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Organ transplantation and COVID-19

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The pandemic caused by severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) has transformed the world. Up to May 16, 2021, 162.2 million individuals (2.1% of the world's population) had become infected, of whom 15.5 million were in Brazil (7.3% of this country's population), and 3.36 million of these infected individuals had died (432,628 in Brazil).[1] Thus, in Brazil, the mortality rate up to that date was 2/1,000 of the population and, for 2.8% of the infected individuals, the virus was lethal. This scenario has negatively affected the economy of many countries, causing great losses to thousands of companies, and even bankruptcies; and it has left millions of workers unemployed. The social distancing and isolation that have become necessary to combat the pandemic have harmed social relationships, school activities and non-essential work activities. Meetings and congresses have also been affected.

Organ transplantation could not remain immune to the coronavirus disease (COVID-19). Organ donation and transplantation activities, and the patients receiving these organs, have also been affected in various ways, as we describe in the following list:

1) Impact on donation and transplantation activities and on waiting lists:
   a. Decreased numbers of donors, due to fewer notifications and increased contraindication;
   b. Decreased numbers of transplantations, with variation according to the organ transplanted and the type of donor (living or deceased);
   c. Decreased entry to waiting lists and increased mortality among patients on these lists;
   d. Changes to activities at transplantation centers: with maintenance, diminishment or even temporary suspension of transplantation operations;
   e. Modification of outpatient follow-up for transplant patients, such that a large proportion of these patients started to be attended via teleconsultation.

2) Impact on transplant patients:
   a. Increased mortality;
   b. Increased lethality;
   c. Increased morbidity;
   d. Diminished immunological response to vaccination.

COVID-19 had an immediate impact on donation and transplantation activities in the countries most affected. In the United States, Spain, France, Netherlands and United Kingdom, there were decreases in donation and transplantation rates of between 36% and 90% during the peak months of the first wave of COVID-19.[2] This impact on donation and transplantation rates was regional: for example, New York and northern Italy were among the areas most affected, but this impact was temporary. Activities were then resumed as the pandemic subsided in those areas.[3,4]

In Brazil in 2020, compared with 2019, the donor rate declined by 13%.[5] This drop in donation rates occurred both through a decrease in notification of potential donors, and through an increase in the number of contraindications for transplantation. The decrease in notification of potential donors could have occurred for any of the following reasons:

a) Reduction of the numbers of intensive care unit (ICU) and emergency beds available for potential brain-dead donors because these were occupied by patients with COVID-19;[2]

b) Fear, among the population, of taking family members with severe diseases to hospitals, because of the risk of picking up COVID-19, thus leading to increased numbers of deaths at home;
c) Reduction of the numbers of cases of head trauma caused either by traffic accidents or by firearms.[2]

The increase in the number of contraindications for transplantation may have occurred through a series of factors, especially at the beginning of the pandemic, including the following:

a) Not performing the reverse transcriptase polymerase chain reaction (RT-PCR) test for COVID-19 before removing organs in some places;
b) Not having the result from the RT-PCR test for COVID-19 before removing organs in other places;
c) Potential donors who had been exposed to COVID-19 or who had another respiratory condition, independent of the result from the RT-PCR test for COVID-19, were excluded at the outset of screening.[6]
d) Limitations on air transportation leading to diminished interchange of organs between regions because of prolonged cold ischemia times.[7]

The decline in the transplantation rate also varied according to the type of organ: greater for lung and kidney transplantations and smaller for liver and heart transplantations. It also varied according to the type of donor, such that the decline was greater for transplantations with a living donor. Because this is an elective procedure, many such procedures were postponed so as to avoid the risk of donor contamination during the investigation and organ removal.[2,8]

In Brazil, in 2020, there were declines in the transplantation rates for liver (10%), pancreas (13%), heart (17%), kidney (25%) and lung transplants (39%). The decrease in the number of transplantations with a living donor was greater for kidney transplants (64%) than for liver transplants (13%). There were also variations in the timing of these declines because the pandemic reached different Brazilian states at different times and affected geographical regions differently. Thus, for example, the kidney transplantation rate decreased by 8% in the central-western region and by 80% in the northern region, which has been worst affected by the pandemic.[5]

Analysis on waiting lists is somewhat more complex. On the one hand, with fewer transplantation procedures taking place, there was an accumulation of patients in waiting lists; but on the other hand, the number of patients entering the lists also declined, given that investigations on many patients were postponed.[2] In addition, in many centers, some of the patients, especially those awaiting transplants of non-vital organs (such as kidney and pancreas transplants), were moved from the active to the inactive category to avoid the most severe phase of the pandemic. In Brazil, for example, declines in the numbers of patients entering the lists, of 18% for liver transplants and 13% for kidney transplants, were observed in 2020. There were also increases in the mortality rates among patients in the lists, of 27% for kidney transplants (going up from 5.2% to 6.6%) and 5% for liver transplants.[5]

Activities in transplantation centers either were maintained or were reduced to transplantations only in special cases, or were temporarily suspended, according to the levels of risk for potential recipients, living donors and professionals; and also according to the conditions in these hospitals.[9]rapidly changing pandemic: consequently, evidence-based recommendations in solid organ transplantation (SOT In Brazil, most kidney transplantation centers in the northern and northeastern regions suspended their activities in the first six months of 2020, while this measure was taken by kidney transplantation centers in the southern region in the third three-month period of the year.

Some societies and organizations relating to transplantation have established recommendations for managing these procedures, including with regard to suspension and resumption of activities and increased safety for recipients and living donors.[2,9]

Perhaps the only positive legacy from the COVID-19 pandemic in relation to transplantation in Brazil will be the use of telemedicine, with authorization from the Federal Medical Council (Conselho Federal de Medicina, CFM) and reimbursement from the Ministry of Health and health insurance plans for outpatient follow-up of recipients, so as to diminish the risk of transmission of infection to this patient population. This measure has been beneficial not only for preventing transmission of the virus but also for simplifying attending to patients who live in distant locations, and this benefit deserves to be kept after the pandemic.

The first two articles analyzing the impact of COVID-19 on patients who received kidney transplants provided conflicting results. The first case series, from Wuhan, China, published in March 2020, reported on five cases of COVID-19 in kidney transplant patients that occurred in February 2020. These patients presented good evolution, without any deaths. It was concluded that COVID-19 was not severe in this population and that calcineurin inhibitors were capable of blocking the action of SARS-CoV-2.[10] The second series was published by the transplantation group of Montefiore Hospital, in New York, in April 2020. Thirty-six kidney transplant patients who were affected by COVID-19 in March 2020 were analyzed. Ten of these patients died. It was concluded that the lethality rate among transplant patients (28%) was higher than that of the general population (1%-5%), and higher than that of elderly people over the age of 70 years (8%-15%).[11]

According to some authors, modulation of immunosuppressors may be either harmful or beneficial, depending on the clinical

stage of infection in transplant patients. At the start of the infection, strong immunosuppression may adversely affect specific immunity, thus leading to insufficient control over the viral load and prolonged detection of viral ribonucleic acid (RNA) after the onset of the disease. Later on in the course of the disease, immunosuppressive drugs may be beneficial for suppressing pro-inflammatory processes, through maintaining functional inactivation of the immune system.[2]

However, most case series have shown high mortality rates among transplant patients infected by COVID-19. A meta-analysis[12]however, there remains a paucity of robust data in this population. We conducted a systematic review and meta-analysis of SOT recipients with SARS-CoV-2 infection from January 1st t October 9th, 2020. Pooled incidence of symptoms, treatments and outcomes were assessed. Two hundred and fifteen studies were included for systematic review and 60 for meta-analysis. We identified 2,772 unique SOT recipients including 1,500 kidney, 505 liver, 141 heart and 97 lung. Most common presenting symptoms were fever and cough in 70.2% and 63.8% respectively. Majority (81% on 37 articles about COVID-19 in transplant patients showed that the mortality rate was 18.6%. In an article from the Kidney Hospital (Hospital do Rim) in São Paulo, 11,875 kidney transplant recipients who were followed up as outpatients were analyzed. Among these patients, 491 became infected with COVID-19 and the mean lethality rate was 28.5%, ranging from 6% among young patients without comorbidities to 41% among elderly patients with comorbidities. This demonstrated that immunosuppression, age and comorbidities are important risk factors in this population. In the same study, it was observed that among the patients who recovered from COVID-19, 19% presented permanent dysfunction of the graft and 4%, loss of the graft.[13]

Transplantation in infected candidates and use of organs from donors with COVID-19 are currently only recommended after resolution of the clinical symptoms and with a negative RT-PCR result. Nonetheless, cases of inadvertent transplantation of organs from asymptomatic donors who showed positive RT-PCR results, without transmission to the recipient, have been reported.[14] This may indicate future potential for using donors who are RT-PCR-positive, for life-saving procedures, especially after gaining greater knowledge about the correlation between RT-PCR positivity and infectiveness.[2] There is only one report on transmission from a lung donor infected with COVID-19 to the recipient of that organ.[14]

Initial studies on vaccination against COVID-19 among kidney transplant patients have shown that the immunological response in lower among these individuals, as already seen with vaccination against influenza viruses. In two studies, with 436 and 242 transplant patients, only 17% and 11% presented a serological response, measured 20 and 28 days after the first dose of messenger RNA (mRNA) vaccine.[15,16]1,2 a low proportion (17% Continuation of these studies[17,18] showed that after the second dose of these vaccines, in 658 and 205 patients, a serological response was seen in 54% and 48%, while in the control group it was 100%. In three studies conducted in Israel,[19-21] among kidney (136), liver (80) and lung transplant patients (180), a serological response was observed in 37.5%, 47.5% and 18%, respectively.

These data, if confirmed by other studies, suggest that alternative strategies need to be used in relation to these patients, such as greater numbers of doses; or use of mycophenolate suspension for some days before and after vaccination; or a temporary change to azathioprine or mammalian target of rapamycin (mTOR) inhibitor. These seem to present a better serological response to the vaccine, but this needs to be confirmed.

Thus, organ transplantation has also been dramatically affected by COVID-19, with regard both to transplantation activities and to the severity of cases (with elevated morbidity and mortality) and poor response to vaccination among transplant patients.

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Validity and reliability of the Neonatal Infant Acute Pain Assessment Scale (NIAPAS) in Turkish: prospective study

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ABSTRACT

BACKGROUND: Using pain scales helps nurses in making early diagnoses and in assessing and managing pain symptoms and findings when developing a nursing care plan.

OBJECTIVE: To determine the validity and reliability of the Turkish form of the Neonatal Infant Acute Pain Assessment Scale (NIAPAS).

DESIGN AND SETTING: Prospective study conducted in Istanbul Bakırköy Dr. Sadi Konuk Training and Research Hospital, Istanbul, Turkey.

METHODS: 145 newborns in the 26th to 42nd gestational weeks that were receiving treatment and care in the neonatal intensive care unit were included in this study. A total of 1740 pain assessments were made by two independent observers on these 145 newborns. The research data was collected using a newborn description form, NIAPAS and the Neonatal Infant Pain Scale (NIPS).

RESULTS: The scope validity index of NIAPAS was found to be between 0.90 and 1.00 and its Cronbach's alpha coefficient was 0.914. Correlations between characteristics and total scores (r = 0.20-0.82) were found to be sufficiently high. In an assessment on concurrency validity, there was a strong positive relationship between NIAPAS and NIPS scores (r = 0.73-0.82; P < 0.000). From kappa analysis (0.73-0.99) and intraclass correlation (r = 0.75-0.96), it was determined that there was concordance between the observers.

CONCLUSION: NIAPAS was found to be a valid and reliable scale for evaluating acute pain in newborns.

INTRODUCTION

Newborns are subject to many painful interventions during their stay in neonatal intensive care units (NICUs).[1] Studies have shown that an average of 115 operations are performed in NICUs within a two-week period and that 75% of these operations are painful interventions.[2,3] Newborns are subjected to an average of 7.6-14 painful interventions per day in the first 14 days of their hospitalization.[2,4]

Until recently, it was considered that newborns could not feel pain because their nervous system is not well-developed and myelinization has not yet been completed.[5-7] However, new studies have shown that pain is perceived before the 24th intrauterine gestational week[8] and infants give behavioral, physiological and hormonal responses to painful stimuli during the 25th to 36th gestational weeks.[9] The pain received might result in physiological imbalances in newborns and abnormalities in brain development or response to stress over the short or long term.[10] Untreated pain could have a negative impact on communication between the family and the infant and could also lead to emotional and psychosomatic problems in the future.[11,12]

Accurate assessment of the pain is the first step in enabling effective pain management.[13] The most important problem encountered in understanding pain in newborns is the difficulty in diagnosing pain.[14] Because newborn infants are unable to verbally express pain, any pain assessment is based on the ability of other people to identify pain symptoms.[4]

The American Academy of Pediatrics has recommended that clinical personnel should routinely perform reliable and valid measurements on newborns.[15] In NICUs, pain should be assessed by healthcare professionals who have been trained to identif and interpret pain and to consider factors that impact on newborns' perception of pain and response to pain.[16] Although significant progress in newborn pain management has been made over the last 20 years, pain is still not sufficiently diagnosed among newborns born in clinics, and attempts to reduce pain are only made infrequently.[17]

Many scales are available to assess pain in NICUs. However, only a limited number of scales for assessing acute pain in preterm and term babies are available.

OBJECTIVE

The objective of this study was to determine the validity and reliability of the Turkish form of the Neonatal Infant Acute Pain Assessment Scale (NIAPAS).

METHODS

Type of study

This was a prospective study conducted in Istanbul Bakırköy Dr. Sadi Konuk Training and Research Hospital, Istanbul, Turkey.

Population and sample

The population of the study comprised babies who were followed up in the NICU, at gestational ages of 28-42 weeks and who had not been administered drugs with analgesic, sedative or muscle relaxant impacts that could affect the pain or behavior of the infant. In addition, these babies did not have hyperbilirubinemia, congenital anomalies or neurological diseases and did not undergo surgical interventions.

The sample size for this study was determined in accordance with the principle of taking the sample size to be at least five times the number of scale items, in validity and reliability assessments on study methodologies.[18] Based on this principle, 145 infants were included in this study.

Data collection tools

Three data collection tools were used in this study, as follows:

Newborn description form: This consisted of items describing the characteristics of the infant: gender, gestational age, birth weight, Apgar score, postnatal age, respiration mode and diagnosis.

NIAPAS: The NIAPAS scale was developed in Finland in 2013, by Pölkki et al.[19] It differs from other scales in that it assesses acute pain in babies. It was developed based on feedback from specialist nurses within neonatal intensive care and in close cooperation with other nurses. The NIAPAS scale assesses acute pain through five behavioral and three physiological indicators that are exhibited as contextual factors in the gestational week. These indicators are rated on a scale of 2, 3 or 4 points (0,1; or 0,1,2; or 0,1,2,3), with a potential total of 18 points. Facial expressions, muscle strain, alertness, reaction to action, heart rate, respiration and oxygen saturation are considered in assessing each newborn. Painful operations on newborns are assessed in three stages: for one minute before the painful operation, for the duration of the operation and for one minute following the operation. The pain on the scale is considered to be mild when the score is 0-5, medium when it is 6-9 and sharp when it is 10-18.

Neonatal Infant Pain Scale (NIPS): This was developed in 1993, by Lawrence et al.[20] It is used to assess pain caused by interventional operations in preterm and term newborns, from their behavioral and physiological symptoms. The symptoms assessed are facial expression, crying, respiration mode, movement of arms and legs and alertness. The total score is in the range of 0-7.

Data collection

Research data were collected through observation. Heel-prick blood drawing was chosen as the painful intervention. The infants' response to pain and stress was video recorded by the investigator (BNK), for one minute before the intervention, for the duration of the intervention and for one minute following the intervention.

Each baby was evaluated for pain by two independent observers other than this investigator, by watching video recordings. The observers watched the video recordings separately and scored them independently in accordance with the scale. One of the observers who made this assessment had had 10 years and the other had had 11 years of neonatal intensive care nursing experience. Training on scale and scale assessment before the assessment was provided to the nurses.

Assessment of the data

The research data were analyzed using the Statistical Package for the Social Sciences (SPSS) 22 for Windows (IBM, Armonk, New York, United States). Descriptive statistics on numbers, percentages and arithmetic means were used in assessing the study data. The translation and back-translation method was used to assess language validity. The scope validity index was calculated to determine the content validity. The concordance of the specialist opinions was assessed by means of Kendall's W concordance coefficient. Correlations of total item scores and Cronbach's alpha coefficients were calculated to determine the reliability of the scale. Kappa analysis was conducted to assess the consistency between the observers and an inter-scale correlation test was conducted to assess concurrency validity.

Ethical aspects of the research

Permission was received from Pölkki et al.,[19] who developed the scale, to conduct assessments on the validity and reliability of the scale for use in the Turkish language on September 1, 2019. Approval was obtained from the Clinical Trials Ethics Committee of Istanbul Bakırköy Dr. Sadi Konuk Training and Research Hospital (Ethics Committee Decision No: 2020-03-20). Before collecting the research data, consent was obtained from the parents of the infants who matched the sample criteria.

RESULTS

The infants included in the research had a mean gestational age of 33.30 ± 4.26 weeks, mean body weight of 2188 ± 1129.936 grams

and mean postnatal age of 9.21 ± 7.612 days. The infants' first-minute mean Apgar score was determined as 6.37 ± 0.941 and the fifth-minute mean Apgar score as 8.01 ± 0.764. Certain characteristics of the infants included in the research are presented in **Table 1**.

Examining the validity of the scale

Language validity

The language validity of the scale was assessed in accordance with prescriptions in the literature.[21] For this, one academic staff member who was a specialist in pediatric nursing and fluent in both English and Turkish and one professional interpreter translated the scale from English to Turkish. The scale translated into Turkish was then edited by the investigator by comparing the two translations. The Turkish form thus created was back-translated into English by two academic staff members who were specialists in pediatric nursing and fluent in both languages, and who had not previously seen the original English version of the scale. The expressions used in the back-translation were compared with those in the original scale and, from this analysis to ensure language equivalence, the final version of the Turkish form of the scale was created.

Table 1. Demographics of the infants included in the study (n = 145)

Infant characteristics	Number (n)	Percentage (%)
Gender		
Female	64	44.1
Male	81	55.9
Gestational age		
Less than 28 weeks	18	12.4
28-31 weeks and 6 days	37	25.5
32-36 weeks and 6 days	41	28.3
37 weeks or above	49	33.8
Birth weight		
Less than 1000 g	25	17.2
1000-1999 g	49	33.8
2000-2999 g	34	23.4
3000 g or higher	37	25.5
Respiration mode		
Connected to mechanical ventilation	32	22.1
Continuous positive airway pressure	42	29.0
Spontaneous respiration	71	49.0
Nutrition mode		
TPN	47	32.4
NGS/OGS	54	37.2
Oral	44	30.3
Diagnosis		
Preterm and low birth weight	85	58.6
Mild asphyxia	10	6.9
TTN	20	13.8
Pneumonia	13	9.0
Polycythemia	3	2.1
Hypoglycemia	14	9.7

TPN = total parenteral nutrition; NGS = Nasogastric tube; OGS = Orogastric tube; TTN = Transient tachypnea of newborn.

Content/scope validity

Content validity is used to assess whether a scale and each item on this scale measure the concept that needs to be measured, and whether these contain concepts differing from or other than the concept that needs to be measured. Opinions are received from relevant specialists in order to achieve this. The specialist group is recommended to consist of a minimum of three and a maximum of 20 persons. The scale is then remodeled in accordance with the suggestions and critiques provided by the specialists.[22]

To evaluate the content/scope validity in the present study, opinions were received from 10 specialists, consisting of eight academic staff members who were specialists in pediatric nursing, one academic staff member who was a specialist in gynecology and one neonatal physician who was a specialist in neonatology. These specialists assessed each expression on the scale as 1- "I agree", 2- "The item should be slightly reviewed", 3- "The item should be significantly reviewed" or 4- "I disagree with the item". Subsequently, the scale items were rearranged in accordance with the recommendations of the specialists. The scope validity ratios and the scope validity index (SVI) were obtained for each item on the scale, after implementation of these rearrangements. The SVI values of the scale items were in the range 0.90-1.00.

The concordance level of the specialist opinions was analyzed by means of the nonparametric Kendall's W test (Kendall's W = 0.969; P = 0.000).

Concurrency validity

NIPS was used as the concurrency form in this study. Two observers made three assessments: one before, one during and one after the operation. The relationship between the scores given by the observers on the NIAPAS and NIPS scales are presented in **Table 2**. There was a strong positive relationship between the correlation

Table 2. Relationship between the Neonatal Infant Acute Pain Assessment Scale (NIAPAS) and the Neonatal Infant Pain Scale (NIPS)

Observers	Pearson correlation coefficient (r)		
	Before operation	During operation	After operation
Observer 1	0.78	0.82	0.79
Observer 2	0.73	0.74	0.80
	0.87	0.91	0.94

Note: Pearson's correlation coefficient (r) was used to analyze the correlation between the scores received by newborns using NIAPAS and NIPS before, during and after the intervention. P < 0.001.

values from Observer 1 (r = 0.78-0.82; P = 0.000) and the correlation values from Observer 2 (r = 0.73-0.80; P = 0.000). The correlation values between Observer 1 and Observer 2 were 0.87 before the operation, 0.91 during the operation and 0.94 after the operation, i.e. there was high correlation between the observers.

Examining the reliability of the scale

Internal consistency

Cronbach's alpha coefficient was calculated to assess the internal consistency of the scale. According to the assessment results from the observers, the Cronbach's alpha values were in the range 0.930-0.971 for Observer 1 and in the range 0.913-0.972 for Observer 2. The study's general Cronbach's alpha value was found to be 0.914 (**Table 3**).

Total item score reliability was examined as another method for assessing the internal consistency of the scale. The total item score correlations for the scale before the operation were found to be in the range 0.20-0.77 for Observer 1 and in the range 0.36-0.78 for Observer 2. The total item score correlations during the operation were in the range 0.30-0.82 for Observer 1 and in the range 0.30-0.80 for Observer 2. After the operation, they varied in the range 0.22-0.76 for Observer 1 and in the range 0.25-0.71 for Observer 2 (**Table 4**).

Reliability of concordance between independent observers

The kappa value was calculated to assess the concordance of the scale between observers. Also, the intraclass correlation (ICC) was calculated to assess the concordance between the observers. According to this analysis on concordance, the kappa value was in the range 0.80-0.97 before the operation, 0.63 - 0.99 during the operation and 0.85-0.97 after the operation (P < 0.001).

The intraclass correlation for the scale was found to be in the range 0.76-0.96 before the operation, 0.75-0.95 during the operation and 0.86-0.93 after the operation (P < 0.001) (**Table 5**). It was thus determined that there was good concordance between the observers.

Table 5. Intraclass correlation coefficients of the Neonatal Infant Acute Pain Assessment Scale (NIAPAS)

Characteristics	Intraclass correlation coefficient		
	Before operation	During operation	After operation
Gestational age	0.91	0.91	0.91
Alertness	0.88	0.93	0.88
Facial expressions	0.96	0.81	0.90
Crying	0.96	0.89	0.92
Muscle tension	0.91	0.93	0.87
Breathing	0.93	0.95	0.93
Reaction to handling	0.76	0.75	0.89
Heart rate	0.93	0.94	093
SaO_2	0.94	0.95	0.86

Note: The intraclass correlation coefficient was calculated to assess the concordance between the observers. P < 0.001.
SaO_2 = Oxygen saturation.

Table 3. Score averages and Cronbach's alpha reliability coefficient values of the Neonatal Infant Acute Pain Assessment Scale (NIAPAS)

Observers	Before operation		During operation		After operation	
	Mean score	Cronbach's alpha	Mean score	Cronbach's alpha	Mean score	Cronbach's alpha
Observer 1	2.159	0.930	10.979	0.954	4.751	0.971
Observer 2	2.110	0.913	10.682	0.955	4.675	0.972

Note: The internal consistency of the scale was calculated using Cronbach's alpha.

Table 4. Total item score correlation values of the Neonatal Infant Acute Pain Assessment Scale (NIAPAS)

Characteristics	Observer 1			Observer 3		
	Before operation	During operation	After operation	Before operation	During operation	After operation
Gestational age	0.46	0.32	0.36	0.36	0.30	0.37
Alertness	0.77	0.82	0.76	0.77	0.80	0.71
Facial expressions	0.76	0.71	0.76	0.78	0.77	0.70
Crying	0.63	0.77	0.76	0.70	0.78	0.68
Muscle tension	0.65	0.60	0.70	0.61	0.56	0.50
Breathing	0.54	0.58	0.46	0.60	0.58	0.46
Reaction to handling	0.30	0.66	0.68	0.55	0.63	0.65
Heart rate	0.30	0.72	0.46	0.60	0.58	0.46
SaO_2	0.20	0.48	0.22	0.38	051	0.25

Note: Total item correlation was calculated using Pearson's correlation coefficient (r) between the score achieved from each item and the mean total score.
SaO_2 = Oxygen saturation.

DISCUSSION

Pain is a subjective finding in newborns, who are unable to communicate verbally. Preterm and term newborns treated in NICUs are subject to various levels of painful interventions and this pain is an almost inevitable experience for such babies. Infants are known to feel pain and exhibit behavioral and psychological reactions to painful stimuli.[23]

Many scales are available to assess the pain of preterm and term newborns. Through having a valid, reliable and applicable measurement tool available, nurses will be better equipped to undertake pain management, thereby increasing the quality of patient care and avoiding pain for newborns who are particularly sensitive.

Unlike other scales, the NIAPAS scale assesses acute pain in newborns. Its most important distinction from other scales is that it was developed in close cooperation with specialist nurses in NICUs.[19] Also, the NIAPAS scale enables both more detailed measurement of certain parameters and assessment of physiological changes in addition to behavioral patterns. This scale assesses acute pain through five behavioral and three physiological indicators that are exhibited as contextual factors in the gestational week at birth. It enables reasonable measurement of the pain felt by premature babies, through considering the gestational age in pain assessments on these infants.[19,24] Reaside (2011) argued that oxygen saturation, blood pressure and respiration rate did not have any sensitivity or uniqueness and therefore could not be used independently.[25] Holsti & Granau emphasized that independent measurement of behavioral and physiological reactions was necessary for assessing pain, in order to determine the effects of pain-relieving methods.[26] Pölkki et al. emphasized that a multidimensional approach was the most suitable way for undertaking pain assessment.[19]

Our analysis on the validity of NIAPAS started with examination of its content validity. The SVI values of the scale items varied in the range 0.90-1.00. It has been stated in the literature that the situations that need to be measured using the items on the scale are well expressed by taking the criterion of an SVI value of 0.80.[27]

Concurrency validation is frequently performed in scale validity studies. It consists of assessing the concordance between one newly developed scale that has been cross-culturally adapted and another scale that was previously developed for the same purpose.[21] Concurrency validation was performed in the present study between NIAPAS and NIPS. The correlation between the two scales was high before, during and after the operation. Moreover, there was a strong positive relationship between the correlation values of the two observers. The correlation found (**Table 2**) was close to the correlation values reported by Pölkki et al. (before the operation r = 0.751, during the operation r = 0.873 and after the operation r = 0.804).[19]

The correlation coefficient can range between +1 and -1. A (+) sign shows a positive and a (-) sign shows a negative relationship in the significance level.[28] The correlation coefficient is zero if there is no relationship. It is accepted that the relationship is weak if the correlation coefficient is in the range 0.0-0.50, and strong if it is in the range 0.50-1.00.[29] The concurrency validity of the NIAPAS scale was found to be high.

Cronbach's alpha coefficient was calculated to assess the reliability of the scale. It was reported as 0.723 in the original NIAPAS study.[19] In a study on the reliability of the NIAPAS scale, Huang et al. (2018) found that Cronbach's alpha coefficient was 0.836.[30] In the present study, the Cronbach's alpha value was found to be 0.914, which is a higher value. Cronbach's alpha coefficient indicates the internal consistency and the homogeneity of the items on a scale. According to the literature, the lower limit for Cronbach's alpha coefficient was determined as 0.70 and it was stated that reliability increased as this number approached one.[31] In the present study, Cronbach's alpha coefficient for NIAPAS was found to be 0.914, thus showing that the scale was fairly reliable. This result was in line with data in the literature.[31]

Another method that has been used to test the reliability of a scale is item analysis.[21] A correlation coefficient is calculated for item analysis. The effectiveness of the item increases with higher total item score correlation. Total item correlations are expected to be non-negative and a minimum of 0.20.[28] The total item score correlations for NIAPAS were 0.20-0.82, which was in line with data in the literature,[28] and no item needed to be removed from the scale.

In studies with multiple observers in which data are collected based on observations, concordance between the observers is one of the features that is required in determining the reliability of the scale.[22] The kappa coefficient was used in the present study to test the concordance between the observers. This can range between 0 and +1, and negative values have no value in terms of reliability. The kappa coefficient indicates perfect concordance when it is in the range 0.93-1, very good concordance in the range 0.81-0.92 and good concordance in the range 0.61-0.80.[31] The kappa value in the present study was > 0.73, according to the concordance analyses between the observers, and was therefore at the required level.

The intraclass correlation coefficient was also considered in assessing the concordance between the observers. The intraclass correlation needs to be at least 0.70 for any concordance between multiple assessors to be accepted.[32] In the present study, the intraclass correlation was greater than 0.74, thus showing that there was concordance between the observers (**Table 5**).

CONCLUSION

Through the statistical analyses conducted to ascertain the validity and reliability of the Turkish form of the NIAPAS, it was determined that this scale is valid and reliable for use.

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Influence of unstable shoes on women with lumbopelvic postpartum pain: randomized clinical trial

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ABSTRACT

BACKGROUND: Back pain is a normal symptom during pregnancy and is expected to become worse beyond the first three months after childbirth.

OBJECTIVES: To determine the effectiveness of wearing unstable shoes instead of conventional shoes, regarding pain intensity, low back mobility and stability, among women with lumbopelvic pain (LPP) during the postpartum period.

DESIGN AND SETTING: Prospective, single-blinded, randomized clinical trial conducted at a podiatry and physiotherapy clinical center.

METHODS: A nine-week program of wearing either unstable shoes (A) or conventional shoes (B) was implemented. The following outcomes were measured in three assessments: pain intensity, using a visual analogue scale (VAS); low-back mobility, using a modified Schober test; and stability, using a pressure platform.

RESULTS: The lateral stability speed, anterior stability speed and anterior center of pressure (COP) showed significant ($P < 0.05$) decreases in the unstable shoes group after nine weeks, in relation to the conventional group. Intra-group measurements showed significant differences ($P < 0.05$) in VAS between the second and third assessments and between the first and third assessments in both groups. Intra-group evaluations also showed statistically significant differences ($P < 0.05$) in the lateral stability speed and anterior stability speed.

CONCLUSIONS: Unstable shoes were effective in decreasing the pain intensity at five and nine weeks in women with postpartum LPP. In addition, their use produced decreases in lateral stability speed, anterior stability speed and anterior COP at nine weeks.

INTRODUCTION

Back pain is a normal symptom during pregnancy and is expected to become worse beyond the first three months after childbirth.[1] Several authors have indicated that from 8% to 20% of women present nonspecific lumbopelvic pain (LPP), two to three years after childbirth, which decreases their quality of life and interferes with their daily activities.[2-4] Gutke et al.[5] reported that LPP was related to lumbar instability due to the structural changes produced during the pregnancy.

Postpartum LPP can be assessed based on questionnaires and clinical examinations.[3] In addition, Fritz et al.[6] showed the importance of LPP classification for choosing the optimal intervention strategy. The clinical features of postpartum LPP have been reported to be pain, disability, lack of range of motion (ROM) in the sacroiliac joint, kinesiophobia, reduced quality of life and delayed resumption of doing exercise activities.[5,7]

Several authors have studied the influence of the core muscles on LPP. For example, Hodges et al.[8] found that individuals with low back pain presented decreased transversus muscle activity. Moreover, Teyhen et al.[9] reported that individuals with LPP showed reduction in the thickness of deep abdominal muscles. Exercise programs have been found to be effective in reducing the incidence of LPP, and also in decreasing the number of LPP symptoms, such pain and disability.[10,11] Stuge et al.[12] conducted a physical therapy program focused on specific stabilizing exercises for women with pelvic girdle pain and showed that these exercises produced benefits regarding pain, functionality and quality of life.

Previous studies have found benefits with regard to increasing the muscle activity in different areas through using unstable shoes. Romkes et al.[13] carried out a 3D gait analysis among healthy individuals with and without unstable shoes and reported that changes in movement patterns

occurred in the group wearing unstable shoes, such as increased ankle dorsiflexion ROM and muscle activity. In addition, Nigg et al.[14] reported that there was an increase in electromyography activity in the tibialis anterior in healthy subjects who were using unstable shoes. Regarding the effectiveness of unstable shoes in relation to the trunk muscles and back pain, Nigg et al.[15] reported that unstable shoes may be used to improve low back pain symptoms in golfers, without adverse effects. Lison et al.[16] performed a gait analysis on healthy participants wearing unstable shoes and showed that they presented increased erector spinae and rectus abdominis muscle activity. Moreover, in a comparative study between patients with chronic low back pain and healthy participants, unstable shoes were reported to have the effect of decreasing low back pain.[17]

Currently, there is a lack of randomized clinical trials (RCTs) regarding the effectiveness of unstable shoes, especially among women who suffer from LPP during the postpartum period. We hypothesized that women with LPP during this period could benefit from wearing unstable shoes.

OBJECTIVE

The primary aim of the present study was to determine the effectiveness of wearing unstable shoes instead of conventional shoes, regarding pain intensity, among women with LPP during the postpartum period. Therefore, as a secondary objective, the aim was to assess the effectiveness of wearing unstable shoes with regard to low back mobility and stability in this population.

METHODS

Design

The present study was a prospective, single-blinded, randomized clinical trial (registered at ClinicalTrials.gov: NCT03065270) that was conducted between October 2013 and July 2014. It followed the guidelines of the Consolidated Standards of Reporting Trials (CONSORT).

Participants

Twenty-four women who had been diagnosed with LPP during the postpartum period were included. They were randomly divided into two groups (A and B): group A (n = 12) wearing unstable shoes; and group B (n = 12) wearing conventional shoes. The enrollment of patients was carried out by a specialist medical doctor with more than 15 years in the field of gynecology. All the patients were recruited at the Hospital Quirón, in Madrid, Spain. **Figure 1** presents a flow chart describing the patient recruitment and assessment process.

The inclusion criteria for the study subjects were that they needed to be women aged from 18 to 40 years old, who were primiparous with LPP, had given birth 8 to 12 weeks previously, presented visual analogue scale (VAS) scores of at least 3 out of 10 points and were capable of walking autonomously.[17] The following occurrences were exclusion criteria: implementation of physical therapy interventions, body mass index (BMI) higher than 30 kg/m^2, lower limb injury within the last year, fractures, hemorrhage, induced pregnancy,[18] systemic disease, infections, vaginal prolapses, shoe size smaller than 35 or larger than 42 (European sizes), dizziness or balance disorders.[17]

The sample size was determined to be a convenience sample of 24 subjects, based on data from a previous study.[18]

Ethics

The Research Ethics Committee of the Hospital Universitario de Getafe (Madrid, Spain) approved the study (under protocol no. UEM-DOL-2011-01; dated September 28, 2011). The Declaration of Helsinki was respected throughout the study and a consent statement was signed by all the participants before their inclusion in the study.

Procedure

Prior to the intervention, the subjects performed a short program of dynamic exercises to familiarize themselves with the shoes that they would be using. As recommended by Stewart et al.,[19] the assessments were started only if all the women were accustomed to the shoes and were able to walk comfortably.

In the present study, unstable shoes were assigned to the A group (Masai Barefoot Technology, Masai Marketing and Trading AG, Winterthur, Switzerland) (**Figure 2A**) and conventional shoes were assigned to the B group (Joma, Portillo de Toledo, Spain) (**Figure 2B**). Both groups performed a nine-week program in which the following recommendations were made: the subjects wore their shoes for one hour per day starting on the first day; on the third day, they increased the duration of the intervention to three hours per day; and on the fifth day, they reached four hours of intervention per day. Through this gradual increase in utilization, the patients did not suffer any problems regarding adaptation to the footwear. From the fifth day to the end of the intervention at nine weeks, all the patients wore the shoes for four hours per day.

Randomization

The participants were randomized into an unstable shoes group or a conventional shoes group by means of the free software randomized.org, with a 1:1 ratio. Individuals were informed not to discuss the randomization groups with the outcome measurements evaluator.

Outcome measurements

All measurements were performed by a blinded examiner who did not know the group to which the individuals had been

assigned. For this study, a total of three assessments were carried out: at baseline, five weeks and nine weeks.

Firstly, pain intensity was evaluated using a VAS of 10 cm, ranging from 0 (no pain) to 10 cm (the worst pain imaginable). The subjects marked their pain intensity on the scale using a marker pen. In a previous study, the VAS was considered to be a reliable and valid tool for evaluating pain intensity caused by mechanical stimulation.[20]

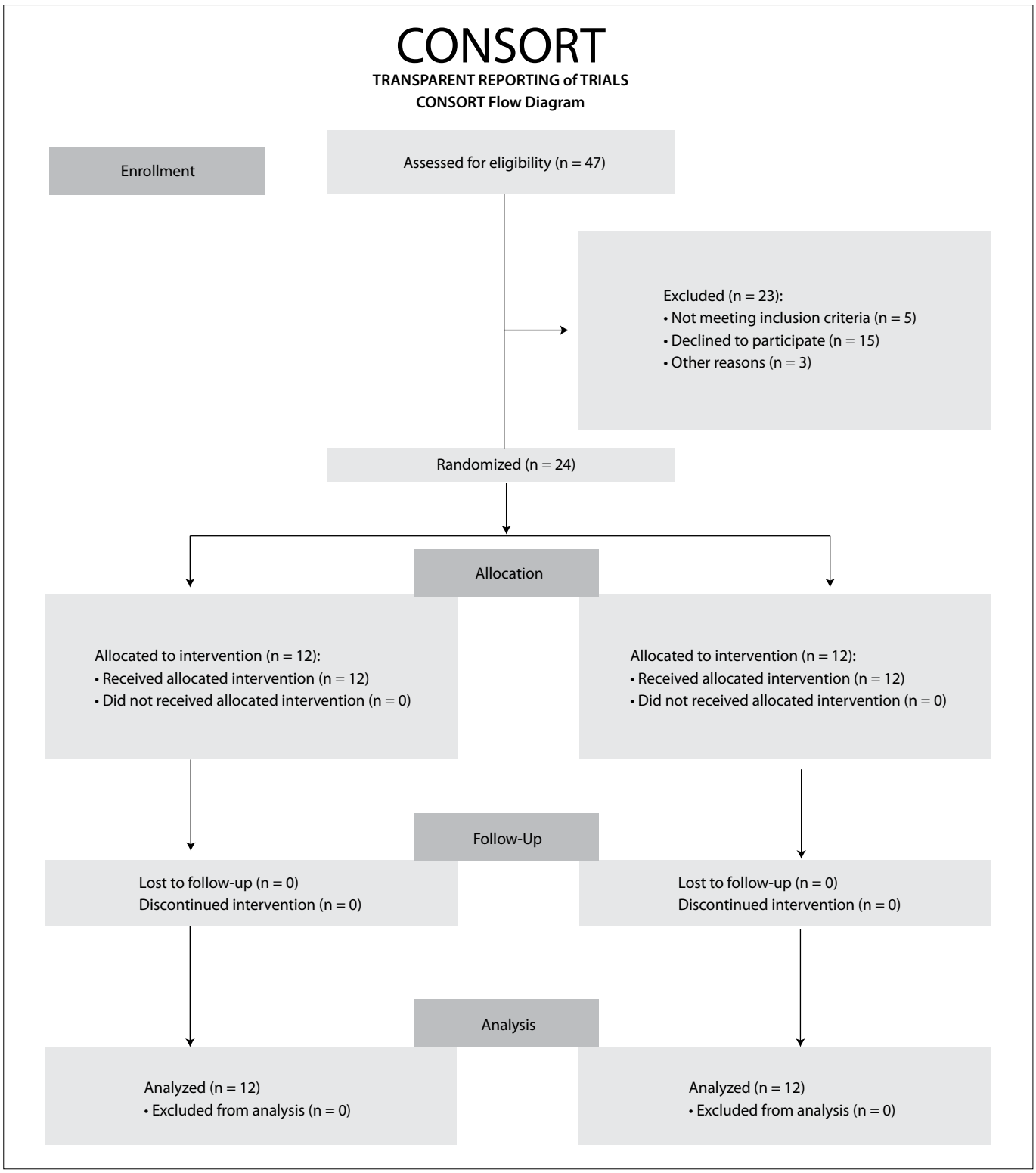

Figure 1. Flow chart describing the patient recruitment and assessment process.

Secondly, low back mobility was assessed by means of a modified Schobert test, following the guidelines of Tousignant et al.[21] The subjects were placed in a standing position and the evaluator marked out the midline of the lumbar spine at the posterosuperior iliac spine (lower landmark) at the level of L4/L5, using a pen. The evaluator also marked out a second line at a distance of 15 cm from the original one (higher landmark). Then the patient performed active anterior trunk flexion, without reaching pain, under the following order: "keep your knees straight and bend forward to touch your toes". The new distance between the lower and higher landmarks was measured and the subject then returned to the neutral position. The difference in the distance between the skin marks initially made in the neutral position and the new marks made in the trunk flexion position was used to indicate the quantity of flexion.[21] After each assessment, the marks were removed from the skin using alcohol.

Lastly, center of pressure (COP) measurements to assess stability were made using a floor-mounted capacitance transducer platform (Medicapteurs, Balma, France). The patients were placed in a standing position with their feet at the width of their pelvis. They were told to stay in a comfortable position, looking straight ahead, with their eyes open during the 30 seconds that the test lasted. The mean of three 30-second tests done in quick succession was recorded for each measurement.[22] This was followed by a five-minute resting period and then another set of tests. The following variables were recorded from the transducer platform: the velocities of the center of gravity developed in the frontal and sagittal planes (lateral and anterior stability speed variables, respectively); the mobility of the center of gravity in the frontal and sagittal planes (lateral and anterior COP mobility variables, respectively).

Statistical analysis

The data analysis was performed using the SPSS package for Windows (version 23.0, IBM Corp., Armonk, New York, United States). Firstly, the Shapiro-Wilk test was used to assess the normality assumption. Secondly, a comparative analysis between groups was performed. For parametric data analysis, Student's t test was used and for nonparametric data analysis, the Mann-Whitney U test was used. Lastly, for intra-group comparisons, the Wilcoxon rank test was performed. For all statistical tests, an α error of 0.05 (95% confidence interval) and a desired power of 90% (β error of 0.1) were used.

RESULTS

The sociodemographic data did not show any statistically significant differences ($P > 0.05$) (**Table 1**). The lateral stability speed, anterior stability speed and anterior center of pressure (COP) were significantly lower ($P < 0.05$) in the unstable shoes group after the nine weeks of the intervention (**Table 2**). The intra-group measurements (**Table 3**) showed significant ($P < 0.05$) differences in VAS between the second and third assessments

Table 1. Sociodemographic data

Data	Unstable shoes	Control	P-value
Age, years	35 ± 4	34 ± 3	0.44
Body mass index, kg/m²	21.82 ± 2.56	22.65 ± 3.17	0.67
Weight increase during pregnancy, kg	12 ± 4	12 ± 5	0.84
Newborn weight, kg	3.11 ± 0.30	2.96 ± 0.40	0.44

Values are mean ± standard deviation unless otherwise indicated.

Figure 2. Unstable shoes (A) and conventional shoes (B).

and between the first and third assessments, in both groups. The intra-group evaluations also found statistically significant differences ($P < 0.05$) in the variables of lateral stability speed and anterior stability speed.

Table 2. Comparison measurements between intervention groups

Measurement	Unstable shoes (n = 12)	Control (n = 12)	P-value
Visual analogue scale			
Baseline	6.17 ± 0.34	5.75 ± 1.54	0.55
Five weeks	4.33 ± 2.23	5.33 ± 2.10	0.27
Nine weeks	2.42 ± 2.54	4.33 ± 2.53	0.11
Lumbar mobility			
Baseline	6.80 ± 1.38	6.52 ± 1.22	0.48
Five weeks	6.67 ± 1.88	6.75 ± 1.89	0.82
Nine weeks	6.72 ± 2.18	6.75 ± 1.46	0.93
Lateral stability speed			
Baseline	1.88 ± 0.34	1.81 ± 0.54	0.50
Five weeks	1.41 ± 0.35	1.71 ± 0.44	0.09
Nine weeks	1.28 ± 0.30	1.72 ± 0.40	0.01*
Anterior stability speed			
Baseline	2.20 ± 0.70	2.07 ± 0.95	0.46
Five weeks	1.56 ± 0.46	1.95 ± 0.62	0.23
Nine weeks	1.43 ± 0.44	1.98 ± 0.55	0.03*
Lateral center of pressure mobility			
Baseline	1.86 ± 0.64	1.57 ± 0.69	0.42
Five weeks	1.33 ± 0.65	1.48 ± 0.57	0.46
Nine weeks	1.24 ± 0.45	1.45 ± 0.46	0.25
Anterior center of pressure mobility			
Baseline	2.70 ± 1.20	2.80 ± 1.57	0.42
Five weeks	2.13 ± 0.83	2.34 ± 1.29	0.81
Nine weeks	1.67 ± 0.80	2.66 ± 1.34	0.04*

Values are mean ± SD unless otherwise indicated; *P-value showing statistically significant difference.

Table 3. Comparison of intra-group measurements between the intervention group (unstable shoes) and control group (conventional shoes)

Comparison	Unstable shoes P-value (n = 12)	Control P-value (n = 12)
Visual analogue scale		
Baseline - five weeks	0.07	0.34
Five weeks - nine weeks	0.00*	0.03*
Baseline - nine weeks	0.00*	0.03*
Lumbar mobility		
Baseline - five weeks	0.08	0.93
Five weeks - nine weeks	0.39	0.72
Baseline - nine weeks	0.47	0.62
Lateral stability speed	0.01*	0.98
Anterior stability speed	0.01*	0.86
Lateral center of pressure mobility	0.15	0.86
Anterior center of pressure mobility	0.06	0.21

*P-value showing statistically significant difference.

DISCUSSION

To our knowledge, this was the first study to observe the effectiveness of unstable shoes among postpartum women. All the participants included in the present study presented LPP and showed decreases in pain intensity in the intervention at five and nine weeks. However, no significant differences were found between the groups with regard to VAS. Like in our study, Vieria et al.[23] reported that there was a significant decrease in lumbar pain in subjects who used unstable shoes, in comparison with a control group, over a six-week follow-up period. In addition, Hodges and Mosley[24] argued that altered postural motor control of the core muscles was related to pain episodes in which modified postural patterns were developed. Along the same lines, Nigg et al.[25] showed that there was a low back pain reduction of 1.75/10 points in VAS after six weeks of using unstable shoes. Lisón et al.[16] showed that there was a significant increase in electromyographic activity in the rectus abdominis and erector spinae muscles during gait, among subjects using unstable shoes. In addition, from those findings, these authors suggested that use of unstable shoes could be a potential intervention for strengthening trunk muscles and improving low back pain.

Based on our data, no statistically significant differences were found in either group, regarding lumbar mobility. Armand et al.[17] explained that increased lumbar lordosis and co-contraction of the trunk muscles in patients using unstable shoes could constitute an inhibitory mechanism against low back pain. Consequently, use of unstable shoes could have potential implications regarding lumbar spine ROM both in healthy and in low-back-pain populations.[16,26]

Our findings showed that there was a significant decrease in imbalance in the sagittal and frontal planes in the intervention group (unstable shoes). The values were more conclusive regarding stability speed and anterior mobility at nine weeks, between the groups. In addition, our findings suggested that changes to lower-limb biomechanics in postpartum women, produced through training on unstable surfaces, had benefits regarding imbalance of the COP. Ruhe et al.[27] showed in a systematic review that imbalance of the COP was related to subjects who suffered low back pain. Thus, use of unstable shoes for improving COP imbalances could be a new interventional approach for patients with lumbar disorders. Moreover, in several studies, use of unstable shoes not only showed benefits for balance, but also showed benefits with regard to enhancement of shock absorption of ground reaction forces.[25,28,29]

The current study suggested that use of unstable shoes had benefits regarding pain intensity and improvement of COP imbalances, while being a relatively inexpensive and portable intervention. Treatment was implemented while the patients were performing other activities, such work or activities of daily life. In addition, unstable shoes training should be carried out within a physical therapy protocol.

Several limitations were observed in this study. Firstly, no straight-leg-raise test was performed in this study, although this might have been useful for evaluating lower-limb and low-back disturbances. Secondly, the effects of wearing unstable shoes before childbirth have not yet been studied. It may be of interest to observe the effectiveness of use of unstable shoes by pregnant women.

CONCLUSIONS

Use of unstable shoes was effective for decreasing pain intensity at five and nine weeks among women with postpartum LPP. In addition, their use produced decreases in lateral stability speed, anterior stability speed and anterior COP at nine weeks.

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Influence of foot pain on frailty symptoms in an elderly population: a case-control study

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ABSTRACT

BACKGROUND: Frailty is a condition that can increase the risk of falls. In addition, foot disorders can negatively influence elderly people, thus affecting their condition of frailty.

OBJECTIVE: To determine whether foot pain can influence a greater degree of frailty.

DESIGN AND SETTING: Cross-sectional descriptive study conducted at the University of Valencia, Valencia, Spain.

METHODS: A sample older than 60 years (n = 52), including 26 healthy subjects and 26 foot pain patients, was recruited. Frailty disability was measured using the 5-Frailty scale and the Edmonton Frailty scale (EFS).

RESULTS: There were statistically significant differences in the total EFS score and in most of its subscales, according to the Mann-Whitney U test ($P < 0.05$). In addition, foot pain patients presented worse scores (higher 5-Frailty scores) than did healthy patients, regarding matched-paired subjects (lower EFS scores). With regard to the rest of the measurements, there were no statistically significant differences ($P > 0.05$). The highest scores ($P < 0.001$) were for fatigue on the 5-Frailty scale and the EFS, and for the subscale of independence function in EFS.

CONCLUSIONS: These elderly patients presented impairment relating to ambulation and total 5-Frailty score, which seemed to be linked to the presence of frailty syndrome and foot disorders.

INTRODUCTION

Aging and chronic illness processes like hyperglycemic disease, musculoskeletal disorders and heart processes can produce frailty syndrome. Consequently, these degenerative processes produce alterations that can affect mental and general health.[1] For example, aging and frailty can affect gait speed and increase the risk of falling due to balance alterations.[2-4] Furthermore, the presence of frailty symptoms affects health-related quality of life (HQoL)[5] in this population group.

Frailty syndrome can be defined as a group of health alterations that can affect several aspects of the aging process. These alterations are a consequence of a dynamic process that has psychological, biological and social characteristics and which reduces health status.[6] The frequency of frail states among people older than 65 years has been estimated to be between 4% and 59.1%.[7]

Among foot conditions in the elderly population, foot disorders and diseases are present most frequently in the frail population group, comprising approximately 25% of foot disorders.[8,9]

Consultations with general practitioners relating to ankle and foot conditions involving osteoarticular pain account for 8% of all consultations.[10] Accordingly, distress caused by pain may raise this percentage. Elderly people have characteristic foot complaints that can be likened to bigger disorders.[11] Foot health forms part of health-related quality of life (HQoL)[12] and poor foot health gives rise to a risk of falls.[13,14]

Clinimetric health questionnaires for measuring the degree of frailty degree are necessary in order to correlate foot disabilities and the level of frailty.

The 5-Frailty scale is a questionnaire of five items that was set up to be self-administered.[6] Respondents can provide affirmative or negative answers, and one point is given for a positive response. Thus, the total score can range from zero to five points, and subjects are classified as robust if the score is zero points, pre-frail with one to two points, or frail with three or more points. These classifications represent the subjects' respective tiredness, resistance, ambulation, disease and weight loss.

Tiredness is evaluated by asking subjects if they feel tired; resistance is determined from their self-reported capacity to climb stairs; ambulation consists of their self-reported ability to move around; illness is determined as the presence of more than five out of a total of eleven pathological conditions, including cardiovascular diseases and diabetes; and loss of weight as a reduction of 5% during the last year.[15]

The Edmonton Frailty Scale (EFS) assesses nine subscales: 1) cognitive, 2) general health status, 3) independence, 4) social support, 5) pharmacological treatment, 6) feeding, 7) mood, 8) continence and 9) functional performance, using eleven questions. The maximum score is 17 and represents the highest degree of frailty.[16] A score of between zero and four does not represent frailty; scores of five to six represent apparently vulnerability, scores of seven to eight represent mild frailty, scores of nine to ten represent moderate frailty and scores of eleven or more represent severe frailty.[17]

No study has yet correlated the scores of the EFS and the 5-Frailty scale. Therefore, the goal of the present study was to correlate the subscales of the EFS and 5 Frailty Scale among elderly people with and without foot disorders.

We were unable to find any references in the literature to the frailty status of elderly people with foot pain. Therefore, our hypothesis was that differences in levels of frailty exist among elderly people with foot pain.

OBJECTIVE

The objective of this study was to determine whether foot pain can influence a greater degree of frailty.

METHODS

This study was developed in Spain. We recruited elderly patients at a medical center, a rehabilitation service and a podiatry clinic, and all survey data were collected between October 2019 and January 2020. We obtained signed informed consent statements from all subjects. The observations for this study were made in accordance with the Strengthening the Reporting of Observational Studies in Epidemiology (STROBE) statement.[18]

Sample size calculation

To calculate the sample size, the G*Power 3.1.9.2 software (Heinrich-Heine-Universität Düsseldorf; Düsseldorf, Germany) was used. The following assumptions were made: differences between two independent means would be tested; the hypothesis was two-tailed; a large effect size of 0.8 was used; the α error was taken to be 0.05, with a 95% confidence interval; the β error was taken to be 20%; and the 1-β power analysis was taken to be 0.80. From this, a total sample size of 52 subjects was determined, with 26 in each group.

Participants

Before beginning the study, approval for conducting this study was obtained from the Ethics Committee of the University of Extremadura, Badajoz, Spain, under the registration number 1/2020, with the approval date March 16, 2020.

Informed consent was obtained from each participant after the purpose and process of the study had been explained to them. The participants were given an assurance that their information would remain confidential. The fact that their participation was entirely voluntary was also highlighted.

The criteria for including patients were that they needed to be elderly people (60 years of age or over) who presented foot pain during the last six months due to toe or foot deformities (but without wounds), regardless of their origin or cause, with a score of more than five points on a visual analogue scale (VAS); and were able to communicate orally and provide written informed consent. VAS scores above five points, i.e. from moderate to severe, showed intraclass correlation coefficient reliability of 0.870.[19]

The exclusion criteria were presence of major neurocognitive disorder, failure to answer the initial identification questions, inability to understand the rules of participation and refusal to participate in the study (through not signing the consent statement).

To recruit volunteer participants, we posted recruitment flyers in places within an elderly people's center where people would gather together. We also addressed groups of elderly people at the center to invite them to contact us if they were willing to participate in the study. Once a potential participant expressed interested, a cognitive function evaluation was performed by a gerontological nurse practitioner (GNP), to establish the cognitive eligibility of the participant. Following the evaluation by the GNP, the investigators explained the study procedures in detail to the participant.

The interviews comprised questions on general health status, sociodemographic characteristics (sex, age, body mass index, height and weight) and comorbidities (e.g. anxiety, depression, diabetes, obesity, osteoarticular diseases, vascular disorders or kidney illness). Data on comorbidities were collected from the patients' medical records. Furthermore, specific items relating to foot pain, such as current treatment or presence of foot deformities, were assessed by a senior podiatry physician (ENF)

In this study, a total of 65 elderly people expressed interest in participating in the study, and all of them met the cognitive requirements. The participants all attempted to complete the survey questionnaires. Subsequently, all the survey questionnaires were analyzed for this study. However, 14 of them were excluded due to incomplete answers. For participants who were not able to read the questionnaires due to vision problems, the investigators read the questions aloud and marked the participants' answers on the questionnaires. The participants took about 15 minutes to complete the questionnaires. They did not receive any compensation for their participation in the study.

Evaluation of frailty

The EFS was designed to measure frailty on nine subscales: cognitive, general health status, independence, social support, pharmacological treatment, feeding, mood, continence and functional performance.[16,21] Its total scores range from 0 to 17, and higher scores indicate more frailty. The scores were classified into three degrees of frailty.[21] Subjects who scored 0-5 points were designated as non-frail. Those who obtained 6-11 points were designated as ostensibly susceptible to frailty. Those who scored 12-17 points were designated as frail. The questionnaire only took 15 minutes to complete.

The participants also completed the 5-item Frailty scale.[22] This scale measures five subscales: tiredness, resistance, ambulation, disease and weight loss. The frailty subscale scores each range from 0 to 5, and higher scores indicate more frailty. Participants who scored between three and five were considered to be frail; those who scored one or two were considered to be pre-frail, and those who scored zero points were considered to be non-frail.[17]

Statistical analysis

All variables were normally distributed, as determined by the Kolmogorov-Smirnov test ($P > 0.05$).

Among the quantitative variables, nonparametric data were described in terms of their median, interquartile range (IR) and 95% confidence interval (CI). Parametric data were described using their mean, standard deviation (SD) and minimum and maximum (range) values.

A comparison of the quantitative data between men and women for the different questionnaire subscales of the EFS and the 5-Frailty scale was conducted, and significant differences were checked using an independent Student t test. Non-normal data were analyzed using the Mann-Whitney U test.

All analyses were considered statistically significant when the P-value was < 0.05 with a 95% CI. Statistical analyses were developed using the SPSS software, version 26.0 (SPSS, Chicago, IL, United States).

RESULTS

Descriptive data and sociodemographic data

Age, height, weight and body mass index were shown to have normal distribution ($P > 0.05$). On the other hand, none of the items from the 5-Frailty test or EFS showed normal distribution ($P < 0.05$).

The sample included 52 subjects whose mean age was 77.47 ± 10.69 years. The study subjects included 26 with foot pain (50.00%) and 26 healthy subjects (50.00%). **Table 1** shows the sociodemographic characteristics. There were no statistically significant differences ($P > 0.05$) between the foot pain patients and the healthy individuals regarding the sociodemographic characteristics of age or body mass index.

Edmonton Frail Scale and 5-Frailty scale distribution

As shown in **Table 2**, the 5-Frailty scale scores did not manifest any statistically significant difference ($P > 0.05$) for subscales or total scores between the foot pain and healthy groups. Furthermore, the distribution of EFS scores is shown in **Table 3**. The EFS subscales did not show any statistically significant differences ($P > 0.05$).

DISCUSSION

The two scales could be correlated, which confers concurrent validity on each subscale, as used in recent studies, and sustains application of the 5-Frailty score as an acceptable measurement relating to aspects of frailty such as ambulation, illness or weight loss. This can be considered to be an advantage in relation to other frailty scales that have been adapted for use in Spanish to evaluate specific aspects of frailty, like the Frailty Trait Scale (FTS).[23]

The frequency of occurrence of frailty factors, especially among elderly people, requires adequate measurement of frailty scores. Our research has shown that frailty relating to biomechanical parameters

Table 1. Descriptive and sociodemographic data of the sample

Demographic and descriptive data	All participants n = 52 Mean ± SD (95% CI)	Foot pain group n = 26 Mean ± SD (95% CI)	Healthy group n = 26 Mean ± SD (95% CI)	P-value*
Age (years)	76.80 ± 9.99 (74.34-79.26)	72.50 ± 7.83 (67.52-77.47	77.75 ± 10.23 (74.96-80.55	0.088
Weight (kg)	62.27 ± 11.60 (59.42-65.12)	67.41 ± 15.29 (57.69-77.13)	61.12 ± 10.45 (58.27-53.98	0.170
Height (m)	1.60 ± 0.08 (1.58-1.62)	1.64 ± 0.09 (1.58-1.70)	1.59 ± 0.07 (1.57-1.62)	0.083
Body mass index (kg/m^2)	24.02 ± 3.75 (23.10-24.95)	24.75 ± 4.45 (21.92-27.59)	23.86 ± 3.60 (22.88-24.85)	0.612

Comparison of demographic characteristics of the total sample (all participants), subjects with foot pain and healthy subjects matched with normalized reference values.

*Mean ± standard deviation (SD), range (minimum-maximum) and Student's t test for independent samples were applied; In all the analyses, $P < 0.05$ (with a 95% confidence interval, CI) was considered statistically significant.

like gait speed presents lower scores. It has also been shown that women have higher degrees of frailty than do men, when both have foot pain.[24,25] Our present results are along the same lines as in previous studies relating to frailty and foot disorders, which showed similar results relating to frailty scores and foot disorders.[26,27]

Moreover, balance disorders have been shown to increase frailty scores, and the our results coincide with those from previous studies.[28,29] Thus, altered walking ability and balance are characteristics of frailty. Specifically, women with foot disorders exhibited higher frailty scores than men, with the exception of the EFS mood subscale, which seems be related to the existence of foot disorders and the aging process. Our results were similar to those of other authors.[5,8]

Future studies should incorporate all other foot risk factors related to frailty syndrome. Although a frailty score is determined

Table 2. Comparisons of 5-Frailty scale scores between foot pain and healthy groups

Frailty Scale Domains	Foot pain group n = 26 Mean ± SD (95% CI) Median (IR)	Healthy group n = 26 Mean ± SD (95% CI) Median (IR)	P-value
Fatigue	0.91 ± 0.30 (0.71-1.11) 1.00 (0.00)	0.45 ± 0.50 (0.29-0.61) 0.00 (1.00)	0.007
Resistance	0.36 ± 0.50 (0.02-0.70) 0.00 (1.00)	0.50 ± 0.50 (0.34-0.66) 0.50 (1.00)	0.427
Ambulation	0.55 ± 0.52 (0.19-0.90) 1.00 (1.00)	0.43 ± 0.50 (0.26-0.59) 0.00 (1.00)	0.481
Illness	0.64 ± 0.50 (0.30-0.98) 1.00 (1.00)	0.38 ± 0.49 (0.22-0.53) 0.00 (1.00)	0.125
Weight loss	0.64 ± 0.50 (0.30-0.98) 1.00 (1.00)	0.53 ± 0.50 (0.36-0.69) 1.00 (1.00)	0.515
Total Frailty Scale	3.27 ± 1.34 (2.37-4.18) 4.00 (2.00)	2.28 ± 1.48 (1.80-2.75) 2.00 (2.00)	0.059

CI = confidence interval; IR = interquartile range. Mann-Whitney U tests were used. In all the analyses, P < 0.05 (with a 95% confidence interval) was considered statistically significant.

Table 3. Comparisons of Edmonton Frail Scale scores between foot pain and healthy groups

Edmonton Frail Scale Domains	Foot pain group n = 26 Mean ± SD (95% CI) Median (IR)	Healthy group n = 26 Mean ± SD (95% CI) Median (IR)	P-value
Cognition	0.91 ± 0.70 (0.44-1.38) 1.00 (1.00)	0.75 ± 0.63 (0.55-0.95) 1.00 (1.00)	0.488
General health status 2A	0.73 ± 0.64 (0.29-1.16) 1.00 (1.00)	0.65 ± 0.62 (0.45-0.85) 1.00 (1.00)	0.718
General health status 2B	1.09 ± 1.04 (0.39-1.79) 1.00 (2.00)	0.75 ± 0.84 (0.48-1.02) 1.00 (1.00)	0.302
Functional independence	1.18 ± 0.98 (0.52-1.84) 1.00 (2.00)	0.45 ± 0.74 (0.21-0.69) 0.00 (1.00)	0.011
Social support	0.64 ± 0.50 (0.30-0.98) 1.00 (1.00)	0.45 ± 0.59 (0.28-0.64) 0.00 (1.00)	0.238
Medication use 5A	0.73 ± 0.46 (0.41-1.04) 1.00 (1.00)	0.58 ± 0.50 (0.41-0.74) 1.00 (1.00)	0.364
Medication use 5B	0.55 ± 0.52 (0.19-0.90) 1.00 (1.00)	0.55 ± 0.50 (0.39-0.71) 1.00 (1.00)	0.979
Nutrition	0.82 ± 0.40 (0.55-1.09) 1.00 (1.00)	0.63 ± 0.49 (0.47-0.78) 1.00 (1.00)	0.233
Mood	0.55 ± 0.52 (0.19-0.90) 1.00 (1.00)	0.55 ± 0.50 (0.39-0.71) 1.00 (1.00)	0.979
Continence	0.27 ± 0.46 (0.04-0.59) 0.00 (1.00)	0.43 ± 0.50 (0.26-0.59) 0.00 (1.00)	0.364
Functional performance	1.00 ± 0.63 (0.58-1.42) 1.00 (0.00)	1.08 ± 0.65 (0.87-1.28) 1.00 (1.00)	0.728
Total Edmonton Frail Scale	8.09 ± 5.43 (4.44-11.74) 9.00 (9.00)	6.69 ± 4.33 (5.26-8.04) 6.00 (7.00)	0.477

CI = confidence interval; IR = interquartile range. Mann-Whitney U tests were used. In all the analyses, P < 0.05 (with a 95% CI) was considered statistically significant.

through the EFS,[25,30] the Geriatrician's Clinical Impression of Frailty (GCIF) has also been used in a cohort of older acute patients.[31]

Several limitations of this study need to be taken into account. A population from different areas might be useful to improve the strength of this study.

In the present study, it was only determined whether foot pain could influence a greater degree of frailty. We found that foot pain does not affect frailty.

Although gait disorders, balance alterations and the risk of falling are very common among frail people,[2,4] studies like the present one should also be developed for other population groups, in order to determine their degree of frailty. For example, widows usually have higher frailty scores due to psychosocial factors.[30,32,33]

Furthermore, selective sampling can cause bias. For this reason, use of randomized sampling should be considered in future studies.

Lastly, the correlation between different foot disorders, including several genetic and acquired or traumatic alterations and chronic illnesses, was not studied here because our population was not suitable for developing these comparisons. We therefore suggest that future research should be conducted on different pathological conditions of the feet.

CONCLUSIONS

Foot pain greater than five points on the 5-Frailty score scale seemed to be linked to the presence of frailty syndrome and foot disorders, especially the score relating to ambulation.

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Frequency of physical activity and stress levels among Brazilian adults during social distancing due to the coronavirus (COVID-19): cross-sectional study

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ABSTRACT

BACKGROUND: The COVID-19 pandemic may be having many psychological impacts on people, at both an individual and a community level.

OBJECTIVE: To ascertain the relationship between the weekly frequency of physical activity and levels of stress among Brazilian adults during social distancing due to the coronavirus (COVID-19), and the interaction of sex in this association.

DESIGN AND SETTING: Cross-sectional study with a descriptive approach conducted at a public university in Curitiba (PR), Brazil.

METHODS: 2,000 Brazilian adults (average age 36.4 years; 59.6% women) were recruited according to convenience through digital media. They filled out a questionnaire in electronic format that asked for sociodemographic information, health data, food consumption data, weekly frequency of physical activity and stress levels on the 10-item Kessler psychological distress scale. Descriptive statistics and regression analyses were used to evaluate the data.

RESULTS: Associations were observed for the following correlations: male sex * no physical activity (odds ratio (OR): 4.35; 95% confidence interval (CI): 1.14-16.67); female sex * physical activity 4 or 5 times a week (OR: 7.86; 95% CI: 2.28-27.05); female sex * physical activity 3 times a week (OR: 7.32; 95% CI: 2.09-25.58); female sex * physical activity 1 or 2 times a week (OR: 14.57; 95% CI: 4.28-49.57); and female sex * no physical activity (OR: 24.17; 95% CI: 7.21-80.97).

CONCLUSION: The lower the weekly frequency of physical activity during the period of social distancing was, the greater the chances of having stress levels were, especially for women.

INTRODUCTION

The COVID-19 pandemic may be having many psychological impacts on people, at both an individual and a community level.[1,2] The few studies published to date have shown that in the initial phase of the COVID-19 outbreak, more than half of the respondents rated its psychological impact as moderate to severe, and about a third reported having moderate to severe anxiety.[3]

In relation to the current pandemic scenario, both the Brazilian Ministry of Health and the World Health Organization recommend social distancing. However, it is known that long periods in isolation can increase behaviors that lead to physical inactivity, thereby contributing to the development of anxiety and depression.[4-6]

Thus, maintaining some frequency of physical activity in the home (aerobic activities, stretching and muscle and bone-strengthening exercises), during this period of social distancing, could help control stress levels, such as anxiety and depression.[7] It has been suggested that higher levels of physical activity are associated with decreased risk of future anxiety disorders and depression.[8,9] These results have been confirmed through recent meta-analyses, in which regular physical activity was seen to be a protective factor against depression.[9,10]

Based on the numerous health benefits that physical activity may provide,[11-13] and considering the importance of maintaining physical activity during the COVID-19 pandemic, especially for controlling stress levels, such as anxiety and depression,[7-10] it is necessary to expand knowledge about the role of the weekly frequency of physical activity.

OBJECTIVE

The objective of the study was to ascertain the relationship between the weekly frequency of physical activity and the level of stress among Brazilian adults during social distancing due to the coronavirus (COVID-19), and the interaction of sex with this association.

METHODS

Ethical considerations

The present study followed the rules for research involving human beings of the Brazilian National Health Council. It was approved by the local university research ethics committee (CAAE: 30750220.1.0000.0102; date: June 9, 2020).

Procedures

This was a cross-sectional, epidemiological and correlational study carried out using a non-probabilistic sample of Brazilian adults who were selected according to convenience. The sample was invited (from April to May 2020) to participate in the survey through dissemination in digital media (WhatsApp, Telegram, Facebook, Twitter and e-mails). Through these media, those interested in participating in the study had access to a questionnaire (available through Google Forms), named: "Questionnaire on habitual physical activity practices, eating habits and psychological factors during social distancing due to the new coronavirus (COVID-19)".

A total of 2,347 adults were evaluated. Respondents who were under 18 years old (n = 38) and duplicate responses (n = 74) were excluded. Individuals who answered the questionnaires incorrectly were treated as sample loss (n = 235). Thus, the final sample included consisted of 2,000 Brazilian adults.

To verify the statistical power of the sample, an *a posteriori* sample calculation was performed considering a 95% confidence level ($\alpha = 0.05$), an 80% power ($\beta = 20$) and a prevalence of physical activity of three times per week during social distancing of 21.1% (distribution of the sample itself). With these parameters, the sample of 2,000 subjects made it possible to identify prevalence ratios above 1.28 as a risk and below 0.75 as protection. These calculations were performed on the calculator G*Power version 3.1.9.4 (G*Power, Dusseldorf, Germany).

Independent variable – physical activity (PA)

To assess physical activity at home (aerobic activities, stretching and muscle and bone-strengthening exercises) during social distancing, the following question was asked: "How often have you been practicing physical activity during social distancing?" The response options were: No exercise, 1 or 2 times a week, 3 times a week, 4 or 5 times a week or 6 or 7 times a week. The respondents were also asked at what time they performed this physical activity on a daily basis. However, the frequency of physical activity during the week was considered for analysis.

Dependent variable – stress level

The respondents' stress level was assessed using the K10 instrument.[14] This instrument consists of 10 questions and assesses anxiety and depression over the last 30 days. The first nine questions all begin "During the past 30 days, how often did you feel..." and are completed with the following: "... exhausted for no good reason?"; "... nervous?"; "... so nervous that nothing could calm you down?"; "... hopeless?"; "... restless or agitated?"; "... so restless that you couldn't stand still?"; "... depressed?"; "... so depressed that nothing could cheer you up?"; and "... worthless?". Finally, the last question is "During the past 30 days, how often did you feel that everything was an effort?".

The answer options were obtained using a Likert scale (never, a little, part of the time, most of the time and all the time). These answers to the 10 questions were summed to generate a final score, which could range from 10 to 50. These scores were used to estimate the level of anxiety or depression. Thus, the participants were classified as presenting low stress (scores of 10 to 15), moderate stress (16 to 21), high stress (22 to 29) or very high stress (30 to 50). For respondents with a total score greater than 22, there is a greater risk of having a mental disorder.[15]

Sociodemographic and health factors

Sex was self-reported ("male" or "female"). Likewise, age was informed by the participants and was then grouped as: 18-29 years, 30-39 years, 40-49 years, 50-59 years or over 60 years. The body mass index (BMI) was calculated from self-reported weight and height in the questionnaire. It was obtained by dividing weight (kilograms) by height (meters) squared and was classified as specified by the World Health Organization (WHO): "underweight" (< 18.5 kg/m^2); "normal weight" (18.5 to 24.9 kg/m^2); "overweight" (25 to 29.9 kg/m^2); or "obesity" (≥ 30 kg/m^2).[16] The respondents were also asked whether they had increased their food consumption during social distancing, with the following response options: no, sometimes or yes.

Data analysis and statistical procedures

The data were described in terms of simple and relative frequencies, according to the stress level of the subjects. The chi-square test was used to compare the frequencies of factors at different levels of stress.

Possible associations between different levels of stress and sex, frequency of physical activities during social distancing, age groups, body mass index and increased food intake during social distancing were investigated through crude multinomial logistic regression (the proportionality of odds had previously been verified), with their respective 95% confidence intervals.

Subsequently, the interaction of sex was tested in the relationship between weekly frequency of physical activities and stress during social distancing (for example: sex * frequency of physical activity). For this, the interaction term was introduced into the models for multinomial logistic regression analysis (with 95% confidence intervals).

All the analyses were performed using the SPSS software, version 24.0 (Chicago, IL, United States), with a significance level set at $P < 0.05$.

RESULTS

The final sample was 2,000 adults (59.6% women), with predominance of the age group between 30 and 39 years (34.2%). Approximately half of the sample (49.3%) was classified as having normal weight, 42.2% reported not having increased their food consumption and 23.8% were practicing physical activities 4 to 5 times a week. Regarding stress, the low level was seen most frequently in the sample (35.9%) (**Table 1**). Higher levels of stress were associated with the following: females, in comparison with males (OR: 5.30; 95% CI: 3.59-7.82); low frequency of weekly physical activity, in comparison with high frequency of weekly physical activity (4 or 5 times: OR: 2.58; 95% CI: 1.23-5.41; 3 times: OR: 3.01; 95% CI: 1.44-6.28; once or twice: OR: 4.71; 95% CI: 2.27-9.75; and not done: OR: 9.73; 95% CI: 4.80-19.69); and the age groups of 30 to 39 years (OR: 5.99; 95% CI: 1.41-25.32) and 18 to 29 years (OR: 17.61; 95% CI: 4.19-73.94), in comparison with the age group of 60 years and over. Higher levels of stress were inversely associated with the following: overweight, in comparison to obesity (OR: 0.56; 95% CI: 0.35-0.90); and increased food intake: sometimes (OR: 0.49; 95% CI: 0.32-0.73) and none (OR: 0.24; 95% CI: 0.16-0.35), in comparison with increased food intake (**Table 2**).

When sex was inserted as an interaction term in the association between the weekly frequency of physical activity and the stress level, significant values were presented for the following: male sex * no physical activity (OR: 4.35; 95% CI: 1.14-16.67); female sex * physical activity 4 or 5 times a week (OR: 7.86; 95% CI; 2.28-27.05); female sex * physical activity 3 times a week (OR: 7.32; 95% CI %: 2.09-25.58); female sex * physical activity 1 or 2 times a week (OR: 14.57; 95% CI: 4.28-49.57); and female sex * no physical activity (OR: 24.17; 95% CI: 7.21-80.97) (**Table 3**).

DISCUSSION

Regarding the initial hypothesis of this study, the analyses confirmed the premise that the lower the weekly frequency of physical activity during the period of social distancing was, the greater

Table 1. Characteristics of this sample of Brazilians according to their stress levels during the social distancing due to COVID-19 (n = 2,000)

	Stress level								P
	Low		Moderate		High		Very high		
	n	%	n	%	n	%	n	%	
Sex									
Male	335[a]	16.8	400[b]	20.0	290[c]	14.5	167[d]	8.3	< 0.001
Female	383[a]	19.1	275[b]	13.8	114[c]	5.7	36[d]	1.8	
Weekly frequency of physical activities during social distancing									
6 or 7 times	136[a]	6.8	72b	3.6	27[b]	1.4	10[b]	0.5	< 0.001
4 or 5 times	179[a,b]	8.9	182[b]	9.1	80[a]	4.0	34[a]	1.7	
3 times	167	8.3	135	6.8	82	4.1	37	1.8	
Once or twice	127[a]	6.3	151[a,b]	7.5	105[b]	5.3	44[a,b]	2.2	
Not practiced	109[a]	5.5	135[a]	6.8	110[b]	5.5	78[c]	3.9	
Age group									
60 years and over	51[a]	2.5	23[b]	1.1	7[b]	0.4	2[b]	0.1	< 0.001
50 to 59 years	92[a]	4.6	63[a,b]	3.1	23[b]	1.1	9[b]	0.4	
40 to 49 years	172[a]	8.6	137[a,b]	6.9	71[a,b]	3.5	28[b]	1.4	
30 to 39 years	251	12.6	230	11.5	144	7.2	59	2.9	
18 to 29 years	152[a]	7.6	222[b]	11.1	159[b]	8.0	105[c]	5.3	
Body mass index									
Obese	87	4.3	86	4.3	63	3.1	36	1.8	0.713
Overweight	266	13.3	254	12.7	127	6.3	62	3.1	
Normal	356	17.8	325	16.3	206	10.3	98	4.9	
Underweight	9	0.4	10	0.5	8	0.4	7	0.4	
Increased food intake during social distancing									
Yes	129[a]	6.5	189[b]	9.4	147[c]	7.3	82[c]	4.1	< 0.001
Sometimes	192	9.6	221	11.1	137	6.9	60	3.0	
No	397[a]	19.9	265[b]	13.3	120[c]	6.0	61[b, c]	3.0	

[a,b,c,d]differ significantly.

the chances were that the subjects would present high levels of stress, even after considering adjustments for overweight and obesity,[17] age and food consumption,[18] which are factors that can also contribute to higher levels of stress. The Physical Activity Guidelines recommend that all adults, even those with chronic medical conditions, should engage in at least 150 minutes (recommended minimum) to 300 minutes a week of moderate-intensity exercise, if they are able to.[19]

These minimum recommendations are equivalent to something like 30 minutes a day of physical activity, 4 to 5 days a week, in order to obtain health benefits.[19] The present study showed that adults (regardless of sex) who reported doing physical activity at this frequency in a regular week would be twice as likely to experience moderate stress and three times as likely to experience high and very high stress, compared with those who did higher frequencies of physical activities (6 to 7 times a week). These stress

Table 2. Factors associated with stress levels among this sample of Brazilians during the social distancing due to COVID-19 (n = 2,000)

	Stress level								
	Moderate			High			Very high		
	OR	95% CI		OR	95% CI		OR	95% CI	
Sex									
Male	1	-	-	1	-	-	1	-	-
Female	1.66	1.34	2.05	2.90	2.23	3.77	5.30	3.59	7.82
Frequency of physical activities during social distancing									
6 or 7 times	1	-	-	1	-	-	1	-	-
4 or 5 times	1.92	1.35	2.73	2.25	1.37	3.67	2.58	1.23	5.41
3 times	1.52	1.06	2.19	2.47	1.51	4.03	3.01	1.44	6.28
Once or twice	2.24	1.55	3.25	4.16	2.55	6.77	4.71	2.27	9.75
Not practiced	2.33	1.59	3.42	5.08	3.11	8.30	9.73	4.80	19.69
Age group									
60 years and over	1	-	-	1	-	-	1	-	-
50 to 59 years	1.51	0.84	2.73	1.82	0.73	4.53	2.49	0.51	11.98
40 to 49 years	1.76	1.02	3.03	3.00	1.30	6.94	4.15	0.95	18.02
30 to 39 years	2.03	1.20	3.43	4.18	1.84	9.45	5.99	1.41	25.32
18 to 29 years	3.23	1.89	5.52	7.62	3.35	17.31	17.61	4.19	73.94
Body mass index									
Obese	1	-	-	1	-	-	1	-	-
Overweight	0.65	0.44	0.97	0.65	0.44	0.97	0.56	0.35	0.90
Normal	0.79	0.55	1.15	0.79	0.55	1.15	0.66	0.42	1.04
Underweight	1.22	0.44	3.35	1.22	0.44	3.35	1.88	0.65	5.43
Increased food intake during social distancing									
Yes	1	-	-	1	-	-	1	-	-
Sometimes	0.78	0.58	1.05	0.62	0.45	0.86	0.49	0.32	0.73
No	0.45	0.34	0.59	0.26	0.19	0.36	0.24	0.16	0.35

OR = odds ratio; CI = confidence interval; P < 0.05.

Table 3. Interaction of sex in the association between weekly frequency of physical activity and stress levels among this sample of Brazilians during the social distancing due to COVID-19 (n = 2,000)

	Stress level								
	Moderate			High			Very high		
	OR	95% CI		OR	95% CI		OR	95% CI	
Weekly frequency of physical activity * Male									
6 or 7 times	1	-	-	1	-	-	1	-	-
4 or 5 times	2.02	1.18	3.44	1.86	0.82	4.21	1.24	0.30	5.14
3 times	1.35	0.77	2.35	1.92	0.84	4.34	2.98	0.82	10.80
Once or twice	2.01	1.13	3.57	2.76	1.20	6.34	0.95	0.18	4.90
Not practiced	2.22	1.21	4.06	3.62	1.55	8.47	4.35	1.14	16.67
Weekly frequency of physical activity * Female									
6 or 7 times	1.48	0.82	2.65	1.77	0.74	4.23	2.07	0.51	8.35
4 or 5 times	2.93	1.70	5.04	4.95	2.27	10.82	7.86	2.28	27.05
3 times	2.76	1.58	4.81	5.83	2.66	12.78	7.32	2.09	25.58
Once or twice	3.71	2.13	6.46	9.36	4.31	20.30	14.57	4.28	49.57
Not practiced	3.51	2.01	6.13	10.07	4.65	21.80	24.17	7.21	80.97

OR = odds ratio; CI = confidence interval; *Interaction = multiplication of the possible moderating variable (sex) in the relationship between weekly frequency and stress during distancing; P < 0.05.

values (moderate, high and very high) increased as the frequency of physical activity in the week decreased. This explains not only the importance of complying with the minimum recommendations, but also the protective role that regular physical activity can play regarding health, when it is done at frequencies higher than the recommended minimum.[19]

Our results highlighted that individuals who had ceased to do physical activity showed significantly higher levels of stress. These findings were concordant with the results from previous studies in which the benefits of physical activity were investigated. Physical activity has a major role in mental health and cognitive function, because exercise has positive effects with regard to preventing and alleviating depression and anxiety.[10,20,21] Our findings corroborate those of other studies that have investigated mental health and physical activity during COVID-19.[22,23]

For men, this association was not observed for high and very high stress, which would be in line with the recommendations, because with frequencies of physical activity of four to five times a week, the psychological responses seem to improve considerably.[10,20-23] In contrast, if women were to follow the recommendations, this would not be enough to decrease the chances of moderate, high and very high stress. For women, practicing physical activities six or seven times a week did not show any association with different levels of stress. The fact is that, according to the literature, women are more prone to higher levels of stress.[10,20-23] The results from the present survey indicate that, despite the lack of significant values, higher frequency of physical activities during the social distancing period would indicate a lower level of stress.

Despite the recommendations that home confinement (lockdown) should not prevent people from being physically active,[24] the results from our study showed that a portion of the sample investigated did not do any physical activity during the COVID-19 home confinement period. It is likely elderly individuals have difficulty in exercising alone at home and have less access to remote physical activity areas. This may explain the reduction in physical activity among elderly people during this period.[23,24] Further studies are needed to understand why women experience higher levels of stress than those of men.

In short, the present study contributes to enabling better understanding of the literature on the importance of maintaining a regular frequency of physical activity.[24] For individuals who reduce their weekly frequency of physical activity, there is an extremely high chance of having high levels of stress, related to anxiety and depression.[14]

Some limitations of our study need to be considered in order to better understand the results. Reverse causality, which is a common feature in studies with a cross-sectional design, does not allow investigation of a cause-and-effect relationship or determination of the direction of the relationships. Nonetheless, this design has been used in several studies like ours. The use of reported measurements depends on the accuracy and recall power of the respondent's responses. However, because our study was large, and because of the special conditions of distancing currently imposed in the vast majority of countries around the world, the use of questionnaires may be the best alternative. It was not possible to assess the type of physical activity (aerobic activities, stretching or muscle and bone-strengthening exercises), since the questionnaire spoke of physical activity in general. Future studies can ascertain the action of the type of physical activity performed.

CONCLUSION

The lower the weekly frequency of physical activity during the period of social distancing was, the greater the chances were that the subjects would present high levels of stress. The interaction term (sex) showed that, especially for women, the reduction in training frequencies during the week contributed to increases in moderate, high and very high levels of stress, 14-fold for women who maintained physical activity only 1 or 2 times a week and 24-fold for those who did not do any weekly physical activity. In summary, our study presents relevant findings about the importance of maintaining the frequency of physical activity, either at home or away from home.

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Quality of life of Family Health Strategy professionals: a systematic review

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ABSTRACT

BACKGROUND: Individuals' quality of working life and motivation are directly related to their satisfaction and wellbeing. Although studies on the quality of life of family health workers have been conducted, there are none correlating these professionals' wellbeing with this work model.

OBJECTIVE: To review the scientific literature in order to identify the levels of quality of life, in their dimensions, of Family Health Strategy workers.

DESIGN AND SETTING: Systematic review of observational studies developed through a partnership between two postgraduate schools (Piracicaba and Uberlândia).

METHODS: The review followed the PRISMA recommendations and was registered in the PROSPERO database. Ten databases were used, including the "grey literature". Two evaluators selected the eligible studies, collected the data and assessed the risk of biases, independently. The JBI tool was used to assess the risk of bias. A complementary statistical analysis was conducted on the means and standard deviations of the results from the WHOQOL-100 and WHOQOL-bref questionnaires.

RESULTS: The initial search presented 1,744 results, from which eight were included in the qualitative analysis. The studies were published between 2007 and 2018. The total sample included 1,358 answered questionnaires. All the studies presented low risk of bias. The complementary analysis showed that the environmental factor (mean score 56.12 ± 2.33) had the most influence on the quality of life of community health workers, while physical health (mean score 14.29 ± 0.21) had the most influence on graduate professionals.

CONCLUSION: Professionals working within the Family Health Strategy had dimensions of quality of life that varied according to their professional category.

SYSTEMATIC REVIEW REGISTRATION: CRD42019123243.

INTRODUCTION

Over the last decades, Brazil has faced the challenge of changing the public healthcare model, i.e. to migrate from the Flexnerian model focused on procedures and specialized care to a comprehensive care model based on understanding the social determinants of health.[1,2] One of the crucial points in this change is to strengthen primary healthcare, for which the main operational strategy is the family health model.[3-5] This strategy makes it possible to expand access to healthcare services and implement actions towards comprehensive healthcare.[6,7]

Expansion of this model has been associated with a 45% reduction in hospitalizations for conditions that are sensitive to resolution within primary healthcare, over a 15-year period.[5] Data from the Ministry of Health indicated that in 2019 there were 43,754 family health teams operating throughout the country. These teams were responsible for providing primary healthcare to 64.47% of the Brazilian population.[8]

Family health work demands different skills for developing innovative community care practices, which makes the work complex and challenging.[9] Primary healthcare professionals present high prevalence (52.9%) of chronic stress associated with their work.[10] Analysis on this prevalence according to professional category shows that even higher prevalence can be observed: 54% among nurses and 67% among doctors.[11,12] However, studies conducted among Brazilian professionals in family health teams have shown lower prevalence of burnout syndrome, varying according to the region of Brazil. In one municipality in the northeastern region, the prevalence of professionals with medium and high levels of burnout was observed to be 37.9%.[13] In a municipality in southeastern Brazil, the prevalence of this syndrome reached 41.6%.[14]

In this regard, it is important to understand that the way in which work is organized affects both the workers' quality of life and the service provided. These are therefore important objects of investigation.[15,16] It can thus be seen that adequate provision of services requires maintenance of the quality of life of family health professionals.[17]

Individuals' quality of working life and motivation are directly related to their satisfaction and wellbeing. Dissatisfaction in a team harms the evolution and productivity of the institution.[18] Although studies on the quality of life of family health workers have been conducted, there are no studies correlating the wellbeing of these professionals with this work model,[19] or proposing actions directed to the quality of life of these workers.

OBJECTIVE

The aim of the present systematic review was to identify the levels of quality of life, in each of their dimensions, of Family Health Strategy workers.

METHODS

Protocol registration

This systematic review was performed in accordance with the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA)[20] and the Joanna Briggs Institute Manual for Evidence Synthesis.[21] The systematic review protocol was registered in the PROSPERO database under # CRD42019123243.

Study design and eligibility criteria

This systematic review aimed to answer the following research question: "What are the levels of quality of life of professionals working in the Family Health Strategy?" This question was based on the "Population, Variable and Outcome" strategy, in which the population included in the study was primary healthcare professionals, the variable was the work in the Family Health Strategy and the outcome was quality of life, considering its different dimensions.

The inclusion criteria defined for selection of studies were that these should only be cross-sectional observational studies developed in Brazil, with quality-of-life questionnaires applied to professionals working in the Family Health Strategy. There were no restrictions on year or language. The following types of study were excluded: 1) experimental or non-cross-sectional studies; 2) studies that did not answer the research question; 3) studies on instrument validation; and 4) qualitative studies.

Sources of information and search strategies

The primary study sources used were the PubMed (including MEDLINE), Scopus, Embase, SciELO, Web of Science, LILACS (Latin American and Caribbean Literature in Health Sciences) and Science Direct databases. The OpenThesis, OpenGrey, and OATD (Open Access Theses and Dissertations) databases were used to partially capture the "grey literature". The MeSH (Medical Subject Headings), DeCS (Health Sciences Descriptors) and Emtree (Embase Subject Headings) resources were used to select adequate search descriptors. The Boolean operators "AND" and "OR" were used to enhance the research strategy through several combinations, as shown in **Table 1**. The search was performed in January 2020. The results obtained were exported to the EndNote Web™ software (Thomson Reuters, Toronto, Canada), in which duplicates were removed.

Study selection

The studies were selected in three stages. A calibration exercise was performed before the selection of studies, in which the reviewers discussed the eligibility criteria and applied them to a sample of 20% of the results retrieved to determine inter-examiner agreement. After an adequate level of agreement (kappa ≥ 0.81) had been reached, the first stage was started. In this, two reviewers (ACCPB and WAV) analyzed all the titles of the studies, independently. Any divergences between these examiners were discussed with a third reviewer (AMH) to reach a consensus. Studies that were not excluded in this phase continued to the next one. In the second phase, the same reviewers (ACCPB and WAV) read the abstracts, independently. The abstracts that did not meet the eligibility criteria were eliminated. Articles in which the titles met the objectives of the study but for which the abstract was unavailable were fully analyzed in the next phase. In the third phase, the preliminarily eligible studies were fully read to verify whether they met the eligibility criteria. In cases of disagreement between the two reviewers, a third one (AMH) was consulted to make a final decision. The studies rejected were registered separately, with explanations of the reasons for exclusion.

Data collection

To ensure consistency between the reviewers in the data collection process, a calibration exercise was performed, in which the reviewers (ACCPB and AMH) extracted information from an eligible study together. After the selection, the studies were analyzed and the two reviewers (ACCPB and AMH) extracted the following information from each of them: study identification (author, year and location), sex, number of questionnaires answered, occupation, types of questionnaires used, mean results regarding quality of life obtained from the questionnaires, application of additional questionnaires and collection of socioeconomic data from the sample.

Risk of individual bias of the studies

The risk of bias and individual quality of each study included were assessed using the JBI critical appraisal tools for use in systematic reviews on cross-sectional observational studies.[22] Two authors

(AMH and MNO) independently assessed each domain, in accordance with the PRISMA recommendations.[20] The risk of bias was categorized as high when the study reached a "yes" score of up to 49%, moderate when the study reached a "yes" score of 50% to 69% and low when the study reached a "yes" score of more than 70%.

The question assessing the inclusion criteria for the study participants (Q1) was considered to have been answered "yes" (criteria verified) when the studies included the universe of family health professionals. The question referring to exposure factors (Q3) was considered "not applicable" because this systematic review aimed to identify factors that influence the quality of life, but only the dimensions most affected. Similarly, the questions about identification (Q5) and treatment (Q6) of the confounding factors were considered "not applicable" because they would identify the validity of the exposure studied.

Qualitative synthesis and complementary statistical analysis

Data were extracted from the individual studies and then a synthesis of results was performed. Considering that all the eligible studies performed descriptive analyses to determine the levels of quality-of-life domains, without comparison between the groups, it was considered unviable to conduct a meta-analysis on continuous outcomes in order to estimate the effects of differences. Thus, the quality-of-life domains in the WHOQOL-bref questionnaire (physical, social, environmental and psychological) and WHOQOL-100 questionnaire (physical, psychological, level of independence, social, environmental and spiritual) were analyzed complementarily, considering the mean and standard deviation values expressed in the primary studies. It was possible to calculate means that were weighted according to the sample size of the scores reported in each study, with the aim of obtaining an overall estimate of the quality-of-life domains. Hence, the STATA software, version 15.0 (StataCorp, College Station, United States), was used.

RESULTS

Study selection

In the initial phase of study identification, after exploring the ten electronic databases, 1,744 results were found. Next, duplicate articles were excluded, which left 1,373 studies for the analysis on titles and abstracts. From these, 12 remained for full-text reading. After reading the full texts, a further four articles were excluded (**Table 2**).[17,23-25]

Table 1. Database search strategies

Database	Search strategy (January, 2020)
PubMed http://www.ncbi.nlm.nih.gov/pubmed	("Quality of Life"[All Fields] OR "Health Related Quality Of Life"[All Fields] OR "Health-Related Quality Of Life"[All Fields] OR "Life Quality"[All Fields] OR "HRQOL"[All Fields]) AND ("Family Health"[All Fields] OR "Family Health Strategy"[All Fields] OR "Primary Health Care"[All Fields]) AND ("Health Occupation"[All Fields] OR "Health Worker"[All Fields] OR "Health Profession"[All Fields] OR "Health Personnel"[All Fields] OR "Occupational Health"[All Fields])
Scopus http://www.scopus.com/	("Quality of Life" OR "Life Quality") AND ("Family Health" OR "Family Health Strategy" OR "Primary Health Care") AND ("Health Occupation" OR "Health Worker" OR "Health Profession" OR "Health Personnel" OR "Occupational Health") ("Quality of Life" OR "Health Related Quality Of Life" OR "Health-Related Quality Of Life" OR "Life Quality" OR "HRQOL") AND ("Family Health" OR "Family Health Strategy") AND ("Health Worker" OR "Health Profession" OR "Health Personnel")
LILACS http://lilacs.bvsalud.org/	("Quality of Life") AND ("Family Health") AND ("Health Personnel") ("Qualidade de Vida") AND ("Saúde da Família") AND ("Saúde do Trabalhador") ("Quality of Life") AND ("Family Health") AND ("Health Workers")
SciELO http://www.scielo.org/	("Quality of Life") AND ("Family Health") AND ("Health Personnel") ("Quality of Life") AND ("Family Health") AND ("Occupational Health") ("quality of life") AND ("Family Health") AND ("health workers")
Web of Science http://apps.webofknowledge.com/	(("Quality of Life" OR "Health Related Quality Of Life" OR "Health-Related Quality Of Life" OR "Life Quality" OR "HRQOL") AND ("Family Health" OR "Family Health Strategy" OR "Primary Health Care") AND ("Health Occupation" OR "Health Worker" OR "Health Profession" OR "Health Personnel" OR "Occupational Health"))
ScienceDirect https://www.sciencedirect.com/	("Quality of Life" OR "Life Quality" OR "HRQOL") AND ("Family Health" OR "Family Health Strategy" OR "Primary Health Care") AND ("Health Occupation" OR "Health Worker" OR "Health Profession" OR "Health Personnel" OR "Occupational Health")
Embase http://www.embase.com	('quality of life' OR 'health related quality of life' OR 'health-related quality of life' OR 'life quality' OR 'hrqol') AND ('family health' OR 'family health strategy' OR 'primary health care') AND ('health occupation' OR 'health worker' OR 'health profession' OR 'health personnel' OR 'occupational health')
OpenGrey http://www.opengrey.eu/	("Quality of Life") AND ("Family Health" OR "Primary Health Care") AND ("Health Worker" OR "Health Profession" OR "Health Personnel") ("Quality of Life") AND ("Family Health") AND ("Occupational Health")
OpenThesis http://www.openthesis.org/	("Quality of Life" OR "Health Related Quality Of Life" OR "Health-Related Quality Of Life" OR "Life Quality" OR "HRQOL") AND ("Family Health" OR "Family Health Strategy") AND ("Health Worker" OR "Health Profession" OR "Health Personnel")
OATD https://oatd.org/	("Quality of Life" OR "Health Related Quality Of Life" OR "Health-Related Quality Of Life" OR "Life Quality" OR "HRQOL") AND ("Family Health" OR "Family Health Strategy") AND ("Health Worker" OR "Health Profession" OR "Health Personnel")

Thus, eight studies[26-33] were selected for the qualitative analysis, but only five of these were retained for the complementary analysis stage. One of the three studies that were not retained for this final stage[27] differed from the others regarding the instrument for measuring the quality of life. The other studies that were not retained[28,29] did not present the data on quality of life in full. **Figure 1** shows the entire process of identification, selection and eligibility of the studies.

Table 2. Full texts excluded and reasons for exclusion

Author	Reason for exclusion
Martin et al.[25]	The instrument used in the study did not address quality of life
Fernandes et al.[17]	Instrument validation
Mota et al.[23]	Instrument validation
Ejlertsson et al.[24]	Duplicate publication

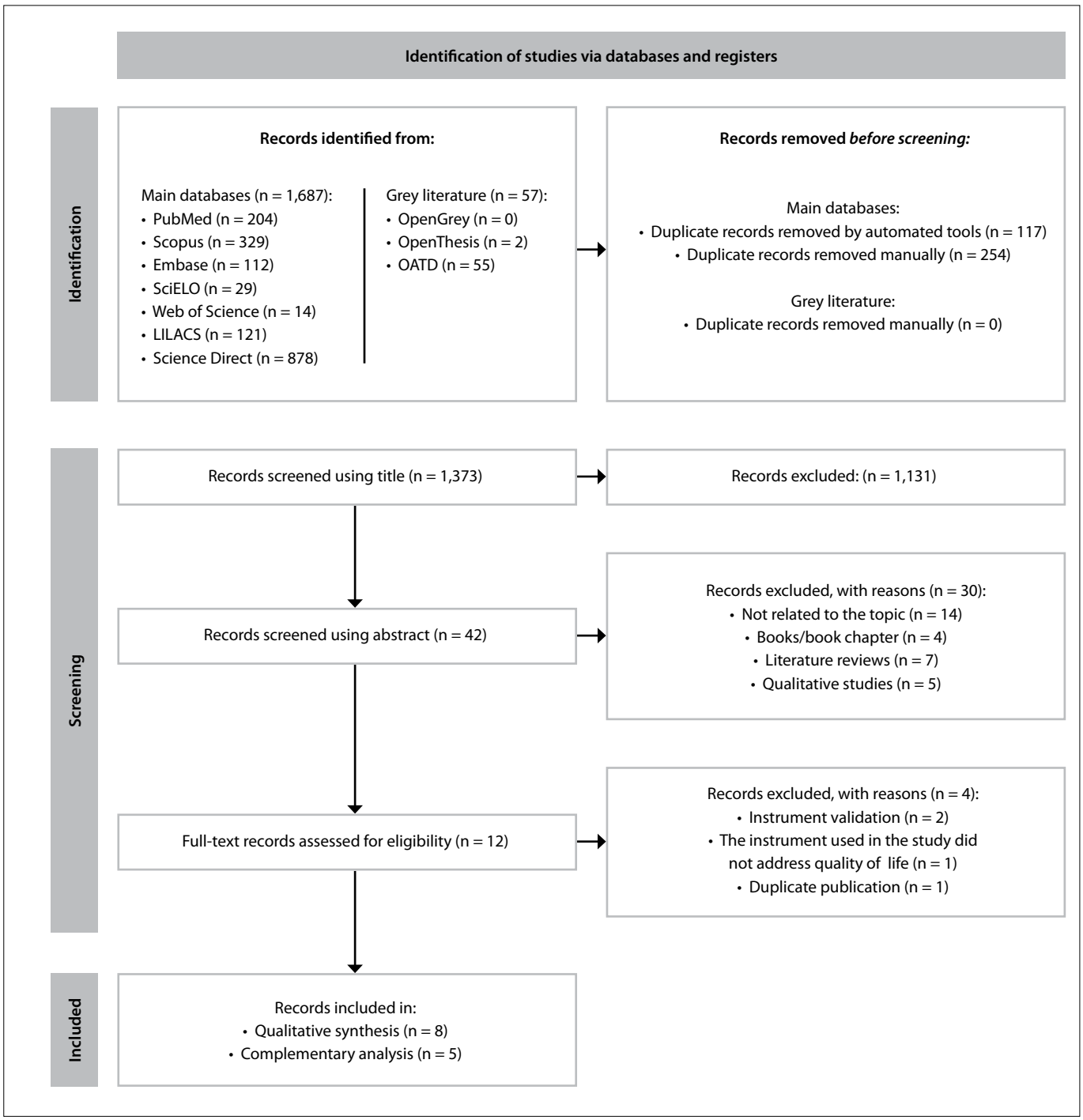

Figure 1. Flowchart of the literature search and selection process adapted from the PRISMA statement.

Characteristics of eligible studies

The eligible studies were published between 2007 and 2018.[26-33] The total sample included 1358 questionnaires answered by Family Health Strategy workers. Their average age ranged from 28 to 33 years (**Table 3**).[26,33] All eight studies had been approved by ethics committees and the workers had signed an informed consent statement. The category of workers with the highest number of participants was community health workers (n = 557), but nurses (n = 180) and physicians (n = 162) also answered the questionnaires. All of the studies were conducted using questionnaires. Five studies[28-31,33] used the WHOQOL-bref protocol, which is a reduced version of the WHOQOL-100 questionnaire, which was used in two studies.[26,32] A single study used Walton's Quality of Work Life scale (Walton's QWL) as the methodology.[27]

Risk of individual bias of the studies

All eight studies presented low risk of bias. The studies by Kluthcovsky et al.,[30] Ursine et al.[33] and Morais et al.[28] obtained positive evaluations in all the criteria analyzed. The studies by Vasconcelos and Costa-Val,[31] Figueiredo et al.,[27] Miranzi et al.,[32] Fernandes et al.[26] and Teles et al.[29] obtained positive evaluations for 80% of their questions. The question assessed as negative in these five studies[26,27,29,31,32] related to the description of study location and subjects (Q2) because the studies did not inform these data, especially concerning study subjects (**Table 4**).

Result measurement and qualitative synthesis

The study by Figueiredo et al.[27] used Walton's QWL, which contains the following domains: adequate and fair compensation,

Table 3. Summary of the main characteristics of the eligible studies

Author	State	Sample size (Total; %F; %M)	Number of questionnaires answered	Professionals assessed	Quality-of-life questionnaire	Other information collected
Kluthcovsky et al.[30]	Paraná	169; 89.3%; 10.6%	169	Community health workers	WHOQOL-bref	Not informed
Vasconcelos and Costa-Val.[31]	Minas Gerais	60; 96.7%; 3.3%	60	Community health workers	WHOQOL-bref	Socioeconomic data
Figueiredo et al.[27]	São Paulo	42; 100%; 0%	42	Community health workers	Walton's QWL perception scale	Not informed
Miranzi et al.[32]	Minas Gerais	77; 54.8%; 45.2%	73	Physicians	WHOQOL-100	Additional questionnaire
Ursine et al.[33]	Paraná	77; 86.3%; 13.7%	73	Community health workers	WHOQOL-bref	Sociodemographic data
Fernandes et al.[26]	Minas Gerais	113; 92.2%; 7.8%	90	Nurses	WHOQOL-100	Sociodemographic data
Teles et al.[29]	Minas Gerais	797; 79.9%; 20.3%	762	Physicians, nurses, dentists, nursing technicians, oral health technicians and assistants, and community health workers	WHOQOL-bref	Sociodemographic and work data
Morais et al.[28]	Minas Gerais	122; 71.9%; 28.1%	89	Physicians	WHOQOL-bref	Sociodemographic work data and burnout questionnaire

F = female; M = male; WHOQOL = World Health Organization Quality of Life instrument; QWL = quality of work life.

Table 4. Risk of bias assessed using the JBI critical assessment tool for systematic reviews, cross-sectional studies version[22]

Author	1	2	3	4	5	6	7	8	% Yes	Risk
Kluthcovsky et al.[30]	√	√	NA	√	NA	NA	√	√	100	Low
Vasconcelos and Costa-Val.[31]	√	--	NA	√	NA	NA	√	√	80	Low
Figueiredo et al.[27]	√	--	NA	√	NA	NA	√	√	80	Low
Miranzi et al.[32]	√	--	NA	√	NA	NA	√	√	80	Low
Ursine et al.[33]	√	√	NA	√	NA	NA	√	√	100	Low
Fernandes et al.[26]	√	--	NA	√	NA	NA	√	√	80	Low
Teles et al.[29]	√	--	NA	√	NA	NA	√	√	80	Low
Morais et al.[28]	√	√	NA	√	NA	NA	√	√	100	Low

1) Were the inclusion criteria in the sample clearly defined?; 2) Were the study subjects and scenario described in detail?; 3) Was exposure measured in a valid and reliable way?; 4) Were objective standard criteria used to measure the condition?; 5) Were confounding factors identified?; 6) Were the strategies to manage confounding factors informed?; 7) Were the results measured in a valid and reliable way?; 8) Was an adequate statistical analysis used?. √ = yes; -- = no; NA = not applicable.

working conditions, work capacities, work opportunity, social integration, respect for workplace laws, working life space and social relevance.[34] These authors[27] observed that the mean overall QWL score was 6.72 points, and fair compensation and working conditions were the domains most affected.

Table 5[26,30-33] presents the results from extraction of the overall quality-of-life scores and the values obtained for each of the dimensions of the WHOQOL-bref and WHOQOL-100 questionnaires. Although these instruments were used in the studies by Teles et al.[29] and Morais et al.,[28] their data were not included in **Table 5** because they were presented as percentages measured in the quality-of-life domains. The study by Teles et al.[29] focused on assessing the results among professionals with low quality of life, and an overall score of 6.72 was obtained. These authors indicated that community health workers had moderate quality of life. Morais et al.[28] observed that physicians presented unsatisfying quality of life in the physical, social and environmental domains and an overall score of 14.5 ± 2.2.

Complementary statistical analysis

Only five studies[26,30-33] presented sufficient mean and standard deviation data for the complementary analysis. Three studies that were included in the descriptive synthesis[27-29] were not included in this stage for the following reasons: one study used a different instrument,[27] another study presented data on workers with low quality of life[29] and another study described its data in a manner that prevented grouping in the complementary analysis.[28]

Figure 2A shows the quality-of-life scores reported in the eligible studies based on the WHOQOL-bref questionnaire. Through estimating weighted means according to sample sizes, it was found that the total quality-of-life score from the WHOQOL-bref questionnaire was 71.74 (SD = 3.27). The environmental domain was the most affected (mean = 56.12; SD = 2.33), followed by the psychological (mean = 73.79; SD = 1.51), social relationships (mean = 75.00; SD = 2.03) and physical health domains (mean = 75.86; SD = 3.46).

Figure 2B presents the quality-of-life scores reported in the eligible studies based on the WHOQOL-100 questionnaire. Through estimating weighted means according to sample size, it was observed that the physical domain was the most affected (mean = 14.29; SD = 0.21), followed by the environmental (mean = 14.32; SD = 0.31), psychological (mean = 15.36; SD = 0.04), social relationship (mean = 15.92; SD = 0.31), spiritual (mean = 16.74; SD = 0.06) and level of independence domains (mean = 17.07; SD = 0.08).

DISCUSSION

This systematic review aimed to identify the levels of quality of life among Family Health Strategy workers. The studies included mainly used the instruments developed by the World Health Organization (WHOQOL-100 and WHOQOL-bref). It was seen

Table 5. Summary of the main results from the eligible studies included in the complementary analysis

Author	Overall quality of life	Dimensions assessed	Results	Main conclusions
Kluthcovsky et al.[30]	69.6 ± 14.5	Physical Social Environmental Psychological	74.2 ± 13.2 75.8 ± 14.2 54.1 ± 12.0 74 ± 11.4	The sociodemographic variables and the domains did not fully explain the variance in quality of life.
Vasconcelos and Costa-Val[31]	3.98 ± 0.65	Physical Social Psychological Environmental	82.8 ± 12 77 ± 18 76 ± 12.7 59.5 ± 12.5	The study presented negative results only for the environmental dimension.
Miranzi et al.[32]	Not informed	Physical Psychological Level of social dependence Environmental Spiritual	14.53 ± 2.35 15.32 ± 2.34 17.16 ± 1.95 15.67 ± 2.24 14.47 ± 1.76 16.67 ± 3.23	The worst results were found in the physical and environmental domains. The main complaints from the participants were lack of bonding, insecurity in the workplace, number of employment links and wages.
Ursine et al.[33]	76.7 ± 13.4	Physical Social Psychological Environmental	74 ± 12.3 71.5 ± 16.7 71.5 ± 13.6 58.0 ± 11.4	The environmental domain presented intermediate results, while the others showed positive results.
Fernandes et al.[26]	16.7 ± 2.2	Physical Psychological Level of social dependence Environmental Spiritual	14.1 ± 1.9 15.4 ± 2.0 17.0 ± 1.6 16.2 ± 2.1 14.2 ± 1.9 16.8 ± 2.6	The results of the questionnaire showed little or no negative impact on the domains.

that graduate professionals and community health workers were affected differently regarding the quality-of-life domains. Most studies using WHOQOL-bref to investigate the quality of life of community health workers showed that the environmental dimension was the one most affected. However, the studies using WHOQOL-100 also included physicians and nurses, and indicated that the physical dimension was the one most affected.

The environmental dimension, which was most affected among community health workers, relates to freedom, safety, financial resources, access to health, social support, recreation, transportation and environmental quality.[35] The qualitative studies by Souza and Freitas[36] and Almeida, Peres and Fonseca[37] corroborated this result, thus showing that community health workers felt unsafe when working with families because they were exposed to urban violence without any type of protection against this reality, which was present in several regions.

There was also a feeling of insecurity and uncertainty regarding the job, which was observed by Souza and Freitas[36] and Figueiredo et al.,[27] which helps to understand the low level of the environmental domain among community health workers. Another important factor in understanding the environmental dimension as the one most affected among community health workers is income (or availability of financial resources). The remuneration of community workers is the lowest among family health professionals[38] and their monthly income may be considered to be close to[38] or below[39] the average wage reality of Brazilians, varying according to the region of the country. Therefore, considering that exposure to violence is an occupational risk for community health workers,[38] these professionals should receive compensatory payment (hazard pay). Although this measurement does not have any direct impact on the quality of life, it may contribute to the remuneration for the work performed by this professional category. Another strategy for improvement of community health workers' quality of life would be for their home visits to be made in pairs.

For physicians and nurses, the physical dimension presented the worst results. This dimension refers to pain, discomfort, sleep quality, fatigue, medication dependence and the ability to work.[35] Physicians and nurses are the professionals working in primary healthcare among whom the highest number of studies on work burnout have been conducted.[40] Compared with other primary healthcare professionals, they present the highest work stress.[42] There is high prevalence of work burnout among graduate professionals.[40,42] Silva et al.[42] indicated that the prevalence of burnout was 64% and the prevalence of inability to work was 32% among nurses, physicians, dentists and social workers. Lima, Farah and Teixeira[40] studied physicians, nurses and dentists working in the Family Health Strategy in a large city in the state of Minas Gerais, Brazil, and found that more than half of the professionals presented burnout syndrome.

The studies included in this systematic review used different instruments to assess the quality of working life, from unspecific ones (WHOQOL-100 and WHOQOL-bref) to a specific instrument for the work environment (Walton's QWL). Regarding the unspecific instruments included in this systematic review, it is worth noting that both were developed by the same group of researchers: WHOQOL-bref is the short version of WHOQOL-100.[35] The authors of these instruments suggested that both are effective in assessing quality of life within the concept determined by the World Health Organization, but that the short version would be indicated for assessing work routines in epidemiological studies.[35]

The existence of several instruments lies within the very essence of the concept of quality of life: polysemic, imperfect and dynamic.[43] The specific instrument used by Figueiredo et al.[27] (Walton's QWL) comes from the conception of work-related quality of life that has been observed within a context of labor movements towards more legal certainty in the workplace, better working conditions and adequate remuneration.[34] However, the creation of this concept, and consequently the instrument, was linked to a historical and cultural particularity of a region, with constant updates and new propositions for the concept of work-related quality of life.[44]

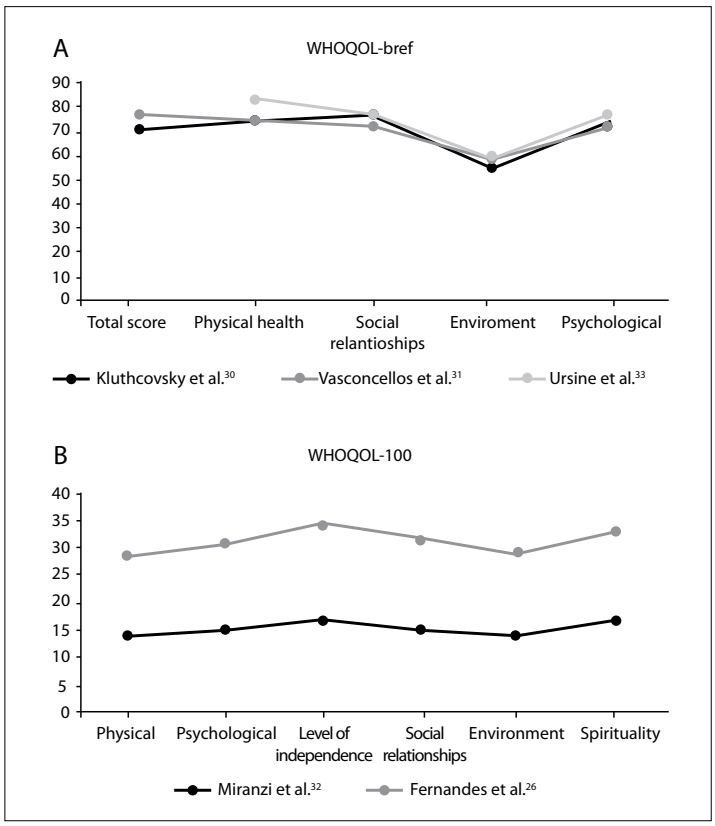

Figure 2. A) Levels of quality-of-life domains reported in the eligible studies based on the World Health Organization Quality of Life (WHOQOL)-bref questionnaire; B) Levels of quality-of-life domains reported in the eligible studies based on the WHOQOL-100 questionnaire.

Therefore, the systematic review and meta-synthesis by Pennisi et al.[45] indicated that assessing the quality of life of Family Health Strategy professionals should include the following factors: working conditions, work processes, interpersonal relationships, personal aspects, work context, work overload and autonomy.

This study is not free from limitations. The first of them related to the heterogeneity observed in the eligible studies, caused by the use of different questionnaires to assess the quality of life (WHOQOL-bref, WHOQOL-100 and Walton's QWL), as previously discussed. Moreover, the results were presented differently (percentages or means and standard deviations), which prevented inclusion of a greater number of studies in the complementary analysis. Another limitation was that the studies were directed towards different professionals, who present professional and social particularities. Lastly, there was an important difference in the number of questionnaires answered in each study, ranging from 42 to 762, which may explain the heterogeneity in the findings. Thus, although the results obtained are consistent, they should be analyzed carefully and further studies are required, in order to assess the true impact of the working conditions of Family Health Strategy professionals on their quality of life.

CONCLUSION

Quality-of-life domains are affected differently among primary healthcare professionals working in family health teams. While physicians and nurses are more affected in the physical domain, community health workers are affected in the environmental domain. This shows that actions in favor of the quality of life of family health professionals cannot be standardized, but the particularities of each professional category must be considered.

Another important factor is the influence of the region covered by the family health team on the quality of life of community health workers. There is an important paradox in considering this relationship and the promotion of quality of life for this professional category because the region is itself the workplace of community health workers, but is also the main factor responsible for interfering with their quality of life.

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Prevalence of burnout and predictive factors among oncology nursing professionals: a cross-sectional study

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Cancer.
Quality of life for professionals.

ABSTRACT

BACKGROUND: Burnout is a syndrome that mostly affects professionals working in contact with patients and their caregivers. In oncology care, nursing professionals are constantly required to provide emotional support for patients and their caregivers, throughout the process of becoming ill, suffering and dying.

OBJECTIVE: To evaluate the prevalence and factors associated with burnout in a sample of nursing professionals at a cancer hospital.

DESIGN AND SETTING: Cross-sectional study conducted at Hospital de Câncer de Barretos.

METHODS: The study population comprised 655 nursing professionals. Burnout syndrome was assessed using the Maslach Burnout Inventory Human Service Survey. Univariate analysis and binary logistic regression models were used to identify independent predictors associated with burnout.

RESULTS: Among 304 nursing professionals included in the study, 27 (8.9%) were classified as presenting burnout according to the two-dimensional criteria, and four (1.3%) were classified based on the three-dimensional criteria. Workplace characteristics were not associated with burnout, while single marital status (odds ratio, OR = 2.695; P = 0.037), perceived workplace stressors, such as impatience with colleagues (OR = 3.996; P = 0.007) and melancholy (OR = 2.840; P = 0.021) were considered to be predictors of burnout. Nursing professionals who would choose the profession again (OR = 0.214; P = 0.001) were least likely to present burnout.

CONCLUSION: Perceived workplace stressors are strongly associated with burnout. Strategies focusing on restructuring of daily work processes and on activities that stimulate positive relationships are important for professionals' health because motivation to continue working in oncology nursing has a protective effect against burnout.

INTRODUCTION

Oncological nursing is a specialty that can be characterized by constant exhaustion, especially emotional, due to the serious nature of cancer and the patient care profile. Nursing professionals within this specialty address patient suffering and death and perform the functions of encouraging and supporting family caregivers.[1,2]

In addition, these professionals' practice can entail work overload, while maintaining institutional norms aimed at humanization and quality work. These factors require a high level of commitment from professionals and can lead to unsatisfactory interpersonal relationships in the work environment. All of these factors may cause professionals to develop burnout syndrome.[1-3]

Burnout syndrome is multifactorial and presents three distinct dimensions, defined as (1) emotional exhaustion (the basic dimension of individual stress, which causes professionals to feel overloaded and exhausted); (2) depersonalization (insensitivity or cynicism toward coworkers and patients); and (3) reduction of personal accomplishment (characterized by a sense of unproductiveness, lack of professional accomplishment and feelings of incompetence).[4-7]

Studies have shown that professionals and students in the field of healthcare have burnout levels that can be considered high in relation to those of other professions.[8-11] A previous study by our research group found that 58.1% of physicians who work in oncology had two-dimensional burnout.[10] In another study, we found that 44.9% of medical students also had levels compatible with two-dimensional burnout.[9]

Specifically, in nursing, a study conducted among nurses at six cancer centers showed that emotional exhaustion from burnout was present in more than 60%, while depersonalization was

present in 28.2%. The study also found that the difficulty that these professionals had in helping patients cope with their illnesses was correlated with the burnout dimensions.[12]

Several studies have suggested that many oncology nurses present burnout or are at risk of this.[13-18] These professionals are part of a specialty that has been recognized as the main clinical area that is exposed to emotional labor.[18] Thus, it can be said that burnout is a matter of worldwide concern, which indicates that there is a need to improve the working conditions of professionals so that they can perform their functions with satisfaction, have good interpersonal relationships and consequently increase their productivity.

In addition, oncology nursing assists cancer patients and their families at all stages starting from diagnosis, including treatment, rehabilitation, dying, death and post-death. These professionals' overburden of work is generated through the complexity and subtypes of the disease and the extension of care to the psychosocial environment. Therefore, understanding the factors associated with high levels of burnout among these professionals forms an essential component of healthcare practice in a philanthropic humanized hospital in a middle-income country.

OBJECTIVE

The objective of this study was to evaluate the burnout levels of oncological nursing professionals and identify the factors that are related to burnout syndrome.

METHODS

Place of study

The Hospital de Câncer de Barretos (HCB), located in the city of Barretos, São Paulo, Brazil, is a public institution that is recognized as a national reference center for cancer treatment. Its hospital attends approximately 6,000 cancer patients daily, from all 27 Brazilian states, through the Brazilian National Health System, which guarantees full, universal and free access for the country's population.[19] It is a care, teaching and research institution and has three oncological units, for provision of various specialties for children, adults and elderly patients (Unit I), for children and adolescents (Children's Unit) and for palliative care (Unit II). These three units have a total of 226 hospital beds, a multiprofessional team and both inpatient and outpatient services.

Ethical aspects

This study was performed in accordance with the regulations of the Brazilian National Health Council (Conselho Nacional de Saúde Brasileiro), under its resolution no. 466/212, and was approved by the Research Ethics Committee of HCB (CEP/HCB no. 1.885.901; January 7, 2017). Nurses who voluntarily agreed to participate in the study provided their consent in writing.

Study design

A descriptive cross-sectional study was conducted between June 2017 and September 2018.

Study population and sample size

Nursing assistants, nurses and nursing coordinators working in Units I and II were included. Professionals who had been hired less than three months prior to the study were excluded.

In accordance with practices in Brazil and at the study site, nursing assistants are professionals with a technical level of education who are responsible for maintaining the patient's hygiene, checking vital signs and administering medications. While nurses provide care directly to patients, plan the assistance and perform medium and high-complexity procedures, nursing coordinators do not have direct contact with patients. The latter are responsible for the bureaucratic and organizational functions of the staff and department.

The study population was composed of nursing assistants, nurses and nursing coordinators from among the total of 655 nursing professionals working in the oncology units (Unit I and Unit II).

Procedures

Initially, informational posters about the research project were posted at strategic points in the oncology units to alert nursing professionals to the research event. Subsequently, the researchers invited all nursing assistants, nurses and nursing coordinators to participate in the study and attend meetings that were scheduled during work shifts in the outpatient, radiology, hospitalization, research and palliative care departments. At these meetings, the study was presented, questions were answered and all nursing professionals who were present were invited to participate in the study. At that time, those who agreed to participate in the study provided written consent and received the study questionnaires to answer. The evaluation questionnaires for this study were completed individually and confidentially by each person who had agreed to participate.

Data collection

The following types of data were collected through the evaluation questionnaire:

- Sociodemographic data – age, gender, marital status, children, school education and other professional activity;
- Data on the professionals' state of health – health problems and the professionals' views of their own health, their own personality and whether they were a happy or unhappy person;
- Data on workplace characteristics – function, time of work, department, time dedicated to direct patient care and whether the work routine was exhausting;

- Data on activities outside of work – family meetings, leisure activities, physical activity, religion and influence of spirituality on work;
- Data on perceived workplace stressors – lack of recognition by the hospital, patients or relatives, difficulties in relationships among the nursing team or with multidisciplinary team members, excessive work, lack of time to perform other work activities, lack of resources for appropriate treatment of patients, institutional rules, lack of knowledge about the strategic planning of the hospital, lack of autonomy at work, constantly dealing with incurable and/or severe diseases, and feelings and symptoms in the work environment;
- Data on professional considerations – happiness with the professional activity, satisfaction with financial achievements, ability to perform professionally, feelings of importance to patients or coworkers, whether the individual would choose to be a nurse professional again, and satisfaction with professional evolution;
- The Maslach Burnout Inventory Human Services Survey (MBI-HSS) – This consists of 22 items that are answered using a seven-point Likert scale. Out of the total of 22 items, nine evaluate emotional exhaustion (EE domain; scored as low = 0-16; moderate = 17-26; high ≥ 27), five evaluate depersonalization (DP; low = 0-6; moderate = 7-12; high ≥ 13) and eight evaluate personal accomplishment (PA, low = 0-31; moderate = 32-38; high ≥ 39). The low, moderate and high scores for each dimension of burnout were obtained by summing the scores of the items in each dimension.[20,21] The bidimensional criterion (high EE and DP scores) and the three-dimensional criterion (high EE and DP scores and low PA score) were used to identify burnout.[22]

The version of the MBI-HSS used in this study had previously been validated and adapted for use in the Portuguese language.[20] The right to use this instrument was purchased from and authorized by Mind Garden, as described on the website http://www.mindgarden.com/.

The instruments used in the study were self-administered in paper format and were completed by the participants in an average of 20 minutes.

Data analysis

The study population was characterized using frequency tables for qualitative variables and means and standard deviations for quantitative variables. Comparisons were made using the non-parametric Mann-Whitney test for continuous variables and the Pearson chi-square test or Fisher's exact test for categorical variables. To identify independent predictors associated with burnout, variables with a P-value < 0.2 obtained in the univariate analysis were included in the binary logistic regression model. To compose the final model, we selected variables with a P-value < 0.05 (stepwise regression, Wald test). The IBM-SPSS software, version 21.0 (IBM Corp., Armonk, New York, United States) was used for statistical analysis, and the significance level was taken to be 0.05.

Missing values in the MBI-HSS were imputed by calculating the average of the responses for each item. Out of the total number of participants, 24 (7.9%) had at least one missing item in the MBI-HSS, and data allocation was used in these situations.

RESULTS

Sample description

Among the 655 nursing professionals potentially eligible to be invited to participate in the study , 11 (1.67%) did not agree to participate in the study, 139 (21.2%) were not approached for the study because they were absent from the department at the time of the meeting, 126 (19.2%) were unavailable on the date and at the time of the meeting and 74 (11.3%) were not included because they were participating in another study using the MBI-HSS instrument.

Thus, the response rate was 46.5%, i.e. 305 nursing professionals were included in this study. However, one participant did not respond to any item of the MBI-HSS and therefore was not included in the analyses relating to burnout.

Demographic profile

The final sample of 305 nursing professionals consisted of 207 (67.9%) nurse assistants, 72 (23.6%) nurses and 26 (8.5%) nurse coordinators. The mean age was 36.0 years (standard deviation, SD = 9.1), and the mean duration of employment at the institution was 92.5 months. For 200 nursing professionals (67.1%), the daily work time dedicated to direct patient care was greater than 75%. In total, 279 (91.5%) of the participants were women, 184 (60.5%) were married or living as married and 192 (63.0%) had children; 193 (63.3%), 44 (14.4%) and 68 (22.3%) had technical, undergraduate education and postgraduate education levels, respectively (**Table 1**).

Burnout scores and prevalence

In total, 27 (8.9%) of the nursing professionals were identified as having two-dimensional burnout (high EE + high DP), and 4 (1.3%) were identified as having three-dimensional burnout (high EE + high DP + low PA).

The scores for each dimension of burnout (EE, DP and PA) were categorized as low, moderate or high. Based on this categorization, high, moderate and low EE were present in 42.1%, 26.6% and 31.2% of the sample, respectively. High DP was present in 11.2%, and moderate

and low DP in 25.3% and 63.5% respectively. For the dimension of PA, 11.8%, 22.7% and 65.5% of the sample presented low, moderate and high scores (**Figure 1**). The mean (with SD) burnout scores were 23.8 (12.1) for EE, 5.8 (5.5) for DP and 39.3 (7.2) for PA.

Factors associated with bidimensional burnout

Table 2 shows that having children (65.0% versus 44.4%; P = 0.039) and considering oneself happy (77.8% versus 55.6%; P = 0.017), along with the majority of the professional consideration variables, were associated with low burnout.

Regarding workplace characteristics, no statistically significant association with burnout was observed. In evaluating the presence of perceived workplace stressors, there was higher prevalence of burnout related to lack of recognition by the hospital (P = 0.006), difficulties in relationships among the nursing team (P = 0.001) and lack of recognition by patients or their relatives (P = 0.004). In addition, the professionals who reported feeling the following, due to the work process, were more susceptible to burnout: sad or anxious (40.7%; P = 0.004); discouraged (63%; P = 0.006); unempathetic with patients (11.1%; P = 0.010); impatient with colleagues (33.3%; P = 0.001); unmotivated (66.7%; P < 0.001); not valued (48.1%; P = 0.029); treated without humanization (18.5%; P = 0.034); that their superiors or colleagues were uninterested in their opinions (25.9%; P = 0.008); professionally impotent (51.9%; P = 0.019); or melancholy (48.1%; P = 0.003) (**Table 2**).

Table 1. Sociodemographic characteristics of nursing professionals working in oncology at a cancer hospital in Brazil (n = 305)

Variables	n (%)
Age	
Years, mean (SD)	36.0 (9.1)
Gender	
Female	279 (91.5)
Male	26 (8.5)
Marital status	
Married/living as married	184 (60.5)
Single	88 (28.9)
Separated/divorced/widowed	32 (10.5)
Children	
Yes	192 (63.0)
No	113 (37.0)
Educational level	
Technical	193 (63.3)
Graduate	44 (14.4)
Postgraduate	68 (22.3)
Department	
Outpatient	93 (30.8)
Hospitalization	85 (28.1)
Palliative care	56 (18.5)
Radiology	46 (15.2)
Research	22 (7.3)
Function	
Nursing assistants	207 (67.9)
Nurses	72 (23.6)
Nursing coordinators	26 (8.5)
Length of time working at the institution	
Months, mean (SD)	92.5 (68.2)
Percentage of time dedicated to direct patient care	
> 75% of working time	200 (67.1)
25%-75% of working time	61 (20.5)
< 25% of working time	37 (12.4)

Hours of daily work for nursing professionals (n = 305; 100%): 7 to 12 hours. SD = standard deviation.

Multivariate analyses

The adjusted multivariate model showed that the nursing professionals who would choose to enter the nursing profession again (odds ratio, OR = 0.214; P = 0.001) had a lower probability of being diagnosed with burnout. In contrast, feeling impatient with colleagues (OR = 3.996; P = 0.007) or melancholy (OR = 2.840; P = 0.021) and being single (OR = 2.695; P = 0.037) were independently associated with a greater likelihood of burnout (**Table 3**).

DISCUSSION

This study evaluated the prevalence of burnout among active oncology nurses at a Brazilian hospital and the potential factors related to the syndrome. Approximately 9% and 1.3% of the participants presented two-dimensional and three-dimensional burnout, respectively. Impatience with colleagues, melancholy and being single were the factors related to greater risk of burnout syndrome. Furthermore, we found that the participants who reported that they would choose to enter the nursing profession again presented lower risk of burnout.

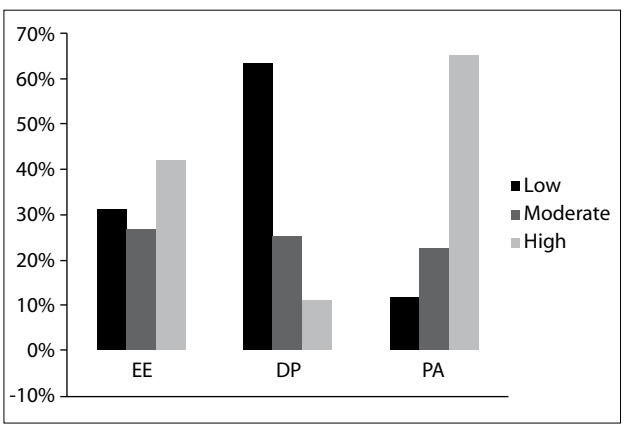

Figure 1. Burnout prevalence rate (%) among nursing professionals, in the different burnout domains and score categories. EE: emotional exhaustion; DP: depersonalization; PA: personal accomplishment. The scores are represented in columns of different shades: black, low levels; dark gray, moderate levels; light gray, high levels.

Table 2. Variables associated with two-dimensional burnout in a sample of nursing professionals working in oncology at a cancer hospital in Brazil (n = 304)

Variable		Burnout		P-value
		No n (%)	Yes n (%)	
Participant characteristics				
Age in years median (minimum-maximum)		35 (20-72)	32 (21-50)	0.163**
Gender	**Female**	254 (91.7)	24 (88.9%)	0.715*
	Male	23 (8.3)	3 (11.1)	
Marital status	**Married/living as married**	173 (62.7)	11 (40.7)	0.090*
	Separated/divorced/widowed	29 (10.5)	3 (11.1)	
	Single	74 (26.8)	13 (48.1)	
Children	**No**	97 (35.0)	15 (55.6)	0.039
	Yes	180 (65.0)	12 (44.4)	
Educational level	**Technical**	175 (63.2)	17 (63.0)	0.839
	Graduate	41 (14.8)	3 (11.1)	
	Postgraduate	61 (22.0)	7 (25.9)	
Other professional activity	**No**	240 (87.3)	25 (92.6)	0.551*
	Yes	35 (12.7)	2 (7.4)	
Health problems	**Not applicable**	185 (67.5)	14 (51.9)	0.134
	Yes	89 (32.5)	13 (48.1)	
How do you consider your health?	**Bad**	64 (23.4)	10 (37.0)	0.158
	Good	209 (76.6)	17 (63.0)	
How do you consider your personality?	**Pessimistic**	77 (27.9)	10 (38.5)	0.263
	Optimistic	199 (72.1)	16 (61.5)	
Do you consider yourself a happy or unhappy person?	**Unhappy**	61 (22.2)	12 (44.4)	0.017
	Happy	214 (77.8)	15 (55.6)	
Workplace characteristics				
Function	Nursing assistants	187 (67.5)	19 (70.4)	1.000
	Nurses	66 (23.8)	6 (22.2)	
	Nursing coordinators	24 (8.7)	2 (7.4)	
Number of months working at the hospital (median (minimum-maximum))		72 (4-360)	72 (8-192)	0.471**
Department	**Outpatient**	84 (30.7)	9 (33.3)	0.105*
	Radiology	44 (16.1)	2 (7.4)	
	Hospitalization	72 (26.3)	13 (48.1)	
	Clinical research	22 (8.0)	0 (0.0)	
	Palliative care	52 (19.0)	3 (11.1)	
Percentage of time dedicated to direct patient care	**< 25%**	35 (12.9)	2 (7.7)	0.552
	25%-75%	57 (21.0)	4 (15.4)	
	> 75%	179 (66.1)	20 (76.9)	
Work routine	**Not exhausting**	25 (9.0)	1 (3.7)	0.490*
	Exhausting	252 (91.0)	26 (96.3)	
Perceived workplace stressors (no versus **yes)**				
Lack of recognition by the hospital		89 (32.1)	16 (59.3)	0.006
Lack of recognition by patients or relatives		25 (9.0)	8 (29.6)	0.004*
Difficulties in relationships among the nursing team		50 (18.1)	13 (48.1)	0.001
Difficulties in relationships with multidisciplinary team members		11 (4.0)	5 (18.5)	0.008*
Excessive work		122 (44.0)	19 (70.4)	0.014
Lack of time to perform other work activities		73 (26.4)	9 (33.3)	0.496
Lack of resources for appropriate treatment of patients		4 (1.4)	1 (3.7)	0.374*
Institutional rules		20 (7.2)	5 (18.5)	0.057*
Lack of knowledge about the strategic planning of the hospital		12 (4.3)	1 (3.7)	1.000*
Lack of autonomy at work		6 (2.2)	1 (3.7)	0.482*
Constantly dealing with incurable and/or severe diseases		51 (18.4)	7 (25.9)	0.440

Continue...

Table 2. Continuation.

Variable		Burnout		P-value
		No n (%)	Yes n (%)	
Feelings at work	Sad/anxious	45 (16.2)	11 (40.7)	0.004*
	Discouraged	96 (34.7)	17 (63.0)	0.006
	No empathy with patients	3 (1.1)	3 (11.1)	0.010*
	Impatience with colleagues	26 (9.4)	9 (33.3)	0.001*
	Not respected	22 (7.9)	3 (11.1)	0.475*
	Unmotivated	79 (28.5)	18 (66.7)	< 0.001
	Not valued	76 (27.4)	13 (48.1)	0.029
	Not encouraged to improve as a professional	36 (13.0)	7 (25.9)	0.081*
	Dehumanized	17 (6.1)	5 (18.5)	0.034*
	Lack of interest from superiors or colleagues about the nurse's opinions	22 (7.9)	7 (25.9)	0.008*
	Lack of interest from superiors or colleagues in relation to their professional capacity	25 (9.0)	4 (14.8)	0.307*
Symptoms in the work environment	Dizziness	121 (43.7)	14 (51.9)	0.425
	Tachycardia	118 (42.6)	13 (48.1)	0.578
	Tachypnea	13 (4.7)	2 (7.4)	0.631*
	Sweating	55 (19.9)	7 (25.9)	0.618
	Frequent headache	130 (46.9)	15 (55.6)	0.425
	Syncope	6 (2.2)	0 (0.0)	1.000*
	Overwhelming desire to cry	124 (44.8)	17 (63.0)	0.104
	Perception of professional impotence	81 (29.2)	14 (51.9)	0.019
	Melancholy	59 (21.3)	13 (48.1)	0.003
Professional considerations				
Happy with the professional activity	Not applicable	82 (29.8)	16 (59.3)	0.003
	Yes	193 (70.2)	11 (40.7)	
Satisfied with financial achievements	Not applicable	144 (52.2)	20 (74.1)	0.042
	Yes	132 (47.8)	7 (25.9)	
Able to perform professionally	Not applicable	66 (24.2)	13 (48.1)	0.011
	Yes	207 (75.8)	14 (51.9)	
Importance to patients	Not applicable	7 (2.5)	3 (12.0)	0.042*
	Yes	268 (97.5)	22 (88.0)	
Importance to coworkers	Not applicable	38 (13.8)	8 (29.6)	0.044*
	Yes	238 (86.2)	19 (70.4)	
Would choose to be a nurse professional again	Not applicable	51 (18.5)	14 (53.8)	< 0.001
	Yes	225 (81.5)	12 (46.2)	
Satisfied with professional evolution	Not applicable	93 (33.7)	13 (50.0)	0.131
	Yes	183 (66.3)	13 (50.0)	
Activities outside of work				
Family meetings	Not applicable	161 (58.1)	22 (81.5)	0.022
	Yes	116 (41.9)	5 (18.5)	
Leisure activities	Not applicable	234 (84.5)	25 (92.6)	0.395*
	Yes	43 (15.5)	1 (7.4)	
Physical activity	Not applicable	182 (65.9)	20 (74.1)	0.522
	Yes	94 (34.1)	7 (25.9)	
Religion	Not applicable	14 (5.1)	1 (3.7)	0.999*
	Yes	263 (94.9)	26 (96.3)	
Influence of spirituality in work	Not applicable	90 (32.8)	9 (33.3)	0.999
	Yes	184 (67.2)	18 (66.7)	

Pearson's chi-square test; *Fisher's exact test; **Mann-Whitney test.

The results shown in the present study have been identified in the worldwide literature.[6,12-18] The high level of burnout among oncology nurses and a growing lack of job satisfaction might negatively affect their quality of life and have an impact on the quality of nursing care and the services to be provided in general.[17,23] A study conducted in hematology and oncology clinics and palliative care units in three different public hospitals in Turkey demonstrated high emotional exhaustion scores among nurses who perceived that their interpersonal relationships were bad and who were not satisfied with workplace. Their emotional exhaustion was higher than that of nurses who were satisfied. In addition, a positive correlation between job satisfaction scores and personal accomplishment scores was identified.[17]

The results from that study in Turkey by Yıldırım and Kocatepe[17] supported the notion that burnout decreases as job satisfaction increases. Furthermore, this can be interpreted as denoting that emotional exhaustion is the most important component of burnout status. In this context, the present study showed that approximately 42% and 27% of the sample had high and moderate EE, respectively. It is noteworthy that Brazilian oncological nurses are more exhausted, considering that EE is the main cause and the initial symptom of burnout syndrome. However, this finding contradicts the data from a quantitative, observational, cross-sectional multicenter study that was conducted in Spain among oncology nurses. A total of 101 oncology nurses were included and 19.2% and 38.4% were found to have high and moderate EE, respectively. Another important finding was that high DP was more prevalent in Spain (21.1%) than in Brazil (11.2%). Low PA was evident in 65.5% of the sample of the present study and in 45.5% of the Spanish professionals, thus showing that there were lower levels of personal fulfillment among the Brazilian nurses.[24]

A meta-analysis study included a total sample of 9,959 nurses from oncology services. The prevalence of EE was 30% and that of low PA was 35%. Thus, the presence and risk of burnout among these employees worldwide are considerable. This needs to be identified and institutional measures need to be implemented to prevent associated conditions.[25]

Factors that have been correlated with two-dimensional burnout were mostly present in the workplace. For example, there was a lack of recognition of nurses' work among patients or family members (P = 0.004). Healthcare professionals dedicate considerable time to integral care of patients and their relatives, especially in place of study.

The main philosophy of nursing is humanized care, according to one of the guidelines of the Brazilian National Health System. However, humanized care and attention has been a one-way street from professionals to patients, and professionals do not always receive the attention and care that they should. Another factor that may contribute to burnout is the professionals' view of their work effort as being for the benefit of patients, often without taking self-care into account, or attention to their limits in relation to work, which leads to psychological distress.[26] This type of stressor, known as overwork, was evident (P = 0.014) in the present study.

The institution's humanization philosophy allows healthcare professionals to have a closer relationship with patients and family members, which can be a protective factor for both patients and workers. On the other hand, this philosophy requires the development of emotional skills to address the emotional excess or burden that results from providing daily care for patients and family caregivers. Thus, nursing professionals are almost always exposed to the stressors of the work environment, which may impair their work-related quality of life.

Oncology is a specialty that requires much from professionals, especially emotionally. This has been identified as the largest clinical field in which nurses are exposed to emotional labor. Nurses in this field are in greater contact with suffering and death than are colleagues in other areas.[18] Constantly coping with serious life-threatening illness generates feelings associated with burnout, such as discouragement (P = 0.006), lack of empathy with patients (P = 0.010), lack of patience with coworkers (P = 0.001), lack of motivation (P < 0.001) and impotence (P = 0.019). Oncology nurses are faced with diseases that generate suffering and that often have an outcome of death. This causes frailty and a feeling of impotence

Table 3. Binary logistic regression analysis on the potential factors associated with two-dimensional burnout (Barretos Cancer Hospital, n = 304)

Burnout				P-value
Variable	Category		OR (95% CI)	
Marital status	Married/living as married		1	------
	Separated/divorced/widowed		2.483 (0.586-10.511)	0.217
	Single		2.695 (1.061-6.844)	0.037
Environmental stressor factors	Impatient with colleagues	No	1	------
		Yes	3.996 (1.470-10.864)	0.007
	Melancholy	No	1	------
		Yes	2.840 (1.168-6.905)	0.021
Daily work variables	I would choose to be a nurse professional again	No	1	------
		Yes	0.214 (0.087-0.526)	0.001

Binary logistic regression analysis. P-value < 0.05. OR = odds ratio; CI = confidence interval.

in professionals, because there is no possibility of reversing the situation.[1] Education and training for dealing with death, and discussion of attitudes towards death, can be a way to decrease the levels of burnout among oncology nurses.[15]

In the binary logistic regression analysis, it could be seen that separated, divorced and widowed individuals (OR = 2.483) and single individuals (OR = 2.695) were more likely to develop burnout than were married individuals. This finding corroborates other studies conducted in Australia and China.[14,27] The emotional support and stability that a family or partner can offer are important protective factors that support mental health and prevent burnout. In addition, it is understood that social support in its different forms is considered predictive of and protective against burnout syndrome.[28]

Another important result from the present study was that relationship difficulties among the nursing team were associated with burnout. In Brazil, nursing is further subdivided into categories. It is a hierarchy, with different positions, functions and salaries. This scenario may not be healthy for relationships among professionals and may cause difficulty and imbalance in the relationships between team members.

The professionals who reported feeling a lack of patience with coworkers (OR = 3.996; P = 0.007) were approximately four times more likely to experience burnout than those who did not report this feeling. One dimension of burnout, i.e. depersonalization, corroborates this finding. The main characteristics of this domain are cynicism and insensitivity toward coworkers, patients and family members, thus indicating that burnout itself leads to a lack of patience with colleagues, which further increases the probability of developing burnout.[5] The feeling of melancholy at work (OR = 2.840) increases the risk of burnout, compared with professionals who do not feel melancholy. It is evident that depression is related to burnout: melancholy is a common feeling among depressive individuals, since it is characterized by mental fatigue.[29]

The professionals were asked whether they would choose to enter the nursing profession again (OR = 0.214), and those who said yes had a lower probability of burnout than those who said no. This finding demonstrates that achievement and job satisfaction are protective factors against burnout.

This study had some limitations. The first was that it was a cross-sectional study, and it was therefore impossible to determine cause-and-effect relationships. The second was that we evaluated work stressors based on the opinions of nursing professionals and did not objectively measure their numbers of appointments or actual working time. However, we believe that perceptions of one's work, and not necessarily the work itself, are more important with regard to the genesis of burnout. Thirdly, the data were based on nursing professionals who were working in a single oncology center, and this may limit the generalizability of our results to other care settings or may not reflect the overall reality of Brazil. Fourthly, the sample consisted mostly of women. Thus, this reflected the demographics of this field, which can be explained by the historical context within which the profession emerged. Although an increasing number of men are entering the profession, women still comprise the majority of nurses in this country. Additionally, the questionnaire that was developed to obtain sociodemographic data relating to nursing professionals' health, perceived stressors in daily work and activities outside of work had not been validated.

CONCLUSIONS

An important number of nursing professionals working in oncology were identified as having possible burnout. The association between perceived workplace stressors and burnout suggested that organizational dynamics had contributed to creation of a stressful work environment that affected these professionals' emotional wellbeing and commitment to the field. In this context, strategies for reorganizing work processes and practices that promote professional interaction, involvement in decision-making and sharing of emotions are relevant for self-management, health promotion and maintenance of care quality.

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Effect of transient obstructive cholestasis on liver histology: a cross-sectional study

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ABSTRACT

BACKGROUND: The role of transient obstructive cholestasis on liver histology remains undetermined.

OBJECTIVE: To investigate whether transient cholestasis impairs liver histology.

DESIGN AND SETTING: Cross-sectional study at a public university hospital (UNICAMP), Brazil.

METHODS: 169 individuals undergoing cholecystectomy, with or without cholestasis. were enrolled. Histopathological findings were correlated with clinical and biochemical characteristics.

RESULTS: Biliary hepatopathy was more frequent in individuals with resolved cholestasis than in those with active obstruction or no jaundice ($P < 0.01$), as also were fibrosis and ductular proliferation ($P = 0.02$). Cholestasis was commoner in individuals with resolved obstruction than in those with no history ($P < 0.01$) or active cholestasis ($P < 0.05$). Biliary hepatopathy was associated with longer duration of cholestasis ($P < 0.001$) and higher bilirubin levels ($P = 0.02$) in individuals with active obstruction; with lower body mass index ($P = 0.02$) and longer cholestasis ($P < 0.001$) in individuals with resolved obstruction; and with longer cholestasis ($P < 0.001$) and longer interval between endoscopic retrograde cholangiopancreatography and surgery ($P = 0.03$) overall. In individuals with active obstruction, duration of cholestasis ($R = 0.7$; $P < 0.001$) and bilirubin levels ($R = 0.6$; $P = 0.004$) were independently correlated with cholestasis severity. Duration of cholestasis ($R = 0.7$; $P < 0.001$) was independently correlated with ductular proliferation severity.

CONCLUSIONS: Transient cholestasis was associated with significant histopathological changes, even after its resolution. Longer duration of obstruction correlated with greater severity of histopathological changes, especially cholestasis and ductular proliferation. This emphasizes the need for early treatment of obstructive cholestasis.

INTRODUCTION

Cholestasis is an impairment of bile formation and/or bile flow that may present with fatigue, pruritus and, in its most suggestive form, jaundice. It can be classified as intrahepatic or extrahepatic.[1-4] It may assume various histological patterns, which present different clinical and diagnostic connotations. The two main patterns, which are canalicular cholestasis and chronic cholestasis, constitute general categories, more suggestive of the progress and degree of cholestasis than of any exact cause. The other two patterns, ductular cholestasis and ductal cholestasis, usually develop within a context of canalicular cholestasis, but are differentiated because of their narrower clinical contexts. Basically, the main histological features observed in cholestasis are occurrences of ductular proliferation and bilirubinostasis.[5] Biliary obstruction is caused by mechanical impairment of bile flow through large ducts, mainly extrahepatic bile ducts. Its structural correspondent is the parenchymal cholestasis with biliary stasis located in zone 3 (perivenular). In cases of incomplete obstruction, a ductular reaction may occur without clear evidence of cholestasis.[6]

Several studies have shown severe consequences of biliary obstruction on liver histology, with changes such as microscopic cholestasis and cholangitis, liver fibrosis and inflammatory changes. Prolonged maintenance may even lead to biliary cirrhosis.[5-7] The vast majority of cases of biliary obstruction are transient, since several treatments can usually be employed to correct the obstructive factor. Treatment may, in most cases, be either surgical or endoscopic. There are cases in which the obstruction resolves spontaneously, such as when small gallstones migrate through the duodenal papilla after a period of obstruction. Commonly, the signs and symptoms of cholestasis cease gradually after the obstructive factor resolves. However, there is no conclusive

evidence regarding the role of transient cholestasis and the duration of obstruction on liver histology.[4-7]

OBJECTIVE

The aims of this study were to investigate whether occurrence of transient cholestasis might lead to significant changes in liver histology and to analyze the influence of the duration of cholestasis on liver histology.

METHODS

Study design

This was a cross-sectional study that enrolled individuals who underwent cholecystectomy at a public tertiary-level university hospital between July 2018 and October 2019. The study protocol was evaluated and approved by the local institutional review board under the reference no. 3.279.991/UNICAMP (CAAE: 10628119.4.0000.5404; date: April 24, 2019). All participants provided informed consent. Liver wedge biopsies were performed on all participants during surgery (cholecystectomy), and samples were collected from hepatic segment III. The findings from histopathological examinations were correlated with the participants' clinical and biochemical characteristics.

Study population

This study included individuals aged 18 years or above, of both genders, who underwent cholecystectomy due to gallbladder disease. The exclusion criteria were the following: past or current history of unrelated biliary liver disease; previous unrelated intervention on the liver or biliary tree; belonging to vulnerable groups; positive serological tests for viral liver disease; past or current use of alcohol or illicit drugs; current or recent use of hepatotoxic drugs or drugs associated with cholestasis; active malignant neoplasm; or incomplete medical records.

The minimum sample size was estimated as 162 individuals, considering an alpha of 0.05, a prevalence proportion of 0.3 and precision of 10%. Out of an initial population of 185 individuals undergoing cholecystectomy, 16 participants were excluded. The causes of exclusion were the following: viral hepatitis (n = 2), liver cirrhosis (n = 3), primary sclerosing cholangitis (n = 1), alcohol use (n = 5), use of hepatotoxic drugs (n = 3) and incomplete medical records (n = 2). Thus, 169 individuals remained included in the study.

Classification into subgroups

The participants were classified according to their clinical histories, laboratory tests and imaging examinations into two large groups: group 1, no clinical cholestasis; and group 2, with a history of clinical cholestasis. Group 2 was subdivided into two other groups: 2A) active cholestasis (clinical history of cholestasis and/or imaging examinations with evidence of obstruction at a date close to surgery and/or ineffective endoscopic retrograde cholangiopancreatography (ERCP) and/or total bilirubin ≥ 2.5 mg/dl); and 2B) resolved cholestasis (clinical history of spontaneously resolved cholestasis and/or imaging examinations with no evidence of obstruction at a date close to surgery and/or effective ERCP and/or total bilirubin < 2.5 mg/dl). The imaging examinations considered in the evaluations included ultrasound scan, computed tomography, endoscopic cholangiography and/or magnetic resonance cholangiography. The participants were then accordingly divided between these groups, as follows: 1 (n = 115); 2 (n = 54); 2A (n = 25); and 2B (n = 29). **Figure 1** shows the flowchart of the study population and the subdivision according to groups.

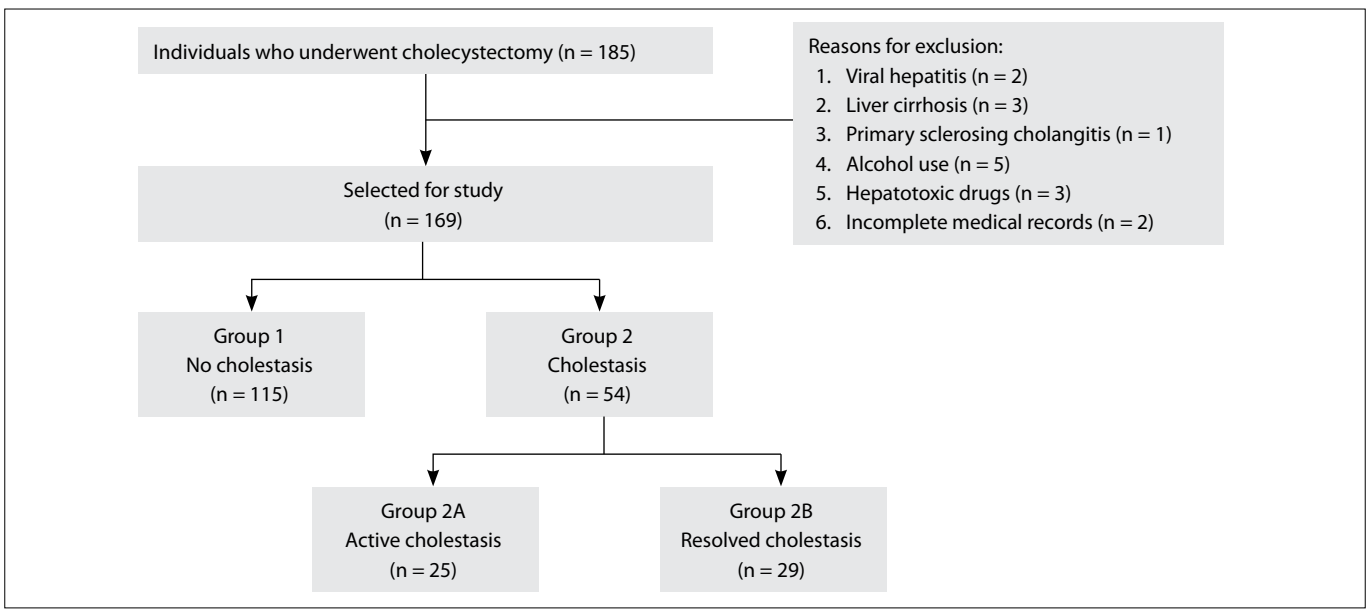

Figure 1. Flowchart of the study population.

Additionally, individuals were divided into groups according to their bilirubin levels (< 3 mg/dl, 3-7 mg/dl or ≥ 7 mg/dl). Those who presented cholestasis were also divided into two groups according to the duration of obstruction (< 15 days or ≥ 15 days).

Variables

The following clinical and demographic variables were analyzed: age (in years); gender (male or female); cholestasis status (active, resolved, overall or no history of cholestasis); endoscopic retrograde cholangiopancreatography (performed or not performed); duration of cholestasis (estimated in days from clinical history information in the medical records); interval between ERCP and surgery (in days); and body mass index (BMI; expressed in kg/m^2).

The following biochemical variables were considered: total bilirubin (in mg/dl); aspartate aminotransferase (AST; in mg/dl); alanine aminotransferase (ALT; in mg/dl); alkaline phosphatase (ALP; in mg/dl); gamma-glutamyl transferase (GGT; in mg/dl); albumin (ALB; in g/dl); and international normalized ratio (INR).

The histopathological variables considered were the present or absence of biliary pattern liver disease and the following specific histological characteristics: fibrosis, ductular proliferation, cholestasis, portal inflammation, steatosis and cholangitis. These characteristics were classified dichotomously as absent or present and were also stratified ordinally according to their degree of severity, as absent (0), mild (1), moderate (2) or severe (3).[5] The histopathological analyses were all performed by the same pathology team and followed the same parameters as defined by Crawford et al.[8]

All specimens were fixed in formalin, embedded in paraffin and sectioned using a microtome at a thickness of 5 µm. Routine specimen processing involved staining the slides with hematoxylin and eosin (15 levels), Masson trichrome (10 levels) and reticulin (5 levels), for a total of 30 levels per specimen. All levels were screened to ensure absence of histological abnormalities.[8]

Statistical analysis

The descriptive analysis consisted of presenting frequency tables for categorical variables and dispersion measurements for numerical variables. For comparison of proportions, we used the chi-square test or Fisher's exact test, when necessary. For comparison of continuous variables between two groups, the Mann-Whitney test was used; for comparison between three or more, the Kruskal-Wallis test was used, with application of the Tukey post-test. For univariate analysis on associations between ordinal endpoints and continuous variables, simple linear regression models were used; for multivariate analysis on significant associations, multiple regression models were used. The significance level used for the statistical tests was 5% ($P < 0.05$). To perform the analyses, the SAS System for Windows computer software (Statistical Analysis System), version 9.2, was used (SAS Institute Inc., 2002-2008; Cary, NC, United States).

RESULTS

Demographic characteristics and nutritional status

There was a predominance of females in the study population (65.7%). There were no differences in gender distribution between the groups (P = 0.9). The average age was 47.2 ± 17.3 years; there were no significant differences in age between the groups studied (P = 0.6). The mean BMI was 27.4 ± 5.2 kg/m^2; there were no significant differences between the groups (P = 0.08). The complete comparison among the groups is presented in **Table 1**.

Biochemical variables

Regarding biochemical variables, group 2A showed significantly higher levels of bilirubin ($P < 0.001$), AST ($P < 0.001$), ALT ($P < 0.001$), ALP ($P < 0.001$) and GGT ($P < 0.001$), compared with groups 1 and 2B. Mean INR was lower in group 1 than in groups 2A and 2B ($P < 0.001$) and ALB was lower in group 2A than in groups 1 and 2B (P = 0.01). The complete comparison among biochemical variables is presented in **Table 1**.

Distribution of histopathological variables

It was observed that the presence of biliary hepatopathy was more frequent in group 2B than in groups 1 and 2A ($P < 0.01$) and also in group 2A compared with group 2 ($P < 0.05$). Fibrosis was more common in group 2B than in groups 1 and 2A (P = 0.02), as also was ductular proliferation (P = 0.02). Cholestasis was more common in group 2B than in groups 2A ($P < 0.01$) and 1 ($P < 0.05$) and was also more frequent in group 2A than in group 1 ($P < 0.05$). There were no significant differences in the distribution of portal inflammation (P = 1.0), cholangitis (P = 0.6) or steatosis (P = 0.3). The complete distribution of histopathological variables is presented in **Table 2**.

Biliary hepatopathy

In the analysis on the presence of biliary hepatopathy, it was observed that, in the overall population, its presence was associated with lower BMI (P = 0.01) and higher bilirubin levels (P = 0.01) and INR (P = 0.04). In a subgroup analysis, biliary hepatopathy was associated with longer duration of cholestasis ($P < 0.001$), higher bilirubin levels (P = 0.02) and higher INR (P = 0.02) in group 2A; with lower BMI (P = 0.02) and longer duration of cholestasis ($P < 0.001$) in group 2B; and with longer duration of cholestasis ($P < 0.001$) and longer interval between ERCP and surgery (P = 0.03), along with higher levels of ALP (P = 0.01) and GGT (P = 0.01) in group 2. In group 1, there was no variable that differed between the groups with or without biliary hepatopathy. The complete comparison between the variables analyzed according to the presence of biliary hepatopathy is presented in **Table 3**.

Table 1. Demographic characteristics, nutritional status and biochemical variables of the study population

N	No cholestasis (group 1)	Active jaundice (group 2A)	Resolved cholestasis (group 2B)	P-value (Post-test P-value when applicable)
	115	25	29	NA
Age (years)	46.9 ± 17.9	45.4 ± 16.9	50.1 ± 19.8	0.6
Gender	F: 77 (67%) M: 38 (33%)	F: 16 (64%) M: 9 (36%)	F: 18 (62.1%) M: 11 (37.9%)	0.9
BMI (kg/m^2)	27.9 ± 5.1	27.1 ± 5	25.4 ± 5	0.08
Bilirubin (mg/dl)	0.6 ± 0.2	5.5 ± 4.5	1 ± 0.5	*< 0.001* *(2A > 2B; P < 0.01)* *(2A > 1; P < 0.01)*
Aspartate aminotransferase (mg/dl)	19.7 ± 7.6	225 ± 210.3	30.1 ± 16.8	*< 0.001* *(2A > 2B; P < 0.01)* *(2A > 1; P < 0.01)*
Alanine aminotransferase (mg/dl)	21.2 ± 13.3	450.1 ± 722.2	46.2 ± 37.6	*< 0.001* *(2A > 2B; P < 0.01)* *(2A > 1; P < 0.01)*
Alkaline phosphatase (mg/dl)	71 ± 25.1	327 ± 295.5	95.3 ± 59.3	*< 0.001* *(2A > 1; P < 0.01)* *(2A > 2B; P < 0.01)*
Gamma-glutamyl transferase (mg/dl)	39.8 ± 35	457.3 ± 380.1	123.6 ± 158	*< 0.001* *(2A > 2B; P < 0.01)* *(2A > 1; P < 0.01)*
Albumin (g/dl)	4.2 ± 0.3	4 ± 0.6	4.2 ± 0.4	*0.01* *(2A < 2B; P < 0.05)*
International normalized ratio	1 ± 0.1	1.3 ± 0.2	1.2 ± 0.1	*< 0.001* *(2A > 1; P < 0.01)* *(2B > 1; P < 0.01)*

N = number of individuals; BMI = body mass index; F = female; M = male; NA = not applicable. Italics indicate statistical significance.

Table 2. Distribution of histopathological variables according to subgroup classification

	No cholestasis (group 1)	Active cholestasis (group 2A)	Resolved cholestasis (group 2B)	Value of P (Post-test value of P when applicable)
Biliary hepatopathy N (%)	25 (21.7%)	11 (44%)	24 (82.8%)	*< 0.001* *(2B > 1; P < 0.01)* *(2B > 2A; P < 0.01)* *(2A > 1; P < 0.05)*
Fibrosis N (%)	63 (54.8%)	13 (52%)	24 (82.8%)	*0.02* *(2B > 1; P < 0.05)* *(2B > 2A; P < 0.05)*
Ductular proliferation N (%)	39 (33.9%)	9 (36%)	18 (62.1%)	*0.02* *(2B > 1; P < 0.05)* *(2B > 2A; P < 0.05)*
Cholestasis N (%)	25 (21.7%)	9 (36%)	16 (55.2%)	*0.001* *(2B > 1; P < 0.01)* *(2B > 2A; P < 0.05)* *(2A > 1; P < 0.05)*
Portal inflammation N (%)	37 (32.2%)	8 (32%)	10 (34.5%)	1.0
Steatosis N (%)	50 (43.5%)	9 (36%)	8 (27.6%)	0.3
Cholangitis N (%)	0	2 (8%)	0	0.6

N = number of individuals. Italics indicate statistical significance.

Table 3. Correlation between occurrence of biliary hepatopathy and variables analyzed in the study population, according to subgroup classification

No cholestasis (group 1)			
	Present	**Absent**	**P-value**
N (%)	25	90	NA
Age (years)	46.6 ± 18	48 ± 17.7	0.7
Gender	M: 6 F: 19	M: 32 F: 58	0.3
BMI (kg/m^2)	23.6 ± 4.6	28.3 ± 5.1	0.1
Bilirubin (mg/dl)	0.5 ± 0.2	0.6 ± 0.3	0.1
Aspartate aminotransferase (mg/dl)	19.6 ± 9	19.7 ± 7	1.0
Alanine aminotransferase (mg/dl)	18.5 ± 9.9	21.9 ± 14.1	0.3
Alkaline phosphatase (mg/dl)	64.1 ± 19.9	72.9 ± 26.2	0.1
Gamma-glutamyl transferase (mg/dl)	28.2 ± 20.4	42.7 ± 37.7	0.07
International normalized ratio	1 ± 0.1	1.1 ± 0.1	0.5
Albumin (g/dl)	4.1 ± 0.3	4.3 ± 0.4	0.1
Overall cholestasis (group 2)			
	Present	**Absent**	**P-value**
N (%)	35	19	NA
Age (years)	47.7 ± 18	48.4 ± 20	0.9
Gender	M: 15 F: 20	M: 5 F: 14	0.2
BMI (kg/m^2)	25.8 ± 5.2	27.1 ± 5.5	0.4
Duration of cholestasis (days)	37.3 ± 12.3	9.9 ± 3	*< 0.001*
ERCP-surgery interval (days) (N = 17)	8.4 ± 2.5	43.7 ± 16.4	*0.03*
Bilirubin (mg/dl)	3.1 ± 4.6	3 ± 1.9	0.9
Aspartate aminotransferase (mg/dl)	93.4 ± 39.1	173.4 ± 39.7	0.1
Alanine aminotransferase (mg/dl)	214.7 ± 113.1	264.2 ± 59.4	0.8
Alkaline phosphatase (mg/dl)	312.5 ± 76.2	144.3 ± 22.5	*0.01*
Gamma-glutamyl transferase (mg/dl)	412.1 ± 96.6	180.9 ± 41.1	*0.01*
International normalized ratio	1.1 ± 0.2	1.1 ± 0.2	0.1
Albumin (g/dl)	4 ± 0.4	4.1 ± 0.6	0.5
Active cholestasis (group 2A)			
	Present	**Absent**	**P-value**
N (%)	11	14	NA
Age (years)	43.8 ± 15.3	46.7 ± 18.5	0.7
Gender	M: 5 F: 6	M: 4 F: 10	0.4
BMI (kg/m^2)	28.6 ± 6.9	26 ± 4.1	0.3
Duration of cholestasis (days)	30 ± 10.5	10.4 ± 2.8	*< 0.001*
ERCP-surgery interval (days) (N = 17)	9.6 ± 10.9	22.7 ± 9.5	0.2
Bilirubin (mg/dl)	7.8 ± 5.9	3.7 ± 1.7	0.02
Aspartate aminotransferase (mg/dl)	222.6 ± 259.4	226.8 ± 172.7	1.0
Alanine aminotransferase (mg/dl)	582.5 ± 1064.4	346.1 ± 254.8	0.4
Alkaline phosphatase (mg/dl)	399.5 ± 348.5	234.6 ± 185.8	0.2
Gamma-glutamyl transferase (mg/dl)	537.6 ± 393.5	355.2 ± 393.5	0.2
International normalized ratio	1.2 ± 0.2	1 ± 0.1	*0.02*
Albumin (g/dl)	3.8 ± 0.5	4.1 ± 0.7	0.4
Resolved cholestasis (group 2B)			
	Present	**Absent**	**P-value**
N (%)	24	5	NA
Age (years)	49.5 ± 19.1	53 ± 25.4	0.7
Gender	M: 10 F: 14	M: 1 F: 4	0.4
BMI (kg/m^2)	24.4 ± 3.5	30.2 ± 8.2	*0.02*

Continue...

Table 3. Continuation.

Resolved cholestasis (group 2B)			
	Present	**Absent**	**P-value**
Duration of cholestasis (days)	40.6 ± 12.1	8.6 ± 3.6	*< 0.001*
ERCP-surgery interval (days) (N = 17)	23.4 ± 39	70 ± 47.9	0.2
Bilirubin (mg/dl)	0.9 ± 0.5	1 ± 0.3	0.7
Aspartate aminotransferase (mg/dl)	31.5 ± 17.7	23.8 ± 10.7	0.4
Alanine aminotransferase (mg/dl)	44.2 ± 38.4	35 ± 36.5	0.6
Alkaline phosphatase (mg/dl)	101 ± 64.2	68.8 ± 4.1	0.3
Gamma-glutamyl transferase (mg/dl)	134.1 ± 172.5	72.8 ± 63.9	0.4
International normalized ratio	1.1 ± 0.1	1.1 ± 0.1	0.7
Albumin (g/dl)	4.1 ± 0.4	4.3 ± 0.3	0.1
Overall study population (groups 1 + 2)			
	Present	**Absent**	**P-value**
N (%)	60	109	NA
Age (years)	47.8 ± 17.7	46.9 ± 18.3	0.7
Gender	M: 21 F: 39	M: 37 F: 72	0.9
BMI (kg/m^2)	26 ± 4.9	28.1 ± 5.2	*0.01*
Bilirubin (mg/dl)	2 ± 3.7	1 ± 1.2	*0.01*
Aspartate aminotransferase (mg/dl)	61.4 ± 133.6	46.4 ± 96.1	0.4
Alanine aminotransferase (mg/dl)	64.2 ± 140.9	129.1 ± 496.7	0.2
Alkaline phosphatase (mg/dl)	109.4 ± 108.3	114.7 ± 165.2	0.8
Gamma-glutamyl transferase (mg/dl)	121.3 ± 198.8	103.8 ± 216.9	0.6
International normalized ratio	1.2 ± 0.1	1 ± 0.1	*0.04*
Albumin (g/dl)	3.9 ± 0.8	4.1 ± 0.9	0.3

N = number of individuals; NA = not applicable; M = male; F = female; BMI = body mass index.
Italics indicate statistical significance.

Subgroup regression analysis

Linear regression analyses were performed between clinical variables in relation to the severity of histopathological characteristics (ordinal outcomes) in the analysis groups and in the overall study population.

In group 1, associations were observed between cholestasis severity and BMI (R = -0.3; P = 0.01) and ALB levels (R = -0.3; P = 0.01) and between severity of ductular proliferation and BMI (R = -0.3; P = 0.005) and ALB levels (R = -0.2; P = 0.04). After multiple regression, it was observed that both ALB (R = -0.2; P = 0.02) and BMI (R = -0.2; P = 0.02) were independently correlated with cholestasis severity and that BMI (R = -0.2; P = 0.008) was independently correlated with the severity of ductular proliferation.

In group 2, significant associations were observed between fibrosis severity and ALP levels (R = 0.4; P = 0.002) and between ductular proliferation severity and duration of cholestasis (R = 0.6; P < 0.001).

In group 2A, significant correlations were observed between fibrosis severity and ALP (R = 0.4; P = 0.03) and GGT levels (R = 0.5; P = 0.01); between cholestasis severity and duration of cholestasis (R = 0.8; P < 0.001), bilirubin levels (R = 0.6; P = 0.004), INR (R = 0.3; P = 0.04) and ALB (R = -0.3; P < 0.001); and between ductular proliferation severity and duration of cholestasis (R = 0.7; P < 0.001), INR (R = 0.7; P = 0.03) and ALB (R= -0.7; P < 0.001). After multiple regression, GGT was independently correlated with fibrosis severity (R = 0.5; P = 0.006); duration of cholestasis (R = 0.7; P < 0.001) and bilirubin levels (R = 0.6; P = 0.004) were independently correlated with cholestasis severity; and duration of cholestasis (R = 0.7; P < 0.001) was independently correlated with the severity of ductular proliferation.

In group 2B, significant associations were observed between fibrosis severity and AST levels (R = 0.4; P = 0.04) and between ductular proliferation severity and duration of cholestasis (R = 0.6; P = 0.002) and ERCP-surgery interval (R = 0.6; P = 0.002). After multivariate analysis, both duration of cholestasis (R = 0.5; P = 0.008) and ERCP-surgery interval (R = 0.4; P = 0.01) were independently associated with the severity of ductular proliferation.

Considering the total study population, associations were observed between cholestasis severity and BMI (R = -0.2; P = 0.03), bilirubin levels (R = 0.3; P < 0.001) and ALB (R = -0.2; P = 0.004); between ductular proliferation severity and BMI (R = -0.3; P < 0.001) and ALB levels (R = -0.2; P < 0.001); between the severity of steatosis and age (R = 0.2; P = 0.009); and between the severity of portal inflammation and age (R = 0.2; P = 0.005). After multiple regression analysis, bilirubin levels (R = 0.3; P < 0.001) were independently correlated with cholestasis severity; and BMI (R = -0.2; P = 0.01) was independently correlated with the severity of ductular proliferation. Complete descriptions of correlation

coefficients and multiple regression in the different subgroups and in the entire study population are presented in **Table 4**.

Liver histology, bilirubin levels and duration of cholestasis

Cholestasis was more frequent in individuals with bilirubin levels over 7 mg/dl (P = 0.04). Other histological features did not differ according to bilirubin levels (**Table 5**).

Among the individuals who experienced biliary obstructions, there were significantly higher frequencies of cholestasis (P < 0.001), biliary hepatopathy (P < 0.001) and ductular proliferation (P < 0.001) (**Table 6**).

DISCUSSION

The presence of biliary hepatopathy in a population without a clinical history of jaundice may indicate occurrence of subclinical and spontaneously resolved cholestatic events (gallstone migration, for example), but with maintenance of the histopathological alteration indefinitely. Rangaswamy et al. previously observed, among

Table 4. Simple and multiple linear regression analyses between the endpoints considered (severity of histopathological characteristics) and study variables, according to subgroup classification

Group 1 (no cholestasis)				
Endpoint: severity of fibrosis				
Variable	**Correlation coefficient (simple regression)**		**P-value (simple regression)**	
Age	0.1		0.2	
BMI	0.02		0.8	
Bilirubin	0.07		0.5	
AST	0.05		0.6	
ALT	0.07		0.5	
ALP	0.1		0.2	
GGT	0.02		0.8	
INR	0.05		0.9	
Albumin	-0.1		0.2	
Endpoint: severity of cholestasis				
Variable	**Correlation coefficient (simple regression)**	**P-value (simple regression)**	**Adjusted coefficient (multiple regression)***	**P-value (multiple regression)***
Age	0.2	0.1	NA	NA
BMI	-0.3	*0.01*	-0.2	*0.02*
Bilirubin	-0.06	0.5	NA	NA
AST	-0.06	0.4	NA	NA
ALT	-0.2	0.3	NA	NA
ALP	-0.2	0.06	NA	NA
GGT	0.04	0.4	NA	NA
INR	-0.2	0.1	NA	NA
Albumin	-0.3	*0.01*	-0.2	*0.02*
Endpoint: severity of ductular proliferation				
Variable	**Correlation coefficient (simple regression)**	**P-value (simple regression)**	**Adjusted coefficient (multiple regression)***	**P-value (multiple regression)***
Age	0.02	0.7	NA	NA
BMI	-0.3	*0.005*	-0.2	*0.008*
Bilirubin	-0.1	0.2	NA	NA
AST	-0.0001	0.9	NA	NA
ALT	-0.1	0.6	NA	NA
ALP	0.2	0.5	NA	NA
GGT	0.1	0.6	NA	NA
INR	0.04	0.2	NA	NA
Albumin	-0.2	*0.04*	-0.1	0.1
Group 2 (overall cholestasis)				
Endpoint: severity of fibrosis				
Variable	**Correlation coefficient (simple regression)**		**P-value (simple regression)**	
Age	0.02		0.9	
BMI	0.07		0.6	
Duration of cholestasis	0.2		0.1	

Continue...

Table 4. Continuation.

Group 2 (overall cholestasis)				
Endpoint: severity of fibrosis				
Variable	**Correlation coefficient (simple regression)**		**P-value (simple regression)**	
Bilirubin	0.2		0.2	
AST	0.3		*0.06*	
ALT	0.08		0.6	
ALP	0.4		0.002	
GGT	0.1		0.5	
INR	0.1		0.3	
Albumin	-0.01		0.9	
Endpoint: severity of cholestasis				
Variable	**Correlation coefficient (simple regression)**	**P-value (simple regression)**	**Adjusted coefficient (multiple regression)***	**P-value (multiple regression)***
Age	0.06	0.7	NA	NA
BMI	0.1	0.5	NA	NA
Duration of cholestasis	0.4	*0.001*	0.3	*0.004*
Bilirubin	0.3	*0.02*	0.2	0.07
AST	0.03	0.8	NA	NA
ALT	0.2	0.2	NA	NA
ALP	0.06	0.7	NA	NA
GGT	0.2	0.1	NA	NA
INR	0.4	*0.01*	0.3	*0.03*
Albumin	-0.1	0.2	NA	NA
Endpoint: severity of ductular proliferation				
Variable	**Correlation coefficient (simple regression)**		**P-value (simple regression)**	
Age	0.07		0.6	
BMI	0.2		0.3	
Duration of cholestasis	0.6		*< 0.001*	
Bilirubin	0.06		0.7	
AST	0.07		0.6	
ALT	0.07		0.6	
ALP	0.3		0.06	
GGT	0.2		0.09	
INR	0.2		0.1	
Albumin	0.01		0.8	
Group 2A (active cholestasis)				
Endpoint: severity of fibrosis				
Variable	**Correlation coefficient (simple regression)**	**P-value (simple regression)**	**Adjusted coefficient (multiple regression)***	**P-value (multiple regression)***
Age	0.03	0.2	NA	NA
BMI	-0.04	0.9	NA	NA
Duration of cholestasis	-0.01	0.4	NA	NA
Bilirubin	0.09	0.7	NA	NA
AST	-0.08	0.7	NA	NA
ALT	0.4	*0.03*	0.3	*0.04*
ALP	0.5	*0.01*	0.2	0.08
GGT	0.5	*0.01*	0.5	*0.03*
INR	0.04	0.2	NA	NA
Albumin	-0.1	0.6	NA	NA
Endpoint: severity of cholestasis				
Variable	**Correlation coefficient (simple regression)**	**P-value (simple regression)**	**Adjusted coefficient (multiple regression)***	**P-value (multiple regression)***
Age	0.1	0.5	NA	NA
BMI	0.1	0.51	NA	NA
Duration of cholestasis	0.8	*< 0.001*	0.7	*< 0.001*
Bilirubin	0.6	*0.004*	0.5	*0.005*
AST	0.04	0.9	NA	NA
ALT	0.04	*0.9*	NA	NA
ALP	0.08	*0.8*	NA	NA
GGT	0.1	*0.6*	NA	NA
INR	0.3	0.04	0.2	0.1
Albumin	-0.3	< 0.001	-0.2	0.1

Continue...

Table 4. Continuation.

Endpoint: severity of ductular proliferation				
Variable	**Correlation coefficient (simple regression)**	**P-value (simple regression)**	**Adjusted coefficient (multiple regression)***	**P-value (multiple regression)***
Age	0.1	0.5	NA	NA
BMI	0.1	0.7	NA	NA
Duration of cholestasis	0.7	*< 0.001*	0.7	*< 0.001*
Bilirubin	0.4	0.08	NA	NA
AST	0.1	0.7	NA	NA
ALT	0.2	0.3	NA	NA
ALP	0.3	0.2	NA	NA
GGT	0.3	0.2	NA	NA
INR	0.7	*0.03*	0.2	0.9
Albumin	-0.7	*< 0.001*	-0.5	0.06
Group 2B (resolved cholestasis)				
Endpoint: severity of fibrosis				
Variable	**Correlation coefficient (simple regression)**	**P-value (simple regression)**		
Age	0.5	0.7		
BMI	0.01	1.0		
ERCP-surgery interval	0.4	0.1		
Duration of cholestasis	0.06	0.8		
Bilirubin	0.07	0.7		
AST	0.4	*0.04*		
ALT	0.3	0.1		
ALP	0.1	0.6		
GGT	0.2	0.3		
INR	0.1	0.8		
Albumin	-0.04	0.6		
Endpoint: severity of cholestasis				
Variable	**Correlation coefficient (simple regression)**	**P-value (simple regression)**		
Age	0.02	0.9		
BMI	0.2	0.3		
ERCP - surgery interval	-0.1	0.6		
Duration of cholestasis	0.3	0.2		
Bilirubin	0.2	0.2		
AST	0.2	0.3		
ALT	0.3	0.2		
ALP	0.3	0.1		
GGT	0.2	0.3		
INR	0.1	0.9		
Albumin	0.1	0.7		
Endpoint: severity of ductular proliferation				
Variable	**Correlation coefficient (simple regression)**	**P-value (simple regression)**	**Adjusted coefficient (multiple regression)***	**P-value (multiple regression)***
Age	0.1	0.7	NA	NA
BMI	0.3	0.1	NA	NA
ERCP - surgery interval	0.6	*0.002*	0.4	*0.01*
Duration of cholestasis	0.6	*0.002*	0.5	*0.008*
Bilirubin	0.01	1.0	NA	NA
AST	0.01	0.9	NA	NA
ALT	0.1	0.7	NA	NA
ALP	0.1	0.7	NA	NA
GGT	0.1	0.6	NA	NA
INR	0.1	0.5	NA	NA
Albumin	-0.1	0.6	NA	NA
Groups 1 + 2 (entire study population)				
Endpoint: severity of fibrosis				
Variable	**Correlation coefficient (simple regression)**	**P-value (simple regression)**		
Age	-0.1	0.2		
BMI	-0.1	0.4		

Continue...

Table 4. Continuation.

Groups 1 + 2 (entire study population)				
Endpoint: severity of fibrosis				
Variable	**Correlation coefficient (simple regression)**		**P-value (simple regression)**	
Bilirubin	-0.04		0.8	
AST	-0.1		0.5	
ALT	0.01		0.7	
ALP	0.2		*0.02*	
GGT	0.01		*0.3*	
INR	0.02		0.5	
Albumin	-0.1		0.07	
Endpoint: severity of cholestasis				
Variable	**Correlation coefficient (simple regression)**	**P-value (simple regression)**	**Adjusted coefficient (multiple regression)***	**P-value (multiple regression)***
Age	0.1	0.1	NA	NA
BMI	-0.2	0.03	-0.1	0.1
Bilirubin	0.3	< 0.001	0.3	< 0.001
AST	-0.05	0.4	NA	NA
ALT	-0.05	*0.4*	NA	NA
ALP	0.1	*0.4*	NA	NA
GGT	0.02	*0.8*	NA	NA
INR	0.01	0.4	NA	NA
Albumin	-0.2	0.004	0.05	0.9
Endpoint: severity of ductular proliferation				
Variable	**Correlation coefficient (simple regression)**	**P-value (simple regression)**	**Variable**	**Correlation coefficient (simple regression)**
Age	-0.01	0.9	NA	NA
BMI	-0.3	< 0.001	-0.2	0.001
Bilirubin	0.2	0.04	0.1	0.1
AST	0.03	0.7	NA	NA
ALT	0.1	0.1	NA	NA
ALP	-0.1	0.1	NA	NA
GGT	-0.1	0.2	NA	NA
INR	0.01	*0.3*	NA	NA
Albumin	-0.2	*< 0.001*	-0.03	0.2
Endpoint: severity of steatosis				
Variable	**Correlation coefficient (simple regression)**		**P-value (simple regression)**	
Age	0.2		*0.009*	
BMI	0.1		0.2	
Bilirubin	-0.04		0.6	
AST	0.01		*0.2*	
ALT	0.06		0.6	
ALP	-0.1		0.2	
GGT	-0.04		1.0	
INR	-0.002		0.5	
Albumin	0.1		0.2	
Endpoint: severity of portal inflammation				
Variable	**Correlation coefficient (simple regression)**		**P-value (simple regression)**	
Age	0.2		*0.005*	
BMI	0.1		0.06	
Bilirubin	0.05		0.4	
AST	-0.003		*0.8*	
ALT	-0.1		0.5	
ALP	0.01		0.7	
GGT	-0.02		0.9	
INR	0.02		0.8	
Albumin	0.1		0.1	

BMI = body mass index; AST = aspartate aminotransferase; ALT = alanine aminotransferase; ALP = alkaline phosphatase; GGT = gamma-glutamyl transferase; INR = international normalized ratio; ERCP = endoscopic retrograde cholangiopancreatography; NA = not applicable. *When applicable; Italics indicate statistical significance.

individuals who underwent cholecystectomy and did not present evidence of biliary obstruction, that histopathological signs of acute cholestasis occurred in 9.1% of their sample. Moreover, Patel et al. also observed histopathological cholestasis in 10% of their patients who underwent uncomplicated cholecystolithiasis cholecystectomy.[9,10] The possibility of occurrences of resolved subclinical cholestatic events or undetected biliary diseases of undetermined clinical importance was raised in these previous studies, and this is reinforced by the findings of the current study.

The presence of biliary hepatopathy was associated with lower BMI and longer duration of cholestasis in both groups with a history of cholestasis, whether resolved or not. This suggested that some degree of nutritional impairment occurred and that the clinical duration of cholestasis is relevant in relation to histopathological evolution. The impact of extrahepatic cholestasis on nutritional status and weight is related to several pathophysiological changes, among which lipid malabsorption stands out, along with poor appetite and reduced intake in certain contexts.[11,12]

In individuals with resolved cholestasis who underwent ERCP, a lengthier time elapsed between the procedures, and cholecystectomy was associated with the presence of biliary hepatopathy. There was also a significant correlation between this interval and the severity of ductular proliferation.

Hence, it seems that performing surgery as early as possible may be beneficial. This may be due to the possibility of undetected subclinical cholestatic events during the time out. This finding reinforces the evidence previously described by Jee et al., Mador et al. and Nebiker et al., who demonstrated in different population studies on individuals who had previous episodes of acute biliary pancreatitis that a delay in performing cholecystectomy was associated with higher occurrence of new biliary complications, especially obstruction, during the waiting period for surgery.[13-15] Similarly, Moody et al., in a meta-analysis study, observed that early cholecystectomy reduced the frequency of readmissions due to biliary complications, among individuals with previous episodes of acute biliary pancreatitis.[16]

The duration of obstruction was significantly associated with the severity of both cholestasis and ductular proliferation. This highlights the progressive aspect of these changes in relation to the duration of the causative condition and, of course, emphasizes the importance of early treatment in order to avoid the development of chronic disease. Previous studies have shown that the severity of functional and structural changes in the liver is time-dependent, but with varying individual susceptibility. Functional recovery after decompression is not immediate in animal models, with persistent short-term hepatocytic insufficiency.[17-19]

Steatosis and portal inflammation were significantly associated with age in the general population and did not differ between groups. This suggested that non-alcoholic fatty liver disease (NAFLD) had a greater influence on these changes than did biliary conditions. Older age is a recognized risk factor for occurrence of NAFLD and also for progression to the most deleterious components of its histopathological spectrum, especially steatohepatitis and fibrosis/cirrhosis.[20,21]

Table 5. Frequencies of liver histological features according to bilirubin levels

	Bilirubin < 3 mg/dl	Bilirubin 3 – 7 mg/dl	Bilirubin > 7 mg/dl	P-value
N	150	15	4	NA
Steatosis, N (%)	60 (40%)	6 (40%)	1 (25%)	0.8
Fibrosis, N (%)	90 (60%)	8 (53.3%)	2 (50%)	0.8
Biliary hepatopathy, N (%)	50 (33.3%)	7 (46.7%)	3 (75%)	0.2
Cholestasis, N (%)	40 (26.7%)	7 (46.7%)	3 (75%)	*0.04*
Cholangitis, N (%)	0	1 (6.7%)	1 (25%)	0.2
Ductular proliferation, N (%)	58 (38.7%)	6 (40%)	2 (50%)	0.9
Portal inflammation, N (%)	47 (31.3%)	6 (40%)	2 (50%)	0.6

N = number of individuals. Italics indicate statistical significance.

Table 6. Frequencies of liver histological features according to duration of cholestasis

	Cholestasis < 15 days	Cholestasis ≥ 15 days	P-value
N	15	39	NA
Steatosis, N (%)	8 (53.3%)	9 (23.1%)	0.05
Fibrosis, N (%)	8 (53.3%)	8 (20.5%)	0.04
Biliary hepatopathy, N (%)	0	35 (89.7%)	*< 0.001*
Cholestasis, N (%)	0	23 (59%)	*< 0.001*
Cholangitis, N (%)	0	2 (5.1%)	1.0
Ductular proliferation, N (%)	0	27 (69.2%)	*< 0.001*
Portal inflammation, N (%)	6 (40%)	12 (30.8%)	0.8

N = number of individuals. Italics indicate statistical significance.

In the study population, treatment and resolution of the obstruction did not lead to full reversal of the histopathological changes associated with cholestasis, in a significant number of patients. There is evidence of mitigation of fibrosis and other liver histological abnormalities later on, after resolution of complete biliary obstructions, but complete resolution does not occur in all affected individuals.[22,23] Olguín et al. demonstrated in a murine model that the time elapsed between the obstruction and its correction is determinant for the possibility of histological reversal.[24] In addition, the correlation between the observed changes and laboratory tests was not appropriate, thus demonstrating the importance of histopathological examination in these cases.

Based on the results from the present study, it is advisable that any individual with a history of biliary obstruction, even if undergoing treatment and with evidence of resolution in laboratory and imaging examinations, should be accompanied through long-term follow-up. It needs to be borne in mind that the reversal of such biliary obstruction-associated liver changes may not be complete and that long-term changes are possible in this context.

The current study presents limitations that should be taken into consideration. Its retrospective design precludes ultimate conclusions on possible causal connections. Moreover, liver biopsies are subject to sampling error, since histopathological changes may be heterogeneously distributed in the liver parenchyma. Nevertheless, the findings of this study are significant and should be considered within their proper context.

CONCLUSIONS

Transient cholestasis was associated with significant histopathological changes, even after its resolution. The duration of obstruction correlated with the severity of histopathological changes, especially cholestasis and ductular proliferation. This emphasizes the need for early treatment of obstructive cholestasis.

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Cardiovascular risk factors and major depressive disorder: a cross-sectional study in São Paulo, Brazil

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ABSTRACT

BACKGROUND: Cardiovascular risk factors can mediate the association between depression and cardiovascular diseases.

OBJECTIVE: To evaluate cardiovascular risk factors in adult individuals with and without histories of major depression in the metropolitan region of São Paulo, Brazil.

DESIGN AND SETTING: Cross-sectional study in São Paulo (SP), Brazil.

METHODS: This study evaluated 423 individuals without any lifetime diagnosis of major depression and 203 individuals with a previous diagnosis of major depression (n = 626). The participants underwent a psychiatric evaluation using a structured clinical interview (SCID-1), an anthropometric evaluation and a clinical evaluation that included blood pressure measurement and assessment of fasting blood glucose, lipid profile and physical activity levels.

RESULTS: Individuals with histories of major depression were more likely to be female (P < 0.0001). Individuals with lifetime diagnoses of major depression were more likely to be current smokers (odds ratio, OR 1.61; 95% confidence interval, CI 1.01-2.59) and to have diabetes (OR 1.79; 95% CI 1.01-3.21); and less likely to be obese (OR 0.58; 95% CI 0.35-0.94).

CONCLUSION: Individuals with major depression had higher odds of presenting tobacco smoking and diabetes, and lower odds of being obese. Healthcare professionals need to be aware of this, so as to increase the rates of diagnosis and treatment in this population.

INTRODUCTION

Cardiovascular diseases are the leading cause of death worldwide and in Brazil.[1] Mortality rates relating to cardiovascular diseases have also been found to be higher in a psychiatric population than in an age-matched general population, with a hazard ratio (HR) of 4.16 (95% confidence interval, CI 1.22-14.25).[2] There is reasonable data describing the association between depressive disorders and cardiovascular disease incidence and mortality, especially with regard to coronary heart diseases.[3,4] Nicholson et al. reviewed 54 observational studies and conducted a meta-analysis regarding depression as an etiological factor among individuals with coronary heart diseases. They found that depression increased the risk of incident coronary heart disease (pooled relative risk, RR 1.81; 95% CI 1.53-2.15).[5]

Individuals' profile of cardiovascular risk factors can explain, at least partially, the higher incidence of coronary heart disease and related mortality among individuals with depressive disorders. Appleton et al. evaluated 8,138 men and found higher incidence of cardiovascular diseases in individuals with depressive disorders (HR 2.36; 95% CI 1.39-4.0). However, the association lost significance after cardiovascular risk factors were included in the model for adjustment (HR 1.73; 95% CI 0.99-2.99).[2] Therefore, cardiovascular risk factors might be important mediators of the causal model linking depressive disorders and cardiovascular mortality.

Depressed individuals might have unhealthier lifestyles than the general population, with higher rates of smoking and greater physical inactivity.[6,7] Strine et al. evaluated 217,379 individuals in a survey in the United States and found that individuals with previous major depression had higher odds of current smoking (odds ratio, OR 1.9; 95% CI 1.8-2.1) and physical inactivity (OR 1.3; 95% CI 1.2-1.4).[7] There are also data showing higher prevalence of metabolic syndrome in patients with major depression[8] and, more consistently, in depressed women.[9,10]

Studies that have evaluated the relationship between cardiovascular risk factors and depressive disorders in the general population are less common, especially in low and middle-income countries.

OBJECTIVE

The aim of this study was to evaluate cardiovascular risk factors (hypertension, diabetes, dyslipidemia, smoking, obesity and metabolic syndrome) and their association with lifetime major depression in a subsample of individuals from the São Paulo Megacity Mental Health Survey, in the metropolitan area of São Paulo, Brazil.

METHODS

Study design

The São Paulo Megacity Mental Health Survey is a population-based cross-sectional study with the aim of evaluating the prevalence of psychiatric morbidity. It focuses on non-institutionalized Portuguese-speaking adults aged 18 or older, living in the metropolitan area of São Paulo, state of São Paulo, Brazil, and it forms the Brazilian component of the World Mental Health Survey (WMH). This is an initiative from the World Health Organization (WHO) that comprises a series of population-based epidemiological studies of adult resident populations in over 30 participating countries around the world. It is conducted with the same methodological framework, using the same instruments as in the WMH. The study protocol has been detailed elsewhere.[11]

Study sample

The current study was based on a subsample of the Brazilian WMH, with a cross-sectional design and was conducted in parallel with the main household survey. Out of the 5,037 individuals who were evaluated in their households, a random subsample of 780 individuals was selected. Eight individuals (1%) with symptoms that needed emergency evaluation, who did not complete the protocol, were excluded. We also excluded 146 (18.7%) who had substance use disorders or eating disorders and, thus, 626 individuals (80.3%) remained included in the final analysis (**Figure 1**). The only missing data consisted of body mass index (BMI) values for individuals. The remainder of the data was 100% complete.

Psychiatric and clinical assessments

In the hospital outpatient setting, trained psychiatrists assessed participants through the Structured Clinical Interview for DSM-IV Axis I Disorders (SCID-I).[12] The SCID-I makes it possible to generate current and lifetime diagnoses on psychiatric conditions. For this analysis, we only included individuals with lifetime diagnoses of major depressive disorder (MDD), with or without associated anxiety disorders.

In addition, the onsite evaluation included a questionnaire that was used to collect the following sociodemographic data: age, sex, marital status, number of years of formal education (measured as number of school years), current job status (worker, housekeeper, student, retired or other) and annual household income. A clinical evaluation focusing on cardiovascular risk factors and cardiovascular diseases was performed by two physicians. All subjects were asked about smoking status (never, past or current), alcohol intake and personal histories of hypertension, diabetes, coronary heart disease or cerebrovascular disease. The level of physical activity was measured using the long version of the International Physical Activity Questionnaire (IPAQ).[13] Inadequate physical activity was defined as being sedentary or insufficiently active according to the IPAQ, considering two domains separately: leisure-time and journey-to-work (commuting) physical activity.

Definition of cardiovascular risk factors

Hypertension was defined as mean systolic blood pressure ≥ 140 mmHg, mean diastolic blood pressure ≥ 90 mmHg, medical history of hypertension and/or current use of medication to treat hypertension.[14] Diabetes was defined as fasting blood glucose ≥ 126 mg/dl, medical history of diabetes and/or use of medication to treat diabetes.[15]

Individuals were considered to have dyslipidemia if they had one or more lipid profile alterations: high-density lipoprotein-cholesterol (HDL-c) levels lower than 40 mg/dl for men and lower than 50 mg/dl for women; triglyceride (TG) levels higher than 150 mg/dl; or low-density lipoprotein-cholesterol (LDL-c) levels higher than 130 mg/dl. Metabolic syndrome was defined as the presence of three or more of the following criteria: abdominal obesity (waist circumference ≥ 102 centimeters (cm) in men and ≥ 88 cm in women); TG blood level ≥ 150 mg/dl; HDL-c cholesterol blood levels lower than 40 mg/dl in men or lower than 50 mg/dl

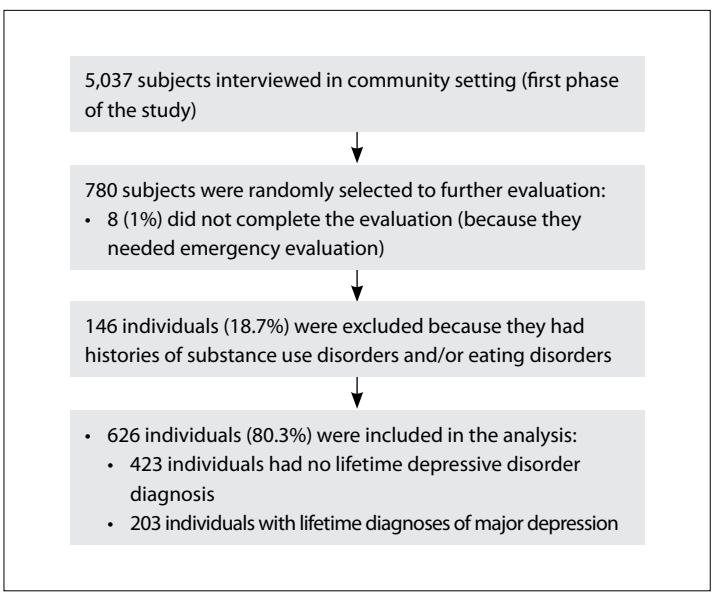

Figure 1. Subjects included in the second phase of the São Paulo Megacity Survey.

in women; blood pressure (BP) ≥ 130 mmHg of systolic blood pressure and/or ≥ 85 mmHg of diastolic blood pressure; or fasting glucose blood level ≥ 100 mg/dl.[16]

Anthropometric and blood pressure measurements

The anthropometric evaluation (weight, height and waist circumference) was performed using standardized equipment and techniques.[17] Blood pressure was measured three times using a standardized technique in the seated position after a five-minute rest. Body mass index (BMI) was calculated as weight in kilograms divided by height in meters squared.[18] Overweight was defined as BMI between 25 and 29.9 kg/m^2. Obesity was defined as BMI greater than or equal to 30 kg/m^2.

Laboratory measurements

Venous blood samples were obtained after a 12-hour overnight fast. The blood samples were analyzed for the following: glucose levels (hexokinase method); total cholesterol (TC) (enzymatic colorimetric assay); HDL-c (HDL - homogeneous cholesterol); triglycerides (enzymatic colorimetric assay); high-sensitivity C-reactive protein (nephelometry); thyroid-stimulating hormone (TSH); and free thyroxine (immunoenzymatic assay - third generation). LDL-c values were obtained using the Friedewald formula.[16]

Statistical analysis

Data entry was carried out twice and a validity check was done in order to identify and correct any data entry errors. Groups were compared using the chi-square test or Fisher's exact test for categorical data, whenever applicable. Continuous variables were tested for normality, and one-way ANOVA (analysis of variance) or nonparametric tests were performed, whenever applicable. We used logistic regression to evaluate comparisons among individuals with and without depression and the results were presented crudely and adjusted for age and sex. The significance level was set at 0.05. We used the SPSS for Windows software, version 16.0 (SPSS Inc., Chicago, United States), and the R software, version 3.0.0 (Vienna, Austria) for the analyses.

Ethical considerations

The Institutional Review Board of Hospital das Clínicas, Universidade de São Paulo approved the study under the protocol number 234/03 (on April 24, 2003), and all the participants signed a written informed consent statement.

RESULTS

Among the 626 participants, 383 (61.2%) were female, 423 had no lifetime history of MDD (67.6%; 95% CI 63.8-71.2) and 203 had lifetime histories of MDD (32.4%; 95% CI 28.9-36.2). The mean age was 40.5 years among the individuals without any lifetime diagnosis of major depressive disorder and 41.5 years among the individuals with lifetime histories of major depressive disorder (P = 0.24). A total of 423 individuals (67.6%) had no lifetime history of depressive disorder, while 203 (32.4%) had a SCID-I diagnosis of lifetime depressive disorder. Individuals with lifetime depression were more likely to be current smokers than were individuals who had never been depressed, with borderline significance (20.3% versus 13.0%; P = 0.056) (**Table 1**).

There were no differences between the individuals with and without lifetime diagnoses of major depressive disorder regarding cardiovascular risk factors, except for a borderline difference for current tobacco smoking (13.0% among individuals without MDD and 20.2% among individuals with MDD; P = 0.056*)*. Most of the individuals were obese or overweight (64.5% of the individuals without MDD and 61.0% of the individuals with MDD; P = 0.12). High frequencies of hypertension (37% in both groups; P = 0.99), metabolic syndrome (34.8% versus 33.5% in individuals without and with MDD, respectively; P = 0.79) and dyslipidemia (62.4% of individuals without MDD and 55.2% of individuals with MDD; P = 0.10) were observed. There was high frequency of sedentary behavior, particularly with regard to physical activity during leisure time (**Table 1**).

In the logistic regression, crude analysis showed that individuals with lifetime histories of MDD had odds ratios for body mass index, hypertension, diabetes mellitus, dyslipidemia, metabolic syndrome and leisure-time physical activity that were similar to those of individuals without MDD. Also in the crude analysis, individuals with MDD had higher odds ratios for current smoking (OR 1.65; 95% CI 1.04-2.62) and lower odds of active commuting-related physical activity (OR 0.60; 95% CI 0.39-0.93) (**Table 2**).

In the age and sex-adjusted logistic regression model, individuals with lifetime major depression had higher odds of being current smokers (OR 1.61; 95% CI 1.01-2.59) and higher odds of presenting diabetes (OR 1.79; 95% CI 1.01-3.21). In addition, individuals with lifetime major depression had lower odds of presenting obesity (OR 0.58; 95% CI 0.35-0.94). No differences were found for other cardiovascular risk factors (hypertension, dyslipidemia, metabolic syndrome and physical activity) (**Table 2**). Further adjustment for cardiovascular risk factors did not change the results (data not shown).

DISCUSSION

In our study, we found that current smoking and diabetes showed associations with lifetime histories of major depression. We also found lower odds of being obese among individuals with lifetime histories of major depression, compared with nondepressed individuals.

Our study found that individuals with lifetime major depression had higher odds of being diabetic. Most studies have found this same association between diabetes and major depression, including evidence for a bidirectional association.[19,20-23] Mommersteeg et al. found among 231,797 individuals from 47 countries that diabetes increased the odds

of depressive symptoms (OR 2.36; 95% CI 1.91-2.92).[24] Mezuk et al. found that diabetes could enhance the risk of incident depression (OR 1.15; 95% CI 1.02-1.30). They also found higher risk of new-onset diabetes among depressed subjects (RR 1.60; 95% CI 1.37-1.88).[23]

There are multiple explanations for the association between diabetes and depression, as mediated by long-term use of antidepressants[25] and increased inflammation and insulin resistance.[26] The recent discussion on syndemics has indicated that the association between diabetes and depression is more complex than it would seem through explanations that invoke exclusive biological pathways. The dynamics of poverty and sociocultural contexts influence lifestyle and the health and disease process that links these two diseases.[27-30] Because the present study was a cross-sectional analysis, it is impossible to draw any conclusions relating to causality. Nevertheless, our data confirm the presence of this association in a Brazilian population sample.

We also found higher odds of current tobacco use among individuals with lifetimes of depressive disorder. Other studies have reported similar results.[7,31] Strine et al. found higher odds of tobacco use among currently depressed subjects (OR 2.2; 95% CI 2.0-2.3) and previously depressed subjects (OR 1.9; 95% CI 1.8-2.1).[7] Goodwin et al. found that among smokers the prevalence of past-year depression was 10.45%, compared with 5.51% among never-smokers.[32] Previous Brazilian studies confirmed the association between tobacco smoking and depressive symptoms.[33,34] Borçói et al. found a prevalence ratio of 2.69 (95% CI 1.62-4.46) for being a current smoker, among individuals with depressive disorder in a sample at a primary care service in a Brazilian municipality (Alegre, Espírito Santo).[33] Rocha et al. evaluated 1,054 individuals in a population-based survey in a southern municipality (Florianópolis, Santa Catarina) and found that 29% of current smokers had depressive symptoms.[34]

Table 1. Cardiovascular disease risk factors according to the presence of lifetime histories of major depressive disorder (MDD)

	Lifetime history of major depressive disorder				P
	No (n = 423)		Yes (n = 203)		
	N	% (95% CI)	N	% (95% CI)	
Sex					< 0.001
Female	228	53.9 (49.1-58.6)	155	76.4 (70.1-81.8)	
Male	195	46.1 (41.4-50.9)	48	23.6 (18.2-29.9)	
Mean age in years (SD)	40.5 (11.1)	40.5 (39.4-41.6)	41.5 (10.6)	41.5 (40.0-43.0)	0.243
Smoking status					0.056
Never	257	60.8 (56.0-65.3)	116	57.1 (50.3-63.8)	
Past	110	26.0 (22.0-30.4)	45	22.2 (16.9-28.3)	
Current	55	13.0 (10.1-16.5)	41	20.2 (15.1-26.1)	
Body mass index					0.118
Normal < 25.0 kg/m^2	149	35.2 (30.8-39.9)	78	38.4 (31.9-45.3)	
Overweight: 25.0-29.9 kg/m^2	164	38.8 (34.2-43.5)	86	42.4 (35.7-49.3)	
Obese ≥ 30.0 kg/m^2	107	25.3 (21.3-29.6)	36	17.7 (12.9-23.5)	
Hypertension					0.990
No	265	62.6 (58.0-67.2)	128	63.1 (56.3-69.5)	
Yes	158	37.4 (32.8-42.0)	75	36.9 (30.5-43.8)	
Diabetes mellitus					0.105
No	390	92.9 (89.3-94.5)	179	88.2 (83.2-92.1)	
Yes	33	7.8 (5.5-10.7)	24	11.8 (7.9-16.8)	
Dyslipidemia					0.098
No	159	37.6 (33.1-42.3)	91	44.8 (38.1-51.7)	
Yes	264	62.4 (57.7-66.9)	112	55.2 (48.3-61.9)	
Metabolic syndrome					0.788
No	276	65.2 (60.6-69.7)	135	66.5 (59.8-72.7)	
Yes	147	34.8 (30.3-39.4)	68	33.5 (27.3-40.2)	
Commuting-related physical activity					0.058
Inactive/sedentary	179	42.3 (37.7-47.1)	105	51.7 (44.9-58.6)	
Insufficiently active	131	31.0 (26.7-35.5)	58	28.6 (22.7-35.1)	
Active	113	26.7 (22.7-31.1)	40	19.7 (11.7-25.6)	
Leisure-time physical activity					0.140
Inactive/sedentary	292	69.0 (64.5-73.3)	155	76.4 (70.1-81.8)	
Insufficiently active	56	13.2 (10.3-16.7)	18	8.9 (5.5-13.4)	
Active	75	17.7 (14.3-21.6)	30	14.8 (10.4-20.2)	

95% CI = 95% confidence interval.

We found lower odds of obesity among individuals with lifetime histories of major depression. The results in the medical literature regarding this association are divergent, with positive results,[35,36] negative results[37-39] and inverse associations.[40] A systematic review by Luppino et al. including 15 studies and 58,745 individuals found higher odds of major depression among individuals with obesity (OR 1.57; 95% CI 1.23-2.01) and also reported that individuals with major depression had higher odds of obesity (OR 1.40; 95% CI 1.15-1.71), although no association with overweight was found (OR 0.98; 95% CI 0.83-1.16).[35] However, Luppino et al. pointed out that differences in study populations might explain the heterogeneous results and suggested that some American studies had a positive association, whereas European studies did not show any significant associations between depression and obesity.[35] An Asian study also reported an association of depression with underweight among men.[40] A Brazilian cohort in Pelotas (Rio Grande do Sul) found that individuals with major depressive disorder had higher odds of obesity (OR 1.9; 95% CI 1.09-3.46).[41] The Brazilian National Health Survey (Pesquisa Nacional de Saúde, PNS 2013) also found a bidirectional association between depression and obesity.[42] Paulitsch et al. found that the association of depression and obesity was mediated by weight perception, i.e. believing oneself to be fat. They also found that some groups were more vulnerable: being non-single, having more schooling and not engaging in physical activity.[43]

Our data contrasted with different Brazilian studies showing regional heterogeneity. In our study, the association between higher rates of commuting-related physical activity and lifetime history of MDD lost its significance after adjustment. Because our sample had a higher number of women than of men and commuting physical activity occurs more frequently among men than among women,[44,45] our results probably lost significance after adjustment for sex.

Our study had some methodological strengthens. Trained psychiatrists made the psychiatric diagnoses of all participants, using a gold-standard instrument (SCID-I). The cardiovascular risk factors were evaluated using medical history and using clinical and laboratory assessments from onsite evaluation made by trained physicians.

The results from the study highlight the importance of diagnosing and treating depression within primary and secondary care.[46]

Table 2. Logistic regression models of the association between cardiovascular risk factors and lifetime history of major depression (crude and age and sex-adjusted)

	Presence of lifetime history of major depressive disorder - OR (95% CI)	
	Crude	**Age and sex-adjusted**
Body mass index		
Normal	1.0 (Reference)	1.0 (Reference)
Overweight	1.00 (0.69-1.46)	1.03 (0.69-1.53)
Obese	0.64 (0.40-1.02)	0.58 (0.35-0.94)
Hypertension		
No	1.0 (Reference)	1.0 (Reference)
Yes	0.99 (0.70-1.40)	0.98 (0.67-1.44)
Diabetes mellitus		
No	1.0 (Reference)	1.0 (Reference)
Yes	1.58 (0.91-2.76)	1.79 (1.01-3.21)
Dyslipidemia		
No	1.0 (Reference)	1.0 (Reference)
Yes	0.74 (0.53-1.04)	0.77 (0.54-1.12)
Metabolic syndrome		
No	1.0 (Reference)	1.0 (Reference)
Yes	0.95 (0.66-1.35)	0.87 (0.59-1.27)
Smoking status		
Never	1.0 (Reference)	1.0 (Reference)
Past	0.91 (0.60-1.37)	0.88 (0.58-1.36)
Current	1.65 (1.04-2.62)	1.61 (1.01-2.59)
Leisure-time physical activity		
Inactive/sedentary	(Reference)	(Reference)
Insufficiently active	0.61 (0.34-1.07)	0.73 (0.41-1.30)
Active	0.75 (0.47-1.20)	0.79 (0.49-1.28)
Commuting-related physical activity		
Inactive/sedentary	(Reference)	1.0 (Reference)
Insufficiently active	0.75 (0.51-1.12)	0.80 (0.54-1.20)
Active	0.60 (0.39-0.93)	0.66 (0.42-1.03)

OR = odds ratio; 95% CI = 95% confidence interval.

Depression is an important risk factor for noncompliance with treatment of chronic diseases. Therefore, for effective control of cardiovascular risk factors, it is mandatory to recognize and treat depression. Depressive individuals are less active, with higher frequency of smoking and less adherence to prescribed medication.[47] In addition, practicing physical activity can also be part of depression treatment. On the other hand, the effect of treating depression can have some impact regarding weight gain, which has been shown to have an important relationship with depression and cardiovascular risk factors and chronic diseases. Healthcare professionals can manage treatment of depression using better cardiovascular-profile drugs or considering other treatment options, such as psychotherapy, whenever possible.[48]

Our study also had some limitations, given that the cross-sectional study design did not permit evaluation of causality. Moreover, the diagnosis of diabetes was made based on only one measurement of fasting plasma glucose, as a consequence of budget limitations and logistic limitations on performing some laboratory tests such as hemoglobin A1c. Another important point is that our sample was young, with a mean age of around 40 years. The prevalence of cardiovascular risk factors increases with age, which may explain the lower frequency in our sample. In addition, although the sample in the first phase of the study with home interviews was representative of the population living in the metropolitan region of São Paulo, only a subsample of participants was invited in the second phase, and many of them refused to participate, thus introducing some selection bias. However, even considering the young age, we reported that there was higher prevalence of diabetes and smoking among the depressive participants than among the nondepressed participants.

CONCLUSIONS

In this sample of individuals living in the metropolitan region of São Paulo, the biggest city in Brazil, we found that individuals with lifetime major depression had higher odds of current tobacco use and of presenting diabetes mellitus. They also had lower odds of being obese, compared with nondepressed individuals. Healthcare professionals need to increase their awareness of the diagnosis of cardiovascular risk factors among individuals with major depression, in order to enhance preventive strategies and thus reduce morbidity and mortality in this high-risk group.

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Physical activity and sedentary behavior as multimorbidity discriminators among elderly Brazilians: a cross-sectional study

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ABSTRACT

BACKGROUND: Associations between behaviors and individual chronic diseases have been demonstrated. However, the relationship between time spent on sedentary behavior and multimorbidity remains less clear.

OBJECTIVE: To identify the predictive power of various intensities of physical activity versus sedentary behavior, as discriminatory factors for cardiometabolic multimorbidity (cardiovascular diseases and diabetes) in the elderly.

DESIGN AND SETTING: Cross-sectional study in different residential census tracts and residential households in Florianópolis (SC).

METHODS: The participants were 425 elderly people (65% women) from the EpiFloripa Aging study in 2014. Sociodemographic variables and self-reported incidence of cardiovascular diseases and diabetes were obtained via a questionnaire. Light physical activity (LPA), moderate-to-vigorous physical activity (MVPA) and sedentary behavior (SB) were measured using accelerometers. The analyses were stratified according to sex and included a diagnosis for interpretation. Behaviors were taken into consideration if their predictive power in terms of area under the receiver operating characteristic (ROC) curve was greater than 0.50. The time cutoff point was defined from sensitivity and specificity.

RESULTS: For older adult men with diabetes, the predictive value of MVPA for absence of multimorbidity was an area of 0.75 (95% confidence interval, CI: 0.538-0.962), and a cutoff of 17 minutes per day. Older adult women with diabetes had an area of 0.71 (95% CI: 0.524-0.866) and a cutoff of 10 minutes per day. LPA and SB did not present predictive values.

CONCLUSION: The time spent on MVPA is a predictor of absence of multimorbidity in elderly people with diabetes, for both sexes.

INTRODUCTION

Multimorbidity is the existence of two or more diseases simultaneously. Its presence may lead to a 5.5-fold higher public healthcare cost per patient.[1] Involvement of multimorbidity, such as cardiovascular disease and concomitant diabetes, has higher prevalence among the elderly, and is the main cause of hospitalizations in Brazil.[2,3] Diabetes combined with hypertension increases the chances of having coronary heart disease and/or cerebrovascular disease threefold, compared with presence of diabetes alone.[4] This reflects mortality rates for all causes, given that the prevalence of hypertension grows at population levels.[5] Among the consequences of multimorbidities in the elderly are the risk of falls, depression and declines in physical function performance and in daily activities.[6]

Hence, reduction of the prevalence of these diseases is included in the agendas of international governmental bodies, such as the Global Strategy on Healthy Eating, Physical Activity and Health[7] and, in Brazil, the Strategic Action Plan for the Fight against Chronic Noncommunicable Diseases (NCDs).[8] Actions are planned to meet the goal of increasing the prevalence of physical activity in the population.[8] However, sedentary behavior is disregarded as an important outcome in health conditions.[9] Sedentary behavior and physical activity form patterns that may be reflected in health in different ways.[10] Objective measurements of physical activity and sedentary time may be useful for ascertaining cutoff points within these behaviors as risk factors for occurrence of cardiometabolic multimorbidity. This has a significant impact on guidance for healthy behaviors at the population level, as a form of prevention and for health promotion.[11,12]

Physical activity recommendations (150 to 300 minutes per week at moderate intensity) for prevention of cardiovascular disease in the elderly and in people with chronic conditions are well established.[13] Likewise, the amount of time spent on sedentary behavior has been shown to be a harmful factor proportional to the presence of the disease.[14] It has been recommended that sedentary time should be replaced by physical activities of any intensity.[13] Although the importance of achieving the physical activity recommendations is clear, some evidence of precisely how much time should be spent on PA and SB would guide proposals for attenuating the risk of having more than one chronic condition, seen in clinical practice.

Receiver operating characteristic (ROC) curve analysis is an important resource for ascertaining the presence or absence of cardiometabolic risks.[15,16] In previous studies, some cutoff points for physical activity and sedentary behavior for disease prediction were proposed, and questionnaires were used to measure these behaviors.[17] Subjective measurements may underestimate the accumulated time spent on sedentary behavior and overestimate the time spent on physical activity among older people, even though such measurements are easy to apply and have low cost. However, objective tools such as accelerometers provide reliable and valid physical activity measurements that make it possible to more faithfully capture different intensities of movement (sedentary, light, moderate and vigorous).[18]

OBJECTIVE

Therefore, the aim of the present study was to identify the predictive power of different intensities of physical activity and sedentary behavior in relation to non-simultaneous occurrence of cardiovascular disease and diabetes in elderly men and women with one of the diagnosed diseases.

METHODS

This was a population-based longitudinal study, carried out in the urban area of Florianópolis (SC), that used data from a study named EpiFloripa Idoso.[19] That study was based on home interviews and had the aim of investigating "the relationships between cognitive and functional status, and violence and general conditions of health in the elderly aged 60 years and over".[19] EpiFloripa Idoso was approved by the Ethics Committee for Research on Human Beings (CEPSH) of the Federal University of Santa Catarina (Universidade Federal de Santa Catarina, UFSC) under registration number 352/2008, dated July 8, 2013.

The first wave of data (baseline) was collected between September 2009 and June 2010. The sample size was estimated based on a prevalence calculation according to the size of the population size over 60 years of age (4,460). From this calculation, the minimum number of elderly people to be interviewed was determined to be 1,599. For this, we used a 95% confidence level, sampling error of four percentage points, unknown prevalence of the phenomenon (50%) and a cluster design effect estimate of two. A further 20% were added for possible estimated losses and 15% for the purpose of testing associations. Through these design effects, while taking into account the availability of funding, the final sample was expanded to 1,911 elderly people.[19]

The sampling method used consisted of two-stage conglomerates, in which the first step was to select census tracts and the second, residential households. We identified 420 urban and residential census tracts, among which 80 were systematically drawn, considering the average monthly family income. Each census tract consisted of 61 to 725 households. Tracts with fewer than 150 households were grouped and those with more than 500 households were divided according to their location and income in order to reduce the coefficient of variation (52.7% for 80 sectors, to 35.2% for 83 sectors). For the second stage, it was considered that the average number of residents per household was 3.1 and that the individuals in the study age group corresponded to 11% of the population.[20] Thus, it was estimated that it would be necessary to visit 60 households per sector from the list of addresses in order to find 20 seniors. All the elderly residents in the households selected were considered eligible, except for institutionalized elderly people who were housed in nursing homes, hospitals or prisons.[20]

The second wave sample (2013-2014) was composed of the elderly people (over 60 years) who had participated in the first wave. To form the second wave sample, home visits and calls were made and posters were put up, with the purpose of inviting the participants of the first wave of the study (1,705) to participate in this second stage. The elderly people who were not found after three visits on different days and at different times, or who refused to participate, had relocated, had become hospitalized or had died were excluded. Consequently, a final sample of 1,197 participants remained in the study.[19] For the present study, data from this stage of EpiFloripa were used.

After potential participants had received explanations about the research and had agreed to participate through signing an informed consent statement, face-to-face interviews were conducted and a questionnaire was filled out. The participants were then invited to attend the Health Sciences Center facilities for the clinical examination and accelerometry stage. Six hundred and four elderly people participated in this stage and, among these, 484 agreed to use an accelerometer. Seventy-one individuals with reduced mobility or with any disability (intellectual, physical and/or sensory) that impeded them from using accelerometers were excluded. The remaining 49 people, who would have been eligible to use an accelerometer, were excluded due to a technical error.

Accelerometer data were collected using the GT3X or GT3X+ models (Actigraph, Pensacola, Florida, United States) and were

analyzed using the Actilife software (Actigraph, Pensacola, Florida, United States). The participants were instructed to use the accelerometer for seven consecutive days and could remove it for sleep and in situations where the monitor would come into contact with water (e.g. bath, pool or beach). The device was attached to an elastic belt and fixed to the right hip above the iliac crest. On the second and fifth day of use of the accelerometer, telephone calls were made as a form of quality control. The accelerometers were programmed for a data sampling frequency of 30 Hz and these data were analyzed in 60-second windows. For data to be considered valid, the accelerometer needed to be used for four days a week (10 hours/day; or for weekend days, 8 hours/day). Consecutive zero periods of 60 minutes or more (with 2 minutes of tolerance) were considered to be non-use time and were excluded from the analysis.[21] The cutoff points for the intensities of physical activity were taken from the model of Freedson et al.,[22] as follows: light physical activity (LPA) (100-1951 counts/minute), moderate-to-vigorous physical activity (MVPA) (≥ 1952 counts/minute) and sedentary behavior (SB) (0-99 counts/minute). The minutes/week data of the variables were adjusted for the number of days of use. Valid data from accelerometer use were obtained from 425 elderly people (87.8%).

Sociodemographic variables (gender, age in years, marital status and education) came from a questionnaire. Information on the outcome of the present study, i.e. the multimorbidity variable for cardiometabolic diseases, was collected from the participants by means of a self-reported questionnaire, based on the following questions: "Has any doctor or healthcare professional ever said that you have or have had heart or cardiovascular disease?" and "Has any doctor or healthcare professional ever said that you have or have had hypertension (high blood pressure)?"; and for diabetes: "Has any doctor or healthcare professional ever said that you have or have had diabetes?" The answer options were yes or no, thus indicating the presence or absence of morbidities. People were considered to have cardiovascular diseases if they self-reported having a diagnosis of heart or cardiovascular disease and/or hypertension. The exposure variables, i.e. LPA, MVPA and SB, were defined in minutes/week and minutes/day through objective measurement using accelerometers.

Statistical analysis was performed using descriptive analysis with absolute and relative frequencies, 95% confidence intervals (95% CI), means and standard deviations, and medians and interquartile ranges (IQR). For the inferential analysis, receiver operating characteristic (ROC) curves were applied. ROC curves are a data attribute that is used to determine cutoff points in diagnostic or screening tests.[23] The area under the ROC curve provides an assessment of the discriminatory power of PA intensities for determining absence of cardiometabolic multimorbidity and the power of SB for determining its occurrence. Multimorbidity was considered to be the occurrence of cardiovascular disease in the presence of diabetes, or the occurrence of diabetes in the presence of cardiovascular disease. The construction of the ROC curve was given by the positioning of the sensitivity on the y axis as a function of [1 - specificity] on the x axis.[23] Sensitivity reports the percentage of affirmative outcomes that were correctly diagnosed using the indicator (true positives), while specificity describes the percentage of individuals who did not present the outcome and were correctly diagnosed using the indicator (true negatives). Thus, the values below the ROC curve represented the balance of the specificity and sensitivity pairs with all possible combinations. In determining a cutoff point, expressed as a bisector variable, the value of 0.5 was considered to be undetectable and 1.0, perfect detection.[24] Thus, for the times spent on LPA, MVPA and SB to be considered to be significant predictors of cardiometabolic multimorbidity, the lower limit of the confidence interval was taken to be greater than or equal to 0.50.[24] The 95% CI also determined predictive values. The analyses were stratified according to sex and whether or not diabetes and cardiovascular disease were present. The data were analyzed using the Stata software, version 13.0 (Stata Corporation, College Station, United States).

RESULTS

The study included 425 elderly people, and 65.0% of them were women. The average age of the men was 73 years (standard deviation ± 7.41). Most of them reported having a partner (83.1%) and their mean schooling level was 9 years (standard deviation ± 6.7). The women's mean age was 74 years (standard deviation ± 7.4). A majority of them were living without a partner (60.2%) and their mean schooling level was 7 years (standard deviation ± 5.2). The median LPA was 1,851 minutes/week (IQR: 1,358-2,283) among men and 1,887 minutes/week (IQR: 1435-2362) among women. The median MVPA was 121 minutes/week (IQR: 50-221) among men and 66 minutes/week (IQR: 18-133) among women. The median SB was 3,930 minutes/week (IQR: 3121-4746) among men and 3,688 minutes/week (IQR: 2971-4490) among women.

The values for the area under the ROC curve for the times spent on the PA and SB that had discriminatory power regarding cardiometabolic multimorbidity are presented in **Table 1**. The area under the ROC curve among men with diabetes that had predictive value was found within MVPA, with a value of 0.75 (95% CI: 0.538-0.962). Among women with diabetes, the area under the ROC curve with predictive value was found within MVPA with a value of 0.71 (95% CI: 0.524-0.886). Neither men nor women with cardiovascular disease presented areas under the ROC curve with predictive value or discriminatory power.

Among men and women with diabetes, the time spent on MVPA discriminated with regard to presence or absence of cardiovascular disease (**Figure 1**). Among elderly people of both sexes with cardiovascular diseases, there was no predictive length of time for physical

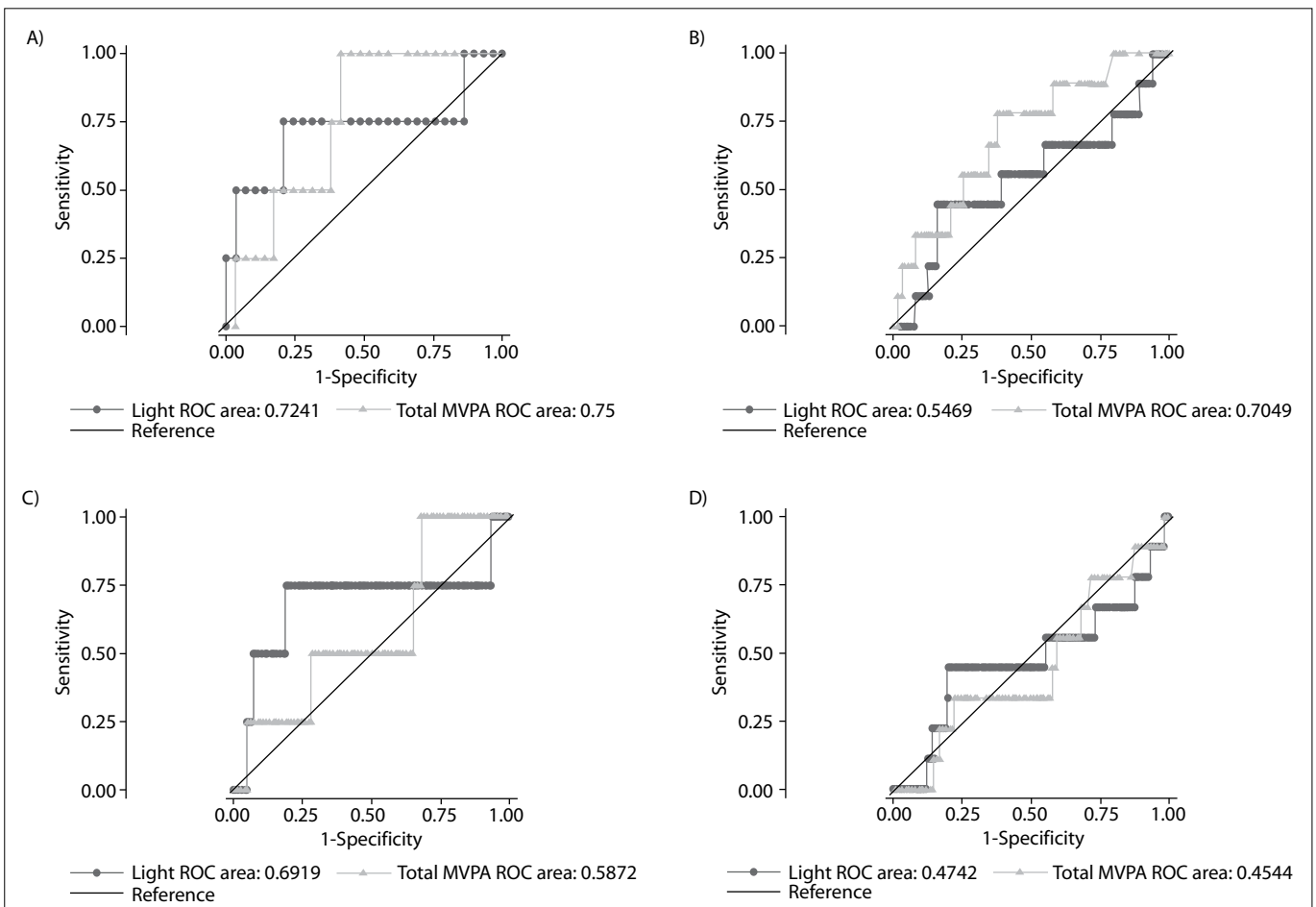
activity (**Figure 1**). Lastly, SB did not have predictive value for either men or women regarding the risk of cardiometabolic multimorbidity among those with diabetes and cardiovascular disease (**Figure 2**).

The values that were found to discriminate cutoff points for time spent on MVPA time, between presence and absence of multimorbidity, are highlighted in **Table 2**. Among the elderly participants

Table 1. ROC curve referring to weekly times spent doing different intensities of physical activity and sedentary behavior, for predict the presence or absence of cardiometabolic multimorbidity among elderly people, 2014 (n = 425)

Groups	Men (n = 160)				Women (n = 265)			
	Area under the ROC curve	95% CI of area	Sensitivity (%)	Specificity (%)	Area under the ROC curve	95% CI of area	Sensitivity (%)	Specificity (%)
With diabetes								
LPA	0.724	(0.326-1.000)	75.0	75.9	0.547	(0.310-0.784)	55.6	56.3
MVPA	0.750*	(0.538-0.962)	75.0	62.1	0.705*	(0.524-0.886)	66.7	65.6
SB	0.681	(0.284-1.000)	55.2	50.0	0.519	(0.273-0.766)	56.3	55.6
With cardiovascular diseases								
LPA	0.692	(0.277-1.000)	75.0	74.4	0.474	(0.228-0.721)	44.4	44.6
MVPA	0.587	(0.274-0.900)	50.0	51.2	0.454	(0.239-0.670)	44.4	42.9
SB	0.591	(0.482-0.699)	58.6	58.3	0.450	(0.187-0.714)	44.4	44.6

*Lower limit of confidence interval ≥ 0.50). LPA = light physical activity; MVPA = moderate-to-vigorous physical activity; SB = sedentary behavior; 95% CI = 95% confidence interval; ROC = receiver operating characteristic.



ROC = Area under the receiver operating characteristic; MVPA = moderate-to-vigorous physical activity.

Figure 1. ROC curve describing weekly time spent engaging in different levels of physical activity as a preventive discriminator for cardiovascular disease occurrence in men (A) and women (B) with diabetes; and for diabetes in men (C) and women (D) with cardiovascular disease, 2014 (n = 425).

with diabetes, it was seen that approximately 17 minutes of MVPA per day for men and 10 min per day for women were required for absence of multimorbidity.

DISCUSSION

The results from this study showed that only time spent on MVPA showed discriminatory power for presence or absence of cardiometabolic multimorbidity among elderly people with diabetes, of both sexes. The cutoffs for absence were minimums of approximately 17 minutes/day for men and 10 minutes/day for women. LPA and SB did not present predictive value for cardiometabolic multimorbidities in the elderly.

The daily MVPA cutoff point for absence of multimorbidity among elderly people with diabetes of both sexes was lower than the PA recommendations (150 to 300 minutes/week for moderate activities and 75 to 150 minutes/week for vigorous activities), based on subjective measurements for PA.[13] The differences in these findings may be due to the type of measurement for PA evaluation. The data of the present study were based on accelerometer measurements, which are considered to be the gold standard for analyses.[9]

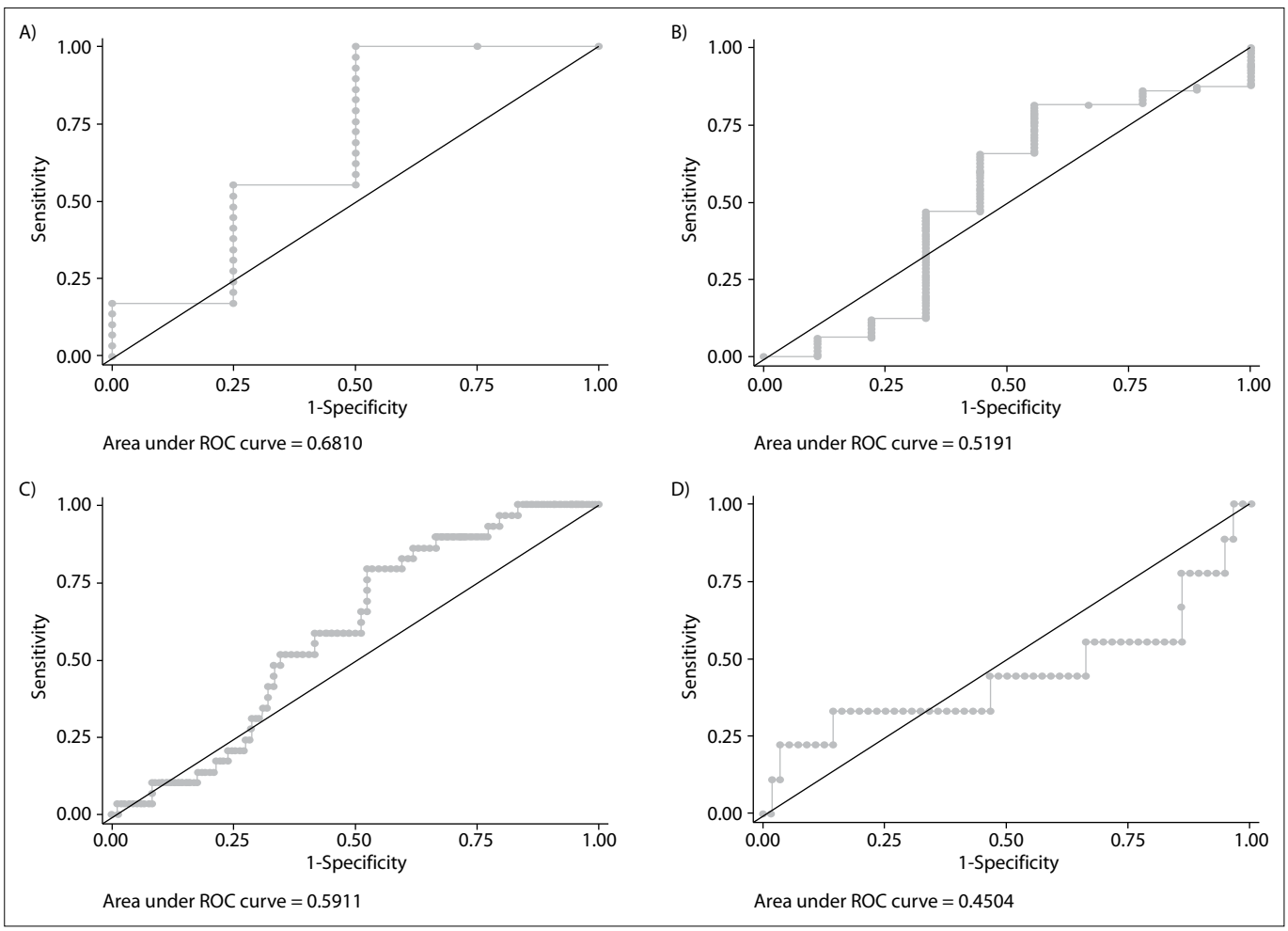


Figure 2. Area under the receiver operating characteristic (ROC) curve describing weekly time spent engaging in sedentary behavior as a risk discriminator for cardiovascular disease occurrence in men (A) and women (B) with diabetes; and for diabetes in men (C) and women (D) with cardiovascular disease, 2014 (n = 425).

Table 2. Time values and cutoff points for the estimated weekly and daily times spent engaging in moderate-to-vigorous physical activity, for predicting occurrence of cardiometabolic multimorbidity among elderly people in southern Brazil, 2014 (n = 425)

Groups	Men (n = 160)			Women (n = 265)		
	MD	Minutes*	Cutoff point**	MD	Minutes*	Cutoff point**
With diabetes						
MVPA	179	122	17.4	91	67	9.6

*Per week; **Minutes per day. MVPA = moderate-to-vigorous physical activity; MD = median.

Thus, the present study suggests that women with diabetes who accumulate at least 9.6 minutes/day or 67 minutes/week of MVPA are at lower risk of cardiometabolic multimorbidity; and that men will achieve this with at least 17.4 minutes/day or 122 minutes/week. These findings are concordant with the recommendation that any duration of physical activity is reflected in healthy outcomes.[13] For elderly people with diabetes, there is evidence showing that MVPA can reduce microvascular complications,[25] such as retinopathy, nephropathy and neuropathies, which are inherent to the disease.[26] Hence, the cutoff points identified in the present study may act as a facilitator for engaging elderly people in MVPA and, thus, minimizing the incidence of diseases affected by occurrence of multimorbidities.[27]

Our findings did not identify predictive values for time spent on LPA and SB for absence of multimorbidity for either sex, diagnosed either with diabetes or with cardiovascular disease. However, there is evidence showing the preventive effect of LPA on multimorbidities, as well as on improvement of functional capacities,[28] and its significant clinical effects on blood pressure, body weight and glucose among the elderly.[29]

Regarding SB, it has been recognized in the literature that long times spent on SB pose risks of multimorbidity,[30] regardless of PA engagement.[14] Although there are no cutoff points for SB, recommendations for replacing it with any level of physical activity have been shown to result in health benefits.[13] A study among elderly women showed that a transfer of 30 minutes from SB to MVPA reduced body mass index by 1.5 kg/m^2.[31] In the case of elderly people diagnosed with cardiometabolic disease, this effect may contribute to lifestyle improvements[9,27] and mental health,[11] as well as circumventing the effects of biological and genetic risks in this population.[27] It is possible that in this group, LPA and SB were not predictive because of the diseases considered, which are more responsive to high-intensity actions, such as MVPA. It is known that among elderly people who reach light levels of physical activity in at least one weekly practice, the prevalence of multimorbidity is lower; however, this reduction is proportional to the increase in activity intensity.[32]

The strength of the present study is that makes a contribution to the small amount of evidence among elderly people in which objective measurement of PA were used.[9] Its practical application is that the cutoffs presented can assist healthcare professionals, researchers and managers in planning and implementing interventions to reduce evidence-based disorders with multimorbidity. Moreover, these data contribute to both population-based and clinical contexts and may guide prescription of PA as a means for complementing treatment of these diseases.

However, some caveats are necessary in reading these data. They refer to a population-based sample residing in a region of Brazil with a high human development index (0.847), compared with the national average (0.727).[33] The self-reporting of diseases may have been biased, given that this was dependent on recalling a doctor's diagnosis. However, we excluded elderly people from our sample if they had a diagnosis of dementia or cognitive problems and would be unable to use an accelerometer. Lastly, multimorbidity was considered only in terms of cardiovascular disease (combined with hypertension) and diabetes, which limits comparability with other studies in which additional diseases were considered in the investigation.

CONCLUSION

The accumulated time that elderly people with diabetes spent on MVPA was a predictor of cardiometabolic multimorbidity. Therefore, as a practical application in the future, it is recommended that elderly men with diabetes should perform moderate-to-vigorous physical activity for at least 17 minutes/day, and elderly women with diabetes for 9.6 minutes/day, to predict absence of multimorbidity. LPA and SB were not predictors for the absence of multimorbidity in either sex for diagnoses of either diabetes or cardiovascular diseases.

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Prevalence of xerostomia and its association with systemic diseases and medications in the elderly: a cross-sectional study

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AUTHORS' KEY WORDS:
Elderly.
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Effect of drugs.
Hyposalivation.
Dry mouth.

ABSTRACT

BACKGROUND: Dry mouth syndrome or xerostomia is defined as decreased salivary flow or hypofunction of salivary glands. Its origins are multicausal and might be the result of a change in the salivary glands or a systemic imbalance.

OBJECTIVE: To ascertain the prevalence of self-reported xerostomia and to identify associated factors.

DESIGN AND SETTING: Cross-sectional study on the entire population of 293 elderly people over 60 years of age living in a Brazilian municipality.

METHODS: Data were gathered from a questionnaire that asked about demographic data, chronic diseases and use of continuous medications, and which used the Xerostomia Inventory (XI) to evaluate dry mouth sensation. Our analysis consisted of multivariate regression and estimation of odds ratios (OR) and their respective 95% confidence intervals (CI) in binary logistic regression models.

RESULTS: The prevalence of self-reported xerostomia was 19.1%. Elderly people with diabetes had higher odds of having self-reported xerostomia (OR: 3.59; 95% CI: 1.48-8.68; P < 0.001) as did those who had chronic diseases and used continuous medication (OR: 2.3; 95% CI: 1.19-4.67; P = 0.009). Elderly people who used continuous medication for the gastrointestinal tract were more likely to have xerostomia (OR: 2.14; 95% CI: 1.03-1.44; P = 0.030).

CONCLUSIONS: Elderly people with diabetes and chronic diseases who were using continuous medication were more likely to have dry mouth. Use of continuous medications for the gastrointestinal tract led to a greater chance of having self-reported xerostomia.

INTRODUCTION

Saliva plays an important role in oral health. Besides being involved in protection against bacteria and fungi, it transports nutrients and digestive enzymes, lubricates the mucosa, facilitates mastication, swallowing and speech, and acts in the process of tooth remineralization.[1,2] Saliva is produced by salivary glands, which are exocrine, such as the parotid, submandibular and sublingual glands. These are the most important pairs of glands and are responsible for 95% of saliva production.[3] In addition, there are other smaller-sized glands throughout the oral cavity, lips and tongue, which help in the process of salivation. These structures produce saliva at certain moments and respond to a series of sensory, taste and olfactory stimuli.

The volume of saliva production may vary according to stimulation. The salivary flow is greater after meals and lower during sleep. In healthy individuals, there is, on average, 1000 ml to 1500 ml of saliva secretion in a day.[3] However, there are several consequences of decreased salivary flow. These include some diseases and problems such as cavities, periodontal disease, various infections, dysphagia, halitosis and difficulties with the stability of dental prostheses.[4]

Dry mouth syndrome or xerostomia is defined as decreased salivary flow or hypofunction of the salivary glands.[5] Its origins are multicausal and might be the result of a change in the salivary glands or a systemic imbalance.[5-7] Some determinants such as continuous use of medication, radiation, systemic diseases and factors common to aging might be associated with a dry mouth condition.[8] Xerostomia is not considered to be a disease but, rather, a manifestation of a series of pathological conditions that considerably alter patients' quality of life. It can affect chewing, swallowing, use of prostheses and speech.[9] Villa et al. reported that xerostomia that is secondary to hyposalivation may also result in fungal infections such as candidiasis, tooth decay, halitosis, changes to the sense

of taste and a burning sensation in the mouth.[10] In addition, they reported that xerostomia may be a consequence of head and neck radiotherapy, depression, anxiety, stress and even malnutrition. It needs to be emphasized that some of the most common chronic conditions today are symptoms of depression and anxiety.[10]

There is some evidence that certain chronic diseases might be determinants of xerostomia and/or hyposalivation.[11-15] One of the diseases most investigated today is diabetes mellitus (DM), a chronic disease characterized by hyperglycemia and insufficient insulin production by the pancreas.[8] The insulin that is produced has the function of regulating carbohydrate metabolism, and its absence causes glucose to remain in the bloodstream, thus characterizing a state of hyperglycemia. Hyposalivation in patients with uncontrolled diabetes might be caused by an increase in diuresis, which could affect saliva production,[16] but it might also be caused by a condition called neuropathy.[17-20] Therefore, there still seems to be much doubt concerning the cause-and-effect relationship between this pathological condition and xerostomia.[21]

In addition to correlations with chronic diseases, a relationship between xerostomia and use of continuous medication has been highlighted. Wiener et al.[22] and Van der Putten et al.[23] added anticholinergic, diuretic and antipsychotic drugs to the list of associated factors. Freitas et al.[6] also included some types of analgesic and xerostomia-associated antibiotics.

Xerostomia is an important condition but is still little-known by the population and has been neglected by health professionals. In addition, studies on this condition are scarce and unenlightening. The absence of explanations about the determining factors of this condition can be highlighted, especially in relation to the non-institutionalized elderly population. The prevalence of xerostomia in the population has been reported to range from 5.5% to 46%.[10] Gender and age-related differences have been observed, such that older individuals may have more symptoms of xerostomia. However, this could be due to the higher number of xerogenic drugs used to treat chronic diseases and might not only be related to age.[10,21] Nonetheless, these associations still seem unclear.

OBJECTIVE

Based on these scientific data, the objective of the present study was to ascertain the prevalence of self-reported xerostomia and to identify its association with chronic diseases, continuous medication use, age and gender, among elderly people in a municipality in southern Brazil.

The hypothesis for this study was that the presence of chronic systemic diseases and use of medications among the elderly people investigated would show associations with self-reported xerostomia.

METHODS

This study was submitted to and approved by the Research Ethics Committee of Faculdade Meridional (IMED), under the approval no. 2,711,544 and CAEE 90966718.0.0000.5319, on June 13, 2018, in accordance with the rules of resolution 466/12. All individuals participating in the research signed an informed consent statement in which they agreed to be part of it. Care was taken in this study to ensure confidentiality regarding identity and privacy, and also the confidentiality of the data obtained.

The present work was compiled in accordance with the recommendations of the STROBE statement (Strengthening the reporting of observational studies in epidemiology).[24]

Design, sample and location of study

The present study took a quantitative approach, with a cross-sectional design. The study population consisted of the elderly population of the municipality of Vanini, which is located in the northwest of the state of Rio Grande do Sul. It has an estimated total population of 2,104 inhabitants and a total area of 69.9 km².[25]

The population of Vanini over 60 years of age consisted of 300 people.[25] All of this population was eligible, but seven people were excluded from the study (see criteria, below). Thus, the study population was formed by 293 elderly people aged 60 years and over. There were no losses in this study.

Inclusion and exclusion criteria

All the elderly population aged 60 years and over participated in this study. Only those with neurological conditions and patients with head and neck cancers undergoing radiotherapy were excluded from the study.

Data collection procedures

Data collection was performed through home visits to all houses in the municipality, made by a team composed of four students of the dentistry course, between August and September 2018. First, a pilot test was performed on twenty elderly people in order to train the researchers to collect data and to check for possible doubts or problems relating to completion of the research instrument by the elderly subjects, thus minimizing possible bias in the research methodology. However, there were no changes to the procedures and, later on, these data from the pilot study were included in the final sample.

The data relating to the variable of self-reported xerostomia were collected by means of a validated questionnaire for xerostomia and dry mouth sensation that is used to verify cases of self-reported xerostomia. The Xerostomia Inventory (XI) includes eleven items.[26] A previous study validated this questionnaire for use among Brazilian individuals.[27] Each item in this questionnaire has five response options: never, hardly ever, occasionally, fairly often and very often. The questions are the following: "Do you have difficulties swallowing any foods?", "Do you have difficulties eating dry foods?", "Does your mouth feel dry when eating a meal?", "Does your nose feel dry?", "Does your face feel dry?", "Do you suck sweets or cough

lollies to relieve dry mouth?", "Do you get up at night to drink?", "Do your eyes feel dry?", "Do your lips feel dry?", "Does your mouth feel dry?" and "Do you sip liquids to aid in swallowing food?"

We added questions asking for demographic data (gender and age) and questions asking about chronic diseases and continuous medication use, consisting of the following: "Do you use continuous medications?", "Do you have diabetes, thyroid dysfunction, rheumatoid arthritis, depression and/or anxiety, HIV, hypertension and/or any other diseases?" and "Do you use medications for the stomach, cholesterol or diuretics, or do you use anticoagulants?" In addition, we also included a question on "Difficulty in using a dental prosthesis".

Outcome variable

We composed the outcome variable of this study based on studies conducted by Thomson et al. in 1999[26] and 2006,[28] which used a single question from the XI questionnaire to ascertain the prevalence of xerostomia. In the present study, we did not perform an oral clinical evaluation.

We combined the responses to the questions of the XI questionnaire into negative answers (no) = never, hardly never and occasionally; and positive answers (yes) = fairly often and very often. Thus, people who answered positively to the XI question "My mouth feels dry" were included in the self-reported xerostomia group.[28]

Covariables

The variables considered were gender (female or male), age (60 to 69 years old or 70 years old or over), diabetes (yes/no), thyroid dysfunction (yes/no), rheumatoid arthritis (yes/no), depression and/or anxiety (yes/no), arterial hypertension (yes/no), HIV (yes/no), other chronic diseases and continuous medication (yes/no), use of medicine for cholesterol (yes/no), use of gastrointestinal tract medication (yes/no), use of diuretic (yes/no), use of anticoagulants (yes/no) and difficulty in using a dental prosthesis (yes/no).

The variable "other chronic diseases and continuous medication" (yes/no) was composed of diseases other than the most prevalent diseases mentioned previously and was considered together with use of drugs to control these diseases. This formed a reliable way of knowing whether the elderly individual was being medicated. The diseases included in this variable were fibromyalgia, Parkinson's disease, hypothyroidism, osteoporosis, cardiac arrhythmia and multiple sclerosis.

Data analysis

For the data analysis, we performed descriptive analyses and bivariate and multiple regressions. In the multiple analysis, we estimated odds ratios (OR) and their respective 95% confidence intervals, with crude variables and variables adjusted for exposure in binary logistic regression models (P-value < 0.05). The data were analyzed using the Statistical Package for the Social Sciences (SPSS) software, version 20.0 (IBM, Armonk, New York, United States).

RESULTS

Table 1 describes the results regarding demographic variables, chronic diseases, difficulties and use of continuous medications. Most of the elderly people were between 60 and 69 years old, and a majority of the population (56%) was male.

Among these elderly people, 12.6% presented diabetes; 10.2%, diseases relating to thyroid dysfunction; 23.2%, depression and anxiety; 57%, arterial hypertension; and 10.2%, rheumatoid arthritis. Moreover, 40.3% of them reported having other diseases, i.e. in addition to those being researched in this study. Thus, in addition to the medications used for the chronic diseases that they reported (diabetes, thyroid dysfunction, rheumatoid arthritis, depression and anxiety, HIV and hypertension), they also used cholesterol-lowering drugs (27%) and medicines for stomach and circulatory problems (17.1%). These elderly people also had other chronic diseases and used continuous medications for their control (40.3%).

Table 2 shows the results relating to Xerostomia Inventory (XI) variables. Presence of dry mouth sensation was reported by 19.1% of the participants when asked the question "Does your mouth feel dry?" Furthermore, 13.3% had difficulty in swallowing food, 14.7% sipped liquids to aid in swallowing food and 30.4% habitually got up at night to drink. In the question about having difficulty in using a dental prosthesis, only 2% of the elderly people answered yes; however, 100% of them were using some type of dental prosthesis.

To perform the binary logistic regression, all variables that had an association with a P-value < 0.20 were entered into the crude model: gender, depression or anxiety, diabetes, other chronic diseases with continuous medication, gastrointestinal tract medication, cholesterol drugs and use of anticoagulants. After multivariate adjustment, the variables of diabetes, other chronic diseases and gastrointestinal tract medication remained significant (P < 0.05), but the other variables lost their associations in the final adjusted multivariate regression analysis model (**Table 3**). Elderly people with diabetes had higher odds of having self-reported xerostomia (OR: 3.59; 95% CI: 1.48-8.68; P < 0.001), as did those who had chronic diseases and used continuous medication (OR: 2.3; 95% CI: 1.19-4.67; P = 0.009). The elderly people who continuously used medication for the gastrointestinal tract also had higher odds of having xerostomia (OR: 2.14; 95% CI: 1.03-1.44; P = 0.030).

DISCUSSION

The purpose of this study was to ascertain the prevalence of self-reported xerostomia and to identify its associations with chronic diseases, continuous medication use, age and gender, among the elderly, in order to learn about these data, which had never been investigated in this location. The results showed that the prevalence of self-reported xerostomia was 19.1%, through using the XI question "Does your mouth feel dry?". It is also important to point out that 13% reported feeling "difficulties in swallowing certain

foods" and 14.7% "sipped liquids to aid in swallowing food", which are important responses for indicating the presence of xerostomia. Xerostomia is a subjective sensation of dry mouth and is assessed by asking individuals directly about their experience with this disease. According to other studies, the question " Does your mouth feel dry" reveals the prevalence of dry mouth.[26,28] Thus, salivary flow was not measured in this study. Dry mouth is an important condition that negatively impacts people's daily lives, so the results presented here should be considered with caution.

The study conducted by Thomson et al. among adults and the elderly showed that the prevalence of xerostomia was 10%, with no difference between the genders.[28] Perotto et al.[12] evaluated 117 dental patients, among whom 24.8% reported having xerostomia, which was associated with medication use. This differed from the results found by Freitas et al.,[6] in which 59% of the elderly subjects reported having a feeling of dry mouth during most of the day, and this sensation was associated with the medication that they were using. The estimated global prevalence of dry mouth was found to be 22% among adult and elderly individuals in a systematic review study.[29] However, the prevalence was higher in studies conducted exclusively among elderly people, and presence of xerostomia in these studies was correlated with

Table 1. Description of demographic variables, chronic diseases and use of continuous medications among elderly people in the municipality of Vanini, Brazil, 2019 (n = 293)

Variables	n	%
Age		
60-69 years	175	59.7
70 or over	118	40.3
Gender		
Female	127	43.3
Male	166	56.7
Diabetes		
Yes	37	12.6
No	256	87.4
Thyroid dysfunction		
Yes	30	10.2
No	263	89.8
Rheumatoid arthritis		
Yes	8	2.7
No	285	97.3
Depression and/or anxiety		
Yes	68	23.2
No	225	76.8
HIV		
Yes	6	2.0
No	287	98.0
Hypertension		
Yes	167	57.0
No	126	43.0
***Other chronic diseases and continuous medication**		
Yes	118	40.3
No	175	59.7
Use of medicine for cholesterol		
Yes	80	27.3
No	213	72.7
Use of gastrointestinal tract medication (antacids/H2/ IPB antagonists)		
Yes	50	17.1
No	243	82.9
Use of diuretic		
Yes	92	31.4
No	201	68.6
Use of anticoagulants		
Yes	50	17.1
No	243	82.9
Difficulty in using dental prosthesis		
Yes	6	2.0
No	287	98.0

***Other chronic diseases/medication** – fibromyalgia, Parkinson's disease, hypothyroidism, osteoporosis, cardiac arrhythmia, multiple sclerosis.

Table 2. Distribution of responses to questions regarding dry mouth (xerostomia) from the Xerostomia Inventory (XI), among elderly people in the municipality of Vanini, Brazil, 2019 (n = 293)

Variables	n	%
I have difficulties swallowing certain foods		
Yes	39	13.3
No	254	86.7
My mouth feels dry when eating a meal		
Yes	38	13
No	255	87
I sip liquids to aid in swallowing food		
Yes	43	14.7
No	250	85.3
I get up at night to drink		
Yes	89	30.4
No	204	69.6
I suck sweets or cough lollies to relieve dry mouth		
Yes	40	13.7
No	253	86.3
My eyes feel dry		
Yes	42	14.3
No	251	85.7
My lips feel dry		
Yes	42	14.3
No	251	85.7
I have difficulty in eating dry foods		
Yes	39	13.3
No	254	86.7
My mouth feels dry		
Yes	56	19.1
No	237	80.9
The skin of my face feels dry		
Yes	26	8.9
No	267	91.1
The inside of my nose feels dry		
Yes	26	8.9
No	267	91.1

older age and the need for continuous-use drugs with high xerostomic potential, among which most were used to treat chronic diseases.[29]

In a study conducted by Islas-Granillo et al.,[30] 68.3% of the elderly subjects had xerostomia. Niklander et al.,[31] in a survey on 566 individuals, observed that 42.4% of them took some type of medication and, of these, 17.92% reported having dry mouth. According to Lopes et al.,[32] out of 20 women surveyed, 50% reported having xerostomia. Another study, conducted by Wiener et al.,[22] showed that among 252 elderly individuals surveyed, 28% had xerostomia associated with sociodemographic conditions, medication use and systemic conditions. The complaint of dry mouth needs to be taken seriously by healthcare professionals and, thus, individuals with this complaint should be asked about what they feel, their medical history and the medicines that they are taking, considering that indefinite-cause xerostomia is an undiagnosed systemic imbalance.

In the present study, there was a statistically significant association between self-reported xerostomia and presence of the chronic disease diabetes mellitus. The chances that an individual with DM who uses continuous medication for this condition will have xerostomia or dry mouth are 3.59 times higher than among other

Table 3. Bivariate (crude) and multivariate (adjusted) binary logistic regression model for the self-reported xerostomia variable, among elderly people in the municipality of Vanini, Brazil, 2019

	Crude OR (95% CI)	P-value*	Adjusted OR (95% CI)	P-value**
Age				
60 to 69	1		-	-
≥ 70	0.95 (0.52-1.72)	0.867		
Gender				
Male	1			
Female	1.63(0.88-2.99)	*0.116*	1.63 (0.83-3.20)	0.152
Difficulty in using dental prosthesis				
No	1		-	-
Yes	2.15 (0.38-12.0)	0.380		
Depression or anxiety				
No	1			
Yes	0.62 (0.32-1.20)	*0.160*	0.82 (0.39-1.72)	0.614
Diabetes				
No	1		1	
Yes	3.12 (1.41-6.90)	*0.005*	3.59 (1.48-8.68)	***< 0.001***
Arterial hypertension				
No	1			
Yes	0.68 (0.37-1.25)	*0.222*		-
Thyroid dysfunction				
No	1			
Yes	1.62 (0.68-3.87)	*0.272*	-	-
Other chronic diseases and continuous medication				
No	1			
Yes	2.34 (1.29-4.23)	*0.005*	2.3 (1.19-4.67)	***0.009***
Gastrointestinal tract medication				
No	1		1	
Yes	2.38 (1.20-4.73)	*0.013*	2.14 (1.03-1.44)	***0.030***
Medicine for cholesterol				
No	1			
Yes	1.99 (1.08-3.68)	0.270	-	-
Use of diuretic				
No	1			
Yes	1.27 (0.69-2.35)	0.440	-	-
Use of anticoagulants				
No	1		1	
Yes	1.86 (0.92-3.75)	*0.083*	1.17 (0.54-2.54	0.676

*Chi-square test; **Wald test (P < 0.05 - statistically significant and shown in italics).

OR = odds ratio; 95% CI = 95% confidence interval; % = frequency-percentage.

Adjusted according to the following variables: gender, depression or anxiety, diabetes, other chronic diseases, gastrointestinal tract medication, cholesterol medication, anticoagulant use (P < 0.05).

elderly people. It should be noted that all the elderly people in the present study were using medication at the time of data collection.

In another study, presence of xerostomia among patients with decompensated DM was explained by increased diuresis or polyuria, which could affect saliva production.[13] Carda et al.[33] surveyed 33 patients with type 2 DM and found that 76.4% of them had symptoms of xerostomia. However, it has been reported that it remains undetermined whether the presence of xerostomia is higher in patients with or without diabetes.[14] In a further study, the prevalence of xerostomia among 120 elderly people diagnosed with type 2 diabetes (60 insulin-dependent individuals and 60 who did not require it) who had been undergoing treatment for at least one year using continuous medication was surveyed. Dry mouth or xerostomia was evaluated on a visual analogue scale. Among these patients, 92.5% presented hyposalivation and 49.2% had moderate to severe dry mouth or xerostomia.[15]

Although the present study did not show any significant relationships with depression and anxiety, high blood pressure or thyroid dysfunction, several other studies have highlighted this association. Thomson et al.[28] found relationships between xerostomia and the use of antidepressants, iron supplements and analgesics. The complaint of dry mouth was more frequent among adults who were using antidepressants, and also among those using other medications such as iron and narcotic painkillers. The individuals who were taking antidepressants were 22 times more likely to feel dry mouth or proper xerostomia.[28] Perotto et al.[12] observed other predisposing factors for xerostomia, consisting of age 50 years and over and presence of diabetes and hypertension.

A study by Bulthuis et al.[34] estimating the possible role of stress in salivary secretion showed a correlation between stress and xerostomia, and it was concluded that stress was related to dry mouth sensation and consequently had an impact on quality of life. A study among adults showed a strong association between xerostomia and quality of life.[35] According to Abrão et al.,[36] alterations such as xerostomia and hyposalivation are common in rheumatic diseases, such that xerostomia affects 1% of patients with rheumatoid arthritis. That study evaluated 604 patients with rheumatological disorders and showed that 43% of them had hyposalivation; this hyposalivation and dry mouth/xerostomia increased with increasing severity of the rheumatological condition.[36]

In the present study, there was an association with the presence of other chronic diseases in the survey questionnaire and their continuous medication. These elderly individuals were 2.3 more likely to have self-reported xerostomia, with a prevalence of 42%. Thus, it can be inferred that, in addition to chronic diseases, the continuous medication itself might have been the cause of these results. Korn et al.[5] observed that various systemic disorders could cause xerostomia or the feeling of dry mouth, among them Sjögren's syndrome. Regarding the results from the present study, it is important to stress that the amount of medication used by the elderly individuals was not investigated, given that there could have been significant differences relating, not to other diseases, but to the higher number of drugs used to treat different chronic illnesses.[5]

Chronic diseases are the ones that most affect the elderly, and they lead to use of large-scale continuous medication.[37] In addition to medications for diabetes, depression and anxiety, others can be considered, such as medications for cardiovascular diseases, nervous system disorders, gastrointestinal tract diseases and metabolic disorders. Therefore, there is an interaction of factors that might cause dry mouth sensation or hyposalivation. In addition to the chronic diseases already mentioned, some drugs could cause xerostomia as a side effect of the treatment.

In the present study, there was a statistically significant association between medication for the gastrointestinal tract and xerostomia. The elderly individuals who used continuous medication for the gastrointestinal tract were 2.14 times more likely to have the condition of xerostomia (28.6%). A study to assess the side effects of several drugs showed an association between the presence of xerostomia and a digestive tract drug called ondansetron.[6] However, it has been reported that medications that cause dry mouth sensation could mainly be those with antisialogogic effects, including anticholinergics, antidepressants, diuretics, antihypertensives, antipsychotics and anxiolytics.[22]

In another study, dry mouth sensation was correlated with the drugs used. It was observed that 11 out of 20 medications used by the elderly subjects had side effects of xerostomia and/or hypofunction of the salivary glands, namely: dipyrone, clonazepam, morphine, ondansetron, enalapril, clonidine, metronidazole, tramadol, clindamycin, diazepam and fluoxetine.[6] Similar results were found in a study by Van Der Putten,[23] in which the medications that could be the cause of dry mouth sensation or xerostomia were investigated, namely: anticholinergics, antihistamines, antipsychotics, diuretics, sympathomimetics, bronchodilators, benzodiazepines, hypnotics, opioid analgesics, muscle relaxants and antidepressants. According to Perotto et al.,[12] the symptoms of xerostomia occurred in individuals using antidepressants, anticonvulsants and antihypertensives. According to Villa et al.,[10] the main cause of hyposalivation and/or xerostomia was the use of medications that included antidepressants, antihypertensives, anticoagulants, antiretrovirals, levothyroxine, supplements and multivitamins, hypoglycemics, steroid inhalers and non-steroidal anti-inflammatory drugs.

It needs to be borne in mind, as a limitation of the present study, that its design was cross-sectional and therefore cause and effect could not be verified, considering that data were analyzed at a single moment. Another limitation that needs to be acknowledged is the fact that memory bias is possible among elderly people when they answer questions. In addition, the variable "chronic diseases and continuous use of medicines" was very broad. Nonetheless, this formed a way of including other diseases and the medicines indicated for their

control. Furthermore, this study did not identify risk factors for the self-reported xerostomia analyzed here. If we had been able to evaluate long-term reports on these individuals and their salivary levels, it might have been possible to observe the incidence and factors that could interfere with this condition. Another limitation was the fact that the municipality analyzed is small and we cannot extrapolate the results to other municipalities that are not similar to this one. However, it is important to highlight that the entire population aged 60 years and over that was living in this location participated in this research.

Knowing the causes of xerostomia from self-reports given by the participants in this study will enable implementation of guidance interventions to improve these individuals' quality of life. However, the data on causality remains uncertain and more information is required in order to be able to reach conclusions regarding the determinants of xerostomia. Nonetheless, the present study is of great relevance and importance for the population surveyed, given that it provides real current data on the elderly people living in this municipality.

CONCLUSIONS

From the results we obtained in this study, it was possible to conclude that the prevalence of self-reported xerostomia among the elderly people in this municipality is moderate, which corroborates the findings in the literature.

Elderly people with diabetes and other chronic diseases using continuous medications are more likely to have dry mouth. Use of continuous medications for the gastrointestinal tract gives rise to a greater chance of having self-reported xerostomia among elderly people.

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Computed tomography with low-dose radiation versus standard-dose radiation for diagnosing fractures: systematic review and meta-analysis

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KEYWORDS (MeSH terms):
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Radiation dosage.
Tomography, X-ray computed.

AUTHORS' KEYWORDS:
Low-dose CT.
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X-ray.
ALARA.
Detection rate.

ABSTRACT

BACKGROUND: Computed tomography (CT) accounts for 13% of all radiological examinations in the United States and 40-70% of the radiation that patients receive. Even with the advent of magnetic resonance imaging (MRI), CT continues to be the gold standard for diagnosing bone fractures. There is uncertainty as to whether CT with a low radiation dose has a fracture detection rate similar to that of standard-dose CT.

OBJECTIVE: To determine the detection rate of low-dose radiation CT and standard-dose radiation CT for fractures, in patients with suspected fractures.

DESIGN AND SETTING: Systematic review of comparative studies on diagnostic accuracy within the evidence-based health program at a federal university in São Paulo (SP), Brazil.

METHODS: We searched the electronic databases Cochrane Library, MEDLINE, EMBASE and LILACS up to June 29, 2020, for studies evaluating the detection rates of low-dose CT and standard-dose CT for diagnosing bone fractures. The Research Triangle Institute (RTI) item bank tool was used for methodological quality evaluation.

RESULTS: The fracture detection rate according to the number of bones evaluated, using CT with low-dose radiation was 20.3%, while with standard-dose radiation it was 19.2%, and the difference between the methods was not significant. The fracture detection rate according to the number of patients, using CT with low-dose radiation was 56.0%, while with standard-dose radiation it was 58.7%, and this difference between the methods was not significant, either.

CONCLUSION: CT with low-dose radiation presented detection rates similar to those of CT with standard-dose radiation, regardless of the bones evaluated.

REGISTRATION NUMBER: CRD42019148491 at the PROSPERO database.

INTRODUCTION

Ionizing radiation such as X-rays is a singular form of energy that surmounts the binding energy of electrons that orbit atoms and molecules.[1] In biological material exposed to X-rays, the most common consequential scenario is that this creates hydroxyl radicals from interactions between X-rays and water molecules. These radicals, in turn, interact with deoxyribonucleic acid (DNA) to cause breakage of bonds or damage to the base.[1] Thus, mutations, chromosomal translocations and fusions between genes can occur, which in some cases may lead to cancer.[1]

All X-ray-based imaging methods have the characteristic in common of a trade-off between image quality and radiation dose, since all forms of ionizing radiation can damage tissues.[2] In patients undergoing radiographic and/or tomographic monitoring, the patient's exposure to radiation needs to be considered, and this poses a challenge to radiologists regarding dose reduction.[3,4]

The main concern in diagnostic imaging is that a stochastic lesion of radiation-induced cancer could develop, which can occur with any radiation dose.[5-7] Conversely, deterministic effects occur only when the threshold has been exceeded and, above that, the incidence and severity of the injury increase with the radiation dose.[6,7] It also needs to be taken into account that the pediatric population is 10 times more sensitive to radiation than adults.[8]

To date, no safe dose of ionizing radiation, below which there is no risk of cell damage and subsequent risk of cancer, has been established.[9,10] However, it has been estimated in the United States that about 1.5%-2.0% of all malignancies can be attributed to radiation from computed tomography (CT) scans.[1,6] Taking all imaging examinations into account, this proportion ranges

from 0.6% to 3.6%.[11] The risk of cancer increases by 0.01% for each mSv emitted in imaging tests.[12]

Thus, there is a growing awareness of the need to use the lowest possible radiation dose level that is capable of providing appropriate diagnostic information, also known as the ALARA principle (As Low As Reasonably Achievable).[9,11-24]

CT is the gold standard for diagnosing fractures,[10,25-27] characterizing them in greater detail, identifying hidden fractures and showing incomplete union.[27,28] In musculoskeletal radiology, low-dose CT has shown good results in studies with pre and postoperative scoliosis evaluations, as well as in diagnosing lytic injuries and fractures in patients with multiple myeloma.[5,29,30] However, when metallic components are present in the bones studied, standard-dose CT scans have better image quality, with fewer artifacts, than low-dose CT scans.[31]

OBJECTIVES

The aim of this study was to determine the detection rates of computed tomography with low radiation dose and computed tomography with standard radiation dose for fractures, independent of the bone suspected, in patients with suspected fractures.

METHODS

Study model

The study model followed the guidelines for systematic reviews of diagnostic accuracy studies, in the Cochrane Diagnostic Reviewer's Handbook version 5.1.

Inclusion criteria

The search of the literature was performed in accordance with the guidelines for Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA). Studies evaluating the diagnostic accuracy and detection rates of fractures in patients with suspicion of fractures, evaluated using low-dose CT and standard-dose CT were included regardless of publication status and regardless of severity and time of disease. We did not put any restrictions on patient age, origin, language or publication status of the study. There was no exclusion regarding population size or patient age. In cases of missing information, the authors were contacted by email.

Participants

The participants in this study were men and women of all ages with suspected bone fractures who underwent low-dose CT or standard-dose CT.

Selection of studies and data extraction

The studies selected were those that were potentially eligible for inclusion in terms of relevant articles or abstracts from reference journals. Two authors performed independent selections for eligibility. In cases of disagreement, a third author was consulted. Data extraction was performed using a standardized form.

Evaluation of methodological quality

Eligible studies with a control group were evaluated using the QUADAS 2 tool (Quality Assessment of Diagnostic Accuracy Studies).[32] In all eligible studies, the RTI Item Bank questionnaire was used. This is a tool that focuses on evaluation of biases and precision).[33,34]

All forest plots were made using the Review Manager software (RevMan), version 5.3, in order to obtain sensitivity and specificity values and the respective 95% confidence intervals (CI). We expressed dichotomous data as odds ratios (OR) with a 95% CI and continuous data as mean differences (MDs) with 95% CI. The study was approved by our institutional review board, under the approval number 7184070819, dated October 2, 2019. The review was approved by the PROSPERO database. No funding or support was provided for this study.

Research methods for choosing studies

A thorough systematic search of the literature was performed in June 2020, in the PubMed, EMBASE, Cochrane Library and LILACS online scientific publication databases, for all original-language publications. The search was conducted using the medical subject headings (MeSH). The MeSH terms used included the following: fractures, bone; radiation dosage; tomography, X-ray computed. The reference lists of the studies included and the main reviews on the subject were also evaluated. Manual searches were also carried out in the lists of references. The full search strategy is presented in **Table 1**.

RESULTS

Studies selected

The search for this systematic review yielded 468 studies using the following MeSH terms: fractures, bone; radiation dosage; tomography, X-ray computed.

There were no studies in which low-dose CT and standard-dose CT were performed on the same patient. Also, no study had a control group. Therefore, it was not possible to assess accuracy, and only the detection rate could be evaluated in the meta-analysis. A total of five studies fulfilled the inclusion criteria and were included in qualitative analysis (**Figure 1**).[16,17,18,35,36] Two studies did not provide all the data.[16,35] Konda et al. was not used because it did not have the necessary blinding for inclusion in this systematic review.[28]

Analysis on the studies

Lee et al. conducted two studies: one published in 2017[17] and another in 2018.[18] In both, the period between January

and September 2016 was assessed. However, these studies were performed using different devices, with 64 channels and 320 channels, respectively. In Lee et al.,[18] there were evaluations by two doctors: one from the emergency department and one radiologist. For the statistical evaluation, we use the data from the radiologist because this specialist has the responsibility for issuing reports.

Four studies reported the numbers of patients evaluated and how many had fractures.[17,18,35,36] Four studies reported the numbers of bones evaluated and how many had fractures.[16–18,36] There was no study with a control group.

All the studies reported that the reduction in the radiation dosage of the CT scans was around 50%. The CT devices, bones evaluated and radiation dosages in the studies reviewed are shown in **Table 2**.[16-18, 35,36]

Table 1. Search strategies used in each of the databases

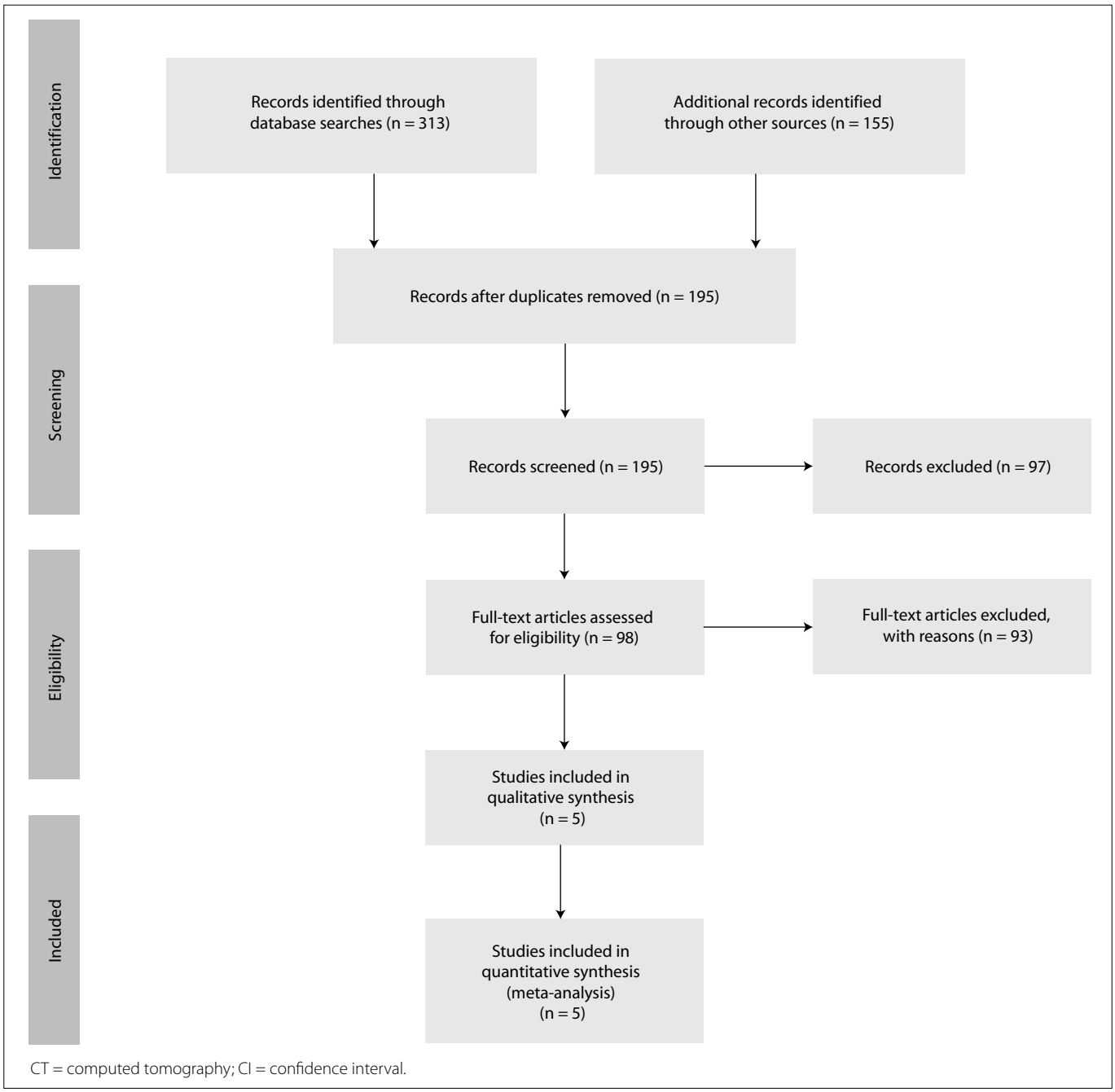
Database	Search strategy
Cochrane Library	#1: MeSH descriptor: [Fractures, Bone] explode all trees. #2: MeSH descriptor: [Radiation Dosage] explode all trees. #3: MeSH descriptor: [Tomography, X-Ray Computed] explode all trees. #4: #1 AND #2 AND #3
MEDLINE	#1: "Fractures, Bone"[MeSH] OR (Broken Bones) OR (Bone, Broken) OR (Bones, Broken) OR (Broken Bone) OR (Bone Fractures) OR (Bone Fracture) OR (Fracture, Bone) OR (Spiral Fractures) OR (Fracture, Spiral) OR (Fractures, Spiral) OR (Spiral Fracture) OR (Torsion Fractures) OR (Fracture, Torsion) OR (Fractures, Torsion) OR (Torsion Fracture) #2: "Radiation Dosage"[MeSH] OR (Dosages, Radiation) OR (Radiation Dosages) OR (Dosage, Radiation) OR (Sievert Units) OR (Units, Sievert) OR (Sv Radiation Dose Equivalent) OR (Gray Units) OR (Units, Gray) OR (Gy Radiation) #3: "Tomography, X-Ray Computed"[MeSH] OR (X-Ray Computed Tomography) OR (Tomography, X-Ray Computerized) OR (Tomography, X Ray Computerized) OR (Computed X Ray Tomography) OR (X-Ray Computer Assisted Tomography) OR (X Ray Computer Assisted Tomography) OR (Tomography, X-Ray Computer Assisted) OR (Tomography, X Ray Computer Assisted) OR (Computerized Tomography, X Ray) OR (Computerized Tomography, X-Ray) OR (X-Ray Computerized Tomography) OR (CT X Ray) OR (CT X Rays) OR (X Ray, CT) OR (X Rays, CT) OR (Tomodensitometry) OR (Tomography, X Ray Computed) OR (X Ray Tomography, Computed) OR (X-Ray Tomography, Computed) OR (Computed X-Ray Tomography) OR (Tomographies, Computed X-Ray) OR (Tomography, Computed X-Ray) OR (Tomography, Xray Computed) OR (Computed Tomography, Xray) OR (Xray Computed Tomography) OR (CAT Scan, X Ray) OR (CAT Scan, X-Ray) OR (CAT Scans, X-Ray) OR (Scan, X-Ray CAT) OR (Scans, X-Ray CAT) OR (X-Ray CAT Scan) OR (X-Ray CAT Scans) OR (Tomography, Transmission Computed) OR (Computed Tomography, Transmission) OR (Transmission Computed Tomography) OR (CT Scan, X-Ray) OR (CT Scan, X Ray) OR (CT Scans, X-Ray) OR (Scan, X-Ray CT) OR (Scans, X-Ray CT) OR (X-Ray CT Scan) OR (X-Ray CT Scans) OR (Computed Tomography, X-Ray) OR (Computed Tomography, X Ray) OR (X Ray Computerized Tomography) OR (Cine-CT) OR (Cine CT) OR (Electron Beam Computed Tomography) OR (Electron Beam Tomography) OR (Beam Tomography, Electron) OR (Tomography, Electron Beam) OR (Tomography, X-Ray Computerized Axial) OR (Tomography, X Ray Computerized Axial) OR (X-Ray Computerized Axial Tomography) OR (X Ray Computerized Axial Tomography) #4: #1 AND #2 AND #3
EMBASE	#1: ('fracture'/exp OR 'bone cement fracture' OR 'bone fracture' OR 'closed fracture' OR 'fracture' OR 'fractures' OR 'fractures, bone' OR 'fractures, closed' OR 'skeleton fracture' OR 'unstable fracture') #2: ('radiation dose'/exp OR 'dose rate, radiation' OR 'dose, radiation' OR 'radiation dosage' OR 'radiation dose' OR 'radiation dose absorption' OR 'radiation dose output') #3: ('x-ray computed tomography'/exp OR 'ct scan' OR 'ct scanning' OR 'tomography, x-ray computed' OR 'x-ray computed tomography') #4: #1 AND #2 AND #3
LILACS	#1: mh: "Fraturas Ósseas" OR (Fractures, Bone) OR (Fracturas Óseas) OR (Fratura) OR (Fraturas) OR (Fraturas de Ossos) OR (mh:C26.404) #2: "Dose de Radiação" OR (Radiation Dosage) OR (Dosis de Radiación) OR (Dosage, Radiation) OR (Gray Units) OR (Gy Radiation) OR (Sv Radiation Dose Equivalent) OR (Dosages, Radiation) OR (Radiation Dosages) OR (Units, Gray) OR (Units, Sievert) OR (Sievert Units) OR (mh: E05.799.513) OR (mh: G01.750.740) OR (mh: N06.850.810.250) OR (mh: SP8.473.654.412.062.116.157) #3: mh:"Tomografia Computadorizada por Raios X" OR (Tomography, X-Ray Computed) OR (Tomografía Computarizada por Rayos X) OR (TAC por Raios X) OR (Tomografia por Raios X Computadorizada) OR (Tomografia Axial Computadorizada por Raios X) OR (TC por Raios X) OR (Tomografia Computadorizada por Transmissão) OR (Tomografia Computadorizada por Transmissão de Raios X) OR (Tomografia Computadorizada Dinâmica) OR (Cine-TC) OR (Tomodensitometria) OR (Tomografia Computadorizada de Feixe de Elétrons) OR (Tomografia de Feixe de Elétrons) OR (Tomografia Computadorizada) OR (mh: E01.370.350.350.810) OR (mh: E01.370.350.600.350.700.810) OR (mh: E01.370.350.700.700.810) OR (mh: E01.370.350.700.810.810) OR (mh: E01.370.350.825.810.810) #4: #1 AND #2 AND #3

Detection rate in relation to number of bones

Bone evaluations were provided and cited with regard to each method, in four studies: Jin et al.,[16] Lee et al.,[17] Lee et al.[18] and Yi et al.[36] A total of 7719 bones were evaluated. Out of the 3876 bones evaluated by means of standard-dose CT, 744 had fractures: a detection rate of 19.2%. Out of the 3,843 bones evaluated by means of low-dose CT, 782 showed fractures: a detection rate of 20.3%. All of this information is shown in **Figure 2**.

Detection rate in relation to number of patients

Patient assessments were provided and cited with regard to each method, in four studies: Lee et al.,[17] Lee et al.,[18] Mulkens et al.[35] and Yi et al.[36] A total of 996 patients were evaluated. Out of the 453 patients assessed by means of standard-dose CT, 266 had fractures: a detection rate of 58.7%. Out of the 543 patients evaluated by means of low-dose CT, 304 had fractures: a detection rate of 56.0%. All of this information is shown in **Figure 3**.



CT = computed tomography; CI = confidence interval.

Figure 1. Summary of the study selection process.

DISCUSSION

The detection rate of low-dose CT in relation to evaluation of the number of fractured bones was 20.3%, while standard-dose CT yielded a rate of 19.2%. The difference between the methods was not significant. The detection rate of low-dose CT in relation to evaluation of the number of patients with fractures was 56.0%, while standard-dose CT yielded a rate of 58.7%. Here too, the difference between the methods was not significant.

A separate assessment on joints, done in only a single study, showed a similar conclusion. Yi et al.[36] demonstrated that fractures of the bones of the shoulder, pelvis, ankle and wrist had a similar detection rate through both low-dose CT and standard-dose CT, in terms of the evaluations on both the number of patients and the number of bones.

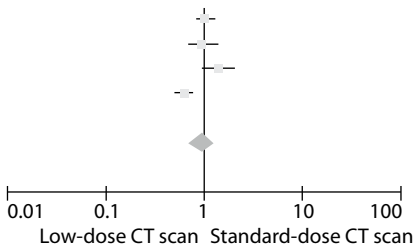
Lee et al.[18] demonstrated good reproducibility among the evaluators, including between those from different specialties (a doctor in the emergency department and a radiologist). All the evaluators

Table 2. Radiation doses used in computed tomography in each of the studies reviewed

Study	CT device	Bone evaluated	Low-dose CT radiation	Standard-dose CT radiation
Jin et al.[16]	64 MDCT	Rib	1.24 mSv	5.75 mSv
Lee et al.[17]	64 MDCT	Lumbar vertebra	2.1 mSv	4.9 mSv
Lee et al.[18]	320 MDCT	Lumbar vertebra	2.1 mSv	5.4 mSv
Mulkens et al.[35]	6 MDCT	Cervical vertebra	1.57 mSv	3.75 mSv
	16 MDCT	Cervical vertebra	1.37 mSv	3.57 mSv
Yi et al.[36]	64 MDCT	Ankle	0.8 mSv	1.4 mSv
		Pelvis	3.9 mSv	7.4 mSv
		Shoulder	2.9 mSv	5.8 mSv
		Wrist	0.7 mSv	1.2 mSv

CT = computed tomography; MDCT = multi-detector computed tomography.

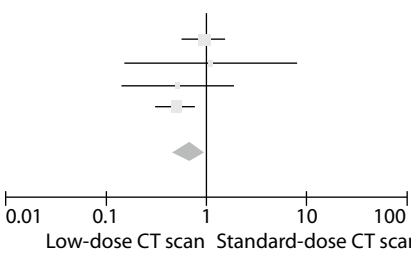
Standard-dose CT scan			Low-dose CT scan			Odds ratio	Odds ratio
Study or subgroup	Events	Total	Events	Total	Weight	M-H, Random, 95% CI	M-H, Random, 95% CI
Jin et al.[16]	187	862	184	862	26.6%	1.02 [0.81, 1.28]	
Lee et al.[17]	72	630	81	685	23.4%	0.96 [0.69, 1,35]	
Lee et al.[18]	312	380	260	340	22.6%	1.41 [0.98, 2.03]	
Yi et al.[36]	173	2,004	257	1,956	27.3%	0.62 [0.51, 0.77]	
Total (95% CI)		3,876		3,843	100%	0.95 [0.67, 1.34]	
Total events	744		782				
Heterogeneity. $Tau^2 = 0.10$; $Chi^2 = 19.19$, df = 3 (P = 0.0002); $I^2 = 84\%$							
Test for overall effect: Z = 0.31 (P = 0.76)							



CT = computed tomography; CI = confidence interval.

Figure 2. Forest plot: comparison demonstrating that there was no significant difference between low-dose CT and standard-dose CT regarding the detection rate for bone fractures.

Standard-dose CT scan			Low-dose CT scan			Odds ratio	Odds ratio
Study or subgroup	Events	Total	Events	Total	Weight	M-H, Random, 95% CI	M-H, Random, 95% CI
Lee et al.[17]	60	126	67	137	41.1%	0.95 [0.59, 1.54]	
Lee et al.[18]	74	76	66	68	4.5%	1.12 [0.15, 8,18]	
Mulkens et al.[35]	3	51	15	140	10.0%	0.52 [0.14, 1.88]	
Yi et al.[36]	129	200	156	198	44.4%	0.49 [0.31, 0.77]	
Total (95% CI)		453		543	100%	0.67 [0.43, 1.04]	
Total events	266		304				
Heterogeneity. $Tau^2 = 0.06$; $Chi^2 = 4.30$, df = 3 (P = 0.23); $I^2 = 30\%$							
Test for overall effect: Z = 1.80 (P = 0.07)							



CT = computed tomography; CI = confidence interval.

Figure 3. Forest plot: comparison demonstrating that there was no significant difference between low-dose CT and standard-dose CT regarding the detection rate for patients with fractures.

analyzed all the CT scans, in terms of both the number of patients and the number of bones. The detection rate for the emergency room physician was 80% in the bone assessments using standard-dose CT whereas with low-dose CT it was 73%. The detection rate for the radiologist was 82% in the bone assessments using standard-dose CT and 76% using low-dose CT. The detection rates in the evaluation according to patients was exactly the same for the two professionals: 97% with both standard-dose CT and low-dose CT.

Mulkens et al.[35] assessed the quality of the images in low-dose CT compared with the quality in standard-dose CT. In analysis on the images done by different evaluators, it was found that although low-dose CT had lower image quality than standard-dose CT, the examination with low-dose CT preserved sufficient quality for accurate assessment of fractures. This study also demonstrated good reproducibility among the evaluators with regard to diagnosing fractures, as shown by Lee et al.[18]

Trauma is responsible for 19% of all fractures, and the incidence of these fractures also increases with age. Brazil, for example, leads the world statistics on traffic accidents, which are the predominant cause of trauma in this country.[37,38] Thus, high numbers of fractures occur in Brazil, which requires large numbers of CT scans. Reduction of the radiation dose from CT scans in Brazil is valuable and important because this will diminish costs.

CT accounts for 13% of all radiological examinations in the United States and between 40% and 70% of the radiation that patients receive.[39-41] It also needs to be taken into account that CT is responsible for the greatest exposure to radiation among trauma patients, since they frequently undergo CT scans.[7,9,15,22,42,43] Although bones are only minimally affected by radiation, the bone marrow is the most radiosensitive organ in the body.[36] Although CT is responsible for 40-70% of patients' radiation doses,[39-41] this percentage goes up to 97.5% in the case of hospitalized patients.[12] In the pediatric population, the effective dose can be up to three times higher than in the adult population.[24] The risk of developing cancer later in life is more powerfully predicted when effective doses of 5.6 mSv for the lumbar spine and 10.0 mSv for the whole dorsal spine are administered through CT, measured by means of radiography.[1,10,44]

Given that, so far, no feasible safe dose of ionizing radiation that does not present a risk of cell damage and consequently cancer has been determined,[9] there is great interest in reducing radiation levels while maintaining the rate of fracture detection. This is even more so in the pediatric population, given that reducing the doses administered to children reduces the incidence of cancer decades after exposure. In 2007, four million CT scans were performed among children in the United States.[1]

CT can be performed with much lower doses of radiation than the standard radiation dose, despite the consequent increase in image noise and reduced image quality.[5,45–47] It can even be done using the same radiation dose as in radiography.[30,48] It seems to be particularly advantageous to indicate a reduced radiation protocol for CT on the extremities, because the area scanned is smaller than that of other regions of the human body, like the abdomen, for example.[49]

Moreover, it needs to be borne in mind that multislice CT tubes have a production life of around 800,000 slice and their average cost is 30,000 pounds (approximately 41,667.00 US dollars or 227,334.00 reais).[50] If the radiation dose were to be halved, the useful life of the CT tube would be increased fourfold, thereby giving rise to important savings.[50] In this regard, it also needs to be remembered that the number of CT scans performed is constantly increasing, year by year. In the United States, 70 million CT scans were performed in 2014, which was 20 times more than had been documented in 1980.[5]

The following methods can be used to reduce the patient's radiation dose received through computed tomography:

- Reducing the milliampere-second setting: if the milliampere-second value is reduced by 50%, the radiation dose will be reduced by the same amount.[51]
- Increasing the pitch: the radiation dose is inversely proportional to the pitch when all other factors are kept constant.[51]
- Changing the milliamp setting according to the patient's size: the milliamp-second value can be reduced proportionally with smaller sizes of patients.[51]
- Reducing the x-ray beam energy (kilovolt peak): reducing the beam energy results in a reduced radiation dose when all other factors are kept constant.[51]
- Model-based iterative reconstruction: this provides lower image noise and fewer artifacts; it has been designed to complement other dose-reduction methods while preserving diagnostic image quality.[52]
- Deep learning: this can distinguish noise from signal in CT images and, consequently, can boost signal while diminishing noise.[53]
- Machine-learning algorithms, as a subfield of artificial intelligence: different types of machine learning (linear regression, regression trees, bagged regression trees, Gaussian process regression, support vector machine (SVM) regression or neural networks) can reduce the radiation dosage, to adapt to new circumstances and identify and rate standards.[4]

Within the scope of public health interest, the importance of reduction of this radiation dose is in relation to the following:

- Reduction of long-term incidence of malignancies.
- Reduced spending on high-cost medications and procedures for malignant neoplasms, i.e. chemotherapy, radiotherapy, surgery, hospitalization, etc.
- Increasing the population's quality of life.
- Reduced expenditure on CT tubes.

These changes would give rise to significant savings. They would enable reallocation of funds to areas that need more attention. Thus, this is a matter of enormous administrative relevance since, in addition to the savings already mentioned, new investments would cease to be necessary (exchange of devices, purchase of software and relocation of devices), given that only adjustments to the regulation of CT examination protocols are needed.[51]

In addition, in cases of patients with diseases that require CT monitoring, low-dose CT scans provide the possibility of shorter time intervals between examinations, thus making it possible to adjust the treatment when necessary and, hence, making it possible to avoid worsening of the disease.[54]

The present findings have some implications for future research. Low-dose CT was shown here to maintain the bone fracture detection rate and was previously shown to be effective for evaluation of pulmonary nodules[55,56] and lithiasis in the urinary tract.[57] In the latter, moreover, ultra-low-dose CT is already being used.[57,58] Therefore, low-dose CT should begin to be evaluated for assessment of other structures, such as the appendix, pancreas and sinuses, among others.

Even with the advent of MRI, CT remains the gold standard for diagnosing bone fractures.[25-27] Therefore, regarding evaluation of bone fractures, we believe that further studies are needed to assess the use of ultra-low-dose CT, which so far has only been analyzed by Konda et al.[28]

Ultra-low-dose CT uses a radiation dose similar to that of radiography and, consequently, further reduces the incidence of malignant neoplasms caused by standard-dose CT. Today, standard-dose CT is the cause of 1.5-2% of cases of malignant neoplasms.[1,6] This proportion is higher among children under 15 years old,[1,12,28] and even more so among children younger than 5 years.[6] Moreover, use of ultra-low-dose CT implies lower spending on medications and CT tubes. It would lead to increased quality of life for this population, over the long term.

However, as quoted by Lee,[19,39] only 9%-16% of doctors are aware of the risk of malignant neoplasms caused by radiation. Furthermore, 75% of radiologists and on-call staff in emergency departments underestimate the radiation dose of CT, and 91% of emergency room doctors do not know that CT increases the risk of cancer throughout life. Added to this is the fact that more than 90% of patients are not informed about the dangers of radiation before they undergo CT.[19,39] Therefore, it is extremely necessary to inform both healthcare professionals and patients about the risks of radiation and the ways in which its use in CT can be improved.

CONCLUSION

According to the results from this systematic review and meta-analysis, it can be suggested that, in evaluating trauma victims (cases due to falls, traffic accidents, etc.) and for patients undergoing tomographic monitoring of fractures, low-dose CT should be used within clinical practice. This will reduce the radiation dose delivered to patients while maintaining the rate of fracture detection, in addition to reducing costs. Through this, it will be possible to maintain the quality of fracture diagnosis, while still avoiding complications of misdiagnosis, such as chronic arthritis, painful non-union or osteonecrosis. A decrease in CT radiation exposure is required, but image quality needs to be maintained for diagnostic accuracy.

It should be taken into account that, in our review, studies using multislice computed tomography devices with between 6 and 320 channels were evaluated, as there were no studies on other devices (helical or multislice with fewer channels) of sufficient quality for their inclusion. Evaluation of low-dose CT in patients with metallic structures was not possible since all the studies examined had excluded patients presenting metallic components (nails, screws, prostheses, etc.), from their selection of patients.

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Could serum total cortisol level at admission predict mortality due to coronavirus disease 2019 in the intensive care unit? A prospective study

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ABSTRACT

BACKGROUND: Critical diseases usually cause hypercortisolemia via activation of the hypothalamic-pituitary-adrenal axis.

OBJECTIVES: To investigate the relationship between serum total cortisol level and mortality among coronavirus disease 2019 (COVID-19) patients in the intensive care unit (ICU), at the time of their admission.

DESIGN AND SETTING: Prospective study developed in a pandemic hospital in the city of Şırnak, Turkey.

METHODS: We compared the serum total cortisol levels of 285 patients (141 COVID-19-negative patients and 144 COVID-19-positive patients) followed up in the ICU.

RESULTS: The median cortisol level of COVID-19-positive patients was higher than that of COVID-19 negative patients (21.84 µg/dl versus 16.47 µg/dl; P < 0.001). In multivariate logistic regression analysis, mortality was associated with higher cortisol level (odds ratio: 1.20; 95% confidence interval: 1.08-1.35; P = 0.001). The cortisol cutoff point was 31 µg/dl (855 nmol/l) for predicting mortality among COVID-19-positive patients (area under the curve 0.932; sensitivity 59%; and specificity 95%). Among the COVID-19 positive patients with cortisol level ≤ 31 µg/dl (79%; 114 patients), the median survival was higher than among those with cortisol level > 31 µg/dl (21%; 30 patients) (32 days versus 19 days; log-rank test P < 0.001).

CONCLUSION: Very high cortisol levels are associated with severe illness and increased risk of death, among COVID-19 patients in the ICU.

INTRODUCTION

The new virus infection that first appeared in Wuhan, China, at the end of December 2019 spread to most countries across the world, causing a global pandemic. In February 2020, the World Health Organization (WHO) named the virus severe acute respiratory syndrome-coronavirus-2 (SARS-CoV-2) and the associated infectious disease, novel coronavirus 2019 (COVID-19).[1]

Acute stress from critical illness increases serum cortisol levels via activation of the hypothalamic-pituitary-adrenal (HPA) axis.[2-4] This is the body's adaptive survival mechanism. SARS-CoV-2 enters pneumocytes using the host's angiotensin-converting enzyme 2 (ACE2) receptors. This enzyme is also found in the arterial and venous endothelial cells of several endocrine organs, including the adrenals.[5-7] Therefore, the HPA axis may be affected during the course of SARS-CoV-2 infection.

The relationship between cortisol release caused by COVID-19 and mortality in the intensive care unit (ICU) is yet to be adequately studied.

OBJECTIVE

The present prospective study was designed with the aim of investigating the relationship between mortality and serum total cortisol levels, measured in a sample collected from COVID-19 patients on the first morning of admission to the ICU of the hospital.

METHODS

This prospective study was conducted among 285 patients hospitalized in the ICU of the Şırnak State Hospital (a pandemic hospital in Turkey), over the period from March 15, 2020, to August 15, 2020. Group 1 included 141 COVID-19-negative patients, and group 2 comprised 144 COVID-19-positive patients.

The study protocol was approved by the Clinical Research Ethics Committee of the Health Sciences University Gazi Yaşargil Training and Research Hospital (Diyarbakır, Turkey) (September 11, 2020; number: 546).

COVID-19 positivity was based on positive results from real-time reverse transcriptase polymerase chain reaction (RT-PCR) tests on nasopharyngeal and oropharyngeal swabs, or on the presence of strong clinical and radiological signs, even in cases in which the swab result was negative.

Samples were collected in the morning, between 7 AM and 8 AM, of the day when the patient was admitted to the ICU. These were used to evaluate the complete blood count, creatinine level, aspartate aminotransferase (AST) level, alanine aminotransferase (ALT) level, albumin level, C-reactive protein (CRP) level, D-dimer level and serum total cortisol level.

Cortisol levels were analyzed using the Cobas 6000 analyzer (Roche Diagnostics, Mannheim, Germany). The reference range for serum total cortisol measured using this device was 0.018-63.4 μg/dl.

Exclusion criteria

Patients with a history of previously known pituitary disorder, adrenal gland disorder, use of corticosteroids (inhaler, topical, oral or parenteral) or use of other drugs that could have disrupted the HPA axis during the previous 3 months, and those on mechanical ventilation at the time of sample collection were excluded from the study. All other patients aged > 18 years were enrolled.

Statistical analyses

The data were analyzed statistically using the Statistical Package for the Social Sciences (SPSS) for Windows software, version 22 (IBM, Chicago, Illinois, United States). Continuous variables were presented as medians with the corresponding interquartile range (IQR), and categorical variables were presented as frequencies and percentages. The chi-square test was used to analyze the categorical variables. Comparisons were made using the Mann-Whitney U test, Kruskal-Wallis test and one-way analysis of variance (ANOVA) test. Spearman's correlation test was used to examine the relationships between pairs of variables. Univariate and multivariate logistic regression analyses were used to detect predictors of mortality. Receiver operating characteristic (ROC) analysis and the area under the curve (AUC) were used to examine the serum total cortisol levels with regard to predicting patient mortality. Sensitivity and specificity values were calculated, and the optimal cutoff levels for serum cortisol were defined. Kaplan-Meier survival curves and the log-rank test were used to examine overall survival. $P < 0.05$ was considered to indicate statistical significance.

RESULTS

In group 1 (COVID-19-negative patients), 63% (89/141) were male patients, while in group 2 (COVID-19-positive patients), 61% (88/144) were men. The predominance of male patients in the groups was noteworthy. The median age of the group 1 patients was 61 years (IQR, 50.5-73.5 years), while that of group 2 was 63.5 years (IQR, 52.25-69 years).

While the proportion of the patients who died was 12% (n = 17) in group 1, it was 30.5% in group 2 (n = 44; $P < 0.001$). The median length of stay in the ICU was 7 days (IQR, 5-12 days) in group 1, while it was 17 days (IQR, 11-24.5 days) in group 2 ($P < 0.001$). The CRP level was significantly higher in group 2 than in group 1 ($P < 0.001$). The median cortisol level was 16.47 μg/dl (IQR, 13.73-19.13 μg/dl) in group 1 and 21.84 μg/dl (18.22-30.11 μg/dl) in group 2 ($P < 0.001$). The demographic, clinical and laboratory parameters of the groups are shown in **Table 1**.

The COVID-19-positive group was divided into subgroups, as survivors (n = 100) and non-survivors (n = 44). The median age of the survivors was 64 years (IQR, 56.25-68 years), while that of the non-survivors was 61 years (IQR, 43.5-69 years). The majority of the patients in both groups were men. The CRP level was 18.76 mg/dl (IQR, 14.69-28.84 mg/dl) in the survivor group and 25.81 mg/dl (17.18-33.1 mg/dl) in the non-survivor group ($P < 0.05$). The demographic, clinical and laboratory results of the survivor and non-survivor COVID-19 patients are shown in **Table 2**.

In the COVID-19-positive group, the cortisol and CRP levels were positively correlated (rho: 0.482; $P < 0.001$) (**Figure 1**). The patients in the groups were divided into subgroups as survivors and non-survivors, and their cortisol levels were compared. The median cortisol level of group 1 survivors (n = 123) was 16.3 μg/dl, while that of group 1 non-survivors (n = 17) was 18.4 μg/dl. Group 2 survivors (n = 100) had a median cortisol level of 19.05 μg/dl, while group 2 non-survivors (n = 44) had a median cortisol level of 31.8 μg/dl. The box plot of the cortisol distribution of the subgroups is presented in **Figure 2**. Group 2 non-survivors had the highest cortisol level, according to multiple comparisons of the serum cortisol levels of the subgroups using the Kruskal-Wallis and one-way ANOVA tests ($P < 0.001$) (**Table 3**).

Univariate logistic regression analysis on the factors that influenced mortality among the COVID-19-positive patients in the ICU, including male sex, cortisol level, CRP level and albumin level, showed significant results (**Table 4**). Multivariate logistic regression analysis on the factors affecting mortality showed that the cortisol level (odds ratio: 1.20; 95% CI: 1.08-1.35; $P = 0.001$) was a significant factor (**Table 5**).

ROC curve analysis on cortisol was performed to predict mortality among COVID-19-positive patients. The cortisol cutoff point

was found to be 31 μg/dl (855 nmol/l) (AUC 0.932; sensitivity 59% and specificity 95%). The positive predictive value was 57% and the negative predictive value was 95%, for the cortisol level 31 μg/dl (**Table 6**). With the cortisol level set at 31 μg/dl as the cutoff point, the median survival of those with cortisol level ≤ 31 μg/dl in the Kaplan-Meier life analysis was 32 days (114 patients [79%]; 95% CI: 24 to undetermined), and the median survival of those with cortisol level > 31 μg/dl was 19 days (30 patients [21%]; 95% CI: 20.69-29.31) (log-rank test, P < 0.001) (**Figure 3**).

Table 2. Characteristics of COVID-19-positive patients

Parameters		Survivors (n = 100)	Non-survivors (n = 44)
Age, years		64 (56.25-68)	61 (43.5-69)
Age (stratified)	< 45	13 (13%)	11 (25%)
	45-64	38 (38%)	14 (32%)
	65-74	41 (41%)	12 (27%)
	≥ 75	8 (8%)	7 (16%)
Sex	Male	55 (55%)	33 (75%)
	Female	45 (45%)	11 (25%)*
Length of stay, days		17.5 (11.25-22)	16.5 (9-25)
CRP, mg/dl		18.76 (14.69-28.84)	25.81 (17.18-33.1)**
D-dimer, ug/l		1360 (1007-2460)	1212 (1062-1871)
Creatine, mg/dl		1.03 (0.76-1.69)	1.29 (0.93-2.08)
AST, U/l		34 (24.25-50.75)	40.5 (26-64.25)
ALT, U/l		26.5 (18-45)	20.5 (14.25-50.25)
Albumin, g/dl		2.74 (2.39-3.02)	2.61 (1.77-3.11)
Neutrophil-to-leukocyte (N:L) ratio		8.97 (3.97-13.29)	8.64 (4.08-15.68)

CRP = C-reactive protein; AST = aspartate aminotransferase; ALT = alanine aminotransferase. Categorical data shown as number (percentage). Non-normally distributed continuous variables displayed as median (interquartile range [IQR]). P < 0.05: significant; *P < 0.05 (chi-square test; **P < 0.05 (Mann-Whitney test).

DISCUSSION

Despite all the support and treatments for COVID-19, the mortality rates among patients admitted to ICUs remain high across the world. In a study on 3,988 patients in Italy, the mortality rate in the ICU was 48.7%.[8] A study on 3,001 patients admitted to ICUs in the United Kingdom found a mortality rate of 31 %.[9] In a study on patients in 178 ICUs in Turkey, the mortality rate was 55.6%.[10] In our study, the mortality rate was 12% among COVID-19-negative patients who were admitted to the ICU, while it was 30.5% among COVID-19-positive patients. Development of acute, progressive respiratory failure caused by COVID-19 infection over a short time is associated with a high risk of mortality.

Similar to what was observed in previous studies,[11-13] our study showed that male sex, high CRP level and low albumin level were associated with high risk of mortality. Although the COVID-19-negative and COVID-19-positive patients did not differ in terms of age, there were more patients aged > 65 years in the COVID-19-positive group. Furthermore, the levels of inflammatory markers (CRP, d-dimer and neutrophil-to-leukocyte ratio), creatinine level and AST level were higher and albumin levels were lower in the COVID-19-positive group than in the COVID-19-negative group.

In stress-free individuals, cortisol is secreted in a daily pattern, with levels peaking in the early morning and dropping to their lowest level in the late evening. Any kind of acute illness or trauma leads to changes in daily cortisol secretion,[14,15] often accompanied by hypercortisolemia in proportion to disease severity, in cases of critical illness that causes severe acute physical stress.[16-18] The increase in cortisol release owing to acute stress in the ICU

Table 1. Demographic, clinical and laboratory parameters of the groups

Parameters		Group 1 (n = 141) COVID-19-negative	Group 2 (n = 144) COVID-19-positive	P-value
Age, years		61 (50.5-73.5)	63.5 (52.25- 69)	0.852
Age (stratified)	< 45	17 (12.1%)	24 (16.7%)	0.268
	45-64	63 (44.7%)	52 (36.1%)	0.14
	65-74	34 (24.1%)	53 (36.8%)	**0.02**
	≥ 75	27 (19.1%)	15 (10.4%)	**0.038**
Sex	Male	89 (63%)	88 (61%)	0.727
	Female	52 (37%)	56 (39%)	0.727
Length of stay, days		7 (5-12)	17 (11-24.5)	**< 0.001**
Death		17 (12%)	44 (30.5%)	**< 0.001**
Cortisol, μg/dl		16.47 (13.73-19.13)	21.84 (18.22-30.11)	**< 0.001**
CRP, mg/dl		12.14 (9.27-14.24)	19.7 (15.87-31.29)	**< 0.001**
D-dimer, ug/l		680 (482-1050)	1250 (1055-2400)	**< 0.001**
Creatine, mg/dl		0.92 (0.79-1.25)	1.04 (0.81-1.78)	**0.025**
AST, U/l		31 (19.5-42)	36.5 (25-56)	**0.001**
ALT, U/l		28 (14.5-39)	26 (17-46.5)	0.167
Albumin, g/dl		2.91 (2.46-3.59)	2.7 (2.38-3.05)	**< 0.001**
Neutrophil-to-leukocyte (N:L) ratio		5.62 (3.26-10.33)	8.83 (4.00-13.87)	**0.002**

CRP = C-reactive protein; AST = aspartate aminotransferase; ALT = alanine aminotransferase.
Categorical data shown as number (percentage). Non-normally distributed continuous variables displayed as median (interquartile range [IQR]). P < 0.05: significant (shown in bold).

is an adaptive mechanism of the body that triggers regulation of cardiovascular, immune and metabolic functions. An appropriate response from the HPA axis to the severe stress of critical illness is essential for survival because both very high cortisol responses and low responses (relative adrenal insufficiency) have been associated with higher mortality rates.[19-21] In our study, the total serum cortisol level on the first morning of hospitalization in the ICU was significantly higher in the COVID-19-positive patients than in the COVID-19-negative patients (21.84 versus 16.47 μg/dl; P < 0.001).

This may be attributable to the fact that COVID-19-positive patients had more severe disease and higher CRP level. Specific cytokines, such as CRP, which presents elevated concentrations in critical illness, activate the HPA axis and modulate the activity of 11β-hydroxysteroid dehydrogenase (an enzyme involved in steroid hormone physiology) and the number, affinity, or both, of glucocorticoid receptors.[19,22] Moreover, the spread of COVID-19 infection has been termed a fatal pandemic by news channels and newspapers; therefore, it is likely to cause fear of death among COVID-19-positive patients, thus leading to greater severity of acute stress and higher stimulation of cortisol release.

A comparison of the baseline cortisol levels of 403 COVID-19-positive patients and 132 COVID-19-negative patients by Tan et al. showed significantly higher cortisol levels in COVID-19-positive patients than in COVID-19-negative patients (619 nmol/l versus 519 nmol/l; P < 0.0001).[23] The COVID-19-positive group in that previous study had higher CRP levels, similar to those of our study; thus, we can conclude that cortisol elevation may be related to disease severity. In another study on 62 patients with severe sepsis and 63 with septic shock who were admitted to an ICU, the baseline total cortisol levels were 728 ± 386 nmol/l and 793 ± 439 nmol/l, respectively. Non-survivors had higher calculated total cortisol concentrations (980 ± 458 nmol/l) than the survivors (704 ± 383 nmol/l).[24]

The lowest median cortisol level was in group 1 survivors, while the group 2 non-survivors had the highest cortisol level in the multiple-group comparisons that were performed by dividing the study subjects into subgroups of survivors and non-survivors. In the multivariate logistic regression analysis, in which we examined the effect of clinical parameters on mortality among COVID-19-positive patients, only the cortisol level was significant.

The cortisol cutoff point was 31 μg/dl (855 nmol/l) in the ROC curve analysis that was performed to predict mortality among the COVID-19-positive patients (sensitivity 59% and specificity 95%). It is challenging to predict, on the day of ICU admission, which patients are likely to die. In fact, it is difficult for clinicians to select patients for whom more time should be devoted, given the limited time and resources. In such cases, the serum total cortisol level could facilitate and guide the decision-making process for clinicians.

Through using the cutoff point of 31 μg/dl for our patients' cortisol level, the median length of survival for cortisol levels ≤ 31 μg/dl was 32 days, while that for cortisol levels > 31 μg/dl was 19 days. We found that this significant value was an important

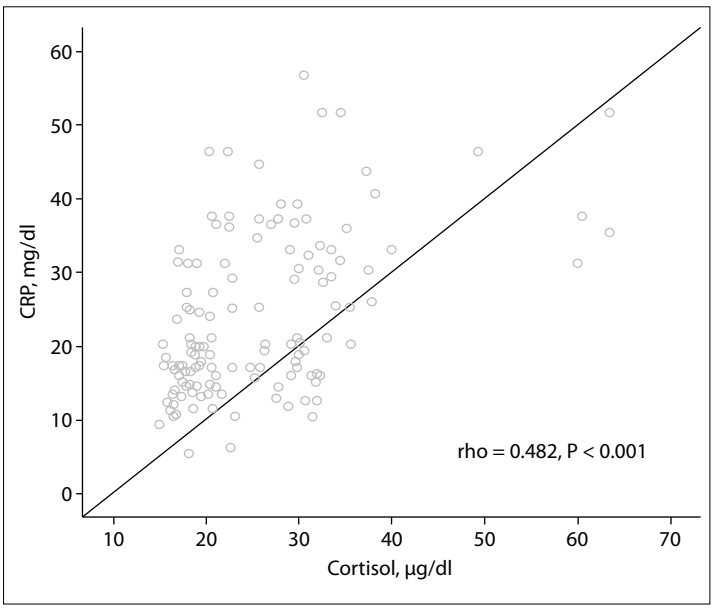

Figure 1. Positive correlation of cortisol with C-reactive protein (CRP) levels in the COVID-19-positive group in the intensive care unit (Spearman's correlation).

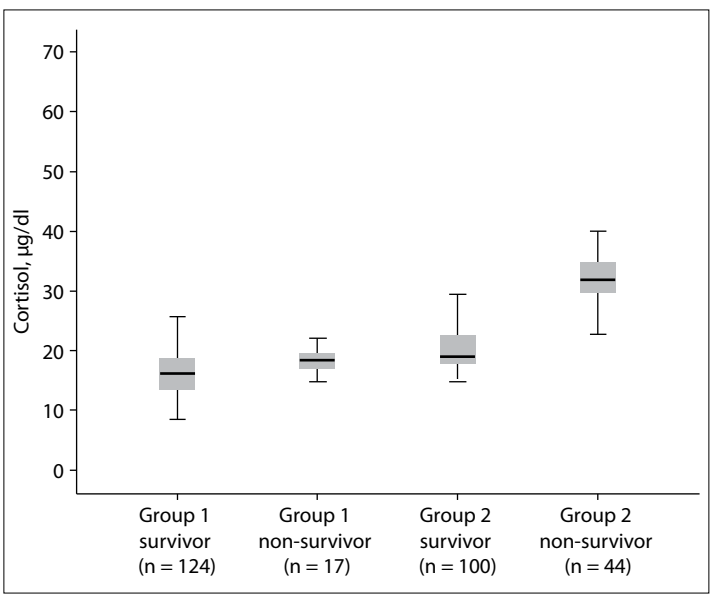

Figure 2. Boxplot of cortisol distribution of the groups (Group 1, COVID-19-negative; Group 2, COVID-19-positive). The thick line in the middle of each box is the median. The top and bottom lines of each box indicate the first and third quartiles.

Table 3. Comparison of the median cortisol levels of survivors and non-survivors

Groups	Median cortisol level	Interquartile range	Groups	P-value
Group 1 survivor (n = 123)	16.3	13.45-18.92	Group 1 non-survivor	0.624
			Group 2 survivor	**< 0.001**
			Group 2 non-survivor	**< 0.001**
Group 1 non-survivor (n = 17)	18.4	16.11-19.56	Group 1 survivor	0.624
			Group 2 survivor	**0.006**
			Group 2 non-survivor	**< 0.001**
Group 2 survivor (n = 100)	19.05	17.76-22.54	Group 1 survivor	**< 0.001**
			Group 1 non-survivor	**0.006**
			Group 2 non-survivor	**< 0.001**
Group 2 non-survivor (n = 44)	31.8	29.64- 34.92	Group 1 survivor	**< 0.001**
			Group 1 non-survivor	**< 0.001**
			Group 2 survivor	**< 0.001**

Group 1 = COVID-19 negative patients, Group 2 = COVID-19 positive patients
Comparisons between groups were made using the Kruskal-Wallis test and one-way analysis of variance. Multiple comparisons between groups were made using the post-hoc Tamhane T2 test.
P < 0.05 = significant (shown in bold).

Table 4. Univariate logistic regression analysis on clinical parameters related to in-hospital mortality among patients diagnosed with COVID-19 in the intensive care unit

Parameter	B	Wald	P value	Odds ratio	95% CI	
					Lower	Upper
Sex (male)	-0.898	4.989	**0.026**	0.407	0.185	0.896
Age, years	-0.013	0.756	0.385	0.987	0.958	1.017
Length of stay, days	0.001	0.004	0.952	1.001	0.961	1.043
Cortisol, µg/dl	0.221	32.811	**0.000**	1.247	1.156	1.345
CRP, mg/dl	0.039	5.228	**0.022**	1.040	1.006	1.075
D-dimer, ug/l	0.000	1.219	0.270	1.000	0.999	1.000
Creatine, mg/dl	0.118	0.760	0.383	1.125	0.863	1.465
AST, U/l	0.001	0.750	0.386	1.001	0.998	1.005
ALT, U/l	0.001	0.100	0.751	1.001	0.996	1.006
Albumin, g/dl	-0.622	4.171	0.041	0.537	0.296	0.975
N:L ratio	-0.021	1.938	0.164	0.979	0.950	1.009

CI = confidence interval; CRP = C-reactive protein; AST = aspartate aminotransferase, ALT = alanine aminotransferase; N:L ratio: neutrophil-to-leukocyte ratio.
P < 0.05: significant (shown in bold).

Table 5. Multivariate logistic regression analysis on clinical parameters related to in-hospital mortality among patients diagnosed with COVID-19 in the intensive care unit

Parameters	B	Wald	P-value	Odds ratio	95% CI	
					Lower	Upper
Age, years	-0.017	0.610	0.435	0.983	0.940	1.027
Sex (male)	-0.240	0.172	0.678	0.787	0.253	2.447
Length of stay, days	-0.022	0.438	0.508	0.979	0.918	1.043
Cortisol, µg/dl	0.190	11.397	**0.001**	1.209	1.083	1.350
CRP, mg/dl	-0.032	1.104	0.293	0.968	0.912	1.028
D-dimer, ug/l	0.000	1.219	0.270	1.000	0.999	1.000
Creatine, mg/dl	-0.003	0.000	0.989	0.997	0.644	1.543
AST, U/l	0.001	0.033	0.856	1.001	0.987	1.016
ALT, U/l	-0.008	0.364	0.546	0.992	0.967	1.018
Albumin, g/dl	-0.489	1.154	0.283	0.613	0.251	1.497
N:L ratio	-0.019	0.693	0.405	0.981	0.938	1.026

CI = confidence interval; CRP = C-reactive protein; AST = aspartate aminotransferase; ALT = alanine aminotransferase; N:L ratio: neutrophil-to-leukocyte ratio.
P < 0.05: significant (shown in bold).

Table 6. Receiver operating characteristic curve analysis on cortisol to predict mortality among COVID-19-positive patients

Parameter	Cutoff point	AUC	Sensitivity	Specificity	PPV	NPV
Cortisol	31 µg/dl (855 nmol/l)	0.932	59%	95%	57%	95%

AUC = area under the curve; PPV = positive predictive value; NPV = negative predictive value.

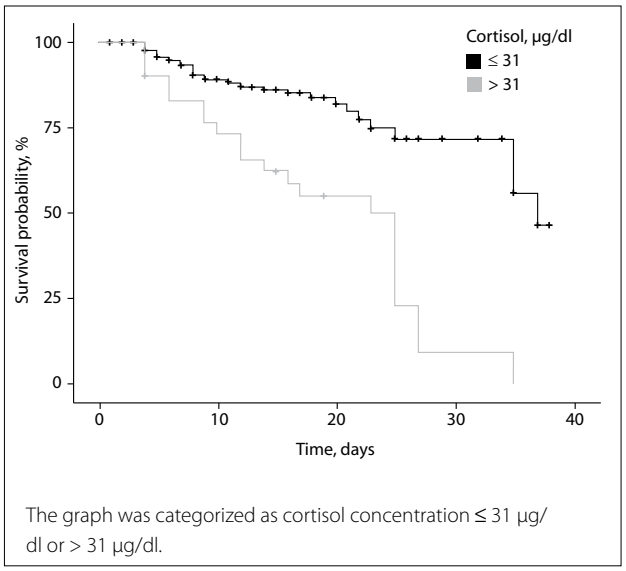

Figure 3. Kaplan-Meier plot of survival probability over time.

marker that could be used to estimate mortality among COVID-19-patients admitted to the ICU.

The present study had certain limitations. First, we only performed analysis using a single baseline cortisol level that was measured on the first morning of admission to the ICU due to COVID-19. In our ICU, corticosteroid treatment is frequently applied from the first day of admission; therefore, measuring the serum cortisol levels under corticosteroid treatment may have provided inaccurate results. Second, we did not measure the level of adrenocorticotropic hormone (ACTH), cortisol-binding globulin or free cortisol. Therefore, it was not possible to comprehensively evaluate the effects of COVID-19 on the HPA axis. Third, no ACTH stimulation test (synacthen test) was performed on the patients before starting this study. Therefore, an unknown state of adrenal insufficiency may have been overlooked. Lastly, this study was conducted in a single center. Larger, multicenter studies are required, in order to obtain more conclusive evidence.

CONCLUSION

Elevated cortisol level is an independent biomarker that enables prediction of adverse outcomes and mortality among COVID-19-positive patients admitted to the ICU. The ability to predict which patients in the ICU may deteriorate faster will help clinicians to allocate resources appropriately and raise the standard of patient care. Furthermore, we can consider a patient's cortisol levels while making a decision regarding the treatment approach.

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Association between handgrip strength and bone mass parameters in HIV-infected children and adolescents. A cross-sectional study

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ABSTRACT

BACKGROUND: Low bone mineral content (BMC) and bone mineral density (BMD) have been identified in human immunodeficiency virus (HIV)-infected children and adolescents. The direct adverse effects of HIV infection and combined antiretroviral therapy (ART) negatively contribute to bone metabolism. A direct relationship between muscle strength levels and BMD in HIV-infected adults and older adults has been described. However, it is unknown whether handgrip strength (HGS) is associated with bone mass in pediatric populations diagnosed with HIV.

OBJECTIVE: To ascertain whether HGS levels are associated with BMC and BMD in HIV-infected children and adolescents.

DESIGN AND SETTING: Cross-sectional study conducted in Florianópolis, Brazil, in 2016.

METHODS: The subjects were 65 children and adolescents (8-15 years) diagnosed with vertically-transmitted HIV. Subtotal and lumbar-spine BMC and BMD were obtained via dual-emission X-ray absorptiometry (DXA). HGS was measured using manual dynamometers. The covariates of sex, ART, CD4+ T lymphocytes and viral load were obtained through questionnaires and medical records. Sexual maturation was self-reported and physical activity was measured using accelerometers. Simple and multiple linear regression were used, with $P < 0.05$.

RESULTS: HGS was directly associated with subtotal BMD ($\beta = 0.002$; $R^2 = 0.670$; $P < 0.001$), subtotal BMC ($\beta = 0.090$; $R^2 = 0.734$; $P = 0.005$) and lumbar-spine BMC ($\beta = 1.004$; $R^2 = 0.656$; $P = 0.010$) in the adjusted analyses. However, no significant association was found between HGS and lumbar-spine BMD ($\beta = 0.001$; $R^2 = 0.464$; $P = 0.299$).

CONCLUSION: HGS was directly associated with BMD and BMC in HIV-infected children and adolescents.

INTRODUCTION

Low bone mineral content (BMC) and bone mineral density (BMD) have been identified in human immunodeficiency virus (HIV)-infected children and adolescents.[1] This occurs because of the direct adverse effects of HIV infection and combined antiretroviral therapy (ART), which negatively contribute to bone metabolism.[2-4] The marked reductions in BMC and BMD are directly associated with increased proinflammatory cytokines, delayed growth and maturational development, decreased muscle mass levels and endocrine disorders, which reduce osteoblast activity and stimulate osteoclasts.[2,3]

Damage to bone mass is especially worrisome in pediatric populations, whether diagnosed with HIV or not, since during this phase of life, there is greater bone mineral increase.[5] Approximately 85%-90% of final adult bone mass is reached during childhood and adolescence, and losses from bone accumulation during this critical period may compromise peak bone mass, which is recognized as the determinant for the risks of osteoporosis and fractures in adulthood.[6]

Although major efforts to attenuate bone loss have been based on pharmacological interventions (bisphosphonates)[7] and vitamin D and calcium supplementation, non-pharmacological strategies based on physical activity that promote gravitational overload (running and jumping) or muscle tension (strength training) have the capacity to induce bone formation stimuli and inhibit bone resorption.[8,9] Handgrip strength (HGS) enhancement exercises have been suggested as a strategy in HIV treatment because they improve cardiorespiratory fitness, body composition

and weight control.[10] In the literature, a direct relationship between HGS levels and BMD in HIV-infected adults[11,12] and older adults[12] has already been described. However, it is unknown whether HGS is associated with bone mass in pediatric populations diagnosed with HIV.

Investigations relating to the association between HGS and bone mass in HIV-infected children and adolescents are important and can support non-pharmacological interventions to reduce complications resulting from infection and prolonged use of ART, with regard to functional capacity and body composition (bone mass, fat mass, etc.). These complications may include development of osteopenia, early osteoporosis and, possibly, related fractures due to falls, which would increase the risk of morbidity in adulthood. In children and adolescents without a diagnosis of HIV, HGS has been described as a marker of bone health and overall health.[8] Among the strategies available for measuring HGS levels, use of manual dynamometers has been highlighted as a simple and widely applicable method, due to its low cost, speed and association with general HGS.[13]

OBJECTIVE

The aim of the present study was to ascertain whether HGS levels are associated with BMC and BMD in HIV-infected children and adolescents.

METHODS

Study design

The present study was conducted in the city of Florianópolis (SC), Brazil, in 2016. The study was approved by the Research Ethics Committee of the Universidade Federal de Santa Catarina (UFSC) (protocol number 49691815.0.0000.0121; date: October 10, 2015). All parents/guardians of the children and adolescents signed an informed consent statement authorizing participation in the research.

Participants

Children and adolescents (8 to 15 years old) with a diagnosis of HIV that had been acquired via vertical transmission, who were under clinical follow-up at the "Joana de Gusmão" Children's Hospital, were recruited for the study. The eligibility criteria were the following: a) presentation of a record of HIV infection by means of vertical transmission in the medical records; b) age between 8 and 15 years; c) availability of clinical and laboratory information in the medical records; and d) ability to stand and to communicate. The exclusion criteria were the following: a) motor impairment or contraindication for vigorous exercise; b) speech, hearing and/or cognition impairment; c) presence of diseases that alter body composition, except for HIV infection; and d) occurrence of regular use of diuretic medications or immunotherapies. Participants presenting any pathological condition other than HIV infection that changed body composition were excluded from the study.

Dependent variables

Total, subtotal (all sites except head) and lumbar-spine BMD and BMC were obtained by means of dual emission X-ray absorptiometry (DXA) (Lunar Prodigy Advance Model Discovery Wi-Fan-Beam - S/N 81593; GE Medical Systems, Madison, United States). X-ray attenuation in body tissues was computed using the Encore 13.60.033 software, pediatric version 8.10.027 (GE Medical Systems, Madison, United States). Internal quality control was ensured by performing a standard daily calibration process provided by the manufacturer of the DXA machine. During the DXA assessments, the participants were barefoot, wearing appropriate clothing and not wearing any metallic accessories.[14] The reading of the biometric pattern by means of a specific body-wide sensor (head to toe) lasted approximately 10 minutes, while the individual remained supine on the device stretcher with arms extended along the sides of the body, with palms facing downwards.[15,16]

Independent variable

HGS was measured using a Saehan dynamometer (Model SH5001, Saehan Corporation, Masan, Korea), which has been concurrently validated with the Jamar dynamometer ($r = 0.976$), with high intra-examiner reliability ($r = 0.985$).[17] This test was chosen because HGS levels have been strongly correlated with total muscle strength (correlation coefficient 0.736 to 0.890) in children, adolescents and adults.[18]

The evaluation procedures followed the protocol described by the Canadian Society for Exercise Physiology.[19] During the evaluation, the participants were instructed to stand with their arms extended at their sides, holding the device in one hand without it touching the corresponding thigh. The device was gripped between the distal phalanges and the palm of the hand.[19] The subject was asked to breathe in and then exhale as much as possible, followed by exerting greater pressure with the hand on the device. The test was performed twice in each hand, alternating hands between tests. The full strength was calculated as the sum of the largest reading from each hand.

Control variables

Sex (male or female) was ascertained at interviews. Information on CD4+ T lymphocyte count (%), HIV viral load (logarithmic) and antiretroviral therapy (ART) (categorized as not using ART, using ART without protease inhibitors (PI) or using ART with PI) was obtained from the medical records. These variables

relating to treatment and infection were used as controls in analyses because previous studies had identified an inverse association with bone mass.[1] Sexual maturation was self-reported by the participants by using pubic hair images, in accordance with Tanner's procedures.[20]

Moderate to vigorous-intensity physical activity (MVPA) was investigated using the Actigraph accelerometer (model GT3X-Plus; Manufacturing Technology Inc., Fort Walton Beach, United States), with continuous use for 7 to 14 days, including weekends. The participants were instructed to wear the equipment on the right side of the waistline from early morning until the end of the day, taking it off only during water activities and sleep. For the data analysis, records of at least four days (three on weekdays and one on weekends) for a period of 10 hours or more on each day, after removal of non-use time of at least 60 consecutive zeros (60 minutes), were taken into consideration. The number of minutes of MVPA minutes was obtained from cutoff points described by Evenson[21] and was proportionally adjusted to the average length of time for which the adolescents stayed awake (14 hours). Verbal and written instructions were made available to participants and guardians before the device was used. MVPA was used as the adjustment variable because less physically active HIV+ individuals tend to have lower BMD and BMC values.[22]

Statistical analysis

Descriptive analysis (median and interquartile range) was performed on the data. Kurtosis and asymmetry were used to verify data normality (range from -2 to + 2), and histogram analysis was used to identify normality in data distribution. Pearson's linear correlation and multiple linear regression were used to test correlations and associations between outcome and exposure, respectively. For multiple regression analysis, control variables (sex, sexual maturation, skin color, viral load, type of medication used and level of habitual physical activity) were entered. Regression coefficients (β), 95% confidence interval and determination coefficients for each model analyzed (R^2), multicollinearity diagnosis (VIF), Akaike information criterion (AIC), Bayesian information criterion (BIC) and effect size (Cohen's D) were estimated. For all analyses, the STATA software, version 14.0 (StataCorp LLC, College Station, Texas, United States), was used. The statistical significance level was set at $P \leq 0.05$.

RESULTS

Sixty-five adolescents (30 males and 35 females) aged 8-15 years who had been diagnosed with HIV participated in the study. The participants' characteristics are highlighted in **Table 1**.

Pearson's linear correlation analysis demonstrated that HGS was directly correlated with total BMD ($r = 0.60$; $P < 0.01$), total BMC ($r = 0.77$; $P < 0.01$) and subtotal BMC ($r = 0.78$; $P < 0.01$). **Figure 1** shows correlations between HGS and subtotal BMD ($r = 0.71$; $P < 0.01$) and lumbar-spine BMD ($r = 0.55$; $P < 0.01$) in these HIV-infected children and adolescents, along with the association between HGS and subtotal BMC corrected for height ($r = 0.75$; $P < 0.01$) and lumbar-spine BMC ($r = 0.70$; $P < 0.01$).

Single and multiple linear regression analyses are presented in **Table 2**. In these HIV-infected children and adolescents, HGS was directly associated with subtotal BMD ($\beta = 0.002$; $P < 0.001$), even after adjustment for sex, sexual maturation, skin color, viral load, type of medication used and level of habitual physical activity. HGS was directly associated with lumbar-spine BMD ($\beta = 0.003$; $P < 0.001$), but after adjusting for covariates, the association lost statistical significance. Regarding subtotal BMC and lumbar spine BMC, single and multiple analyses showed direct

Table 1. Characteristics of the children and adolescents diagnosed with human immunodeficiency virus (HIV)

	Median	Interquartile range (p25; p75)
Chronological age (years)	12.7	10.5; 14.0
Bone age (years)	12.5	10.0; 14.0
Height (cm)	149.8	139.3; 156.4
Body mass (kg)	38.4	31.7; 49.6
Body mass index (kg/m²)	17.4	16.0; 19.9
LSTM (kg)	29.0	23.4; 33.8
BMD total (g/cm²)	0.930	0.881; 1.007
BMC total (g)	1461.9	1158.9; 1819.0
Z-score BMD total (SDS)	-0.028	-0.242; 0.146
Z-score BMC total (SDS)	-0.332	-0.991; 0.709
BMD subtotal (g/cm²)	0.823	0.756; 0.912
BMC subtotal (g)	1108.8	848.3; 1449.3
BMC subtotal/height (g/cm)	7.481	6.106; 9.152
BMD lumbar spine (g/cm²)	0.801	0.707; 0.889
BMC lumbar spine (g)	121.5	85.1; 159.6
Handgrip strength (kg)	19.0	14.0; 26.0
Moderate-vigorous physical activity (min/day)	43.8	26.6; 64.2
Viral load (log)	1.6	1.6; 2.5
CD4+ T lymphocytes (cell/mm³)	819.0	575.0; 1091.0
CD8+ T lymphocytes (cell/mm³)	1088.0	790.0; 1422.0
	n	**(%)**
Skin color		
White	29	44.6
Brown, black, East Asian and indigenous	36	55.4
Current ART		
Yes, with PI	39	60.0
Yes, without PI	15	23.1
Not used	11	16.9
Sexual maturation		
Pre-puberty	15	23.1
Puberty	47	72.3
Post-pubertal	03	4.6

n = sample; % = percentage; g = grams; kg = kilograms; cm = centimeters; mm = millimeters; min = minutes; p25 = 25th percentile; p75 = 75th percentile; ART = antiretroviral therapy; PI = protease inhibitors; BMD = bone mineral density; BMC = bone mineral content; LSTM = lean soft tissue mass; SDS = standard deviation score.

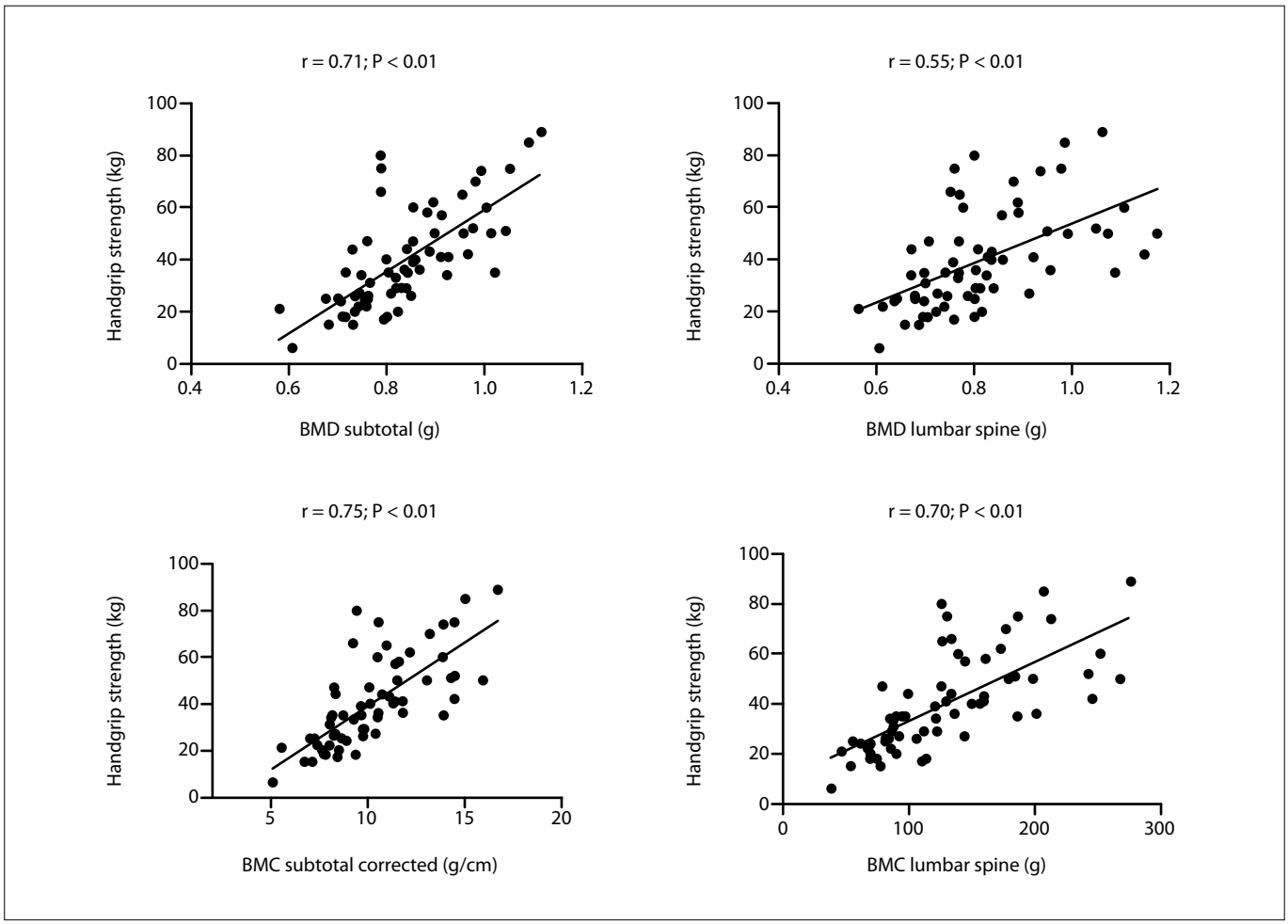

Figure 1. Pearson's linear correlation for total and regional bone parameters (bone mineral density [BMD] and bone mineral content [BMC]) in relation to handgrip strength, among children and adolescents diagnosed with HIV (n = 65).

Table 2. Simple and multiple linear regression on bone mineral density and bone mineral content in relation to handgrip strength in children and adolescents diagnosed with human immunodeficiency virus (HIV)

	β (95% CI)	β standardized	R^2	P	VIF	AIC*n	BIC	Cohen's D
BMD subtotal								
HGS	0.004 (0.003; 0.005)	0.711	0.500	< **0.001**				
Adjusted model	0.002 (0.001; 0.003)	0.380	0.670	**0.003**	1.75	-156.619	-398.348	2.03
BMD lumbar spine								
HGS	0.003 (0.002; 0.005)	0.550	0.290	< **0.001**				
Adjusted model	0.001 (-0.001; 0.002)	0.166	0.464	0.299	1.75	-103.253	-344.982	0.85
BMC subtotal*								
HGS	0.096 (0.075; 0.118)	0.755	0.563	< **0.001**				
Adjusted model	0.053 (0.025; 0.080)	0.427	0.734	**0.001**	1.75	213.388	-28.341	2.70
BMC lumbar spine								
HGS	2.086 (1.554; 2.618)	0.702	0.485	< **0.001**				
Adjusted model	1.004 (0.246; 1.762)	0.351	0.656	**0.010**	1.84	629.718	387.989	1.86

HGS = handgrip strength; CI = confidence interval; VIF = diagnosis of multicollinearity; AIC*n = Akaike information criterion; BIC = Bayesian Information Criterion; BMD = bone mineral density; BMC = bone mineral content; BMC subtotal* = corrected for height; Adjusted model = adjusted for sex, sexual maturation, skin color, viral charge, type of medicine used, CD4+ T lymphocytes and level of habitual physical activity.

associations with HGS (β = 0.090 and P = 0.005; and β = 1.004 and P = 0.010, respectively).

DISCUSSION

The main findings from the present study were that HGS was directly associated with BMD and BMC (total, subtotal and lumbar-spine) in HIV-infected children and adolescents. These results are unprecedented in the pediatric population diagnosed with HIV and demonstrate the importance of HGS for bone mass. In HIV-infected adults, it has been shown in the literature that HGS was directly associated with different health outcomes, such as cardiometabolic risk,[12] phase angle[23] and overall quality of life.[24]

Our results were consistent with those from previous studies among adults[11,12] and older adults[11] diagnosed with HIV. In those studies, a direct relationship was found between greater HGS and better indicators for bone parameters. The present study showed that this relationship is also true for HIV-infected children and adolescents.

In the present study, the physiological mechanisms that explain the direct association between HGS levels and bone mass were not evaluated, but the results can be explained in terms of several factors. First, the mechanostatic theory postulates that HGS is a predictor of bone mass in different populations.[25,26] With the exception of trauma, muscles cause the largest loads and deformations on major bones, with potential osteogenic stimulation, which helps control the biological mechanisms that determine bone strength. This promotes bone structure strength in children and adolescents, depending on increasing HGS and how bones respond to it.[27] Second, hormones and other non-mechanical agents that affect bone strength may affect the muscle-bone unit strength relationship; however, the effect that HGS exerts on bone strength cannot be replaced. In addition, some biological agents that directly exert effects on bones through actions on bone cells (e.g. growth hormones, androgenic hormones, calcium, vitamin D and their metabolites) also perform different functions that stimulate HGS.[27] Third, activities that develop HGS positively contribute to leptin secretion, which is directly related to greater stimulation, proliferation and differentiation of osteoblasts and osteoclasts. These provide the best balance in the process of absorption and remodeling of bone structures.[28]

However, even though HGS and bone mass are directly interrelated, thus suggesting the possibility of interventions consisting of physical exercise, children and adolescents with chronic conditions may have restrictions on participating in more intense physical activity, due to both real and perceived limitations.[29] In fact, in previous research using the same sample as in the present study, Lima et al.[30] identified that HIV-infected children and adolescents accumulated lower bouts of moderate-to-vigorous physical activity, compared with healthy controls. This may result in reduced total physical activity, which in turn may impair the development of HGS and skeletal impact load, thereby compromising full bone development.[3,4] In addition, ART may negatively affect bone parameters, which may compromise bone health.[2] However, correct and continuous use of ART is indispensable, as it enables longer survival for HIV patients. Although there is no consensus regarding the volume and intensity of muscle strength exercises and habitual physical activity that are necessary for mitigating the negative effects of ART,[7] strategies aimed at improving muscle strength, as well as increasing the time spent on physical activity, are necessary.

There is a consensus that physical activity is important for bone mass in the first two decades of life because it assists in the mineralization process of the growing bones.[22] Moreover, structural improvements can be achieved by increasing mechanical load through habitual physical activity.[22] Involvement in activities that require maximum strength or resistance (for example, weight lifting) or those involving large body motion (for example, individual or team sports with high-intensity motion) can lead to increased stimulation of the bone matrix. Thus, it might be theorized that physical activities, especially those requiring HGS, can attenuate or even reverse the deleterious effect of HIV and ART on bone mass, which would minimize the subsequent risk of osteoporosis in adulthood.[27] However, exercise-based intervention studies that simulate strength are needed to test this hypothesis.

In the present study, HGS presented lower explanatory power regarding lumbar-spine BMD variability, compared with whole-body BMD. Trabecular bone (e.g. the lumbar spine) is mainly affected by general and systemic factors such as hormonal status. However, cortical bone (e.g. femurs) is more likely to be affected by regional mechanical influences, such as the force of gravity, muscle mass and strength, which may explain the lower explanatory power of HGS regarding lumbar-spine BMD, compared with whole-body BMD.

This research had limitations that suggest that caution is needed in interpreting the results, such as its sample heterogeneity due to the variability of age, clinical condition and use of ART. The lack of information about calcium and vitamin D intake and blood concentration may also be considered to be a study limitation. In addition, the cross-sectional design does not allow cause-and-effect inferences among study variables. The study also had strengths such as the precision and reliability of the instruments used, in addition to the representativeness of the pediatric patients in the region researched (78% of the patients were treated at the reference hospital).

CONCLUSIONS

It was concluded that HGS was directly associated with BMD and BMC in HIV-infected children and adolescents, regardless of sex, sexual maturation, skin color, viral load, type of medication used

and level of habitual physical activity. Randomized clinical trials should be carried out to confirm whether exercises that stimulate HGS promote bone mass improvements in HIV-infected children and adolescents.

Practical applications

The results from the present study demonstrated the direct association between HGS levels and bone mass in HIV-infected children and adolescents. Based on these results, physical activity promotion strategies aimed at improving HGS levels can be designed to contribute to maintenance or improvement of bone mass parameters. Physical activities that increase strength levels, such as those performed with one's body mass (calisthenics), performed individually (e.g. rope jumps, push-ups or bar pulls) or in pairs/groups (e.g. wheelbarrow, tug of war or arm wrestling) can be encouraged by healthcare and exercise professionals working with HIV-infected children and adolescents. These can form an integral part of non-pharmacological strategies aimed at maintaining or improving bone parameters in this population.

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Use of CentriMag for refractory cardiogenic shock in a puerperal woman: case report

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AUTHORS' KEY WORDS:
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ECMO.
Puerperal.
Refractory cardiogenic shock.

ABSTRACT

CONTEXT: Heart failure in Brazil is a major public health problem and, even with advances in treatment, it still presents high morbidity and mortality. As a treatment option, mechanical circulatory assist devices (MCADs) have greatly increased in importance over the last decade.

CASE REPORT: This report concerns a case of refractory cardiogenic shock due to acute myocarditis in a 35-year-old puerperal female patient who presented with retrosternal pain, fatigue and dyspnea. At the hospital, she was diagnosed with myocarditis. There was no improvement in perfusion even after receiving dobutamine, intra-aortic balloon passage (IAB) and venoarterial extracorporeal membrane oxygenation (VA-ECMO). Therefore, it was decided to implant a MCAD (CentriMag). During hospitalization, recovery from the bi-ventricular dysfunction was achieved. The CentriMag device was removed 10 days after it had been implanted, and the patient was discharged after another 8 days. The myocarditis was proven to be due to the Coxsackie virus.

CONCLUSIONS: The decision to implant a MCAD should be individualized, as patient profiles do not always match the indications in the guidelines and protocols. In this study, clinical discussion of the case among the medical and multi-professional teams was essential in order to be able to successfully reverse the patient's severe clinical condition without sequelae, through using a CentriMag implant.

INTRODUCTION

Worldwide, there were approximately 26 million people with heart failure in 2014. This therefore represents a major public health problem.[1] In Brazil, the scenario is not different and, even with advances in treatment, heart failure still presents high morbidity and mortality. The incidence of heart failure in Brazil is 199 cases per 100,000 person-years, and the one-year mortality rate is 24.5% (95% confidence interval, CI, 19.4%-30.0%).[2] Recent data from the Department of Information Technology of the Brazilian National Health System (DATASUS) have shown that in Brazil the number of heart failure deaths was 27,461 just in 2017.[3]

As a treatment option, mechanical circulatory assist devices (MCADs) have greatly increased in importance over the last decade. Although there are solid guidelines for indication of MCAD implantation,[4] some particular cases still need to be studied, such as cases of refractory cardiogenic shock due to myocarditis. The objective of this case report was to present a case of refractory cardiogenic shock due to acute myocarditis in a young puerperal woman.

CASE REPORT

This present case report was approved on April 13, 2020 (#1599; CAAE 30403220.7.0000.5461). A 35-year-old married female patient who was in the early puerperal period (childbirth in April 2019) sought emergency assistance with flu symptoms that she had had for approximately six days. At the emergency room, she was diagnosed with tonsillitis and was treated with azithromycin and prednisone. In the absence of symptom improvement, she presented retrosternal pain, fatigue and dyspnea. In a new medical evaluation, markers for myocardial necrosis were examined, with positive results, suggesting a diagnostic hypothesis of myopericarditis.

After admission to the coronary unit, she presented signs of low cardiac output with precordial pain, nausea and peripheral perfusion and was then referred to the advanced heart failure unit. She used vasoactive drugs (VAD), but without improvement in perfusion and clinical

presentation. After her case has been discussed by the team, it was decided to perform intra-aortic balloon (IAB) passage. Because of progression of dysfunction and worsening of her general condition, it was decided to install peripheral venoarterial extracorporeal membrane oxygenation (ECMO). The patient maintained the signs of low output and low flow in ECMO, in addition to poor perfusion in the right lower limb after cannulation. It was therefore decided to replace the ECMO with a ventricular assist system (VAS) (CentriMag; Levitronix LLC, Waltham, MA, United States), on July 1, 2019. The procedure was performed by means of median sternotomy, with decannulation of the ECMO and myocardial biopsy.

During the hospitalization with the device, she received corticotherapy and immunotherapy lasting five days. During this time, she required correction of a pseudoaneurysm in the right femoral artery. In addition, she underwent decompression fasciotomy in a right anterior tibial store because of presentation of compartmental syndrome. She evolved with progressive hemodynamic stability and, on July 8, 2019, she presented aphasia of momentary expression, shown by transcranial doppler microembolization in the left middle cerebral artery. Her anticoagulation was adjusted, but the microembolization was maintained.

On July 11, 2019 (10 days after implantation), she was decannulated from the CentriMag. An intracavitary left ventricle (LV) thrombus from the device (**Figure 1**) was seen, which evolved with progressive weaning from VAD and corticotherapy, with clear recovery from the bi-ventricular dysfunction (ejection fraction, EF: 17% to 58%) and recovery of strength in the right forefoot. Analysis on the myocardial biopsy confirmed that the cause of the myocarditis was positivity for the Coxsackie virus (viral load of *Erythroparvovirus* and HHV6 type 6B).

Eight days after implant removal (July 19, 2019), the patient was discharged from the hospital with preserved bi-ventricular function (**Figure 2**). Currently, the patient is in outpatient follow-up without complaints, presenting good quality of life and preserved heart function (EF 62%).

DISCUSSION

In this case report, we present a peculiar case of a 35-year-old puerperal woman who progressed with significant worsening of cardiac function within a few hours, even with passage of an IAB and ECMO. The decision to install a CentriMag device in this patient was crucial for enabling myocardial recovery and significant improvement of cardiac output. Reports involving use of CentriMag to treat heart failure in the postpartum period remain rare. **Table 1** shows the results from a systematic search for similar studies using the PubMed and EMBASE databases.

Temporary mechanical circulatory assist devices (MCADs) are important for re-establishing the hemodynamic condition and should be indicated individually. In addition, they serve as an aid for decision-making up to the point of defining the approach to be taken in cases where immediate hemodynamic support is required (as a bridge to decision); or for recovery of ventricular function in cases of acute myocardial infarction (as a bridge to recovery); or as hemodynamic support and clinical stabilization of patients in a severe condition who are in a transplant queue (as a bridge to transplantation).[4]

It is known that IAB is widely used as the first option for treating heart failure,[5] but in some cases in which refractory cardiogenic shock occurs, ECMO is an excellent and rapid option. CentriMag provides a temporary option for ventricular function support until the myocardium recovers,[6] thus preventing low output from leading the heart to irreversible cellular conditions.

Faced with the clinical picture of worsening of our patient's cardiac function, the decision to implant CentriMag was made in a matter of hours. This was in accordance with the recommendations of the Interagency Registry for Mechanically Assisted Circulatory Support Classification (INTERMACS),[7] in which use of MCADs is strongly indicated for patients with the profiles INTERMACS 1 (severe cardiogenic shock) and INTERMACS 2 (progressive decline in renal, hepatic, nutritional and lactatemia function, despite use of inotropes).

Figure 1. Left ventricular intracavitary thrombus of the device.

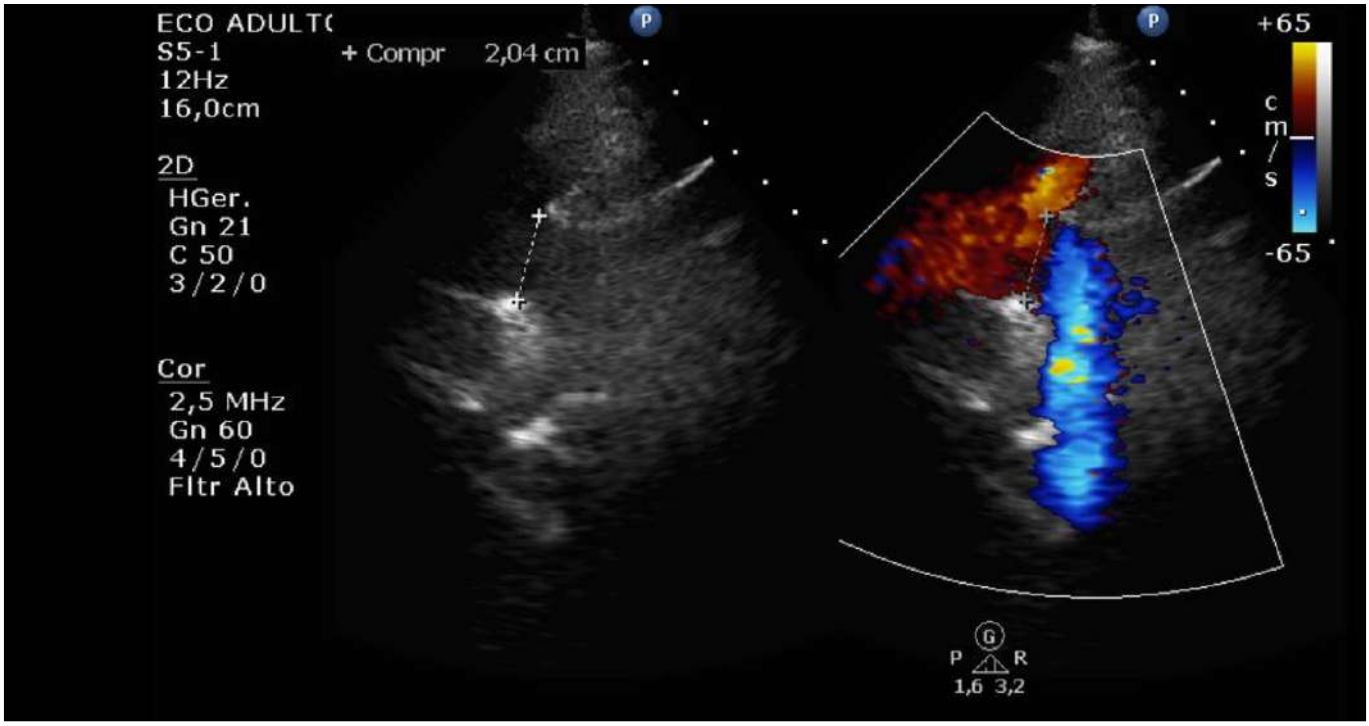

Figure 2. Bi-dimensional echocardiogram with N-flow mapping after explantation of CentriMag device, showing preserved bi-ventricular function (July 16, 2019).

Table 1. Systematic review of the literature

Database	Search strategy	Results
MEDLINE/PubMed	(("heart failure" [Mesh]) OR "myocarditis"[Mesh]) AND "Heart-assist devices"[Mesh] AND "Postpartum Period"[Mesh]	Case report: 4 Original article: 1
	((heart failure) OR Refractory cardiogenic shock) AND ((centrimag OR heart-assist devices)) AND (postpartum)	Case report: 9 Original article: 15 Review: 3
EMBASE	('heart failure'/exp OR 'heart failure' OR 'myocarditis'/exp OR myocarditis) AND ('centrimag'/exp OR centrimag) AND ('postpartum'/exp OR postpartum)	Original article: 3 Conference abstract: 4

CONCLUSIONS

The decision to implant a MCAD should be individualized, as patient profiles do not always match the indications in the guidelines and protocols. In this study, clinical discussion of the case among the medical and multi-professional teams was essential in order to be able to successfully reverse the patient's severe clinical condition without sequelae, through using a CentriMag implant.

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Would it be possible to have better ways and routes of administration for vaccines against COVID-19?

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Dear Editor,

While celebrating with joy the evidence of the effectiveness of several vaccines against coronavirus disease 2019 (COVID-19), we are faced with the reality that billions of people in all regions of the planet will need to be vaccinated in order to achieve plausible control of the pandemic.

Scientific debates on which vaccine would be the best for COVID-19 have been given priority by scientific publications and news reports, with less emphasis than necessary on discussion of what the best vaccine administration routes might be.

Until such time that better evidence is available, we believe that research on new routes of administration is as important as proving the individual effectiveness of each vaccine. In these times of a pandemic, this is an opportunity to carry out randomized clinical trials to test different types of intradermal immunization in comparison with intramuscular immunization.

As a covering organ, the skin has mechanisms to protect the organism against physical, chemical or biological aggressions. Keratinocytes, Langerhans cells, fibroblasts, T lymphocytes, macrophages and dendritic cells are the first line of defense in the immune, cellular or humoral response.[1]

This immunological defense is not observed in the hypodermis or in the underlying muscles. Consequently, it is assumed that cutaneous microbiomes would have the function of "educating" the body's immune system.[2]

Over recent years, injection of vaccines into the intradermal compartment has been considered. The logic is that vaccines injected into the dermis would provide greater immune stimulation.[2]

Several techniques for percutaneous immunizations have been described, among which three can be listed: superficial manual punctures with microneedles; intradermal Mantoux injection (the Mantoux method, which was first described in 1910 and has become the clinical standard for intradermal injection); and "DNA tattooing", described by Bins et al.in 2005.[3] In our view, this last method could be the most effective technique in a national vaccination campaign.[3]

What are the differences between these intradermal vaccination techniques?

Manual punctures with microneedles consist of dripping the vaccine on the skin and puncturing the site with needles. The diffusion of the vaccine in the dermis is passive.[2,4,5] Assuming that two dozen perforations should be performed on the skin of each patient, the procedure could be exhausting for the technician, thus losing effectiveness.[6]

Intradermal injection with a syringe and needle (Mantoux method) requires technical skill. Moreover, the volume that needs to be injected is greater, with the aim of forming a bolus.

DNA tattooing[3] uses tattoo machines to inject vaccines into the skin instead of inks. This vaccine delivery method was inspired by the ancient technique of artistic dermopigmentation. It was innovated and implemented by Brazilian dermatologists eight years ago, under the name MMP (Portuguese-language acronym for Micro-Infusion of Drugs into the Skin).[4-5]

Tattoo machine procedures are accurate and reproducible. The protocol for injecting medications with tattoo machines has already been established, consisting of 570 perforations per cm^2, with a needle speed of between 60 Hz and 120 Hz and a needle depth of 300 microns.[5] The rapid movement of the needles causes diffusion and active dispersion of the vaccine in the dermis.[4]

This gives rise to a greater area of immunological exposure that may extend to regional lymph nodes.[7]

We estimate that to immunize a patient, we need to puncture 1 cm^2 of skin. We performed an experimental assay (unpublished results) in which we injected 1.0 ml of saline into artificial skin using a tattoo machine. This amount was enough to cover 20 to 50 cm^2 of artificial skin, meaning that 20 to 50 patients could be immunized with this volume, depending on the skill of the technician.

We propose to launch randomized, well-designed clinical trials that will aim to describe the effectiveness of intradermal vaccination in its three forms and compare them with each other and with traditional intramuscular vaccination.

These studies may be carried out in different scenarios and be brought together later, in syntheses of appropriate evidence.

It is essential to carry out analyses on cost-effectiveness and budgetary impacts, and to explore the possibilities of attaining greater efficiency, in order to cope with limited resources and enable better access to treatments for less developed countries.

Through such studies, data for clinical decisions can be provided, so as to be better prepared to face the challenges of comprehensive worldwide immunization; and, of course, to improve patients' experience.

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Conflict of interest: Samir Arbache: Tattooing is an ancient technique under public domain done mainly by tattoo artists. We have chosen to copyright the acronym MMP® in Brazil, United States and Europe and we grant free use exclusively to dermatologists who are members of the Brazilian Society of Dermatology and equivalent entities around the world. Dr Arbache's commercial involvement in this investigation was required in order to obtain approval of the equipment for medical use under Brazilian health legislation (as enforced by Agência Nacional de Vigilância Sanitária, ANVISA) and to render this investigation acceptable for the relevant ethics committee. We hereby inform that the clinical results described and documented herein can be achieved using any available tattoo machine. Dr Arbache is a member of the staff that trains Brazilian dermatologists in the use of this technique. Álvaro Nagib Atallah is an Adjunct Editor of the Sao Paulo Medical Journal

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Does use of nonsteroidal anti-inflammatory drugs increase patients' clinical severity of COVID-19?

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Dear Editor,

Since the emergence of the first cases of coronavirus disease 2019 (COVID-19) at the end of 2019, understanding of this disease has been advancing rapidly. Updates on this subject are crucial to healthcare professionals who are engaged in the battle against this disease. However, it is noteworthy that the emergence of updates not based on evidence has generated difficulties in the clinical management of patients in the midst of this pandemic, especially when dealing with cases of misleading information.

In March 2020, the French Minister of Health (Oliver Veran) used the social network Twitter to announce that unpublished data indicated that use of nonsteroidal anti-inflammatory drugs (NSAIDs) could increase the severity of COVID-19, possibly due to viral replication mechanisms. This comment seems to have originated in part from the clinical opinion of an infectious disease specialist in southwestern France, where it was observed that four cases of previously healthy young patients with COVID-19 progressed to the severe stage of the disease after previous use of NSAIDs to combat the initial phase symptoms. This announcement had worldwide repercussions and led to clinical insecurity regarding drug therapy for patients with COVID-19, despite the lack of any scientific evidence.[1,2]

Given this scenario, regulatory authorities have tried to investigate the association between use of NSAIDs, especially ibuprofen, and patients' severity of COVID-19.[1,2] Some studies have been conducted in different populations, but failed to show any significant association between use of NSAIDs and increased risk of severe clinical disease among patients with COVID-19.[1,3,4] Among these, Drake et al. developed a prospective cohort study between 17 January and 10 August 2020, on 78,674 hospitalized patients with a confirmed diagnosis of COVID-19 at 255 healthcare services in England, Scotland and Wales. After adjusting the sample, it was noted that use of NSAIDs was not associated with worsened mortality (odds ratio, OR 0.95; 95% confidence interval, CI 0.84-1.07; P = 0.35), starting to need intensive care (OR 1.01; 95% CI 0.87-1.17; P = 0.89), requirement of oxygen therapy (OR 1.0; 95% CI 0.89-1.12; P = 0.97), invasive ventilation (OR 0.96; 95% CI 0.80-1.17; P = 0.69), non-invasive ventilation (OR 1.12; 95% CI 0.96-1.32; P = 0.14) or occurrence of acute renal injury (OR 1.08; 95% CI 0.92-1.26; P = 0.33). However, despite the limitations of that study, it should also be noted that rational use was made of this pharmacological group, especially among elderly individuals and patients with multimorbidity.[1]

NSAIDs are considered to be potentially inappropriate medicines (PIMs) for use among the elderly, due to these individuals' senescence. They should be prescribed with caution, given that the risk might be greater than the clinical benefits provided, while safer and more effective alternatives may be available. Thus, they can be considered potentially inappropriate.[5]

Consumption of NSAIDs is commonplace, especially in age groups ≥ 60 years, since they are dispensed readily in pharmacies in Brazil, without any requirement to restrict medical prescriptions. This access to medications that are considered to be over-the-counter (OTC) drugs by Brazil's national regulatory agency facilitates occurrence of self-medication, polypharmacy, drug interactions and imminent risk of adverse reactions. However, it has been recognized that use of NSAIDs potentially gives rise to health risks, through promoting salt and water retention, reducing inhibition of chloride absorption and reducing the action of the antidiuretic hormone,

thus facilitating a propensity to hyperkalemia, edema and decompensation of blood pressure levels, especially in hypertensive individuals. In addition, there are risks of dyspepsia, heartburn, gastric and duodenal ulceration, increased risk of bleeding time due to disorders of platelet function, acute renal injury due to renal hypoflux and decreased glomerular filtration rate.[5]

In view of the above, it is noteworthy that, to date, there has been no significant evidence for any increase in clinical severity of COVID-19 among patients who use of NSAIDs, especially ibuprofen. Nonetheless, this scenario brings a need to review the form of prescription among patients with COVID-19 and the form of dispensing this pharmacological group.

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INSTRUCTIONS FOR AUTHORS

Scope and indexing

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

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

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

Editorial policy

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

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

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

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

São Paulo Medical Journal does not charge authors any "open access fees" and submission is free for all. Associação Paulista de Medicina provides financial support for the Journal.

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

Transparency and integrity: guidelines for writing

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

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

Conflicts of interest

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

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

Acknowledgements and funding

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

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

Authorship

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

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

The corresponding author is the primary guarantor of all ethical issues relating to the manuscript, before, during and after its publication. However, *São Paulo Medical Journal* and ICMJE consider that all authors are held fully responsible for the study, regarding the accuracy or integrity of data and data interpretation in the text. Contributions such as data collection only do not constitute authorship.

The addition or deletion of authors' names in the manuscript byline is possible only if the corresponding author provides the

reason for the rearrangement and a written signed agreement from all authors. Modifications to the order of the authors are possible, but also need to be justified. Authors whose names are removed or inserted must agree with this in writing. Publication of the article cannot proceed without a declaration of authorship contributions signed by all authors.

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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;
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 in the PROSPERO database. 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);
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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.
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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 "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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