confidence interval; [a]95% CI OR = 95% confidence interval for odds ratio.

A notable decline in breastfeeding rates was observed six months postpartum, even among WH participants. This finding underscores the necessity of not just educating mothers about breastfeeding but also providing sustained social support, especially for adolescent mothers. A qualitative study involving young mothers identified four primary obstacles to breastfeeding: stigma, role, place, and support. Stigma relates to the embarrassment of breastfeeding in public and the identity of being a young mother. Role refers to the difficulties of juggling the dual responsibilities of being an employee or student and a mother. The place barrier involves the lack of time or support at school or work, coupled with the absence of facilities to store expressed milk. Lastly, the support barrier is tied to the lack of adequate breastfeeding support within the broader community or from unsupportive family members.[5,21]

Participants in the WH were more adequately prepared to breastfeed their infants upon first holding them. Additionally, adolescent participants in the WH reported an increased intention to breastfeed following their involvement in the antenatal education group. Other research involving both adolescent and adult mothers has suggested that frequent attendance at support group meetings leads to improved attitudes toward breastfeeding, reduced barriers to breastfeeding, and increased breastfeeding rates.[3,20,22]

Emphasizing the significance of a higher breastfeeding rate is crucial, as it contributes to the attainment of the Sustainable Development Goals (SDG.) Research has demonstrated that breastfeeding can enhance educational achievement and income in adulthood, thereby addressing SDG1: no poverty, SDG4: quality education, and SDG8: decent work and economic growth. Furthermore, breastfeeding can help prevent hunger, malnutrition, and obesity, aligning with SDG2: zero hunger and SDG3: good health and well-being.[23] Additionally, the right of women to breastfeed and express milk in public spaces is recognized, supporting SDG5: gender equality.

Our observation revealed that a significant proportion (64.4%) of PC adolescents did not receive any information about breastfeeding during antenatal care. The majority of these adolescents obtained breastfeeding information from their family and friends. However, health professionals are deemed the most qualified individuals to provide adolescents with breastfeeding advice. The internet was another significant source of breastfeeding information reported. It is crucial to underscore that the participants in our study are adolescents from "Generation Z." Consequently, the internet and social media play a substantial role in their lives and can also serve as a valuable platform for healthcare professionals and organizations to advocate for exclusive breastfeeding practices.[24]

We observed a minor, albeit insignificant, difference in the prematurity rate between adolescents in the PC group and those in the WH group. Prematurity often poses a significant challenge to successful breastfeeding due to the increased suckling difficulties experienced by premature infants.[25] At the Women's Hospital, all mother-infant pairs in the rooming-in setting have the opportunity to breastfeed. Premature infants who are unable to breastfeed are accommodated in the Neonatal Care Unit. Therefore, in our study, prematurity was not deemed a source of bias.

Both groups included adolescent mothers with partners. The literature extensively documents the beneficial impact of a father's presence

on a child and the breastfeeding regimen.[18,26] Regular interaction, such as cohabitation, with grandmothers, has been linked to a decrease in breastfeeding initiation and an increased risk of early weaning. Conversely, support from maternal grandmothers for breastfeeding has a positive correlation with the maintenance of breastfeeding.[18]

The adolescent demographic in WH was slightly younger compared to that in PC. This could be attributed to WH being a tertiary referral hospital, offering specialized antenatal care for teenagers. A notable difference between the two groups was the number of ANC visits. Nevertheless, the number of antenatal visits in both groups adhered to the WHO recommendation of eight health visits for pregnant women.[27]

Our study is subject to certain limitations. Primarily, the healthcare professionals disseminating information to the multidisciplinary and BFHI groups could vary on a weekly basis. Nevertheless, all healthcare professionals involved in breastfeeding promotion and support have undergone BFHI training and certification, independent of this study. This is to mitigate potential discrepancies in guidance within the group and to ensure uniformity in the approaches to the topics discussed. Secondly, akin to other studies,[28] a substantial number of missed follow-up appointments were noted. Factors such as sociodemographic, cultural, and logistical determinants could potentially contribute to higher rates of missed follow-ups among adolescents. To counteract this, adolescents who missed their postpartum care visit were promptly contacted via telephone to reschedule. Lastly, the retrospective questions posed during the hospital stay may have induced recall bias, as the adolescent mothers were physically exhausted and preoccupied with newborn care.

CONCLUSIONS

We advocate for all expectant women, particularly adolescent ones, to receive antenatal education on breastfeeding to boost breastfeeding rates. When group participation is impractical, it falls to healthcare professionals to guide and support expectant and postpartum mothers through their breastfeeding journey. Antenatal education groups, being cost-effective and capable of accommodating a larger number of women, can act as a catalyst in low- and middle-income countries.

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The influence of hemodialysis on intracranial pressure waveform in patients with chronic kidney disease: an observational study

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Intracranial pressure waveform.

ABSTRACT

BACKGROUND: Among the complications related to chronic kidney disease (CKD), those of a neurological nature stand out, and for a better quality of life for patients, the diagnosis and treatment of these complications is fundamental.

OBJECTIVES: This study aimed to assess the effect of hemodialysis on intracranial pressure waveform (ICPw) in patients with chronic kidney disease undergoing hemodialysis and those who are not yet undergoing substitutive therapy.

DESIGN AND SETTING: An observational study was conducted in two stages at a kidney replacement therapy center in Brazil. The first was a longitudinal study and the second was a cross-sectional study.

METHODS: Forty-two patients on hemodialysis were included in the first stage of the study. In the second stage, 226 participants were included. Of these, 186 were individuals with chronic kidney disease (who were not undergoing substitutive therapy), and 40 did not have the disease (control group). The participants' intracranial compliance was assessed using the non-invasive Brain4care method, and the results were compared between the groups.

RESULTS: There was a significant difference between the hemodialysis and non-hemodialysis groups, with the former having better ICPw conditions.

CONCLUSIONS: Hemodialysis influenced the improvement in ICPw, probably due to the decrease in the patients' extra-and intracellular volumes. Furthermore, ICPw monitoring can be a new parameter to consider when defining the moment to start substitutive therapy.

INTRODUCTION

Chronic kidney disease (CKD) has become one of the main causes of death and suffering in the 21st century, affecting approximately 10% of the worldwide population, accounting for approximately 843.6 million ill individuals, with a higher prevalence among older adults, women, racial minorities, and those with diabetes mellitus and hypertension.[1]

Kidney disease has become a public health concern due to its increasing prevalence and high treatment costs for the public. In clinical terms, kidney disease is characterized the loss of kidney function occurs over time. Diagnosis is based on the mean glomerular filtration rate (GFR) (GFR < 60 mL/min/1.73 m^2 for ≥ 3 months), and the presence of kidney damage is determined through biopsy or other markers of kidney damage.[2] The classification of the progression of this disease is based mainly on the GFR, and five stages have been established, as shown in **Figure 1**. The prevalence of the initial stages of chronic kidney disease is significantly higher than that of end-stage kidney disease (ESKD).[3] The consequences of the illness, besides the loss of kidney function, include cardiovascular disease and premature death,[3] in which the risk of death due to a cardiovascular event is higher than that of requiring hemodialysis or a transplant. Approximately 4 million people worldwide depend on kidney replacement therapy, of which 89% undergo hemodialysis.[2] The complications related to hemodialysis are common. Some are even expected due to the hemodialysis process itself, in which the patient bears hours of extracorporeal blood flow, forced ultrafiltration, and exposure to large quantities of dialysate. Unexpected complications include infectious diseases, mineral metabolism disorders, and neurological complications, such as hemodialysis imbalance syndrome.[4]

Neurological complications may be responsible for the incapacity and mortality of patients with CKD and may affect both dialytic and pre-dialysis patients. Additionally, they may affect both the central and peripheral nervous systems and are frequently neglected and rarely acknowledged. Laboratory tests, imaging studies, and neurophysiological tests are some of the tools available for diagnosis. Treatment involves a multifactorial approach, and prognosis depends on the availability of treatment and its precocious start.[5]

A non-invasive intracranial pressure waveform (ICPw) monitoring tool was developed by the Brazilian company Brain4care Inc. (São Carlos, São Paulo, Brazil). This novel approach to studying neurological disturbances has already been applied in hemodialysis patients. The technology is based on capturing small variations in the skull caused by ICP alterations through a voltage sensor in contact with the lateral region of the sagittal suture, providing real-time ICPw data. This ICPw is composed of three peaks (**Figure 2a**), and from the morphology of this wave, it is possible to infer intracranial compliance (**Figures 2b – normal** and **2c – altered**).[6]

A first cross-sectional study using this technology in patients with ESKD undergoing hemodialysis indicated that these patients frequently experience alterations in intracranial compliance and that high-quality hemodialysis (according to Kt/V) might be effective in normalizing intracranial compliance.[7] Kt/V is a formula used to measure dialysis adequacy, in which K is urea clearance by the dialyzer, t is the time of treatment, and V is the volume of urea distribution in the patient. The recommended Kt/V is maintained above 1.2 during hemodialysis.[8] A subsequent follow-up study evaluated the intracranial compliance (by means of the ratio between the peaks P2/P1) pre-dialysis and post-dialysis, demonstrating that the P2/P1 ratio was less than that observed before the dialysis was done, reinforcing the previous finding that hemodialysis generates a positive effect on intracranial compliance.[9]

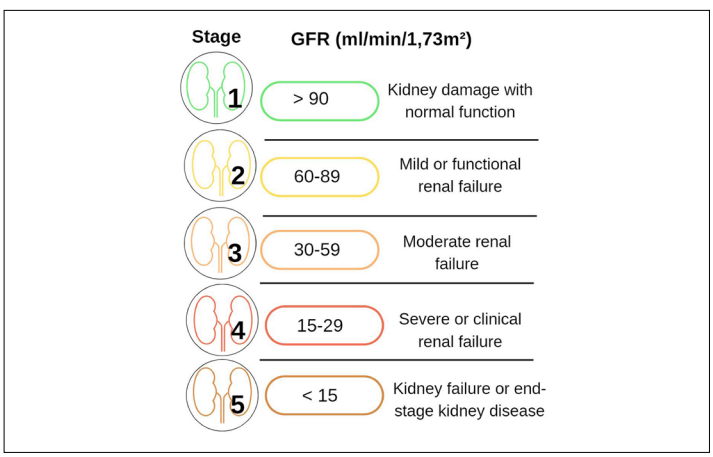


Figure 1. Stages of chronic kidney disease based on the glomerular filtration rate.

Based on these results, the need to investigate alterations in intracranial compliance in the initial stages of CKD as well as in those patients in stage 5 who do not undergo dialysis is required. Patients with CKD enter stage 5 when their GFR is < 15 mL/min/1.73 m^2, but dialysis is usually indicated when the GFR is < 10 mL/min/1.73 m^2.[10]

OBJECTIVE

The aim of this study was to analyze intracranial compliance in different CKD stages (stages 1, 2, 3, 4, and 5 non-dialytic) compared with the results obtained in patients undergoing dialysis[9] and a control group.

METHODS

This study was conducted in two stages at a substitutive kidney therapy center (KTC) of a hospital in southern Brazil. Both protocols were approved by the Research Ethics Committee of Universidade Estadual de Ponta Grossa (protocols: 1.834.627, approved on 2016, Nov. 24; 4.039.453, approved on 2020, May 20) and the study followed the STROBE.[11]

Participants

The participants were patients with chronic kidney disease from the southern region of the state of Paraná, most of whom have diabetes and high blood pressure and were being treated by the Unified Health System (in Portuguese, Sistema Único de Saúde – SUS). The first stage was an observational,

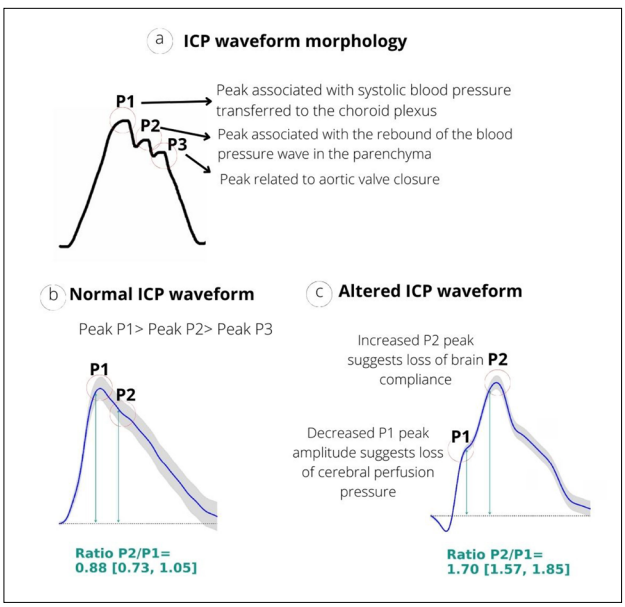


Figure 2. (a) Morphology of an intracranial pressure wave composed of three peaks; (b) Morphology of a normal intracranial pressure wave; (c) Morphology of an intracranial pressure wave with alteration.

longitudinal, prospective study of 42 patients with terminal kidney disease who underwent hemodialysis periodically, three times a week, for six months.[9] The study started in January 2017 and ended in August 2018. The second stage was an observational, cross-sectional study that included 226 participants. Of those, 186 were patients with CKD in stages 1–5 but who still did not undergo any kind of substitutive kidney therapy, and 40 did not present with CKD and were classified as the control group. The choice of control group participants was randomized, including individuals of similar age groups as those in the CKD group. The second stage began in October 2019 and ended in October 2021. During both stages, the sampling was convenient because this was an unprecedented study according to the number of patients admitted at the KTC.

Every participant received information about the study and willingly participated after signing the two-part form of the Consent Term (Termo de Consentimento Livre e Esclarecido). As inclusion criteria, it was established that participants should be ≥ 18 years and considered legally capable. The clinical characteristics of patients were obtained using questionnaires and consultations with online medical records from the KTC. The study was conducted in accordance with the Code of Ethics of the World Medical Association (Declaration of Helsinki).

Monitoring of intracranial compliance

Intracranial compliance was monitored using non-invasive equipment provided by the company Brain4care. Two examiners participated in the research, one for each stage, and they underwent previous training provided by the company. This method is innovative, validated,[12] safe, and detects micrometric deformation of the cranial bones through a mechanical extensometer attached to a sensor. This sensor is fixed to a band and coupled to the lateral position of the patient's head, approximately 2 cm above the ear. The detected deformations were transformed into electrical signals and displayed on a monitor. The amplification stage then occurs in which the equipment filters, amplifies, digitizes, and records the signals. The monitor displays are saved and sent to the Brain4care Analytics software, which provides us with a report of each display in which the wave morphology of the ICP and the amplitude of its peaks can be observed.[13] The equipment used was properly calibrated by Brain4care.

At the moment of monitoring, the individuals stood still, sat down, and were monitored for approximately 3–5 min. The patients in the first stage, who underwent hemodialysis, were monitored pre- and post-dialysis in every session during the 6-month period in which they were assessed. Patients in the second stage underwent one monitoring session.

Statistical analysis

Two comparison models were created for the P2/P1 ratio. The first included three groups: 1) individuals without CKD; 2) individuals with CKD who did not undergo substitutive treatment; and 3) individuals who underwent hemodialysis. The second model differs from the first because it includes three levels of CKD severity among patients with the disease who did not undergo hemodialysis. The levels of severity were: mild, which includes individuals at stages 1 and 2; moderate, which includes individuals at stages 3a and 3b; and severe, which includes individuals at stages 4 and 5. In this way, Model 2 included five groups: 1) individuals without CKD; 2) individuals with CKD in the mild form; 3) individuals with CKD the moderate form; 4) individuals with CKD in the severe form; and 5) individuals undergoing hemodialysis.

The average P2/P1 ratio of each patient undergoing hemodialysis was calculated pre- and post-dialysis monitoring. Pre-dialysis values were selected for a more reliable analysis, as post-dialysis values could be affected by all dialysis procedures.

Analysis of the quantitative value of the ICPw P2/P1 ratio in both models utilized an analysis of variance (ANOVA) with Tukey's post-hoc test. We conducted the Shapiro-Wilk test to verify the normality of the data ($P > 0.05$).

To assess the discriminative power of ICPw in CKD patients undergoing enhanced hemodialysis compared with those who still required it, we generated a receiver operating characteristic (ROC) curve using the P2/P1 ratio as a factor. The ROC curve plots the sensitivity (true positive rate) against 1-specificity (false positive rate) for different cut-off values of the P2/P1 ratio, displaying the relationship between sensitivity and specificity across a range of cut-off values. We calculated the area under the curve (AUC) to evaluate the overall diagnostic accuracy of non-invasive intracranial pressure measurements. The optimal cut-off value was determined by maximizing the Youden index, which combines sensitivity and specificity to measure the overall diagnostic accuracy. By comparing the ROC curves of patients with CKD not undergoing hemodialysis with those of patients with CKD undergoing hemodialysis, we assessed the discriminative power of non-invasive intracranial pressure measurements between the two groups. Statistical significance was set at a significance level of 5% ($P < 0.05$). All calculations were performed using GraphPad Prism version 9.00 Windows (GraphPad Software, La Jolla, California, USA).

RESULTS

Clinical parameters

The clinical parameters of the patients included in this study are shown in **Table 1**. The largest group we studied was patients with CKD undergoing hemodialysis (n = 42), and the smallest group

was patients with stage 5 CKD not undergoing dialysis (n = 19). The age of the volunteers varied between 18 and 90 years.

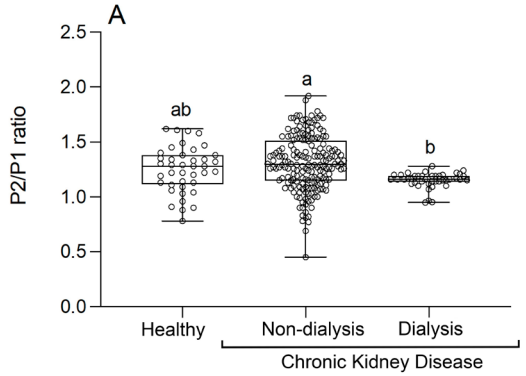
Comparative analysis of the P2/P1 ratio results between the groups

There was a significant difference between the analyzed groups (**Figure 3**); the patients undergoing dialysis mostly presented a P2/P1 ratio close to 1 (ratio P2/P1 ≤ 1 = normality). The group of patients not undergoing dialysis had the highest P2/P1 ratio. An alteration in intracranial compliance was also observed in the control group (healthy); the average P2/P1 ratio in these patients was > 1.

Table 1. Mean age and percentage of individuals of each sex within each group (control group, stages 1–5 of chronic kidney disease who do not undergo hemodialysis, and stage 5 who undergo hemodialysis)

Clinical parameter	n	Age, in years, mean (range)	Sex, n (%)	
			Men	Women
Control group	40	45.0 (23–90)	45%	55%
CKD Stage 1	26	39.6(18–66)	35%	65%
CKD Stage 2	33	49.4 (26–73)	39%	61%
CKD Stage 3a	34	66.3 (28–78)	53%	47%
CKD Stage 3b	39	63.1 (36–81)	39%	61%
CKD Stage 4	35	64.54 (35–90)	43%	57%
CKD Stage 5 non-dialysis	19	60.6 (41–79)	47%	53%
CKD Stage 5 dialysis	42	55.8(21–87)	55%	45%

CKD = chronic kidney disease.



Box plot with the average and interquartile break of non-invasive intracranial pressure values obtained from healthy volunteers and patients with different stages of chronic kidney disease without and with hemodialysis. (A) ratio P2/P1, significant difference (P = 0.0002). Different letters represent significant differences (P < 0.05). The circles represent volunteers. Analysis of variance (ANOVA) with Tukey's post hoc test

Figure 3. Comparison of the intracranial pressure P2/P1 ratio values of control participants, patients with chronic renal failure who do not undergo hemodialysis, and patients who undergo hemodialysis.

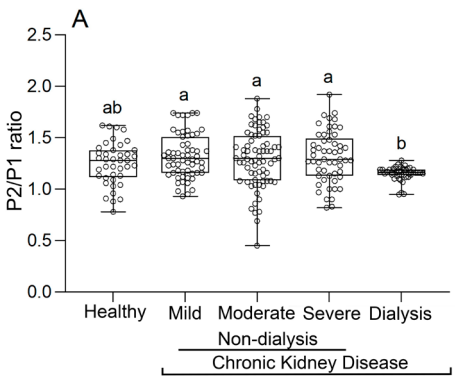
The graph ahead (**Figure 4**) brings a wider analysis of the results presented in the previous graph (**Figure 3**). The patients in the group "without hemodialysis" were classified into three categories: mild CKD, moderate CKD, and severe CKD, for a thorough analysis of what happens during intracranial pressure in the different stages of kidney disease.

The mild, moderate, and severe CKD groups had similar P2/P1 ratios. However, there was a significant difference between the CKD groups without hemodialysis and patients undergoing hemodialysis. The healthy patients had similar results to the patients in the groups "mild," "moderate," and "severe," undergoing hemodialysis.

An ROC curve was generated for the P2/P1 ratio to assess its diagnostic performance in patients with CKD in both the hemodialysis and non-hemodialysis groups. The P2/P1 ratio demonstrated discriminative power, with an AUC value of 0.728 (P < 0.0001). Hence, the P2/P1 ratio serves as a good marker for distinguishing between hemodialysis and non-hemodialysis patients with CKD (**Figure 5**).

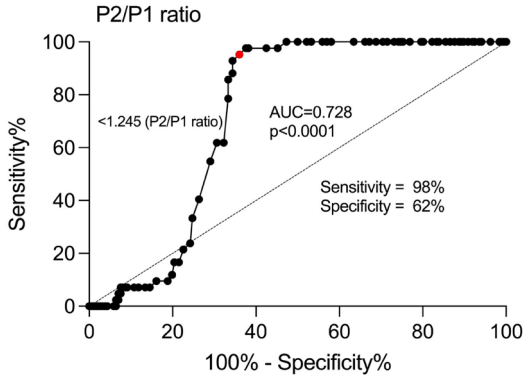
DISCUSSION

In this study, we demonstrated that the group of individuals undergoing hemodialysis presented better intracranial compliance than the group of individuals with CKD who did not undergo substitutive kidney therapy. One of the most affected organs by CKD is the brain, and varied neurological damages are commonly observed in kidney patients, such as cognitive



Legend: Box plot showing the average and interquartile interval of non-invasive intracranial pressure values obtained from healthy volunteers and patients at different stages of chronic kidney disease. (A) ratio P2/P1, significant difference (P = 0.0018). Comparison between the groups: Different letters represent significant differences (P < 0.05). The circles represent volunteers. Analysis of variance (ANOVA) with Tukey's post hoc test

Figure 4. Comparison of the ICP P2/P1 ratio values of control participants, patients with chronic renal disease in mild, moderate, and severe stages who do not undergo hemodialysis, and patients who undergo hemodialysis.



Legend: The ROC curve of the P2/P1 ratio was used to assess the distinguishing power between patients with CKD undergoing hemodialysis and not undergoing hemodialysis. The area under the curve (AUC): 0.728, sensitivity: 98%, specificity: 62%, cut-off: 1.245 (red dot), P < 0.0001.

Figure 5. Receiver operating characteristic (ROC) curve of non-invasive intracranial pressure (P2/P1 ratio) in hemodialysis and non-hemodialysis patients with chronic kidney disease.

deterioration, encephalopathy, convulsions, and strokes.[14] One of the pathological mechanisms is brain edema, which can be due to the accumulation of uremic toxins[15] and increase in extracellular fluid, progressing as the GFR decreases, causing ICP elevation.[16] Patients who undergo hemodialysis are in the terminal stage of the disease and present a very low GFR. In addition, the ICP in these patients was better, probably because of the decrease in fluid volume due to hemodialysis. This aligns with our results of the ICPw comparison pre- and post-dialysis, indicating improvement after the procedure.[9] Therefore, hemodialysis plays an important role in the improvement of ICPw. The mild, moderate, and severe CKD groups exhibited similar P2/P1 ratios. The hypothesis for this result is the administration of adequate treatment for these patients and the differences in the protocols for each stage. As CKD progresses, the disease management protocol becomes more complex and rigid, requiring better control of laboratory parameters and administration of medications.[10]

An additional interesting finding of this study was the distinction between the groups of patients with CKD who underwent hemodialysis and those who did not. Using the ROC curve, we determined a cut-off point of 1.245 for the P2/P1 parameter, with an AUC value of 0.728 and a sensitivity of 98%. AUC is a widely used performance measure for assessing the accuracy of a binary classification model. AUC values close to 1.0 indicate excellent performance in correctly classifying true categories; values between 0.7 and 0.9 are considered indicative of moderate to good performance; and AUC values between 0.5 and 0.7 are deemed poor to moderate performance.[17] Hence, our findings suggest that the P2/P1 ratio serves as a reliable marker for distinguishing between the two groups.

Neurological manifestations may appear in any CKD stage, with higher chances in the late stages.[18] In the early stages, the main symptoms reported are: difficulty focusing, lack of attention, emotional unbalance, depression, and recent memory impairment.[14] In the more advanced stages, the accumulation of organic waste and toxins causes loss of consciousness, convulsions, and coma.[15] Although the neurological symptoms become more evident in the terminal stage of the disease, their identification and adequate management in the early stages delay the progression and effects of these complications.[19] Usually, initiating dialysis in patients with chronic kidney disease is determined based on the presentation of typical symptoms of kidney insufficiency, which often occur with a GFR 5–10 mL/min/1.73 m^2, and include mental confusion and loss of consciousness.[20] In this context, the monitoring of the ICPw might aid in investigating neurological disturbances at every stage of CKD. In summary, the ICPw follow-up in the last CKD stage might be one of the determining factors in initiating substitutive renal therapy. Hemodialysis has demonstrated efficient ICPw improvement in these patients, reducing the symptoms and improving the quality of life.

In the control group, a large number of individuals presented with alterations in ICPw. This may be attributed to the presence of diseases such as arterial hypertension, diabetes, and obesity observed in some of these patients, which may interfere with brain self-regulation. Brain self-regulation corresponds to the capacity of the brain to maintain adequate blood flow through variations in arterial pressure,[21] and its limits are an average arterial pressure between 60 and 160 mmHg for healthy adults.[22] Furthermore, thickening of the internal basal membrane of the brain microvasculature and an increase in the P2 peak in mice with diabetes was observed. The hypothesis is that the damage to the brain microvasculature in diabetes mellitus compromises intracranial compliance.[23] In addition, diabetic ketoacidosis, a complication of diabetes, may lead to brain edema, which may cause intracranial hypertension.[24] Moreover, many authors associate obesity with the development of idiopathic intracranial hypertension.[25,26] Idiopathic intracranial hypertension is characterized by increased intracranial pressure of uncertain etiology, primarily affecting obese women of reproductive age.[27] Although its pathophysiological mechanism is unknown, the risk of developing idiopathic intracranial hypertension intensifies according to the body mass index.[25,28] Notwithstanding, overweight and obesity are factors that increase the probability of cerebrovascular diseases, which may lead to intracranial hypertension.[29] Other possibilities for the ICPw alteration in patients of the control group could include undiagnosed medical conditions that may affect intracranial compliance and arterial hypertension, which may exceed the brain's self-regulation limit. Although these

data are noteworthy, they are not the focus of this study, and more studies are being conducted with the objective of clarifying the behavior of the ICPw and related variables.

This research has some limitations, such as convenience sampling of only one KTC, which may generate biased selection. Furthermore, in the second stage, only one monitoring of each patient was performed, providing accurate data without the possibility of following up. Additionally, both stages were not performed concurrently, with the possibility of protocol changes between the years of the study.

Despite its limitations, this study demonstrates the relevance of monitoring ICPw in patients with CKD from the early stages until the terminal stage. The incorporation of the non-invasive monitoring method of the ICPw in the follow-up of patients with chronic renal diseases aids in their treatment, resulting in an improved quality of life and preventing complications such as strokes, which are common in these individuals. In patients in the terminal stage, ICPw monitoring may be an auxiliary tool in the decision to initiate hemodialysis, as it influences ICPw improvement.

CONCLUSION

In conclusion, hemodialysis influences ICPw control in patients with CKD at the terminal stage. In addition, we suggest non-invasive monitoring using ICPw as a new parameter in deciding the moment at which the patient with CKD must initiate substitutive kidney therapy, with the objective of minimizing the risks to the brain and improving the patient's quality of life.

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A comparison of pre- and post-operative outcomes in living donors undergoing transperitoneal laparoscopic nephrectomy and open nephrectomy: a retrospective single-center study

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Live donor.

ABSTRACT

BACKGROUND: Kidney transplantation is often regarded as the preferred therapy for end-stage renal disease. Several surgical procedures have been developed to reduce postoperative donor complications, while maintaining kidney quality.

OBJECTIVE: This study aimed to compare the preoperative and postoperative outcomes of living kidney donors who underwent either transperitoneal laparoscopic nephrectomy or open nephrectomy.

DESIGN AND SETTING: Retrospective study conducted in Istanbul, Turkey.

METHODS: Fifty-five living-related kidney donors underwent nephrectomy and were retrospectively divided into two groups: 21 donors who underwent open nephrectomy (Group 1) and 34 donors who underwent transperitoneal laparoscopic nephrectomy (Group 2).

RESULTS: In comparison to the donors who underwent open nephrectomy, those who underwent transperitoneal laparoscopic nephrectomy had significantly shorter postoperative hospital stays (2.3 ± 0.2 versus 3.8 ± 0.8 days, P = 0.003), duration of urinary catheterization (1.2 ± 0.8 days versus 2.0 ± 0.7 days, P = 0.0001), operating times (210 ± 27 minutes versus 185 ± 24 minutes, P = 0.02), and less blood loss (86 ml versus 142 ml, P = 0.048). There was no statistically significant difference between the two groups with regard to the estimated blood transfusion and warm ischemia time. The preoperative week, first postoperative week, and 1-month postoperative serum creatinine levels were comparable between the groups.

CONCLUSIONS: Laparoscopic donor nephrectomy can be safely performed at centers with expertise in laparoscopic surgery. Laparoscopic donor nephrectomy has better outcomes than open donor nephrectomy in terms of length of hospital stay, duration of urinary catheterization, operating time, and blood loss.

INTRODUCTION

Improvements in technique have resulted in better outcomes for laparoscopic donor nephrectomy.[1,2] Ratner introduced this technique in 1995; it is now performed more frequently, with higher success rates.[3] Donor nephrectomy is distinguished from other surgical procedures in that the surgery is performed on a healthy individual to improve the health of another. This places a strong emphasis on reducing donor morbidity and implementing minimally invasive approaches. There is an increasing gap between organ supply and demand, which has also played a role in the recent trend toward living-donor kidney transplantation.

Transplant recipients receive numerous benefits from living donations, and the operation can be planned. However, donors do not receive the same benefits.[4] Some of the advantages of transperitoneal laparoscopic nephrectomy over open methods are reduced intraoperative blood loss, improved aesthetics, shorter hospital stay, and faster overall postoperative recovery, which allows the recipient to return to normal activity in a shorter period. As a result of these advantages, the number of living-donor kidney transplants has increased.[5,6] Currently, most transplantation centers harvest living-donor kidneys using a conventional laparoscopic surgical approach.[6] Transplantation teams accept living kidney donations under conditions that suggest a safe long-term outcome for the donor.[7]

OBJECTIVE

We aimed to evaluate and compare early complications and renal function following donor nephrectomy performed by an experienced surgeon using either an open or laparoscopic approach.

METHODS

Patients

This study included 55 living-related kidney donors who underwent nephrectomy between March 2010 and March 2014. Twenty-one of these patients underwent open nephrectomy (Group 1), and 34 underwent laparoscopic nephrectomy (Group 2). Donors were interviewed regarding their surgical preferences, which included both open and laparoscopic donor nephrectomies. Patients aged between 18 and 75 years with end-stage renal disease, (defined as an estimated glomerular filtration rate of < 20 mL/min, symptomatic uremia, or dialysis necessity), who received an organ from a live donor from their family were included in the study. The exclusion criteria were nephrectomy of cadaver origin, a follow-up duration less than 1 month, and pre- or post-operative contrast-enhanced imaging. Patient data were collected from the hospital's medical records database and through patient interviews.

The donations were voluntary and in accordance with the Human Organ Transplant policies and regulations in Turkey. This study was approved by the Ethics Committee of the Marmara University School of Medicine (ID: 11.09.2014/15/14, date: 07.11.2014).

Evaluation of donors

A detailed assessment of the donors is routinely performed to ensure long-term safety. According to the United Network for Organ Sharing (UNOS), follow-up and monitoring of serum creatinine levels are required after a post-donation duration of at least 2 years. The functional performance of the kidney is mainly evaluated using the best overall measure: the glomerular filtration rate (GFR). The Modification of Diet in Renal Disease (MDRD) formula was used to calculate and perform a detailed evaluation of pre- and post-operative kidney function using estimated glomerular filtration rates (eGFRs). This formula was developed by the MDRD study group.[8] The ability of the MDRD formula to predict GFRs was analyzed by comparing the results obtained from other prediction equations of healthy participants without any known kidney disease.[9] Age, sex, and serum creatinine levels were recorded for the study participants to estimate GFR using the abbreviated version of the MDRD formula:[10]

$$eGFR\ (ml/\ min/\ 1.73\ m^2) = 175 \times (S_{cr})^{-1.154} \times (age)^{-0.203} \times (0.742\ if\ female).$$

Operative procedures

Before the procedures, the donors and recipients underwent a comprehensive medical assessment, and light bowel preparation was performed before surgery. The renal vessel anatomy of all donors was evaluated using abdominal computed tomography (CT) imaging.

The best use of renal vein length was achieved by left donor nephrectomy, which was routinely performed. A retroperitoneal flank incision was used for classic open nephrectomy. Transperitoneal laparoscopic nephrectomy was performed on the left side with the patient in the decubitus position. The procedure was performed using a video laparoscope and dissecting instruments. The procedure started with the inflation of the abdomen using a Verres needle. The abdominal cavity was inspected to ensure that there was no damage after inserting a 12-mm trocar. Two additional trocars were then inserted, the first superolateral to the umbilicus and the second at the midline of the rib cage. We often preferred using 10-mm trocars because they were easy to interchange with laparoscopic instruments. Dissection started with a Toldt line incision and reflection of the descending colon and continued until Gerota's fascia was seen. The medial gonadal vein was observed, and the dissection was traced up to the renal hilum. The renal artery and gonadal, renal, and adrenal veins were then carefully dissected and transected. The progression of the level of the iliac vessels was made by ureteral dissection, and the ureter was transected distally. Each of the renal arteries, veins, and ureters were stapled across before the kidney could be removed from the bag. In the final step, the completely freed kidney was removed from the Gibson incision.

Statistical analysis

The data were analyzed for frequencies, and the chi-square test was used to compare categorical variables. The mean values of the numerical variables between the groups were compared using the Mann–Whitney U test. SPSS for Windows (version 20.0; SPSS Inc., Chicago, Illinois, United States) was used for the statistical analysis of all data. Statistical significance was set at $P < 0.05$.

RESULTS

Donor demographics, estimated blood loss, operative characteristics, mean hospital stay, mean operative time, warm ischemia time of the graft, number of vessels, reduction rate of donor serum creatinine levels in the first seven days and one month after renal transplantation, and donor complications were compared between the two surgical approaches.

Living-donor nephrectomies were performed on all 55 donors (34 transperitoneal laparoscopic nephrectomies; 21 open nephrectomies). The donor demographics and indications for surgery were

similar in both groups. A comparison of donor characteristics is shown in **Table 1**. Abdominal CT angiography revealed the presence of double renal arteries in two of the 21 donors undergoing open nephrectomy (Group 1) and three of the 34 donors undergoing transperitoneal laparoscopic nephrectomy (Group 2). The mean warm ischemia time was 283 ± 152 s for open nephrectomy and 238 ± 73 s for transperitoneal laparoscopic nephrectomy (P = 0.4). In comparison to the donors who underwent open nephrectomy, the donors who underwent transperitoneal laparoscopic nephrectomy had a significantly shorter postoperative hospital stay (2.3 ± 0.2 versus 3.8 ± 0.8 days, P = 0.003), duration of urinary catheterization (1.2 ± 0.8 versus 2.0 ± 0.7 days, P = 0.0001), operating time (210 ± 27 versus 185 ± 24 minutes, P = 0.02), and significantly less blood loss (86 ml versus 142 ml, P = 0.048) (**Table 2**). There was no statistically significant difference in the estimated blood transfusion and warm ischemia time between the two groups (**Figure 1**). There were no cases of graft loss or conversion from laparoscopic to open surgery. Two patients in Group 1 had fevers > 101.5°F due to atelectasis, which was treated with intravenous antibiotics. In the laparoscopic group, one donor had a pneumothorax that required thoracic drain tube placement, and a small umbilical hernia developed at the hand port site.

Table 1. Patient characteristics

Parameter	Group 1 (ODN)	Group 2 (LDN)	P value
Patient, (n)	21	34	
Age (mean), SD, (years)	45 ± 9.6	45 ± 8.9	0.7
Gender, (n)			
Male	8	12	0.7
Female	13	22	
Laterality, (n)			
Right	2	0	0.1
Left	19	34	
Renal artery, (n)			
Single	19	31	0.9
Double	2	3	
BMI (mean), SD, (kg/m^2)	29.7 ± 4.5	27.1 ± 4.2	0.5

Mann-Whitney U and Chi-Square tests used.
SD = standard deviation; BMI = body mass index; ODN = open donor nephrectomy; LDN = laparoscopic donor nephrectomy.

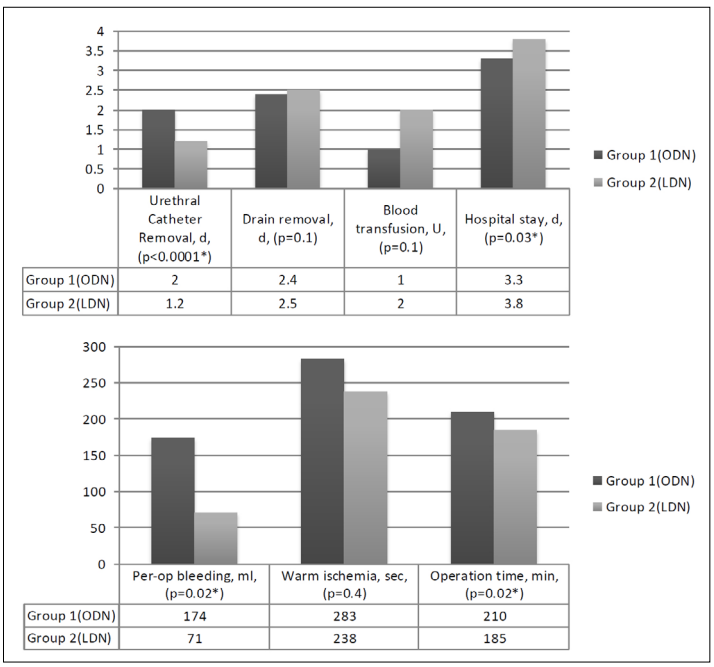


Figure 1. Intraoperative and postoperative parameters.

Table 2. Clinical and laboratory data of the groups

Parameter	Group 1 (SD)	Group 2 (SD)	P value
Preoperative Cre (mg/dl)	0.72 (0.14)	0.75 (0.15)	0.6
Postoperative 1st week Cre (mg/dl)	1.02 (0.23)	1 (0.23)	0.9
Postoperative 1st month Cre (mg/dl)	1.02 (0.24)	1.06 (0.20)	0.5
Preoperative microalbumin (mg/dl)	4.9 (2.93)	2.1 (1.7)	0.19
Postoperative microalbumin (mg/dl)	11.2 (6.69)	2.1 (1.9)	**0.03**
Urethral catheter removal (day)	2 (0.7)	1.2 (0.81)	**< 0.0001**
Drain removal (day)	2.4 (0.75)	2.5 (2.08)	0.1
Blood transfusion (U)	1	2	0.1
Perioperative bleeding (ml)	174 (142)	71 (61)	**0.02**
Warm ischemia time (sec)	283 (152)	238 (73)	0.4
Operation time (min)	210 (27)	185 (39)	**0.02**
Hospital stay (day)	**3.8 (0.85)**	**2.3 (0.2)**	**0.003**

Continuous data presented as mean + standard deviation (SD).
Cre = creatinine; SD = standard deviation; U = unit; Min = minutes; Sec = second.

The creatinine levels in the preoperative week and first postoperative week and month were comparable between the two groups (**Table 2**). The mean eGFRs preoperatively and at postoperative week 1 and month 1 were comparable between the two groups. A statistically significant reduction in eGFR was noted at postoperative week 1.

The mean MDRD values in Group 1 and Group 2 were 107 ± 16.1 and 104.2 ± 14.2 ml/min/m^2, respectively (P = 0.28). After postoperative week 1, the MDRD values decreased to 34 and 34.3 ml/min/m^2 in Group 1 and Group 2, respectively (between-group comparison P = 0.98, within-group comparison P < 0.0001 for both groups) (**Figures 2** and **3**). At postoperative month 1, the MDRD values stabilized for donors in both groups.

A within-group assessment of the surgical learning curve was also performed for Group 2 (laparoscopic nephrectomy), which showed a significant reduction in surgery time following the first 10 cases of living donors (P = 0.0001). From an average of more than 200 min for the first 10 cases, surgery time was reduced to less than 200 min after the initial 10 procedures (249 ± 19 versus 197 ± 13 minutes). No statistically significant differences were found based on the learning curve between the two groups (i.e., the first 10 subjects and the remaining subjects) in terms of laboratory parameters, perioperative blood loss, analgesic requirement, and postoperative clinical parameters. No deaths occurred among the 55 donors included in this study.

DISCUSSION

Limitations in the organ donor supply continue to pose a significant challenge to improving the outcomes of patients with end-stage renal failure. It has become imperative to expand the potential living-donor pool; this has been successfully achieved with the advent of laparoscopic donation because of the rapid recovery and return to normal activities.[11]

Living-donor nephrectomy is considered the most stressful intervention in urology because, by definition, it involves an

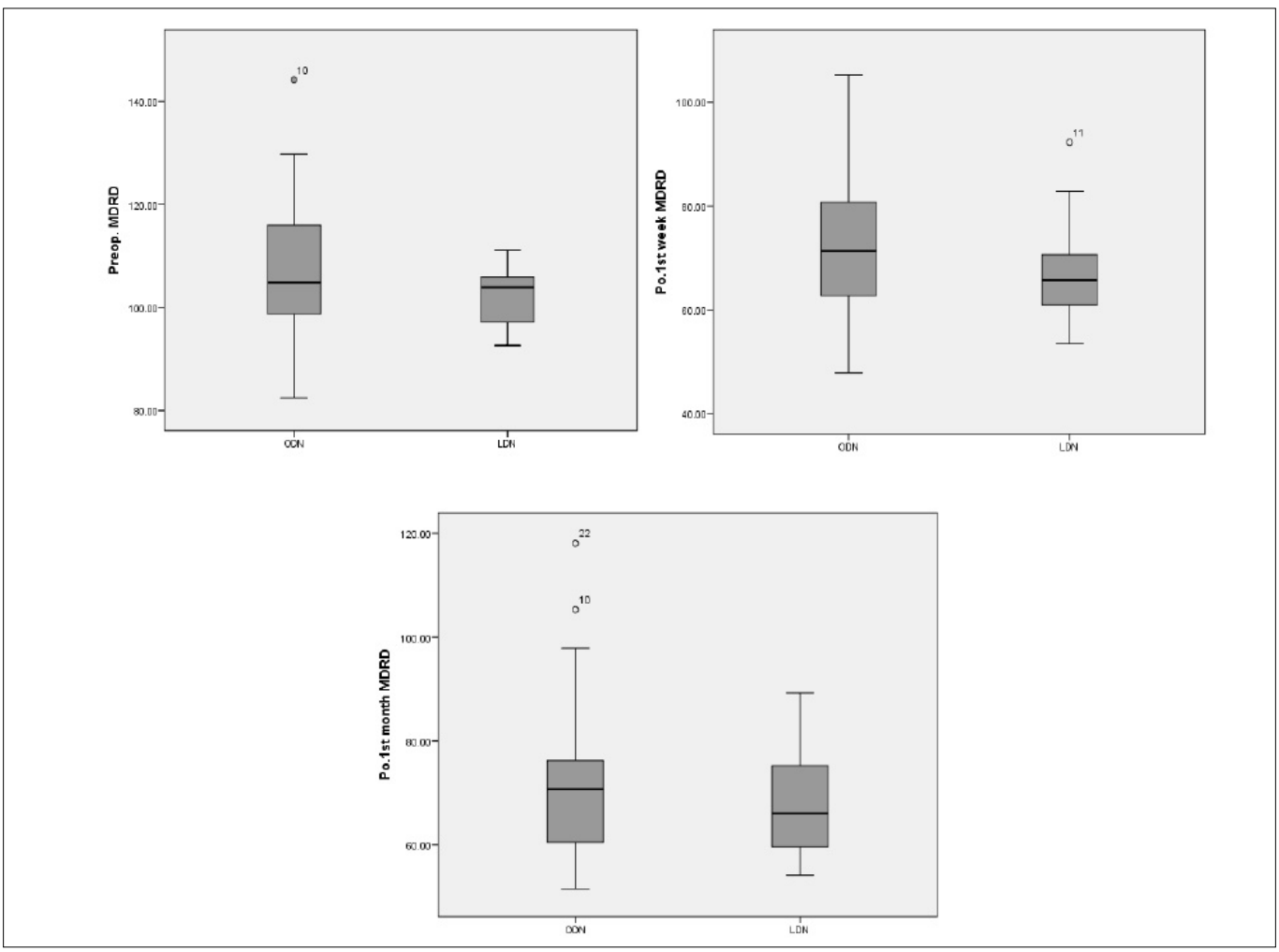
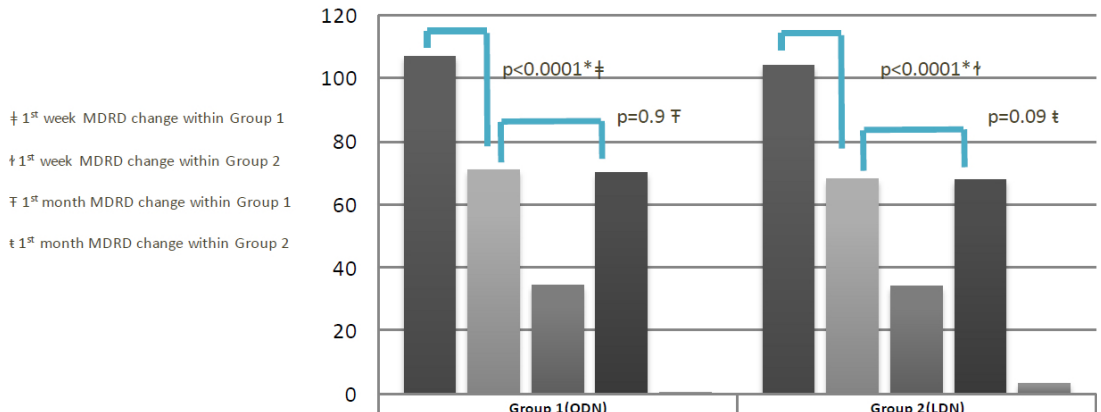


Figure 2. Comparison of the mean Modification of Diet in Renal Disease (MDRD) preoperatively and at postoperative week 1 and month 1.



	Group 1(ODN)	Group 2(LDN)
Preop (p=0.28)	107	104
Preoperative x Postoperative difference (1st week, p=0.98)	71	68
Within Group x Period (1st week, p=0.29)	34.3	34
Preoperative x Postoperative difference (1st month, p=0.31)	70	67.9
Within Group x Period (1st month, p=0.3)	0.3	3.4

Figure 3. Comparison of the groups in terms of estimated glomerular filtration rates (eGFR) using the Modification of Diet in Renal Disease (MDRD) formula.

altruistic organ donation by healthy individuals.[12] Donor nephrectomy is a unique operation in that it exposes a person in complete health to the potential complications of major surgery for the benefit of the recipient. Therefore, donor safety should be the priority in kidney transplantation.[13]

The rate of live kidney donation in the United States, Europe, and Turkey has increased directly with the increased use of living transperitoneal laparoscopic nephrectomy.[14,15] There is an association between the introduction of transperitoneal laparoscopic nephrectomy and the expansion of the living kidney donor pool in particular, and renal transplantation in general; evidence of this has been previously reported.[15]

However, morbidity and complication rates have been found to increase among surgeons just beginning to learn the technique for laparoscopic donor nephrectomy. To minimize the warm ischemia time, careful handling of the vessels and kidney, rapid specimen extraction, and extensive vascular dissection are required, and advanced laparoscopic skills are necessary. The operative time and complication rates were used to measure the surgical learning curve. After significant gains in experience, the incidence of delayed graft function and operative time decreased considerably. Leventhal et al. reported that the majority of complications occurred during the first 30 cases.[2] Additionally, four of the five conversions occurred in the first 40 cases.[2] The learning curve for laparoscopic nephrectomy flattened after 10 cases, even in the hands of an experienced laparoscopic surgeon. Based on the transperitoneal laparoscopic nephrectomy experience gained during this study, we adopted a point of view that seemed promising in terms of minimizing the morbidity associated with the learning curve. Moreover, from the recipients' standpoint, the transperitoneal laparoscopic nephrectomy results were comparable to those obtained using the well-established open approach. From the donors' standpoint, the transperitoneal laparoscopic nephrectomy results were superior to those of the open approach.

The increasing number of living donors has resulted in the need for more information about the potential risks of living with one kidney. Our findings indicate that most kidney donors have a favorable renal course. However, additional donors should be evaluated to confirm these findings. After donation, numerous donors developed increased serum creatinine levels, which may be associated with increased cardiovascular mortality.[16] In a study by Berber et al., the postoperative serum creatinine levels were within normal limits.[17] Therefore, the development of kidney dysfunction or failure in a donor is highly unlikely. Despite the limited follow-up and number of patients, several studies have examined changes in serum creatinine levels.[18] Hartmann et al. reported 1,800 cases of living donors, of which only seven developed end-stage renal disease.[19] Another study reported 402 cases of living donors in Sweden, and only one required hemodialysis due to postoperative renal failure.[20] In our study, the donors did not develop end-stage renal disease in the long-term follow-up, a result consistent with the findings of previous studies.

During transperitoneal laparoscopic nephrectomy, minimization of the warm ischemia time is crucial to avoid renal injury.

In one study, the reported warm ischemia time ranged between 2.6 and 6 min.[21] In a study of 500 cases of laparoscopic donor nephrectomy reported by Leventhal et al., the average warm ischemia time was 2.6 min.[22] Previous studies have reported shorter warm ischemia times for transperitoneal laparoscopic nephrectomy in comparison to open donor nephrectomy. In our study, the mean duration of warm ischemia was 2.7 min. Ideally, the warm ischemia time should not exceed 3 min in transplant surgery.[23] In general, the warm ischemia time is expected to be shorter in minimally invasive donor nephrectomy than in open donor nephrectomy. However, in our study, we observed a longer warm ischemia time in the open donor nephrectomy group than that reported in the literature. Specific factors may have contributed to the longer warm ischemia time such as the complexity of the procedure, surgical team experience, or variations in the technique used. It is also possible that there are issues related to the preservation and handling of the kidney after removal that may affect the warm ischemia time. Another reason could be that open donor nephrectomy involves a larger surgical incision and more extensive dissection of the kidney and its blood vessels, which increases the risk of bleeding and prolongs the warm ischemia time. The longer operative time for open donor nephrectomy differed from that reported in the literature. This discrepancy may be because the duration of open donor nephrectomy varies depending on the surgeon's experience, the patient's anatomy, and the type of surgical technique used.

We found that the results from the donors' standpoint corresponded with those reported in other studies that compared transperitoneal laparoscopic and open nephrectomy. These include shorter hospital stay, less blood loss, and similar rates of complications.[1,11,18,22]

Our study had some limitations. First, although the collection of laparoscopic data was prospective, this study was retrospective, and the majority of open nephrectomy data were historical. Consequently, a significantly longer follow-up period was observed in the open nephrectomy group (Group 1). Second, the higher American Society of Anesthesiologists status of the open nephrectomy group constituted a discrepancy between the two study groups that was unlikely to account for the longer hospital stay. Another limitation was the relatively small sample size of each group. An additional limitation was the inadequacy of our findings, which indicated a difference in the length of the donors' hospital stay between the two groups. Additional outcomes, such as functional status and patients' quality of life, could have been more detailed and informative.

CONCLUSIONS

Transperitoneal laparoscopic living-donor nephrectomy is a less invasive approach than open nephrectomy. This has a significant influence on kidney donor operations. Consequently, donor morbidity decreased while a higher-quality allograft for the recipient was maintained. Transperitoneal laparoscopic donor nephrectomy can be safely performed in centers with expertise in laparoscopic surgery. From the donor's perspective, transperitoneal laparoscopic donor nephrectomy has better outcomes than open donor nephrectomy in terms of the length of hospital stay, duration of urinary catheterization, operating time, and blood loss.

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Cut-off points of neck and waist circumference as predictors of obstructive sleep apnea in the Colombian population: a comparison with polysomnography

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Waist circumference.
Sleep apnea, obstructive.
Area under curve.
Body mass index.

AUTHORS' KEYWORDS:
Obstructive apnea.
Cut-off point.
Neck circumference.

ABSTRACT

BACKGROUND: Neck circumference (NC) is a useful anthropometric measure for predicting obstructive sleep apnea (OSA). Ethnicity and sex also influence obesity phenotypes. NC cut-offs for defining OSA have not been established for the Latin American population.

OBJECTIVES: To evaluate NC, waist circumference (WC), and body mass index (BMI) as predictors of OSA in the Colombian population and to determine optimal cut-off points.

DESIGN AND SETTING: Diagnostic tests were conducted at the Javeriana University, Bogota.

METHODS: Adults from three cities in Colombia were included. NC, WC, and BMI were measured, and a polysomnogram provided the reference standard. The discrimination capacity and best cut-off points for diagnosing OSA were calculated.

RESULTS: 964 patients were included (57.7% men; median age, 58 years) and 43.4% had OSA. The discrimination capacity of NC was similar for men and women (area under curve, AUC 0.63 versus 0.66, P = 0.39) but better for women under 60 years old (AUC 0.69 versus 0.57, P < 0.05). WC had better discrimination capacity for women (AUC 0.69 versus 0.57, P < 0.001). There were no significant differences in BMI. Optimal NC cut-off points were 36.5 cm for women (sensitivity [S]: 71.7%, specificity [E]: 55.3%) and 41 cm for men (S: 56%, E: 62%); and for WC, 97 cm for women (S: 65%, E: 69%) and 99 cm for men (S: 53%, E: 58%).

CONCLUSIONS: NC and WC have moderate discrimination capacities for diagnosing OSA. The cut-off values suggest differences between Latin- and North American as well as Asian populations.

INTRODUCTION

Obstructive sleep apnea (OSA) is highly prevalent among adults. Approximately 425 million (399–450) adults, aged 30–69 years have moderate to severe obstructive sleep apnea globally, with more affected individuals in China, followed by the United States, Brazil, and India.[1] In patients with cardiovascular disease, the prevalence rises to 40%–60%.[2] Additionally, the risk of fatal and non-fatal cardiovascular events is significantly higher in patients with severe untreated OSA (adjusted odds ratio, OR 2.8 for fatal and 3.1 for non-fatal).[3]

Neck circumference (NC) is one of the screening strategies useful for predicting OSA.[4] For this reason, NC is included in widely used questionnaires such as the STOP Bang,[5] which proposes an NC cut-off point of 40 cm. NC is associated with fat deposition in the anterolateral region of the upper airway.[6] Its measurement complements body mass index (BMI) information and correlates with OSA severity, regardless of visceral fat, especially in non-obese patients.[7]

In the North American population, NC larger than 17 inches (43 cm) in men and 16 inches (41 cm) in women has been strongly associated with the risk of OSA.[8] These values are notably higher than the values proposed for Asian populations (38.75 cm in men and 34.5 cm in women).[9] These differences suggest the existence of various obesity phenotypes, partly explained by ethnic factors that also account for geographic differences in OSA prevalence.[10,11] Reported differences between North American and Asian populations highlight the importance of establishing specific cut-off points for each population. In Latin America, there is limited information on anthropometric measurements, prompting the need to determine optimal NC cut-off points that may help to predict OSA.[12]

Similarly, the optimal waist circumference (WC) cut-off point for predicting OSA in Latin America is unknown. Previous studies have proposed cut-off points of 94 cm for men and 90–92 cm for women as markers of visceral adiposity,[13,14] but the value of these measurements in predicting OSA is currently unknown.

Although previous studies in Latin America[15] have described a possible association between sleep disorders and anthropometric measurements, none have compared these measurements with the existing gold standard of polysomnography (PSG).

OBJECTIVE

The goal of this study was to evaluate NC, WC, and BMI as screening tests to identify patients with OSA, and to compare anthropometric measurements with PSG results. This study also aimed to determine the optimal cut-off points for these measurements in a representative sample from three Colombian regions.

METHODS

This multicenter study aimed to assess screening tests and determine cut-off points. We included adults older than 18 years from three cities in Colombia (Bogotá D.C., Santa Marta, and Bucaramanga) who attended primary or secondary prevention programs at the Instituto del Corazón, as well as patients from the general population of those cities who accepted an invitation to participate in the study. Patients with mental illnesses that could interfere with data collection were excluded. The Committee of Ethics and Research of the Pontificia Universidad Javeriana in Bogotá, D.C. (Colombia) approved the research protocol (M-CIE 55761, January 26, record 1-2012).

Each participant completed a form that included questions on demographics and comorbidities along with several screening questionnaires, including the Epworth Sleepiness Scale, Berlin Questionnaire, and Pittsburgh Sleep Quality Index. Patients with scores above the established cut-off points were candidates for PSG.

A trained professional used a nonelastic measuring tape and followed standardized techniques to obtain anthropometric measurements, including body weight, height, NC, and WC. WC was measured at the mid-axillary line, midway between the lowest rib and the iliac crest, with the patient in expiration, as recommended by the International Diabetes Federation.[16] NC was measured at the cricothyroid membrane level; and BMI was established according to World Health Organization (WHO) parameters.[17]

Immediately after the anthropometric measurements, participants underwent conventional type 1 PSG with Alice 5 (Philips Respironics, Murrysville, United States) from 9 p.m. to 6 a.m. The study included readings from nasal and oral flow transducers, a snore microphone, video recordings, electroencephalograms, electrooculograms, electromyograms, electrocardiograms, belts for thoracic and abdominal effort impedance measurements, pulse oximetry, and sensors for position changes during sleep. One certified sleep specialist interpreted all the tests, according to the American Academy of Sleep Medicine (AASM) parameters.[18] This second evaluator was blinded to the results of the screening questionnaires and the anthropometric measurements. The AASM hypopnea criteria require a 30% reduction in airflow accompanied by a 4% oxygen desaturation or a 50% reduction in airflow accompanied by a 3% oxygen desaturation or arousal. Apnea was defined as the cessation of airflow for at least 10 s. Criteria for diagnosing OSA were an Apnea Hypopnea Index (AHI) > 15 with no symptoms, or ≥ 5 in the presence of symptoms. The severity of the condition was classified according to AHI values as mild (AHI > 5 and < 15 per h), moderate (AHI > 15 and < 30 per h), or severe (AHI > 30 per h).[19]

Statistical analysis

The Shapiro-Wilks test was used to assess variable normality. Averages and standard deviations were used for numerical variables with a normal distribution, and medians with interquartile ranges were used for variables with non-normally distributed data. Groups were compared using an unpaired two-tailed t-test, chi-square test, or a Mann-Whitney U test, according to the type of variable.

Sensitivity (S) and specificity (E) were calculated for the NC, WC, and BMI cut-off points and compared to the PSG results as a reference standard. Receiver operating characteristic (ROC) curves were differentially calculated by sex and age group (younger and older than 60 years), and the areas were compared using a nonparametric approach.[20]

The study determined optimal cut-off points for each measurement using the Liu method.[21] Additionally, NC operative characteristics were presented with a 40 cm cut-off point, taking into account values used in the STOP-Bang questionnaire.[5] For WC, a 90 cm cut-off point was established according to previous studies in the Colombian population.[13] For BMI, the cut-off point was set at 30 according to WHO recommendations for diagnosing obesity.[17]

Data were analyzed using the STATA statistical package 14.0 (Stata Corp, College Station, Texas, United States).

RESULTS

The study included 964 patients, mostly men (58%) aged between 18 and 91 years of age. Median ages were 59 years for men and 57 years for women. Most of the participants were overweight, with a median BMI of 26; obesity prevalence was 18.7% in men and 23.1% in women. At assessment, 65.9% of patients had cardiovascular disease, defined as heart disease of any cause, coronary artery disease, or cerebrovascular disease.

Regarding comorbidities, high blood pressure (HBP) was most frequent (57%), followed by coronary disease (44%) and

diabetes mellitus (16%). Of patients with HBP, 15% had AHI > 30. Hypothyroidism and diabetes were more frequent in patients with HBP. **Table 1** describes the clinical and demographic characteristics of the study population according to sex.

A total of 44.1% of men and 42.4% of women fulfilled the PSG diagnostic criteria for OSA. NC (38.75 cm ± 3.99 versus 40.40 cm ± 3.66, P < 0.001), WC (95.91 cm ± 12.16 versus 100.95 cm ± 11.08, P < 0.001), and BMI (25.93 ± 3.86 versus 28.07 ± 4.43, P < 0.001) were higher in patients with OSA. Most patients had mild or moderate OSA according to AHI criteria (**Table 1**).

The discriminatory ability of NC to diagnose OSA was similar for men and women (area under the curve, AUC 0.63 versus 0.66, P = 0.39) (**Figure 1A**). However, an independent analysis of patients by age group revealed that the discriminatory ability of NC was better for women younger than 60 years than for older women (AUC 0.69 versus 0.57, P < 0.05).

The discriminatory ability of WC was better for women than for men (AUC 0.69 versus 0.57, P < 0.001) (**Figure 1B**). In the male subgroup, the discriminatory ability was better for those younger than 60 (AUC 0.62 versus 0.52, P < 0.05).

The discriminatory ability of BMI was between 0.6 and 0.7, (**Figures 1C**), with no significant differences between subgroups. All three anthropometric variables had better discriminatory ability than the positive response to the question about snoring loudly (AUC 0.57 95% confidence interval [CI] 0.54–0.60) proposed in the STOP – BANG questionnaire.

Table 2 presents operative characteristics of NC for the optimal cut-off point and for a 40 cm cut-off point. The selected cut-off point for women was 36.5 cm (S: 56%, E: 62%) and for men, 41 cm (S: 72%, E: 55%).

Selected WC cut-off points for women were 97 cm (S: 65%, E: 69%) and 99 cm (S: 53%, E: 58%) for men. **Table 3** presents the

Table 1. Sociodemographic characteristics of included patients

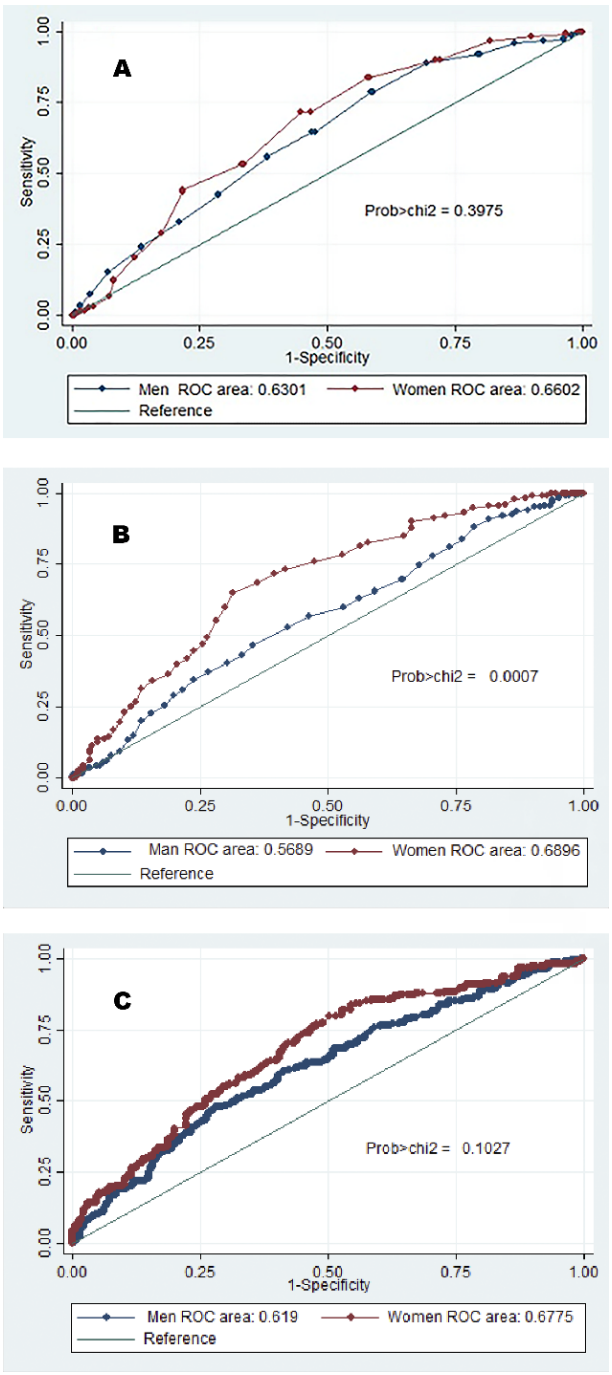
	Women n (%) 408 (42.3)	**Men n (%) 556 (57.7)**	**P value**
Age in years, median (IQR)	57 (45–67)	59 (51–69)	0.01
BMI, Kg/m², n (%)			
< 18	0 (0)	3 (0.5)	
18–24.9	149 (36.5)	190 (34.2)	0.08
25–29.9	165 (40.4)	259 (46.6)	
> 30	94 (23.1)	104 (18.7)	
Neck circumference in cm, median (IQR)	37 (35–48)	41 (39–44)	< 0.001
Neck circumference in cm, mean (SD)	37.2 (3.4)	41.1 (3.5)	< 0.001
Waist circumference in cm, median (IQR)	98 (89–106)	99 (92–109)	< 0.001
Waist circumference in cm, average (SD)	97 (13.16)	99 (10.9)	< 0.001
Snoring*, n (%)			
Yes	260 (63.7)	388 (69.8)	
No	77 (18.9)	107 (19.2)	0.015
Don´t know	71 (17.4)	61 (11.0)	
Snoring loudly , n (%)**	140 (34.1)	239 (43.0)	0.006
****OSA, n (%)**	**173 (42.4)**	**245 (44.1)**	
Mild	99 (24.3)	113 (20.3)	
Moderate	47 (11.5)	73 (13.1)	0.599
Severe	27 (6.6)	59 (10.6)	
Comorbidities n (%)			
Coronary disease	134 (32.8)	289 (52.0)	< 0.001
HBP	216 (52.9)	332 (59.7)	0.035
Diabetes	55 (13.5)	97 (17.4)	0.101
Depression	76 (18.6)	60 (10.8)	0.001
Anxiety	72 (17.6)	64 (11.5)	0.007
Hypothyroidism	93 (22.8)	56 (10.1)	< 0.001
COPD	19 (4.6)	23 (4.1)	0.705
GERD	49 (12.0)	60 (10.8)	0.561

IQR = interquartile range; BMI = body mass index; SD = standard deviation; OSA = obstructive sleep apnea; HBP = high blood pressure; COPD = chronic obstructive pulmonary disease; GERD = gastro esophageal reflux disease.

*According to the question, Do you snore? included in the Berlin questionnaire; **According to the question Do you snore loud? Included in the STOP-BANG questionnaire; **Results by polysomnogram (PSG).

operative characteristics of WC for the optimal cut-off point and for a 90 cm cut-off point.

The BMI cut-off point with the best operative characteristics was 26.6 for men (S: 60%, E: 59%) and 26 for women (S: 71%, E: 58%) (**Table 4**).



ROC area = receiver operating characteristic area under the curve.
A. Neck circumference; B. Waist circumference; C. Body mass index.

Figure 1. Operative characteristics curves for neck circumference, waist circumference, and body mass index, according to sex.

DISCUSSION

This study is the first to determine the operative characteristics of anthropometric variables for predicting OSA in a Colombian population by comparing these characteristics to PSG as the gold standard. The results suggest that BMI, NC, and WC have moderate discriminatory ability (AUC from 0.6 to 0.7), with NC and WC having better discriminatory ability for patients under the age of 60. This study also found that the optimal cut-off points for predicting OSA were lower than those described for the North American population, but higher than those described for the Asian population.

Strikingly, OSA prevalence in this sample was relatively high (43.4%), possibly because many patients came from primary and secondary cardiovascular prevention clinics. Patients at these clinics have a higher frequency of established cardiovascular diseases and cardiovascular risk factors than other cohorts.

Previous studies have evaluated the association between anthropometric measurements and OSA in Asian and Caucasian populations. Similar to our findings, these studies reported that NC is significantly higher in patients with OSA,[10] unlike their findings for WC and BMI, where no significant differences were found. NC has been proposed as a useful OSA screening tool and even as a tool for assessing OSA severity.[22,23] A study in a Colombian population with 5,474 participants reported that BMI, WC, and NC were significantly higher in patients who screened positive for OSA (Berlin and STOP-Bang), but this study did not perform confirmatory tests for OSA.[15]

The present study found that NC and WC had moderate discriminatory ability for predicting OSA, with AUC values superior to those reported for the four different screening scales (Epworth, Pittsburgh, Berlin, and STOP-Bang) in the Colombian population, in which AUC values were between 0.51 and 0.56.[24] The results of the present study suggest that easy measurements such as NC and WC may be even more useful than OSA screening questionnaires, which usually require a longer time to administer. Additionally, anthropometric measures had better discriminatory ability than the simple question about snoring. Further studies are needed to determine if the discriminatory ability of these scores (e.g., the STOP-Bang score) improves when specific cut-off points are included for each population.

A recent meta-analysis determined that obese populations in Latin America and the Caribbean had an average NC of 42.56 cm (95%CI: 41.70 cm–43.42 cm; I^2: 92.40%). However, since the assessed studies used different operative definitions of NC, the meta-analysis could not determine the prevalence of patients with large NCs.[12] This finding stresses the need to define an optimal NC cut-off point for the Colombian population.

The present study found that the optimal NC cut-off points for predicting OSA were 36.5 cm for women (S: 71.7, E: 55.3)

Table 2. Operative characteristics of neck circumference for obstructive sleep apnea screening compared to polysomnography

	Operative characteristics for neck circumference ≥ 40 cm			Operative characteristics at the optimal cut-off point			
	Sensitivity (%) 95%CI	Specificity (%) 95%CI	AUC	Cut-off point (cm)	Sensitivity (%) 95%CI	Specificity (%) 95%CI	AUC
Women general	20.3 (14.6–27.1)	87.7 (82.8–91.6)	0.54 (0.50–0.57)	36.5	71.7 (64.3–78.3)	55.3 (48.7–61.8)	0.63 (0.59–0.68)
Men general	64.5 (58.1–70.5)	52.4 (46.7–58.1)	0.58 (0.54–0.62)	41.0	56.0 (49.5–62.2)	62.0 (56.1–67.2)	0.59 (0.54–0.63)
Women							
< 60	18.0 (10.9–29)	91.0 (85.1–95.1)	0.54 (0.5–0.59)	36.5	65.1 (53.5–75.3)	64.6 (56.2–72.4)	0.65 (0.58–0.71)
> 60	27.2 (18.4–37.4)	74.7 (64.5–83.3)	0.50 (0.44–0.57)	38.5	55.0 (43.5–65.4)	61.0 (49.9–71.2)	0.58 (0.50–0.65)
Men							
< 60	69.7 (61.5–77.1)	54.2 (45.7–62.5))	0.61 (0.56–0.67)	40.5	69.7 (61.5–77.1)	55.6 (47.1–63.8)	0.63 (0.57–0.68)
> 60	57.3 (47.2–67)	50.9 (43.1–58.7)	0.54 (0.48–0.60)	39.0	73.8 (64.2–82)	42.5 (34.9–50.4)	0.58 (0.52–0.63)

AUC = area under the curve; CI = confidence interval.

Table 3. Operative characteristics of waist circumference for obstructive sleep apnea screening compared to polysomnography

	x			Operative characteristics for optimal cut-off point found in the study			
	Sensitivity (%) 95%CI	Specificity (%) 95%CI	AUC	Cut-off point cm	Sensitivity (%) 95%CI	Specificity (%) 95%CI	AUC
Women general	82.6 (76–87.9)	42.1 (35.7–48.7)	0.62 (0.58–0.66)	97.5	65.3 (57.7–72.4)	68.5 (62.2–74.4)	0.67 (0.62–0.71)
Men general	83.7 (78.4–88.1)	23.8 (19.2–28.9)	0.54 (0.50–0.57)	99.5	53.1 (46.6–59.4)	58.0 (52.2–63.4)	0.55 (0.51–0.59)
Women							
< 60	81.3 (71–89.1)	45.8 (37.5–54.3)	0.63 (0.57–0.69)	94	65.0 (53.5–75.3)	64.0 (55.5–71.7)	0.64 (0.57–0.71)
> 60	83.7 (74.5–90.6)	36.3 (26.4–47)	0.60 (0.53–0.66)	97.5	73.1 (62.9–81.8)	59.3 (48.5–69.5)	0.66 (0.59–0.73)
Men							
< 60	85.2 (78.3–90.6)	27.8 (20.6–35.8)	0.56 (0.51–0.61)	98.5	58.0 (49.4–65.9)	60.0 (51.6–67.7)	0.59 (0.53–0.64)
> 60	81.6 (72.7–88.5)	20.4 (14.5–27.3)	0.51 (0.64–0.55)	99.5	52.4 (42.4–62.4)	55.1 (47.2–62.8)	0.53 (0.47–0.59)

AUC = area under the curve; CI = confidence interval.

Table 4. Operative characteristics of body mass index for obstructive sleep apnea screening compared to polysomnography

	Operative characteristics for BMI ≥ 30			Operative characteristics for the optimal cut-off point			
	Sensitivity (%) 95%CI	Specificity (%) 95%CI	AUC	Cut-off point	Sensitivity (%) 95%CI	Specificity (%) 95%CI	AUC
Women general	31.2 (24.4–38.7)	84.3 (79–88.7)	0.58 (0.53–0.62)	26	70.5 (63.1–77.2)	56.6 (50–63)	0.64 (0.58–0.68)
Men general	23.3 (18.1–29.1)	85.2 (80.8–89)	0.54 (0.51–0.57)	26.6	60.0 (53.6–66.2)	59.0 (53.1–64.4)	0.60 (0.55–0.63)
Women							
< 60	35.0 (24.7–46.5)	81.9 (74.7–87.9)	0.58 (0.52–0.64)	25	81.3 (71–89.1)	53.5 (45–61.8)	0.67 (061–0.73)
> 60	28.0 (19.1–38.2)	87.9 (79.4–93.8)	0.57 (0.52–0.63)	27.5	57.5 (46.4–68)	70.1 (59.4–79.5)	0.64 (0.56–0.71)
Men							
< 60	23.9 (17.2–31.8)	84.0 (77–89.6)	0.49 (0.54–0.58)	26.5	60.5 (52.2–68.5)	60.0 (51.6–67.7)	0.60 (0.54–0.69)
> 60	22.3 (14.7–31.6)	86.2 (80.1–91.1)	0.54 (0.49–0.59)	26.6	61.2 (50.8–70.9)	57.2 (49.2–65)	0.60 (0.53–0.65)

BMI = body mass index; AUC = area under the curve; CI = confidence interval.

and 41 cm for men (S: 56, E: 62), which are lower values than those reported for the North American population (41 cm for women and 43 cm for men)[8] or those reported in Romania where the optimal cut point was 41 cm.[25] However, the optimal cut-off points in this study were higher than those reported for the Asian population (34.5 cm for women and 38.75 for men).[9] This suggests that the Colombian population has different ethnic characteristics, possibly associated with different obesity phenotypes.[26,27] Cut-off points in this study are similar to those reported in Brazil (36.2 cm for women and 40.2 cm for men)[28] and Chile (≥ 40 cm of adjusted NC, S: 77.3%, E: 67.2% for OSA diagnosis with AHI > 5).[29] The Chilean study did not differentiate between sexes. Similarly, a sub-analysis of the Sleep Heart Health Study cohort (SHHS) highlighted the NC-to-height ratio as a statistically solid alternative diagnostic method, comparable to other components of the STOP-Bang questionnaire for moderate to severe OSA screening.[30]

The findings of this study suggest similar anthropometric characteristics among Latin American populations. They also suggested that the discriminatory ability of NC may be even better in patients younger than 60 years, with AUC values of close to 0.7.

For WC, this study found that the optimal cut-off point for OSA screening was 97.5 cm and 99.5 cm for women and men, respectively, which are higher values than those established for cardiovascular risk, with acceptable discriminatory ability among women.

A strength of this study was its large sample size. This sample allowed precise optimal cut-off point calculations, even for subgroups classified by age and sex, accounting for differences in fat distribution associated with late hormonal changes in women. However, some limitations of this study should be acknowledged. This study examined a cohort with a high prevalence of cardiovascular diseases, so the possibility of generalizing the results to the broader population is limited. Further studies are required to confirm the findings of the present study. Additionally, the sample may not be fully representative of the Colombian population. However, we included patients from three different regions living at different altitudes to minimize potential bias.

CONCLUSION

In conclusion, anthropometric measurements are simple and easy-to-use tools useful for identifying patients with OSA. The data in this study suggest that the optimal NC cut-off point in the Colombian population, and possibly in Latin America as a whole, is lower than that reported for North American populations. Complementary studies are required to determine whether including population-specific cut-off points would improve the discriminatory ability of screening scores.

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Sedentary behavior, abdominal obesity and healthcare costs in Brazilian adults with cardiovascular diseases: a cross-sectional study

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ABSTRACT

BACKGROUND: Research on the economic burden of sedentary behavior and abdominal obesity on health expenses associated with cardiovascular diseases is scarce.

OBJECTIVE: The objective of this study was to verify whether sedentary behavior, isolated and combined with abdominal obesity, influences the medication expenditure among adults with cardiovascular diseases.

DESIGN AND SETTING: This cross-sectional study was conducted in the city of President Prudente, State of São Paulo, Brazil in 2018.

METHODS: The study included adults with cardiovascular diseases, aged 30-65 years, who were treated by the Brazilian National Health Services. Sedentary behavior was assessed using a questionnaire. Abdominal obesity was defined by waist circumference. Medication expenditures were verified using the medical records of each patient.

RESULTS: The study included a total of 307 adults. Individuals classified in the group with risk factor obesity combined (median [IQ] USD$ 29.39 [45.77]) or isolated (median [IQ] USD$ 27.17 [59.76]) to sedentary behavior had higher medication expenditures than those belonging to the non-obese with low sedentary behavior group (median [IQ] USD$ 13.51 [31.42]) (P = 0.01). The group with combined obesity and sedentary behavior was 2.4 (95%CI = 1.00; 5.79) times more likely to be hypertensive.

CONCLUSION: Abdominal obesity was a determining factor for medication expenses, regardless of sedentary behavior, among adults with cardiovascular diseases.

INTRODUCTION

The use of medicines has been the basis of many clinical interventions to treat a large variety of diseases and represents one of the most relevant components of overall healthcare costs. Healthcare costs related to medicine use increases with age[1,2] and represents a relevant challenge for the management of any national health service.

The prevalence of sedentary behavior and abdominal obesity has increased worldwide, and these phenomenon seems to have been boosted by the coronavirus pandemic.[3] Even before the pandemic, the relevant burden of both abdominal obesity and sedentary behavior on the development of cardiovascular and metabolic diseases has been reported by several authors.[4,5,6,7] Part of this attention directed to abdominal obesity and sedentary behavior is because the diseases associated with these factors put relevant pressure on national health services worldwide.

One hour of sedentary behavior can add up to approximately USD $37 in personal health expenditures.[8] It has been defined as activities that do not increase energy expenditure substantially above the resting level and involves energy expenditure of 1.0 to 1.5 metabolic equivalent units (METs).[9] Sedentary behavior, over the last decade, has been associated with numerous chronic non-communicable diseases (NCDs).[10-12]

An epidemiological study conducted over a span of 12 years on individuals aged 18-90 years in Canada showed that spending excessive time on sedentary behaviors can have a negative impact on various health outcomes, regardless of the individual's physical activity level. Those who reported spending approximately three-quarters of their time, or almost all of their time throughout the day, sitting (hazard ratio, HR = 1.47 [95% confidence interval (CI) = 1.09–1.96]; HR = 1.54

[95%CI = 1.09–2.17]) were at a higher risk for cardiovascular disease-associated mortality when compared to those who reported almost no time sitting.[13]

Obesity has been associated with cardiovascular disease-associated mortality (HR = 1.50, 95%CI = 1.08; 2.08).[14] In addition to the economic burden that ranges between 0.7%-2.8% of a country's total health budget,[15] evidence shows that abdominal obesity increases the probability of higher medication expenditure by 1.66 times.[16]

Obesity has been associated with economic losses in the public and private sectors.[17] However, although sedentary behavior is widely associated with a large variety of health outcomes, its economic impact remains unclear. Moreover, even when related to each other (obesity and sedentary behavior), the combined impact of both on healthcare costs has barely been investigated, mainly in developing nations, the home of most of the world's population.

We hypothesized that the combination of obesity and sedentary behavior impacts the costs attributed to medication. The findings of this study would be useful in motivating stakeholders to prioritize investments in the prevention of these two risk factors (especially sedentary behavior), which would aid in mitigating the healthcare costs.

There is evidence in the literature on how sedentary behavior affects health,[14] but information regarding its impact on economics and healthcare costs is scarce. Moreover, research that explores the economic burden of sedentary behavior and obesity, in aggregate form, on healthcare expenditures associated with cardiovascular disease is also scarce. It is believed that the presence of both risk factors maximizes health expenditures.

OBJECTIVE

The objective of this study was to verify whether sedentary behavior, isolated and combined with abdominal obesity, influences medication expenditure among adults with cardiovascular diseases.

METHODS

Study population

This study presents a descriptive research model and involves cross-sectional evaluation of participants along with a longitudinal cost analysis. These results refer to the first data collection (baseline) of an ongoing cohort study conducted in the city of Presidente Prudente (with approximately 230,000 inhabitants), located in the western region of the State of São Paulo, Brazil.

Patient selection was carried out through the medical records of the Regional Hospital, which offers referral care of medium and high complexity, totally free of charge, to 45 cities and municipalities in the western region of the state, with an average turnover of 447.36 patients/day.

The minimum sample size was calculated taking into consideration the annual number of patients treated at the Regional Hospital (n = 163,288) as well as the number of patients (aged 30-65 years) treated for cardiovascular reasons (Category I of the International Classification of Diseases and Related Health Problems [ICD] [~ 0.74%, n = 1,200]). Thus, considering a percentage of 0.74%, sampling error of 5%, and Z = 1.96, the minimum sample size was estimated to be 106. Finally, by adding an estimated loss of 100% throughout the follow-up period (estimated from previous studies), a minimum of 212 participants were required to participate in this study.

Participants were randomly selected using medical records from the cardiology department (last six months) of the Regional Hospital. After the selection of patients from the records, it was verified whether they met the following inclusion criteria: i) age ranging between 30-65 years (age group with a high prevalence of chronic diseases in Brazil);[18] ii) use of the services offered by the Brazilian National Healthcare System for cardiovascular diseases in the last year; and iii) residing in the city of Presidente Prudente. Researchers could obtain information regarding the use of primary healthcare services. Patients were excluded if they: i) did not meet at least one inclusion criterion; ii) were deceased; iii) had an inactive phone number; and iv) missed at least two scheduled appointments for data collection.

The selected patients were contacted via telephone and invited to participate in face-to-face interviews and evaluations (conducted in July and August 2018). Patients who agreed to participate in the study signed a consent form.

From the list of 1,200 patients provided by the Regional Hospital, random draws in blocks (300 patients per draw) were performed using STATA software version 16.0 (StataCorp LLC, College Station, Texas, USA) (**Figure 1**).

All telephone numbers selected in the first and second draws (n = 600) were verified by the researchers and five attempts were made to contact the patients. A third draw was required, and 194 patients were contacted until the minimum sample size was reached (**Figure 1**). Among the 794 patients contacted, 307 agreed to participate in the study, 316 declined to participate, 31 telephone numbers no longer belonged to the patient, 30 belonged to deceased patients, and 110 missed at least two scheduled appointments for data collection (**Figure 1**).

Ethical Considerations

The study design and methodology was approved on May 22, 2018, by the Ethics Research Committee of São Paulo State University (Protocol number CAAE 82767417.5.0000.5402). The study was conducted in accordance with the tenets of Declaration of Helsinki and informed consent was obtained from all the participants prior to the commencement of the study.

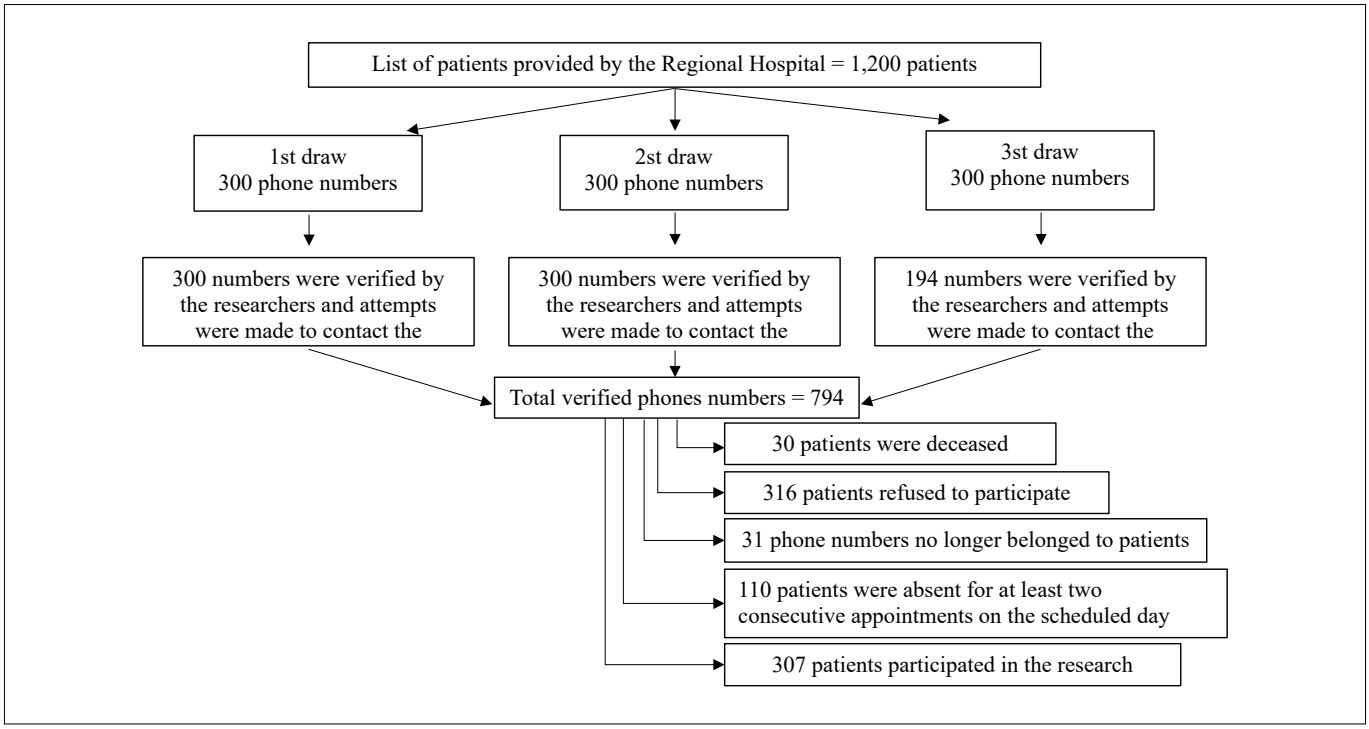


Figure 1. Flow chart depicting the selection of the study population.

Dependent Variables

Medication expenditures

Estimated expenditures refer to medications used by patients in primary healthcare. Medication expenditures were estimated, including information registered in medical records 12 months prior to the date of face-to-face evaluation (July/August 2017 to July/August 2018).[2,19]

Medication expenditures were calculated by multiplying the number of medications with the price and daily quantity. Prices of medication distributed to the patient (funded by the Brazilian National Healthcare System) were based on information from standard tables for reimbursement of services provided to the municipal government for the year of purchase. Monetary values were expressed in Reais (R$) and updated in accordance with the official Brazilian inflation index (Extended National Consumer Price Index, IPCA), from the date of obtaining the data until December 2022, and converted into US dollars (US$) using the official exchange rate of the same date (dollar exchange rate at 5.21) published by the Brazilian Central Bank.[20]

Presence of NCDs

Information regarding chronic diseases such as arterial hypertension, hypercholesterolemia, diabetes mellitus, heart attack, atherosclerosis, and nephritis, was first obtained through medical records in the sampling process and then verified via interview using a questionnaire.[21] The interviewee reported the following: (i) diagnosis of the disease; and (ii) use of medications.

Independent variables

Sedentary behavior and abdominal obesity

Sedentary behavior was assessed using a questionnaire developed by Mielke et al.[22] The instrument included questions regarding time spent on sedentary behavior (activities such as watching television, using a computer, and remaining seated) on a typical weekday in different environments: i) work; ii) educational setting (school or college/university); iii) transportation (car, bus, and motorcycle); and iv) home. This instrument was submitted to test-retest reliability study and the intraclass correlation coefficients and Lin concordance score were ≥ 0.7 for all items and total score.[19]

For the present study, participants were classified according to daily time (hours) spent on sedentary behavior: i) high sedentary behavior (HSB) ≥ 8 h, and ii) low sedentary behavior (LSB) < 8 h. This cutoff point was adopted based on a study that included a similar population and found that HSB (≥ 8 h per day) was associated with higher all-cause mortality risk.[23]

Abdominal obesity was defined by waist circumference (WC), with cutoff points being 102 cm for men and 88 cm for women.[24]

For statistical analysis, a new variable was created considering the cluster of sedentary behavior and abdominal obesity, resulting

in three groups: i) HSB and abdominal obesity (Obese + HSB); ii) HSB or abdominal obesity (Intermediate [Obese + LSB or Non-obese + HSB]); and iii) LSB and no abdominal obesity (Non-obese + LSB).

Adjustment variables and patient characterization

Sex and age of the participants were recorded during the interview. Economic condition (EC) was verified according to the patient's monthly income.[25] These were considered confounding variables due to their association with chronic disease diagnosis.

Weight and the percentage of body fat were measured using bioelectrical impedance (InBody brand model 230, InBody Co., Seoul, South Korea). Height was measured during the interview using Sanny Caprice stadiometer (ES2060, Sanny, Sao Paulo, Brazil). Diastolic and systolic blood pressures were measured using a manual device (BIC brand APO336, CBMED, Itupeva, Brazil.) according to the Brazilian Guideline of Arterial Hypertension.[26]

Statistical analysis

Normality of data was verified using the Kolmogorov-Smirnov test, and further analyses were performed according to the distribution of the dataset. Descriptive statistics were presented as mean values, standard deviation (SD), median, interquartile range (IQ), and 95%CI for numerical variables, and as percentage values for categorical variables. Comparisons between groups were verified using the analysis of variance (ANOVA) test (with Tukey's post hoc) and the Kruskal-Wallis test (with Mann-Whitney as post hoc) when the variables were normal and not normal, respectively. Associations between categorical variables (presence of chronic diseases and the cluster of sedentary behavior and abdominal obesity) were tested using the chi-square test, and when significant, the magnitude of the associations was expressed as OR and its 95%CI using binary logistic regression. Statistical significance (P value) was set at 5%, and all analyses were performed using STATA 16.0 statistical software (Stata LLC, Texas, United States).

RESULTS

The study included a total of 307 adults with cardiovascular diseases. The mean age of the study population was 54.38 (8.29) years, and it comprised 160 (52.1%) men and 147 (47.9%) women. Regarding the level of education, 5.2% of the participants (n = 16) had a college degree, 27% (n = 83) had completed high school, 46.6% (n = 143) had completed elementary school, and 21.2% (n = 65) had not completed elementary education. All participants were classified as having low EC (< R$ 5,000.00 per month, USD$ 1,225.04).

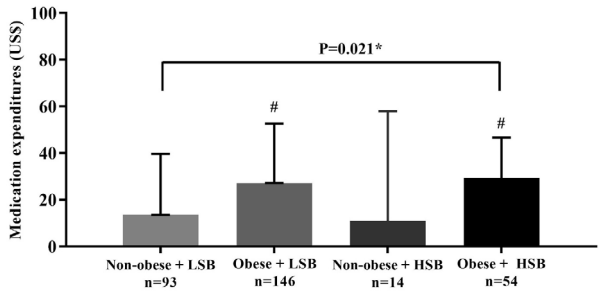
The prevalence of HSB and abdominal obesity in the study population was 22.1% (n = 68) and 65.1% (n = 200), respectively. The general characteristics of the study participants are presented in **Table 1**. Differences were observed among the groups in terms of age, height, weight, body mass index (BMI), WC, and systolic blood pressure (P < 0.05).

When comparing medication expenditures according to sedentary behavior and abdominal obesity grouping, we found that individuals classified in the obese + HSB group had higher expenses than those in the non-obese + LSB group (median [IQ] USD$ 29.39 [45.77] versus USD$ 13.51 [31.42]; P = 0.01). Among those classified in the intermediate group, it was observed that those who were only obese (obese + LSB) had higher expenses than the Non-obese + LSB group (median [IQ] USD$ 27.17 [59.76] versus USD$ 13.51 [31.42]; P = 0.05). However, the same was not observed for those with only HSB (Non-obese + HSB) (median [IQ] USD$ 11.04 [63.54] versus USD$ 13.51 [31.42]; P = 0.97) (**Figure 2**).

Table 1. General characteristics of the study population in terms of the three groups studied

Variable	Non-obese + LSB (n = 93) Mean (SD)	Intermediate (n = 160) Mean (SD)	Obese + HSB (n = 54) Mean (SD)	P value*
Age (years)	52.51 (8.94)	55.54 (7.67)[a]	54.13 (8.46)	**0,019**
Height (cm)	158.16 (7.17)	164.33 (9.50)[a]	169.51 (8.0)[a,b]	**0,001**
Weight (kg)	66.39 (9.88)	86.55 (16.32)[a]	92.06 (17.25)[a]	**0,001**
BMI (kg/m^2)	26.65 (4.33)	32.08 (5.52)[a]	31.92 (5.40)[a]	**0,001**
WC (cm)	87.86 (8.72)	106.12 (13.12)[a]	107.50 (14.15)[a]	**0,001**
%BF (%)	34.81 (9.63)	37.58 (9.67)	35.70 (8.20)	0,070
DBP (mm/Hg)	85.38 (76.10)	84.47 (13.48)	84.34 (15.99)	0,985
SBP (mm/Hg)	118.06 (19.90)	127.86 (19.20)[a]	127.17 (19.64)[a]	**0,001**
Sum of diseases	2.00 (1.89)	2.38 (1.66)	2.28 (1.74)	0,170

* P < 0.05 for the One-Way ANOVA; [a] significant difference (P < 0.05) when compared to the non-obese + LSB group (Tukey Post Hoc test); [b] significant difference (P < 0.05) when compared to the Intermediate group (Tukey Post Hoc test); LSB = Low Sedentary Behavior; HSB = High Sedentary Behavior; SD = standard deviation; cm = centimeters; kg = kilograms; BMI = body mass index; kg/m^2 = kilograms per square meter; WC = waist circumference; %BF = percentage of body fat; DBP = diastolic blood pressure; SBP = systolic blood pressure; mm/Hg = millimeters of mercury.



LSB = Low Sedentary Behavior; HSB = High Sedentary Behavior; * P < 0.05 for Kruskal-Wallis test; # = significant difference (P < 0.05) when compared to the non-obese + LSB group (Mann-Whitney test).

Figure 2. Medication expenditures according to the cluster of sedentary behavior and abdominal obesity.

When analyzing the association between chronic diseases and the cluster of sedentary behavior and abdominal obesity, we found significant results for arterial hypertension (P = 0.004) and heart attack (P = 0.035). Binary logistic regression analysis showed that individuals with abdominal obesity and HSB were 2.4 times more likely to be hypertensive than non-obese + LSB individuals. Age was a significant risk factor in this model for hypertension (OR = 1.07 [95%CI = 1.04; 11.11]) and heart attack (OR = 1.05 [95%CI = 1.01; 1.08]) (**Table 2**).

In addition, it was found that individuals with hypertension had higher expenditures for medication (median [IQ] USD$ 33.85 [55.03] versus USD$ 4.83 [21.69]) when compared with normotensive patients (P = 0.01).

Table 2. Association between presence of chronic diseases and the cluster of sedentary behavior and abdominal obesity

NCDs	%(n)	P value	OR [95%CI]	H-l P value
Arterial Hypertension		**0.004**		0.843
Non-obese + LSB	53.8(50)		1.00	
Intermediate	73.1(117)		1.71 (0.92; 3.19)	
Obese + HSB	74.1(40)		**2.40 (1.00; 5.79)**	
Hypercholesterolemia		0.140		
Non-obese + LSB	34.4(32)		---	
Intermediate	41.3(66)		---	
Obese + HSB	46.3(25)		---	
DM		0.100		
Non-obese + LSB	19.4(18)		---	
Intermediate	24.4(39)		---	
Obese + HSB	31.5(17)		---	
Heart attack		**0.035**		
Non-obese + LSB	22.6(21)		1.00	0.731
Intermediate	37.5(60)		1.01 (0.51; 1.97)	
Obese + HSB	37.0(20)		0.88 (0.37; 2.09)	
Atherosclerosis		0.394		
Non-obese + LSB	17.2(16)		---	
Intermediate	22.5(36)		---	
Obese + HSB	22.2(12)		---	
Nephritis		0.500		
Non-obese + LSB	7.5(7)		---	
Intermediate	4.4(7)		---	
Obese + HSB	5.6(3)		---	

*P < 0.05 for chi-square test followed by binary logistic regression; OR = Odds ratio (OR adjusted for sex, age, and educational level); HSB = high sedentary behavior; LSB = low sedentary behavior.

DISCUSSION

Our study population comprised Brazilian adults with cardiovascular diseases. Our primary finding was that the groups that had higher expenses for medication had abdominal obesity risk factor, and when abdominal obesity and HDB were combined, a robust association with prevalence of arterial hypertension was observed.

We found that 22.1% of the study participants had HSB. This proportion was not very different from the estimates of the World Health Organization study which included six low- and middle-income countries, and reported that sedentary behavior varied from 21%-58% among the adult population.[27] Similarly, a Brazilian study showed that approximately 30% of the adults (≥ 20 years) reported 3 h/day of sedentary behavior, while approximately 20% reported sedentary behavior spanning 6h/day-9h/day. On an average, the participants reported spending 5.8 (SD 4.5) h/day sitting.[22]

Additionally, 65.1% of our study population presented with abdominal obesity. This was similar (approximately 70%) to the proportion reported by a previous research (approximately 70%) with a comparable population.[16] In our study, 17.6% participants had a cluster of sedentary behavior and abdominal obesity. Literature has shown that the likelihood of obesity is 3.21 times higher among sedentary individuals.[28]

The present study showed higher medication expenses for individuals classified in the groups with obesity risk factor (Obese + LSB and Obese + HSB), indicating that this variable was a determinant of medication expenses. The relationship between obesity and healthcare expenditure has been well explored by several previous studies.[16,29,30] An Australian study showed that higher obesity rates correlated with higher expenditures, with costs being 19%-51% higher in comparison to individuals with normal weight.[29]

A Brazilian study reported that an increase in the number of obese individuals in a household was proportional to the increase in healthcare expenditures (P < 0.001), especially in the context of medications.[27] Additionally, among the population assisted by the primary healthcare system, it was observed that medication expenditure represented 35.2% of all expenditures related to health services. Moreover, it has been reported that increased WC and low level of physical activity were related to higher medication expenditures (rho = 0.25, P value = 0.001 and rho = -0.13, P value = 0.001).[16]

Figure 2 show higher expenses for medication when HSB was combined with obesity. However, the group with isolated HSB did not appear to have significantly higher expenses than the Non-obese + LSB group. The total healthcare costs attributable to sedentary behavior in 2016-2017 in the United Kingdom was £ 800 million. In addition, cardiovascular disease costs attributable to sedentary behavior reached £ 424 million (£ 367 to £ 480 million), followed by £ 281 million (£ 233 to £ 327 million) for diabetes.[31] In Finland, healthcare costs attributable to sedentary behavior (≥ 8 h/day) totaled approximately € 1.5 billion in 2017.[32]

To the best of our knowledge, this is one of the first study to describe the potentially harmful impact of sedentary behavior combined with obesity on healthcare costs in developing nations. Therefore, contextualizing the values presented in this study, it is worth noting that individuals who were obese and had HSB spent 12.6% of the national minimum wage on medicines (quotation referring to December 2022 [USD$ 232.6]; 9.65% of average per capita income in Brazil in 2022 [USD$ 304.4]).[33]

The economic impact of the combination of sedentary behavior and obesity can be linked to the onset of NCDs. An Australian study including more than 8,000 adults showed a negative association between sedentary behavior and mortality due to cardiovascular diseases (risk ratio = 1.18, 95%CI = 1.03, 1.35).[34] Obese individuals have a tendency to develop cardiovascular diseases,[35] such as arterial hypertension,[36] due to metabolic dysfunctions, which may promote insulin resistance[37] and consequently result in coronary microvascular dysfunction.[38]

Studies suggest that hypertension is more likely to occur in people with excess weight and sedentary lifestyle (OR = 4.09, 95%CI = 1.93–8.63) or with abdominal obesity and sedentary lifestyle (OR = 4.69, 95%CI = 2.35–9.35) when compared to individuals with normal weight and active lifestyle.[39] We found that sedentary behavior and abdominal obesity increased the likelihood of being diagnosed with arterial hypertension by 2.4 times, a fact that can justify the increase in medication expenditure. Studies in the United States[40-42] have reported that individuals with hypertension spend 6.42 times more on medications in comparison to normotensive individuals ($P < 0.001$),[40] and that annual medical expenses associated with hypertension has increased significantly by 8.3% ($P = 0.015$).[41] In Canada, hypertension accounts for 10.2% of the total health expenditure, $ 13.9 billion in 2010 and projections estimate $ 20 billion by 2020.[42] In Brazil, hypertension is one of the three cardiovascular diseases that imposes high expenditure on the universal health system.[43]

In our study, other relevant diseases, such as diabetes mellitus, atherosclerosis, and dyslipidemia, were not found to be significantly associated with sedentary behavior and abdominal obesity. A potential explanation for this may be an underestimation of the actual prevalence of these diseases in our study population. In fact, all of these disease entities require more complex diagnostic methods than arterial hypertension and heart attack.

A possible non-medical alternative to prevent and minimize health expenditures would be to strengthen public health programs with a focus on healthy lifestyle through physical activity and reduction of risk factors such as obesity. It has been reported that every minute of physical activity can reduce the odds of abdominal obesity by 4% and 2% in men and women, respectively.[28]

Evidence suggests that physical activity promotes numerous health benefits, such as decreased incidence of all-cause mortality, cardiovascular diseases, cancer, and diabetes. Performing physical activity of any sort is recommended for all age groups and is better than doing none. At the same time, it is recommended that sedentary behavior be replaced by physical activity, even that of light intensity.[44]

Therefore, we emphasize the importance of our findings, which would be useful for policymakers when allocating health resources to public health programs targeting risk factors such as obesity and sedentary behavior. Furthermore, future research is important to elucidate the complex relationships between sedentary behavior and health outcomes.

The main limitation of this study was reverse causality due to its cross-sectional design. In addition, a questionnaire was used instead of accelerometers to evaluate sedentary behavior. Moreover, the analyses carried out did not allow the assessment of the burden of each isolated disease, not even the one that had the greatest impact on health expenditure. Sensitivity analyses were not performed. It must also be considered that the prevalence of some diseases may have been underestimated in our sample, limiting the power of associations tested. Finally, the expenditure on medications included in the present study represents only a part of the expenses of these patients, since they could have used medications paid for from their own budget. Moreover, this could also have been the case in terms of use of other healthcare systems (e.g., tertiary and secondary care). However, we have highlighted the importance of our findings in the context of public health, revealing the burden of sedentary behavior and abdominal obesity on the public health system.

CONCLUSION

Abdominal obesity proved to be a determining factor for medication expenses, regardless of sedentary behavior, among adults with cardiovascular diseases.

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Compression pre-stapler firing and post-ignition wait during sleeve gastrectomy: a prospective randomized trial

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ABSTRACT

BACKGROUND: Insufficient research exists on the stapling technique in and duration of laparoscopic sleeve gastrectomy (LSG).

OBJECTIVES: This study aimed to assess the clinical outcomes using a 30-second precompression and post-firing waiting time without extra support for the stapling line.

DESIGN AND SETTINGS: Randomized controlled prospective study at a university hospital.

METHODS: This study included 120 patients treated between January 2022 and February 2023. The patients were divided into the non-waiting group (T0) and waiting group (T1), each with 60 patients. Perioperative complications were analyzed using statistical tests.

RESULTS: The waiting group (T1) showed a significant reduction in the number of intraoperative bleeding points requiring intervention compared with the non-waiting group (T0) (81 versus 134, $P < 0.05$). In T0, postoperative C-reactive protein (CRP) levels increased ($P < 0.05$) and hemoglobin levels decreased significantly ($P < 0.05$). The study recorded 22 postoperative complications, accounting for 18.3% of all cases during the 30-day postoperative period.

CONCLUSIONS: The study concluded that the 30 sec + 30 sec stapling technique reduces perioperative bleeding, length of stay, and serious complication rates and is practical and effective for LSG.

CLINICAL TRIAL REGISTRATION: ClinicalTrials.gov with registration code NCT05703035; link: https://clinicaltrials.gov/ct2/show/NCT05703035.

INTRODUCTION

Laparoscopic sleeve gastrectomy (LSG) is the preferred surgical option to address obesity and is the most widely used procedure.[1] LSG offers several advantages including ease of learning compared to other procedures, short operation time, and minimal changes to the natural anatomy of the gastrointestinal system. Additionally, the surgical outcomes had positive effects on weight loss and comorbidities. However, despite technological advancements, the complication rate for leakage and bleeding remained between 0.5% and 2%.[2] In 90% of cases, leaks occur at the sense angle, and they are likely related to technical errors during stapler firing.[3] Techniques that strengthen the staple line to reduce complications place an economic burden on payment systems by increasing patient costs. Staple malformation is the main cause of leakage and bleeding.[4,5]

OBJECTIVE

This study aimed to examine the potential effectiveness of precompression of 30 s before stapler firing and a waiting period of 30 s after firing, without utilizing any additional support or reinforcement for the staple line, in minimizing both intraoperative and postoperative complications. We hypothesized that the waiting period would result in optimal B formation, thereby reducing bleeding and leakage. Identifying factors such as staple size during LSG and firing technique can assist in improving patient care and optimizing bariatric center outcomes by predicting complications.

METHODS

Study design

A double-blind (patient, postoperative data collector, and statistician), randomized controlled prospective study on class III morbidly obese patients matched for body mass index (BMI)

and comorbidities was conducted in a tertiary education and research hospital between January 2022 and February 2023. The study was approved by the ethics committee of the University of Medeniyet (decision no. 2021/0530, dated August 12, 2021), and the trial was registered at ClinicalTrials.gov with registration code NCT05703035.

Patients were randomly classified into two groups: T0 (patients who did not wait) and T1 (patients who waited). The patients underwent preoperative, intraoperative, and postoperative interventions based on the principles of multimodal enhanced recovery bariatric surgery (ERABS).

The patients underwent preoperative, intraoperative, and postoperative interventions according to the principles of multimodal enhanced recovery bariatric surgery (ERABS). Antithrombotic prophylaxis with enoxaparin was administered until postoperative day 14, and all the patients were followed up based on our routine enhanced recovery protocol, including oral intake beginning on postoperative day 1 and discharge planned on postoperative day 2.

Discharge Criteria:

- Anamnesis
  - Visual analogue score < 4
  - No complaints of nausea or vomiting
  - Oral fluid intake > 1,500 ml in 24 hours
  - Moving and walking independently without support
  - No complaints of leg pain
- Physical Examination
  - Abdominal examination is normal
  - Body fever < 38°C
  - Pulse rate < 100 bpm
  - Oxygen saturation (SatO2) > %95
  - Respiration rate: 10–16
  - Drainage < 50 ml
- Laboratory Results
  - Postoperative hemoglobin decline < 2.0 g/dL
  - White blood cell (WBC) < 12 × 10^3/uL
  - C-reactive protein (CRP) < 20 mg/dL

Postoperative follow-up data were recorded by nursing staff and physicians' assistants who were blinded to the procedures. Our prospective database included the documentation of all medical and surgical complications. In this study, intraoperative parameters, such as leakage, bleeding, reoperation and mortality rates, operative time, number of stapler shots, intraoperative bleeding, number of bleeding points treated with clips on the stapler line, and amount of blood in the aspirator and gauze, were recorded. Laboratory tests were requested from the patients on postoperative days 1, 7, and 30. Bleeding was defined as hemoglobin > 2 g/dL, pure blood drainage > 100 ml, or serohemorrhagic drainage > 200 ml and standing blood pressure < 20 mmHg. Parameters for leaks included purulent drainage from the drain, fever, tachycardia, increased respiratory rate, and severe epigastric pain.

Study Population

With a Cohen's d effect size of 0.5, 46 participants were required in each group for a prospective randomized controlled study of sleeve gastrectomy using staple firing with and without precompression, with 80% power and a 5% alpha level. Assuming a potential 10% loss to follow-up, the required sample size was 102. A 12-month enrollment period was anticipated for patient recruitment. The sample size was increased to reach a total of 120 patients in both groups. The study included 120 patients (60 each in T0 and T1).

Inclusion criteria:

- Age: 18–65 years
- BMI > 40.0–49.90 kg/cm2
- Not using anticoagulant drugs
- Never underwent bariatric surgery before

Exclusion criteria:

- Patients who applied for revision surgery
- Patients with a history of thromboembolism
- Patients with known clotting disorders

The selected patients were given ample time to review the details of the study and answer questions. Those who agreed to participate voluntarily signed an informed consent form. Patients who declined to participate or were not eligible for the study were provided standard patient care according to the protocol.

Interventions of the Study

Surgical Procedure and Stapler Technique

Each patient was administered 40 mg of enoxaparin subcutaneously 12 h before surgery. Pneumoperitoneum was created after routine placement of four ports. A Nathanson liver retractor was routinely used. Stomach dissection was performed using an energy device (LigaSure Atlas; Covidien LLC, United States).[6] Gastric calibration was performed using a 38-French gastric bougie placed in the stomach. Gastric transection was initiated with continuous linear staples approximately 3 cm from the pylorus. In all patients, the first stapler was 60 mm black (leg length (4-4.5-5 mm), followed by 60 mm pink stapler (leg length 3-3.5-4 mm) (Endo GIA™ Articulating Reloads with Tri-staple™ Technology, Covidien LLC, United States of America). The last stapler was used, leaving a sufficient distance (approximately 1 cm) from the sense angle. After transection, the resected stomach was removed through a 15 mm trocar site. The gastric tube was pulled up to 37 cm, and a leak test was performed. This was performed using 120 mL of saline stained

with methylene blue. No reinforcement support was used for the stapler line in any patient. A silicone drain was placed in the operative area for all patients.

In the waiting group, after the staple was locked into the stomach, compression was applied for 30 s, and firing was performed in four continuous motions (15 mm per movement). After firing was completed, the punch jaws were left compressed for another 30 s without opening, after which the jaws were opened and the process was completed. The first stapler was fired at 0°, the second at 9°, and a routine angulation of 18° was given to the third and subsequent staplers. In the non-waiting group, firing and cutting were performed without waiting after tissue locking with the stapler, without changing the order of use.

Randomization

After the eligibility screening was conducted by the research coordinator, each patient was assigned a unique number using the hospital system. The randomization program (https://www.randomizer.org/) stratified patients into blocks 4 and 6, and all the randomized patients received care during the study period according to the intervention they were assigned. The study statistician, service follow-up doctor, care team, and patients were blinded to the procedure.

Study Outcomes

The primary outcome of the study was whether waiting for the stapling procedure reduced the rates of bleeding and leakage during and after surgery. The secondary outcomes were the need for additional interventions outside of standard care, morbidity, mortality, and length of hospital stay without any reinforcement of the stapler line. Patients were followed up in the ward and as outpatients for up to 30 days postoperatively to determine whether they experienced any of the complications included in the composite outcome.

Statistical analysis

Follow-up data were collected by a physician and a statistician who were blinded to the treatment groups. Mean and standard deviation was used to express continuous variables. The baseline characteristics of the patients in both groups were reported using descriptive statistics, such as frequency distributions, central tendency, and measures of distribution. Student's t-test was used for normally distributed numerical variables, the chi-square test was used for categorical variables, and the Mann–Whitney U test was used for non-parametric variables. The adjusted odds ratios (ORs) with 95% confidence intervals were presented as the results of the multivariate logistic regression analysis. Statistical significance was set at $P < 0.05$. Statistical analyses were performed using JMP 11 software (SAS Institute Inc., Cary, NC, USA).

RESULTS

Both groups had similar demographic and clinical characteristics **(Table 1).**

Patients with organ damage or bleeding unrelated to the stapling procedure performed during surgery were excluded. The number of bleeding points on the stapling line was assessed by reducing the intra-abdominal pressure to 8 mm Hg for 5 min. The waiting group (T1) showed significantly fewer stapling line bleeding points requiring intervention than the other group (81 versus 134, $P < 0.05$), resulting in a 28% better performance without additional measures. Metallic clips were used for hemostasis in all cases, and bleeding points were observed as staple firings in both groups **(Figure 1).** However, T1 had significantly fewer bleeding points at the second and third staple-firing stages ($P < 0.05$). Intraoperative blood loss was measured using an aspirator, and pressure was applied with gauze in some cases. T0 had a significantly greater intraoperative loss ($P < 0.05$); however, the overall loss was not significant. Further, T0 had a significantly shorter mean operation time of 8 min ($P < 0.05$).

Table 1. Statistical analysis of patients' demographic and clinical characteristic features

Parameters	T0 (n = 60)	T1 (n = 60)	P
Gender (Female/Male)	48/12 (80.0%/20.0%)	50/10 (83.3%/16.7%)	0.498**
Age (years)	33.8 (20-59)	34.3(21-56)	0.439*
Height (cm)	159 (148–179)	158 (157–182)	0.632***
Weight (kg)	117.2 (105-165)	116.4(107-159)	0.454***
BMI (kg/cm^2)	42.3 (40.1–49.2)	43.1(40.5, 2–48.9)	0.543***
Obesity-related comorbidity			
T2D	22 (36.7%)	20 (32.7%)	0.434***
Hypertension	11 (30.0%)	10 (16.3%)	0.657***
OSAS	5 (8.3%)	6 (9.8%)	0.322***
Hyperlipidemia	14 (23.3%)	15 (24.5%)	0.645***

BMI = body mass index; OSAS = obstructive sleep apnea syndrome; T2D = type 2 diabetes; categorical variables are expressed as n (%) and continuous variables as median (IQR); T0 = non-waiting group; T1 = waiting group.

* Student's t-test (mean, standard deviation); ** Chi-square test; *** Mann–Whitney test; $P < 0.05$, considered statistically significant;.

As regards postoperative outcomes, patients with a decrease in hemoglobin level > 2 mg/dL after surgery in T0 had a higher incidence of bleeding than those in T1 (20% versus 8.6%). Two patients in T0 required 4 units of erythrocyte suspension transfusion (P < 0.05). Complications according to the Clavien–Dindo classification occurred in 22 cases (18.3% of all cases) within the 30-day postoperative period; however, no deaths were recorded. Additional interventions were performed in one patient in T0 because of ineffective drainage and in one patient in T1 because of fever caused by atelectasis. No leakage or thromboembolic events occurred during the 30-day follow-up in either group. Hospitalization duration was significantly longer in T0 than in T1 (P < 0.05) **(Table 2).**

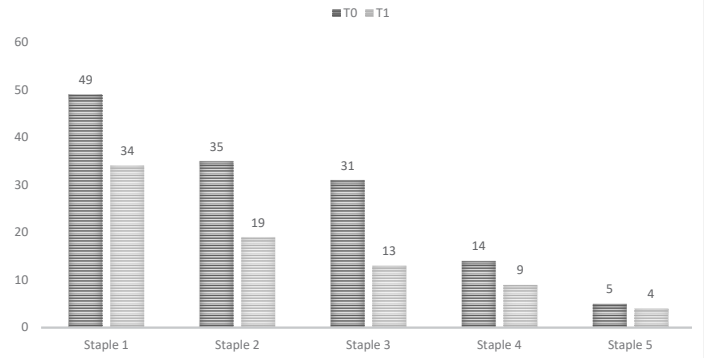

Figure 1. Plot of bleeding points on the punch line.

Regarding laboratory values, the mean hemoglobin decrease was greater in T0 than in T1 (1.9 g/dL vs. 1.5 g/dL, P < 0.05). The acute-phase reactant CRP levels were significantly higher in T0 (P < 0.05). The WBC count and coagulation values increased in both groups after surgery; however, the difference was not statistically significant. Ultrasound controls at 1 week and 1 month post-surgery were normal. Average gastric wall thickness, as determined by pathological evaluation, did not significantly correlate with complications **(Table 3).**

DISCUSSION

Surgical staplers are commonly used in various surgical procedures to facilitate rapid and effortless tissue division and closure. Its use in bariatric surgery is considered the gold standard. Studies have shown that the use of reinforcing products on the stapling line is beneficial.[7] Stapler manufacturers suggest that tissue can be clamped between the jaws of the stapler and cut in a flat position. However, there are no recommendations regarding waiting time.[8]

Research showing the beneficial results of waiting for a certain amount of time before stapling is limited.[9] The optimal waiting and stapling times are unclear. Based on experience, some surgeons recommended waiting a while before firing the stapler to ensure adequate tissue compression for hemostasis.[10] During LSG, bleeding may occur along the stapler line, which may require additional measures such as suturing the edges of the stapler line, using clips, or using electrocautery to stop the bleeding. Difficulty in diagnosis

Table 2. Analysis of patients' intraoperative and postoperative data

Parameters	T0 (n = 60)	T1 (n = 60)	P
İntraoperative			
Operation time(minutes)	52.4 (7.8)*	64.1 (5.3)	< 0,001**
Number of staples used	5.12 (4-6)	5.26 (4-6)	0,452**
Number of bleeding points	134 (0-5)	81 (0-3)*	0,003**
Intraoperative blood loss (mL)	30 (15–25)	15 (10–25)*	0,001*
Clip for hemostasis (median)	3 (0–5)	2 (0–4)	0,116**
Number of patients without bleeding %	11	17	0,002**
Postoperative			
Drain Mean blood loss (ml)	119.4 (30-400)	114.6 (30-225)	0,301*
Clavien-Dindo Classification			
Transfusion %	2 (3.3)	0*	0,042*
Post Op bleeding %	12 (20)	5 (8.3)*	< 0,001*
Postop leak	0	0	1,00*
Thromboembolic event	0	0	1,00*
Hematoma %	1(1.7)	0	0,754*
Vomiting %	1 (1.7)	2 (3.3)	0,342*
Fever %	0	1	0,754*
Length of stay (days)	2.35 (2-5)	2.14 (2-3)*	0,02*
Gastric tissue thickness (mm)	0.27 (0.3)	0.27 (0.2)	0,978*

Categorical variables are expressed as n (%) and continuous variables as median (IQR); * Student's t-test (mean, standard deviation); ** Mann–Whitney test; P < 0.05, considered statistically significant; T0 = non-waiting group; T1 = waiting group.

Table 3. Univariate analysis of laboratory and imaging tests of patients

Parameters	T0 (n = 60)	T1 (n = 60)	P
Preoperative			
WBC (10^3 /uL)	7.7 (2.2)	7.2 (3.5)	0,345*
Hemoglobin (g/dL)	13.2 (3.2)	13.4 (3.1)	0,467*
PLT (10^3 /uL)	231 (114)	234 (98)	0,629**
CRP (mg/L)	2.0 (1.8)	2.1 (0.7)	0.784*
INR	0,98 (0,1)	0.98 (0,1)	0,493**
PT (sn)	14.0 (0.2)	14.1 (0.3)	0,618**
PTT (sn)	83.2 (8.2)	82.9 (7.0)	0,382**
Fibrinogen (mg/dL)	270 (78)	274 (72)	0,234**
USG	N	N	1.00**
Postoperative			
WBC (10^3 /uL)	13.7 (4.9)	12.9 (6.2)	0,237*
Hemoglobin (g/dL)	11.2 (0.6)*	11.9 (1.1)	0,025*
PLT (10^3 /uL)	244 (102)	239 (98)	0,532**
CRP (mg/L)	28.46 (8.5-110.6)	21.3 (7.3-87.6)*	0.014*
INR	0.99 (0.05)	1.0 (0.03)	0.493**
PT (sn)	14.2 (0.2)	14.4 (0.3)	0.578**
PTT (sn)	84.2 (7.0)	83.9 (7.3)	0.382**
Fibrinogen (mg/dL)	274 (72)	277 (74)	0.234**
USG	1 (hematoma)	N	1.00*

WBC = white blood cell; PLT = platelet count; CRP = C-reactive protein; INR = international normalized ratio; PT = prothrombin time; PTT = Partial thromboplastin time; USG = ultrasonography; Categorical variables were expressed as n (%) and continuous variables as median (IQR); * Student's t-test (mean, standard deviation); ** Mann–Whitney test; $P < 0.05$ was considered statistical significance; T0 = non-waiting group; T1 = waiting group.

and indecisiveness in timely intervention during the postoperative period can affect morbidity and hospital stay.[11] An animal model study has shown that the number of bleeding points from the stapler line can be significantly reduced by using waiting times of 0, 1, and 5 minutes before firing as a stapling technique.[12]

In our study, staple line bleeding was observed in 17 (14.1%) patients, with 12 patients in T0 and 5 patients in T1, respectively. These results indicate that the current rate is higher than that previously reported in the literature. We believe that this is due to our comprehensive assessment, which included variables that we believe were associated with bleeding and broad in scope. Two patients in the non-waiting group underwent transfusion because of bleeding, and the other patients were managed conservatively. Better bleeding outcomes were achieved in T1. This can be attributed to the compression–wait–firing–wait–separation technique used, which compresses the tissue to obtain a flatter and thinner tissue, reduces staple slippage from the tissue during firing, and promotes optimal staple formation.

Intraluminal bleeding cannot be observed intraoperatively prior to endoscopic inspection after staple firing. Bleeding at the staple line may indicate bleeding within the lumen of an organ or structure.[12,13] Delaying the firing of a staple for a period of time is a simple method to reduce staple line bleeding, which may be associated with a decrease in the likelihood of intraluminal bleeding.[14] In our study, after a total of 1 min of waiting and approximately 10 min of postoperative observation, no evidence of localized or diffuse ischemia was observed in the gastric tissue. This may be because of the thicker stomach tissue and abundant blood supply. Choosing an appropriate wait time for ignition further helps prevent tissue tension and bending during the procedure. In a study of distal pancreatectomy, this time was approximately 5 minutes.[15]

Major postoperative morbidity after LSG is often associated with staple line leakage, which has two main causes: ischemic or mechanical and technical aspects related to incorrect firing of the stapler and the type of cartridge used.[16] Generally, the leakage rate after LSG is 1–2.7%; however, in our study, no leaks were observed in either group, probably owing to the sample size.

During the postoperative follow-up, 22 patients (18.6% of the total patients) had complications within the first 30 days after surgery. The type and frequency of these complications were similar to those reported in previous research studies.[17,18]

In a limited number of studies on distal pancreatectomy, a waiting time of 10 min has been shown to reduce tissue slippage as the staple legs penetrate the tissue, resulting in proper tissue compression and a smooth staple line by allowing fluid drainage.[19] However, we did not find similar studies on gastric or intestinal tissue in the literature. In studies related to gastric tissue thickness, research has shown that tissue thickness decreases from the antrum to the proximal area, which is crucial in staple selection.[20] We used Tri-Staple technology in all of our patients. Owing to the thicker antral tissue, we chose the first cartridge to be black and all subsequent cartridges to be purple. The average thickness of the stomach wall in our study was measured to be 2.7 mm. Our results suggest that appropriate staple selection in combination with waiting time may reduce bleeding and complication development.

The effects of tissue precompression have been determined in limited studies related to colorectal and pancreatic surgeries.[21,22] However, the optimal waiting time remains unclear. In colorectal surgery, only data on precompression are available. The difference in our application was that we waited both during precompression and compression after firing. Therefore, we believe that the staples formed an optimal B-formation after firing and that the pressure on the tissue prevented protrusion between the staple teeth. Minimal disruption of tissue integrity was associated with reduced bleeding and leakage.

Overall, these findings highlight that stapling techniques should be considered in bariatric surgery to minimize postoperative bleeding and improve patient outcomes.

This study had some limitations. First, although stapler malformation is believed to be the primary cause of bleeding and leakage,

whether optimal stapler formation is associated with improved clinical outcomes remains unclear. Second, the potential effects of precompression on the gastric wall, such as vascularization, bleeding, and tissue damage, were not evaluated. However, these factors are critical and require further investigation. Last, the lack of studies with longer dwell times limits the ability to compare and determine the most effective dwell time.

CONCLUSION

Our study suggests that a 30-second precompression, along with a 30-second post-fire waiting period, possibly results in improved staple formation. In addition, precompression time is a critical factor in optimizing staple formation. Further, the removal of the device from the tissue after the waiting period is shown to have a significant effect on bleeding, hospital stay, and recovery.

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Portuguese Advance Directives-a twist against futility? A cross sectional study

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ABSTRACT

BACKGROUND: Advance Directive documents allow citizens to choose the treatments they want for end-of-life care without considering therapeutic futility.

OBJECTIVES: To analyze patients' and caregivers' answers to Advance Directives and understand their expectations regarding their decisions.

DESIGN AND SETTING: This study analyzed participants' answers to a previously published trial, conceived to test the document's efficacy as a communication tool.

METHODS: Sixty palliative patients and 60 caregivers (n = 120) registered their preferences in the Advance Directive document and expressed their expectations regarding whether to receive the chosen treatments.

RESULTS: In the patient and caregiver groups, 30% and 23.3% wanted to receive cardiorespiratory resuscitation; 23.3% and 25% wanted to receive artificial organ support; and 40% and 35% chose to receive artificial feeding and hydration, respectively. The participants ignored the concept of therapeutic futility and expected to receive invasive treatments. The concept of therapeutic futility should be addressed and discussed with both the patients and caregivers. Legal Advanced Directive documents should be made clear to reduce misinterpretations and potential legal conflicts.

CONCLUSION: The authors suggest that all citizens should be clarified regarding the futility concept before filling out the Advance Directives and propose a grammatical change in the document, replacing the phrase "Health Care to Receive / Not to Receive" with the sentence "Health Care to Accept / Refuse" so that patients cannot demand treatments, but instead accept or refuse the proposed therapeutic plans.

TRIAL REGISTRATION: ClinicalTrials.gov ID NCT05090072

URL: https://clinicaltrials.gov/ct2/show/NCT05090072.

INTRODUCTION

Given the increasing growth in scientific knowledge and the advancements in medical treatments, patients' autonomy regarding end-of-life care must be promoted.[1]

Advance Directives have emerged as self-determination documents enabling patients to participate in end-of-life decision-making when they can no longer manifest their wishes.[2]

In Portugal, Advance Directives were legalized in 2012 (Law 25/2012 of 16th July).[3] This legislative norm enables citizens to nominate a health surrogate and register their preferences on a Living Will[4] document with a five-year expiry date. Every adult citizen capable of providing free and informed consent can register their Living Will with the proper legal authority of the Ministry of Health.[3]

The Portuguese Advance Directives document[4] comprises a two-step formulation of a tick-box type. In the first section (clinical situations to apply Advance Directives), citizens choose clinical scenarios where they wish to apply their end-of-life preferences. In the second section (Healthcare to receive or not), they register their Advance Directives by ticking the boxes according to their preferences (**Table 1**).[4]

Through decades, the Advance Directives were implemented and promoted as a legal document that allowed patients to refuse the treatments they considered unacceptable for themselves, protecting them from therapeutic futility and medical obstination.[5] The Portuguese law reinforces that idea by stating that the citizens can choose not to receive cardiorespiratory resuscitation or invasive organ support, among others.[3] However, the Advance Directives' documents[4] are silent regarding the concept of medical futility and do not raise patients' and citizens' awareness on this issue, although they should, to prevent inadequate expectations and future disagreements or litigations between

patients, caregivers, and the healthcare personnel. Therefore, when patients do not tick the boxes of refusal of blood product administration, cardiopulmonary resuscitation, or invasive organ support, they probably assume they will receive those treatments, ignoring that in some clinical circumstances, those procedures might be considered futile and contrary to "legis artis" and, as such, not be accomplished.

OBJECTIVES

This study aimed to analyze the answers to the Advance Directive formulary[4] of a population of patients receiving palliative care and their caregivers and to understand their decisions when filling the document.

METHODS

Design and setting

This study analyzed the answers of a group of participants enrolled in the DAVPAL (Advance Directives in Palliative Care) trial (available on ClinicalTrials.gov, ID NCT05090072), which was conceived to test the use of the Advance Directive document as an instrument to promote better concordance between patients and caregivers regarding end-of-life care.

All patients were referred to the Palliative Medicine Service between September 2018 and September 2019, and their caregivers were invited to participate. Participants were enrolled in the study if the following inclusion criteria were fulfilled: adult patients who agreed to participate in the DAVPAL Trial, had no cognitive impairment, and could understand and speak Portuguese.

This study adhered to the ethical procedures outlined in the Declaration of Helsinki. The study was approved by the Ethics Committee of the Centro Hospitalar de Trás-os-Montes e Alto Douro on June 18, 2018 (Doc no. 245/2018), and all participants provided written informed consent to participate in the trial.

We asked 60 patients receiving palliative care and 60 caregivers (n = 120) to fill in the Portuguese Advance Directive formulary and express their preferences and expectations regarding the treatments for their end-of-life care.

The Portuguese model of Advance Directives[4] was used to register the participants' preferences. All participants filled in the documents individually and expressed their expectations when deciding whether to tick each sentence.

Table 1. Demographic characteristics of the population

	Patients	Caregivers
Age (years), mean ± SD	70.6 ± 13.2	58.6 ± 13.5
Gender, n (%)		
Male	32 (53.3%)	16 (26.7%)
Female	28 (46.7%)	44 (73.3%)
Education Level, n (%)		
Illiterate	7 (11.7%)	1 (1.7%)
Knows how to write and read	9 (15.0%)	4 (6.7%)
Primary School	30 (50.0%)	15 (25.0%)
Middle School	11 (18.3%)	17 (28.3%)
High School	3 (5.0%)	12 (20.0%)
University	0 (0.0%)	11 (18.3%)
Religion, n (%)		
Catholic	59 (98.3%)	55 (91.7%)
Jehovah's Witness	1 (1.7%)	2 (3.3%)
Agnostic	0 (0.0%)	1 (1.7%)
Other	0 (0.0%)	2 (3.3%)

SD = standard deviation.

RESULTS

The demographic characteristics of the study population are shown in **Table 1**. We observed that the patients were older than the rest of the participants and the caregiver group included a higher proportion of females. The patient group had low literacy levels and most participants were Catholic, as expected in Portugal.

Table 2 shows the Portuguese Advance Directives' formulary.[4] To be officially valid, these documents must be registered on the platform—National Registration of the Living Will[6] (RENTV) by a governmental health employee.

All participants chose the three clinical scenarios in the first section of the document (clinical situations where the Advance Directives apply), and their answers differed only in the second section of the document (Healthcare to Receive / Not to Receive); therefore, only the answers in this section will be presented and analyzed.

We enhanced the answers to the first three sentences of the second part of the document.[4] They concern treatments that might be considered futile in the end-of-life period of most patients facing the scenarios of the first section, and particularly when they have terminal diseases for which they are receiving palliative care. The participants' decisions are presented in **Table 3**.

As expected, in the circumstances of terminal disease such as no expected recovery, or irreversible neurological or psychiatric disease with vital organ dysfunction, most participants refused invasive treatments and CPR. In the patients' and caregivers' groups, respectively, 70.0% and 76.7% chose "Not to receive cardiorespiratory resuscitation," 76.7% and 75% chose "Not to receive artificial organ support," and 60.0% and 65% chose "Not to receive artificial feeding and hydration only to delay the natural death occurrence".

However, a considerable number of patients and caregivers did not refuse to undergo invasive procedures. When asked about their decisions, all the participants expressed that they expected to receive these treatments. In the patient group, despite facing incurable, progressive, or fatal diseases for which they were receiving palliative treatment, 30% wanted to receive cardiorespiratory resuscitation, 23.3% wanted to receive invasive and artificial organ support, and 40% chose to receive artificial feeding and hydration to delay the occurrence of natural death.

A significant number of participants in the caregiver group also chose not to refuse these invasive treatments when faced with previously described clinical scenarios. In this group, 23,3% chose cardiorespiratory resuscitation, 25% chose artificial organ support, and 35% chose artificial feeding and hydration to delay natural death. Similarly, as in the patient group, all these caregivers mentioned that they wanted and expected to receive these treatments if their heart or any vital organ stopped, despite being in a clinical situation of incurable and fatal diseases.

The main reasons for choosing artificial life support were religious and the concept that life must be preserved at any cost, as "miracles happen." Spontaneous commentaries such as "my faith helps me not to give up," "while there is life, there is hope," and "only God knows when it is time to die" were used to justify the decisions made. One participant from the patients' group even claimed that he had previously been on artificial life support and "woke up" to explain his choice of receiving invasive measures to postpone death. However, in both groups,

Table 2. Portuguese Advance Directives (Living Will)[4]

CLINICAL SITUATIONS TO APPLY THE ADVANCE DIRECTIVES

When I am incapable of expressing my will, because of my mental or physical health situation, and one or more of the following hypotheses occur:

☐ Diagnosis of incurable and terminal disease
☐ No expectable recovery, according to state of art
☐ Unconsciousness with irreversible neurologic or psychiatric disease complicated by respiratory, renal, or cardiac disfunction
☐ Other _____

HEALTH CARE TO RECEIVE / NOT TO RECEIVE

Therefore, I manifest my clear and unequivocal will of:

☐ Not receive cardiorespiratory resuscitation
☐ Not be submitted to invasive and artificial organ support
☐ Not be submitted to artificial feeding and hydration for delaying the occurrence of natural death
☐ Participate in experimental studies or investigation trials
☐ Not be submitted to experimental treatments
☐ Not be submitted to experimental studies or investigation trials
☐ Interrupt previously consented experimental treatments or investigation trials participation
☐ Not authorize blood and derivates transfusions
☐ To receive palliative care and minimal oral or subcutaneous hydration
☐ To be administered effective and necessary pain killers and other symptom control drugs
☐ To receive spiritual assistance when invasive life support is about to end
☐ Be accompanied by the following person _____ when invasive life support is about to end

Table 3. Participants' answers to the Advance Directives[4] (healthcare to receive or not)

Based on the scenarios previously described,	**PALLIATIVE PATIENTS (n = 60)**		**CAREGIVERS (n = 60)**	
I manifest my clear and unequivocal will of:	**Selected**	**Did Not Select**	**Selected**	**Did Not Select**
	n (%)	**n (%)**	**n (%)**	**n (%)**
Not to receive cardiorespiratory resuscitation	42 (70.0%)	**18 (30.0%)**	46 (76.7%)	**14 (23.3%)**
Not be submitted to invasive and artificial organ support	46 (76.7%)	**14 (23.3%)**	45 (75.0%)	**15 (25.0%)**
Not be submitted to artificial feeding and hydration for delaying the occurrence of natural death	36 (60.0%)	**24 (40.0%)**	39 (65.0%)	**21 (35.0%)**
Participate in experimental studies or investigation trials	38 (63.3%)	22 (36.7%)	37 (61.7%)	23 (38.3%)
Not be submitted to experimental treatments	22 (36.7%)	38 (63.7%)	21 (35.0%)	39 (65.0%)
Not be submitted to experimental studies or investigation trials	21 (35.0%)	39 (65.0%)	21 (35.0%)	39 (65.0%)
Interrupt previously consented experimental treatments or investigation trials participation	19 (31.7%)	41 (68.3%)	16 (26.7%)	44 (73.3%)
Not authorize blood and derivates transfusions	19 (31.7%)	41 (68.3%)	23 (38.3%)	37 (63.3%)
To receive palliative care and minimal oral or subcutaneous hydration	59 (98.3%)	1 (1.7%)	60 (100.0%)	0 (0.0%)
To be administered effective and necessary pain killers and other symptom control drugs	59 (98.3%)	1 (1.7%)	60 (100.0%)	0 (0.0%)
To receive spiritual assistance when invasive life support is about to be ended	51 (85.0%)	9 (15.0%)	48 (80.0%)	12 (20.0%)
Be accompanied by the following person when invasive life support has ended _____	54 (90.0%)	6 (10.0%)	45 (75.0%)	15 825.0%)

most patients and caregivers chose to receive palliative care and symptom control drugs.

All participants ignored that cardiorespiratory resuscitation, invasive and artificial organ support, and artificial measures to delay natural death, might not be considered good practice in the previously chosen clinical scenarios and for most patients in palliative care. The participants were unaware of the concept of medical utility. They believed that the Advance Directives gave them a choice of treatment, regardless of whether they were indicated in their clinical situation or considered futile. They all stated that they expected to receive these invasive treatments, as they knew that the healthcare staff had to comply with the Advance Directives' content.

DISCUSSION

In palliative care patients, all invasive treatments must be weighted and pursued only when physicians have strong evidence that they will benefit the patients more than harm them. However, when patients are unfamiliar with the futility concept and choose to receive invasive treatments in Advance Directive documents, they may create unrealistic expectations of receiving them, even when they are considered futile.

Although the Portuguese population's health literacy has improved,[7] some patients and citizens may be unaware of what is considered "good medical practice," and legal considerations may emerge if they understand that their autonomy and self-determination are not being accomplished. Health professionals are crucial in raising patient awareness regarding these issues, although the concept of futility is challenging for patients, physicians, and families to define and perceive differently.

The initial concept of futility as a non-beneficial, ineffective, and inappropriate treatment (Ethics Committee of the Society of Critical Care Medicine, 1997)[8] evolved to other definitions such as "an intervention that is unlikely to restore, maintain, or enhance a life that the patient can be aware of"[9,10] or "interventions with a meagre chance of benefitting the patient (quantitative futility), and interventions that will produce benefits with shallow quality (qualitative futility)."[11]

Morata[12] proposed a consensus definition for futility as "interventions or procedures which do not achieve meaningful recovery of the primary ailment based on the patient's and multidisciplinary teams' healthcare goals, yet a latent sense of hope often underlies the situation and patient condition."[12]

Unfortunately, futile treatments are performed worldwide and are well-documented in the literature. In a systematic review of non-beneficial treatments in hospitals at the end-of-life,[13] that included 1,213,171 participants across 10 different countries, the most frequently reported situations were non-beneficial ICU admissions (10% prevalence), newly initiated or ongoing chemotherapy (33% prevalence), cardiorespiratory resuscitation for terminal patients (28,1% prevalence), death in the ICU and on a hospital ward, or after initiating aggressive treatment (58% prevalence), and non-beneficial examinations in patients classified as "Do not resuscitate" (33%–50% prevalence).[13]

The literature is scarce on research emphasizing patients who choose invasive treatments despite the low chance of benefitting them,[14] as we noticed in our trial results. Kobewka et al.[14] analyzed the end-of-life decisions of 13 patients with advanced organ failure diseases or at high risk of death who requested CPR if their heart stopped. In this trial, all 13 patients had previously seen a decision-aid video regarding CPR, its benefits, and harms, and still chose to ask for resuscitation maneuvers. The main reasons for their answers reflected a solid will to prolong life and the sense that refusing CPR meant choosing to die. Similar to this study, most participants lacked sufficient information on CPR and its consequences, and still, they defended this choice as essential and "worth a try."[14] The authors also highlight the high risk of discordance between the patient's preferences and the performed treatments, classifying it as a seriously wrong event that must be prevented.

According to Portuguese law,[3] the preferences stated on the Living Will must be respected by health professionals, with a few exceptions (patients no longer want the registered choices; decisions are outdated considering the scientific evolution; the circumstances that the patient predicted have changed). However, Portuguese law also states that the Advance Directives are invalid when against the law and public order, against good medical practices, or when their accomplishment might induce a non-natural and avoidable death.[3]

In this context, particularly in patients with progressive and incurable diseases receiving palliative care, clinicians have a moral obligation not to initiate ineffective treatments and ensure that both patients and families understand this concept of medical futility and maleficence to prevent future circumstances of displeasure and litigation.

Studies[15,16] have explained that patients and their families must be involved in the decision-making process to respect their autonomy. However, this does not give them the right to receive or demand any desired treatment, as patients may have unrealistic goals for their end-of-life healthcare.[15,16]

The Advance Directives documents are considered a prospective consent form regarding the treatments for the end-of-life period.[17] Some authors[10] describe this document as a "proactive, informed refusal of therapies in a future state of incapacity."[10]

Therefore, as stated by Beauchamp,[18] crucial elements must be considered when an informed consent form is requested and signed. First, citizens must be competent to decide and have the capacity to receive and understand all information regarding the subject. Then, after receiving and integrating the available information, the citizen must be able to decide voluntarily and, finally, consent to the proposed treatment.[18] In Portugal, citizens and patients can register their Advance Directives without mandatory

medical counseling or health care assistance, although some citizens might request it. Consequently, one of the most critical elements of informed consent might not be fulfilled, as we cannot guarantee that citizens have complete knowledge and comprehension of the available healthcare treatments, indications, contraindications, and potentially harmful side effects before registering their Living Will. This assumes particular interest in palliative care patients, as the risk of therapeutic futility is considerable.

The Portuguese Medical Association document on patient rights and duties[19] clearly states that patients can decide, in a free and informed way, whether to accept or refuse any treatment according to their self-determination rights. However, this document does not provide patients the right to choose treatments without benefits in their clinical situation.[19] The Advance Directives' document[4] should be equally clear and not conducive to misinterpretations. These documents should include an explanatory section on the therapeutic futility and elucidate the patients on this subject.

Most legalized Advance Directives in European countries[20] refuse supportive treatment and treatment limitations. In Portugal and many other countries in Europe, the documents are legally binding, and their content must be respected by healthcare teams, whereas in other countries, the documents are merely informative and indicative of the patient's preferences.[20]

Many Advance Directives formularies, in countries such as Canada, England, USA, Spain, Germany or Australia, have an explanatory introduction regarding their content and its purpose.[21-26] However, they lack information regarding the concept of futility and non-beneficial treatments and give the citizens the option to choose or not invasive treatments that might be considered futile.[21-26] Nevertheless, some countries legalized Advance Directives documents that are more objective and less prone to misunderstandings by focusing citizens' choices on refusing invasive and potentially harmful treatments instead of demanding treatments that might be considered futile.

In the Netherlands, the legalized Advance Directives[27] only include a "do not resuscitate order" or a "written treatment prohibition and a request for euthanasia," and the Finnish Advance Directives'[28] formulary consists of a pre-written text refusing invasive treatments and demanding the interruption of previously started treatments if they are later recognized as futile.[28]

The Swiss Advance Directives'[29] document, despite allowing citizens to choose invasive treatments for their end-of-life care, stresses that when citizens choose invasive treatments, they must accept the restrictions associated with the desire to stay alive. Citizens and patients can decide between "do not treat" or "treat as clinically indicated, even in cases of poor prognosis" and implicitly acknowledge that if any treatment is to be done, it must be clinically indicated.[29]

In France, the Advance Directives'[30] document sends a more subtle message, which may reduce the likelihood of patients demanding non-benefitting treatments, because the document only allows patients to accept or refuse treatments. The use of these particular words ("accept and refuse") has broader and deeper consequences than it seems at first sight, insofar as it implies that the treatments must be offered or proposed so that citizens can accept or refuse them. Therefore, if the medical team considers that a treatment is not beneficial and does not propose it to the patient, the patient has no legal way to request it and go against the good medical practice, as they can only "accept or refuse" treatments.[30]

Congruent with other countries, the primary purpose of Portuguese law[3] is to allow citizens to refuse invasive and futile treatments such as non-benefiting reanimation or vital organ support. However, the document might allow a subversive interpretation and convey the idea that citizens can ask for any treatment, even those who might not benefit from them[3,4]

Even among medical teams, the futility concept is hard to define and recognize;[12] therefore, we cannot expect patients to consider futility issues when choosing treatments for their end-of-life care if they are unfamiliar with the subject.

Physicians must be clear and honest when informing patients and caregivers about their clinical situation and prognosis, the treatments that can benefit them, their side effects, and possible influence on their quality of life so that their decisions are made with full conscience.[31]

Citizens and patients must be informed of their right and autonomy to accept or refuse the treatments proposed for their end-of-life care. They must be encouraged to analyze and question their treatment choices and discuss these issues with their loved ones. However, the futility issues must not be left out of the conversations, and the benefits of the good medical practices must be overvalued. These different concepts must be addressed and exhaustively discussed among patients, caregivers, and health professionals to improve their knowledge of the subject. Particularly in palliative care, as patients face progressive and terminal diseases and have poor benefits from curative treatments, discussion of the futility concept must be considered a priority by healthcare teams.[32]

Therefore, good communication habits between patients, families, and healthcare teams are vital for clarifying patients' preferences for their end-of-life period. In addition, reducing their pretension of being subjected to treatments that might be harmful must be a fundamental goal to achieve.[10]

CONCLUSION

The Advance Directive legislation aimed to promote the patient's autonomy and self-determination in refusing invasive and futile treatments that might not benefit them as scientific knowledge is evolving.[5]

However, as observed in one group of 60 patients and 60 caregivers, many participants chose invasive treatments and artificial organ support for end-of-life care (23%-40%). Although these treatments

may be considered futile in the palliative patient group, none of the participants were familiar with this concept or definition.

Healthcare teams have a moral duty to elucidate to patients and caregivers about the futility theme and must consider it a priority when patients face progressive and terminal diseases, defend the patients' best interests, and ensure that their decision-making is conscientious and well-founded.[31]

We advocate that every citizen and patient who manifests the will to register their Advance Directive must be informed by their healthcare physician about their clinical scenario and prognosis, the concept of therapeutic futility, and harmful treatments before filling the document. They should also be informed about the Advance Directives[4] content, its limits, and the circumstances that might question its validity.

Caregivers should also be involved in the decision-making process to help clarify the patients' wishes as legitimate surrogates.[33]

However, the Portuguese Advance Directive document[4] as a legal instrument that empowers patients to exercise their autonomy and that the healthcare team must respect, should be transparent and not prone to misinterpretations, not to give rise to legal issues and disputes. Although in Portuguese law on Advance Directives, the right to refuse treatment is absolute and the right to request is not compulsory, good medical practice must be respected and achieved.

We consider that the Advance Directive document[4] should have an explanatory section that elucidates citizens and patients' rights to accept or refuse the treatments that they are being offered, but should also clearly mention that they must not demand treatments that have no benefit and are considered futile in their clinical situation, as most probably will not receive them.

We propose a simple change of the words that precede section 2 of the Portuguese Advance Directives' document "Healthcare to Receive / Not to Receive," to "Healthcare to Accept / Refuse," as this statement preceding the Advance Directives' questions, will reinforce the idea that treatments must be offered so that the citizens have the right to accept or refuse them.

This subject must also be continuously debated among healthcare professionals, in conferences, meetings, and day-to-day ordinary clinical practice to facilitate its recognition, definition, and worldwide discussion.

We strongly believe that improving citizens', patients, and caregivers' health literacy might reduce their probability of choosing futile treatments and avoid misinterpretations and false expectations when completing Advance Directive documents. Healthcare personnel who are familiar with these concepts and the patient's medical history, family members, and social environment, should have a prominent place in this accomplishment, mediating the decision-making process and promoting a therapeutic strategy consistent with the patients' wishes and good medical practices.

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When the fever will not stop, stop the pills! A case report

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Factor, risk.

ABSTRACT

Neuroleptic malignant syndrome (NMS) is a neurologic emergency potentially fatal. This rare side effect is most commonly associated with first-generation antipsychotics and less frequently with atypical or second-generation antipsychotics. The diagnosis relies on both clinical and laboratory criteria, with other organic and psychiatric conditions being ruled out.

CASE REPORT: A 39-year-old female patient, who is institutionalized and completely dependent, has a medical history of recurrent urinary infections and colonization by carbapenem-resistant *Klebsiella pneumoniae*. Her regular medication regimen included sertraline, valproic acid, quetiapine, risperidone, lorazepam, diazepam, haloperidol, baclofen, and fentanyl. The patient began experiencing dyspnea. Upon physical examination, she exhibited hypotension and a diminished vesicular murmur at the right base during pulmonary auscultation. Initially, after hospitalization, she developed high febrile peaks associated with hemodynamic instability, prompting the initiation of antibiotic treatment. Despite this, her fever persisted without an increase in blood inflammatory parameters, and she developed purulent sputum, necessitating antibiotherapy escalation. The seventh day of hospitalization showed no improvement in symptoms, suggesting NNMS as a differential diagnosis. All antipsychotic and sedative drugs, as well as antibiotherapy, were discontinued, after which the patient showed significant clinical improvement.

CONCLUSION: Antipsychotic agents are commonly employed to manage behavioral changes linked to various disorders. However, their severe side effects necessitate a high degree of vigilance, the cessation of all medications, and the implementation of supportive care measures. A prompt and accurate diagnosis of NMS is crucial to alleviating the severe, prolonged morbidity and potential mortality associated with this syndrome.

INTRODUCTION

Neuroleptic malignant syndrome (NMS) is an uncommon (incidence of 0.01% to 3.23%) but potentially lethal idiosyncratic reaction (**Table 1**) that may emerge in the aftermath of treatments with neuroleptics, demonstrating itself with symptoms ranging from altered consciousness to death.[1,2]

High-potency first-generation antipsychotics (FGAs) are associated with the highest incidence of NMS, e.g., haloperidol. Though second-generation antipsychotics (SGAs) have a lower incidence, low-potency FGAs have not been imputed alone in any case of NMS.[3]

Additional risk factors identified include pre-existing organic pathologies of the central nervous system, lithium treatment, infections, and the cessation of medication with anticholinergic properties or alcohol. Given the rising use of SGAs, it is crucial to remain cognizant of the associated risk of NMS.[4]

The diagnostic criteria for NMS encompass altered mental status, heightened muscle stiffness, fever, autonomic dysfunction, and analytical alterations such as elevated creatine phosphokinase (CPK). However, the presentation of NMS can vary, with some patients developing the syndrome without rigidity.[5-7] Consequently, there is no specific test available for NMS, and diagnosis relies heavily on clinical suspicion.[8]

NMS complications can lead to multiple organ system failure, aspiration pneumonia, pulmonary embolism, disseminated intravascular coagulation, and persistent cognitive sequelae. These long-term cognitive effects are often the result of hypoxia and prolonged hyperthermia.[6]

While it is not always possible to scientifically validate treatment recommendations, the significance of prompt supportive care is universally accepted. Additionally, discontinuing the use of causative antipsychotics is crucial to reducing mortality rates.[9,10]

Significantly reducing the morbidity and mortality of this perilous condition can be achieved through the minimization of risk factors, early identification, and swift management. A multidisciplinary approach could potentially be the key to a successful outcome.[6]

Further research is urgently required to scientifically substantiate the pathophysiology of NMS and formulate evidence-based treatment guidelines.[9]

CASE REPORT

This case report was approved on July 29, 2022 (#05, Ethics Committee of Tondela-Viseu Hospital Center, Viseu). A female patient, 39 years old, was institutionalized in a Continuing Care Unit, totally dependent on her daily life activities, usually conscious, reactive to stimuli, non-collaborating, and with periods of psychomotor agitation. Medical history included percutaneous endoscopic gastrostomy (PEG) and bladder catheter, mental retardation since childhood, epilepsy, recurrent urinary infections, and colonization by carbapenem-resistant *Klebsiella pneumoniae* (KPC). Her regular medications were sertraline 100 mg id, valproic acid 500 mg 3 id, quetiapine 100 mg 2 id, quetiapine 50 mg id, risperidone 2 mg 3 id, lorazepam 5 mg id, lorazepam 2,5 mg 2 id, diazepam 5 mg id, haloperidol oral solution, ipratropium/salbutamol 0.5/0.25 mg id, budesonide 200 mcg 2 id, acetylcysteine 600 mg id, baclofen 10 mg 3 id, lactulose id, ferrous sulfate 329.7 mg id and transdermal fentanyl 12.5 mcg/h. There was no recent history of recent dose changes, evidence of overdose, or the introduction of a new medication. There were no known drug allergies.

The patient was sent to the emergency service for dyspnea and desaturation (82% ambient air) and had no other symptoms (such as cough, fever on admission, nasal obstruction/rhinorrhea), having performed sputum culture 20 days earlier with isolation of *Proteus mirabilis* meropenem-sensible. On physical examination, she was prostrated, non-collaborating, with mucocutaneous pallor, presenting a PEG and bladder catheter, and without pitting edema in her lower extremities. She had a blood pressure of 88/61 mmHg, a pulmonary auscultation with a decreased vesicular murmur at the right base, and a cardiac auscultation without alterations. Blood analysis, urinary screening, and arterial blood gas tests were executed with no analytical changes. Chest X-ray with slight bilateral hilar enhancement and blood cultures without bacterial growth. A head computed axial tomography scan without contrast was performed for "mild signs of ischemic leukoencephalopathy. Mild ventricular enlargement, reflecting diminished encephalic volume and subcortical atrophy, was more than expected for the patient's age. Minor old lacunar strokes in the right striatocapsular region".

Table 1. Bibliography

Reference	Database	Search strategy	Data	Filter	Nº Results	Results
1	MEDLINE/ PubMed	"neuroleptic malignant syndrome" [MeSH] AND "antipsychotic agents" [MeSH] AND "fever" [MeSH]	28-08-2022	2017–2022	26	1. Case Report: 13 2. Original article: 7 3. Narrative Review: 3
2	MEDLINE/ PubMed	"neuroleptic malignant syndrome" [MeSH] AND "antipsychotic agents" [MeSH] AND "neuroleptics" [MeSH]	28-08-2022	2017–2022	131	1. Meta-Analysis: 3 2. Original article: 12 3. Narrative Review: 23
3	MEDLINE/ PubMed	"neuroleptic malignant syndrome" [MeSH] AND "antipsychotic agents" [MeSH] AND "risk factors" [MeSH]	28-08-2022	2017–2022	11	1. Case Report: 1 2. Original article: 1 3. Narrative Review: 9
4	MEDLINE/ PubMed	"neuroleptic malignant syndrome" [MeSH] AND "adverse drug reactions" [MeSH] AND "risk factors" [MeSH]	28-08-2022	2017–2022	4	1. Original article: 1 2. Narrative Review: 3
5	MEDLINE/ PubMed	"neuroleptic malignant syndrome" [MeSH] AND "antipsychotic agents" [MeSH] AND "adverse drug reactions" [MeSH]	28-08-2022	2017–2022	26	1. Meta-Analysis: 1 2. Case Report: 11 3. Original article: 7 4. Narrative Review: 7
6	MEDLINE/ PubMed	"neuroleptic malignant syndrome" [MeSH] AND "autonomic dysfunction" [MeSH] AND "fever" [MeSH]	28-08-2022	2017–2022	3	1. Original article: 1 2. Narrative Review: 2
7	MEDLINE/ PubMed	"neuroleptic malignant syndrome" [MeSH] AND "antipsychotic agents" [MeSH] AND "drug-related side effects" [MeSH]	28-08-2022	2017–2022	7	1. Case Report: 2 2. Original article: 2 3. Narrative Review: 3
8	MEDLINE/ PubMed	"neuroleptic malignant syndrome" [MeSH] AND "autonomic dysfunction" [MeSH] AND "fever" [MeSH]	28-08-2022	2017–2022	4	1. Narrative Review: 4
9	MEDLINE/ PubMed	"neuroleptic malignant syndrome" [MeSH] AND "fever" [MeSH] AND "risk factors" [MeSH]	28-08-2022	2017–2022	3	1. Case Report: 2 2. Narrative Review: 2
10	MEDLINE/ PubMed	"neuroleptics" [MeSH] AND "antipsychotic agents" [MeSH] AND "risk factors" [MeSH]	28-08-2022	2017–2022	812	1. Meta-Analysis: 45 2. Randomized Controlled Trial: 28 3. Narrative Review: 55

The patient was admitted to the hospital for oxygen therapy, presumed to be suffering from a respiratory infection caused by *Proteus mirabilis*. Treatment with amoxicillin-clavulanic acid was initiated.

On D2, the patient began experiencing a fever peak (39–40 °C), accompanied by episodes of psychomotor agitation and hemodynamic instability. This necessitated the use of peripheral cooling and antipyretics to manage the fever. Analytical control revealed no significant deviations from the previous day's results. However, due to the rapid deterioration associated with hemodynamic instability, a decision was made to alter the antibiotic therapy, initiating meropenem.

On D4, the fever peaks (4–4 hours) persisted despite the administration of antipyretics, and analytically, the inflammatory parameters were not elevated. Blood analysis showed leukocytes 7.10 × 10^9/L, segmented neutrophils 79.3%, hemoglobin 11.5 g/dL, sodium 136 mmol/L, potassium 4.2 mmol/L, chloride 101.8 mmol/L, urea 30 mg/dL, creatinine 0.2 mg/dL, reactive C protein 1.0 mg/dL and CK 2,500 U/L. Lumbar puncture was not possible due to the patient's instability and bone deformities of the lumbar spine. At that moment, the patient presented expectoration with a purulent appearance, and a microbiological examination was performed. Vancomycin and fluconazole were started for greater microbiological coverage.

In D7, there was no improvement in fever nor changes in clinical and analytical parameters (showed leukocytes 7.9 × 10^9/L, segmented neutrophils 76.2%, hemoglobin 11.4 g/dL, sodium 138 mmol/L, potassium 4.1 mmol/L, chloride 104.1 mmol/L, creatinine 0.4 mg/dL, reactive C protein 1.2 mg/dL, and CK 2,840 U/L).

NMS was suspected as a differential diagnosis, and all antipsychotics, sedative drugs, and antibiotherapy were suspended. After 24 hours, the patient presented a good clinical evolution with sustained apyrexia, which suggested this syndrome as the most likely diagnosis. Oxygen therapy was slowly withdrawn as the patient became eupneic without oxygen needs. The Psychiatric Team resumed and adjusted psychiatric medication 2 weeks after the event, maintaining only sertraline 100 mg id, valproic acid 500 mg 3 id and stopping all other psychiatric medications (quetiapine 100 mg 2 id, quetiapine 50 mg id, risperidone 2 mg 3 id, lorazepam 5 mg id, lorazepam 2.5 mg 2 id, and transdermal fentanyl 12.5 mcg/h), with favorable evolution and without new clinical worsening.

DISCUSSION

When symptoms no longer present a logical explanation, it is imperative to pause and consider the patient at hand. In this woman's case, overlooking the NMS hypothesis could have led to a fatal outcome, likely due to an iatrogenic cause. A high degree of clinical suspicion and meticulous anamnesis are essential to deducing a differential diagnosis, as demonstrated in this case.

The escalating prevalence of chronic diseases and polymedication underscores the growing need for drug deprescription. Equally crucial is the implementation of appropriate therapeutic management for each patient, a task in which family doctors play a pivotal role. In the differential diagnoses of any polymedicated patient, particularly those on a regimen of both traditional and atypical antipsychotics, the presence of NMS must be considered, as exemplified by our patient's case.

The text also highlights the contemporary issues of quaternary prevention and deprescription, areas that frequently fall short in our clinical practice.

Our case diverges from typical NMS cases due to the absence of rigidity. The patient initially exhibited hypotension, psychomotor agitation, dyspnea, and an unexplained fever during hospitalization. These symptoms, while potentially indicative of other diagnoses, particularly infectious ones, were present in this case. The patient's clinical improvement following the complete discontinuation of medication supported the provisional diagnosis of NMS.

CONCLUSION

The concurrent utilization of multiple medications, known as "polymedication," coupled with physiological alterations impacting pharmacokinetics and pharmacodynamics leads to an increased likelihood of adverse side effects.

The diagnosis of NMS is fundamentally clinical and necessitates a high degree of suspicion. The treatment is primarily supportive.

This case report underscores the significance of the prompt and precise diagnosis of NMS, which is crucial in reducing severe, prolonged morbidity and potential mortality.

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INSTRUCTIONS FOR AUTHORS

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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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