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The importance of multiprofessional care

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Multiprofessional care can be defined as a work methodology involving healthcare professionals "with complementary backgrounds and skills, sharing common health goals and exercising concerted physical and mental effort in assessing, planning, or evaluating patient care. This is accomplished through interdependent collaboration, open communication and shared decision-making. This in turn generates value-added patient, organizational and staff outcomes."[1]

Within the context of Brazilian governmental healthcare actions, this care model is recent. It began through changes in public healthcare policies that led to creation of the National Health System (SUS). SUS took on the challenge of replacing the existing care practices that focused on curing diseases. It brought in plans and strategies aimed towards the principles of universality, equity and comprehensiveness of care. In 1994, the Family Health Program (PSF) was created, which was directed towards the context of primary healthcare. The strategy for attending the population was developed around multiprofessional work that had the aim of developing educative activities focusing on problem-solving and transformation of realities.[2,3]

The teams are generally composed of doctors, nurses, dentists, oral health technicians or auxiliaries, nursing technicians or auxiliaries and community health agents (ACS). The main objectives are to promote autonomy and stimulate self-care, thus seeking better quality of life for individuals and communities, while respecting the realities and the environment that surround these individuals.[4,5]

One of the biggest difficulties in implementing this is the lack of professionals to meet this demand in all the spheres of public healthcare. To overcome this, a change in culture and commitment towards public administration is fundamental, in order to achieve practices governed by preventive actions and health promotion.[6]

One example of multiprofessional care is the palliative care that traditionally forms the therapeutic option for end-stage oncological patients. Within this scenario, multiprofessional teams have an essential role in symptom alleviation, improvement of quality of life and improvement of comfort for patients and their families.[7]

Palliative care teams are frequently composed of doctors, nurses, social assistants, volunteers and religious leaders. Whenever possible, patients should be the ones to make final decisions on their own care, using information from the team and their own values as a guide.[8]

Within all spheres of patient care, teamwork provides direct and indirect improvements for everyone involved in the process. These include reduction of hospital length of stay, shortening of recovery time and improvement of adherence to treatment.[9] A systematic review in the literature examined the actions of multidisciplinary teams at different stages of oncological treatment (diagnosis, treatment, pain control and palliative care). In all the studies analyzed, there was a multidisciplinary team and a control group. The multidisciplinary team improved adherence to treatment and diminished the time taken to do tests, thus enabling higher chances of cure. Discussion of cases among the team members had a positive impact on planning and implementing therapies, making clinical decisions and making referrals to specialists. Within palliative care, there was better pain control and higher adherence to oral medications. The study showed that formation of multidisciplinary teams to act in relation to cancer treatment is a promising development that can improve patients' quality of life and the efficiency of the services provided.[10]

In relation to transplantation, multiprofessional teams are essential at all stages of the process. For organ donation, synchronicity of activities is fundamental given that the tasks of each member of the team are complementary and are all of prime importance.[11]

Some examples of the activities of multiprofessional teams relating to organ donation: The nurse does the active search, notifies the transplantation center, communicates with the medical team, conducts interviews with the family, collects samples for laboratory tests and operates the extracorporeal circulation machine. **The doctor** conducts the protocols for certifying brain death, assesses the viability of the organs and harvests the organs. **The psychologist** provides emotional support for the donor's family and conducts interviews with the family. **The social assistant** aids the family in signing documentation for the donation and provides guidance for the family if the body needs to be moved.

It has now been seen that multiprofessional teams have made great efforts towards combating the pandemic of severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2). In facing up to its disease (COVID-19), development of research and care protocols and dissemination of information have certainly been a challenge.[12]

At the Heart Institute (Instituto do Coração, INCOR) of Hospital das Clínicas, University of São Paulo Medical School (Faculdade de Medicina da Universidade de São Paulo, FMUSP), a multiprofessional committee for managing the COVID-19 crisis was set up. This group has been holding weekly meetings with the executive, clinical and nursing directorates and with the hospital infection committee, in order to discuss and pass on information to the different professionals, regarding new measures at the institution for facing the pandemic, and to draw up care protocols and training schemes to capacitate professionals to care for these patients.

In providing care for patients with COVID-19, pulmonologists, cardiologists, intensive care specialists, nurses, physiotherapists, pharmacists, nutritionists and psychologists together define therapeutic plans for these patients, starting from individual assessments on each case. Actions are implemented in accordance with the priorities and targets that have been established.

Even if there is a favorable outcome after hospitalization, patients with other diseases of high complexity who then go through the COVID-19 experience and require intensive care are generally left with a significant physical and psychological burden. In this regard, multiprofessional teams need to be organized such that they can provide long-term care until these patients' health, or at least their quality of life, is restored.[13]

Multiprofessional care is a recently proposed way of working that has become widely used among healthcare teams in order to face up to the intense process of specialization and fragmentation of care. Formation of teams focusing on meeting needs comprehensively and on seeking solutions that complement each other in an effective manner is a strategy that enables care that is safer and provided by professionals with better qualifications. Moreover, this brings better results for patients.

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Evidence for the efficacy of Tai Chi for treating rheumatoid arthritis: an overview of systematic reviews

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Tai Ji.
Arthritis, rheumatoid.
Exercise therapy.

AUTHORS' KEY WORDS:
Mind-body exercise.
Tai Chi Chuan.
Rheumatoid arthritis exercise.

ABSTRACT

BACKGROUND: Rheumatoid arthritis (RA) is a chronic disease with higher prevalence among women aged between 30 and 50 years and general prevalence of 1% worldwide. Interventions promoting improvement of quality of life for individuals with RA are required. Tai Chi appears to be a low-cost alternative, with studies showing positive results from this technique. However, regarding aspects of RA such as pain and sensitivity, studies remain inconclusive.

OBJECTIVES: To compare the effectiveness of the Tai Chi method for treating patients diagnosed with rheumatoid arthritis, among systematic reviews.

DESIGN AND SETTING: Overview of systematic reviews with Cochrane and non-Cochrane methodology.

METHODS: Systematic reviews involving quasi-randomized and randomized clinical trials (RCTs) on use of Tai Chi, with no restrictions regarding the date and language of publication, were included.

RESULTS: Three systematic reviews were included. The effects of Tai Chi associated with education and stretching exercises versus education and stretching were evaluated in these reviews. They showed that improvements in the variables of mood, depression and functional index were associated with use of Tai Chi.

CONCLUSIONS: The findings suggest that clinical improvement was achieved, although not statistically significant with regard to pain and disease pattern, as assessed using the ACR20 measurement. Improvements relating to disability and quality of life were also seen. There was a low level of evidence and therefore caution in data analysis is recommended. The three studies included showed poor reliability for providing an accurate and complete summary of use of Tai Chi among people diagnosed with rheumatoid arthritis.

PROSPERO: CRD42019125501.

INTRODUCTION

Rheumatoid arthritis (RA) is a chronic inflammatory systemic disease that mainly affects the musculoskeletal system. Its prevalence worldwide is 1%.[1,2] Its occurrence rate peaks at ages between 30 and 50 years and it is primarily seen in females and people with a family history of the disease. Fifty percent of the risk of developing rheumatoid arthritis is attributed to genetic factors.[1,3] Among environmental factors, the biggest trigger is smoking.[3]

Rheumatoid arthritis is further defined as an autoimmune condition, due to expression of autoantibodies such as the rheumatoid factor, which attacks a particular part of immunoglobulin G.[4] Consequently, an inflammatory process occurs, thereby leading to proliferation of synovial cells in joints. The proliferating synovial inflammatory tissue is called "pannus" and leads to destruction of the adjacent cartilage and to bone erosion. Large production of pro-inflammatory cytokines, including tumor necrosis factor and interleukin-6, drives the destruction process,[1] which is associated with persistent pain, deformities and disability, which leads to functional decline and generates social costs.[5,6]

There is a direct association between disease severity and higher treatment costs. It has been estimated that in the United States, US$ 2,000 to US$ 10,000 is spent per patient per year. In addition to this, there are indirect costs that are expected to be at least similar to these figures.[7] De Azevedo et al.[8] estimated the indirect costs of rheumatoid arthritis in a survey conducted at the Federal University of São Paulo and found that the costs ranged from US$ 466,107.81 to US$ 2,423.51 per patient per year. Based on this scenario, interventions that help to mitigate this disease form relevant strategies, both for patients and for public health.[9]

Positive effects on rheumatoid arthritis management through physical exercise programs aimed at maintaining muscle strength, mobility, flexibility, balance, resistance, and aerobic capacity have been demonstrated.[10-13] Such exercises are generally prescribed at low intensities and are adapted to the demands of each patient.[14] In this context, activities that involve both body and mind have shown positive results, as is the case of Tai Chi.

Tai Chi is a Chinese martial art composed of slow and smooth movements that reproduce shapes and postures inspired by nature, with circular and rhythmic movements and great mental focus.[14,15] The intensity of Tai Chi practice is equivalent to walking at a speed of six kilometers/hour, and this gives rise to a moderate increase in heart rate.[2] Practicing Tai Chi improves balance and postural control, increases lower limb strength, improves flexibility and prevents falls, especially among the elderly, in addition to promoting interaction between body and mind.[16-18] Biopsychosocial benefits have also been shown, with improved wellbeing and reduced stress, anxiety, depression and mood disorders.[19] In addition to the points mentioned above, because Tai Chi is a form of exercise that involves unloading of bodyweight, it has the benefit of stimulating bone formation, thus decreasing the risk of osteopenia and osteoporosis.[20]

Although studies have shown positive results from use of Tai Chi, the evidence regarding its effectiveness in treating rheumatoid arthritis remains limited and inconclusive with regard to aspects such as pain, function, sensitivity and edema. Hence, further studies to analyze the effects of this technique are required.

OBJECTIVE

The purpose of this overview was to compare the effectiveness of the Tai Chi method among patients diagnosed with rheumatoid arthritis, among systematic reviews (SRs).

METHODS

Design

This overview included systematic reviews that used either Cochrane or non-Cochrane methodology, involving randomized clinical trials (RCTs) and quasi-randomized trials. There were no restrictions regarding the date or language of publication.

Inclusion criteria

Types of participants

Only systematic reviews on patients diagnosed with rheumatoid arthritis in accordance with the American College of Rheumatology (ACR) criteria, with the diagnostic confirmation clarified in the body of the text, were included. There were no age or sex restrictions, regardless of the time of the disease onset,

Types of interventions

Systematic reviews that included the Tai Chi technique as a form of intervention, whether for prevention or treatment, in comparison with other conservative methods or placebo or no treatment, were assessed.

Types of outcomes

All outcomes involving Tai Chi practice among patients diagnosed with rheumatoid arthritis that were reported in the studies included were considered.

Process of searching for and selecting studies

The searches were conducted in September 2019, using the official terminology of the Health Sciences Descriptors (DeCS) and Medical Subject Headings (MeSH) databases. The search strategy is presented in **Table 1**. The following databases were accessed: Medline via PubMed, Cochrane Library, EMBASE and Virtual Health Library (VHL). The grey literature was also accessed. A manual search on the reference lists found in studies previously included was performed. Two independent reviewers (EF and HP) selected the studies, while observing the inclusion criteria mentioned above. Software available through the Rayyan website[21] was used to remove duplicates and to make the final

Table 1. Search strategy

Database	Search strategy
Virtual Health Library	(tw:("Artrite Reumatoide" OR mh:c05.550.114.154* OR mh:c05.799.114* OR mh:c17.300.775.099* OR mh:c20.111.199*)) AND (tw:("Tai Ji" OR (t'ai chi) OR (tai chi) OR (tai chi chuan) OR (tai-ji) OR (taiji) OR (taijiquan) OR mh:e02.190.525.890* OR mh:e02.779.474.913* OR mh:i03.450.642.845.560.500*)) AND (db:("MEDLINE" OR "IBECS"))
PubMed	((("Arthritis, Rheumatoid"[Mesh] or Rheumatoid Arthritis))) AND (("Tai Ji"[Mesh] or Tai-ji or Tai Chi or Chi, Tai or Tai Ji Quan or Ji Quan, Tai or Quan, Tai Ji or Taiji or Taijiquan or T'ai Chi or Tai Chi Chuan))
Cochrane	#1 MeSH descriptor: [Arthritis, Rheumatoid] explode all trees #2 Rheumatoid Arthritis #3 #1 or #2 #4 MeSH descriptor: [Tai Ji] explode all trees #5 Tai-ji or Tai Chi or Chi, Tai or Tai Ji Quan or Ji Quan, Tai or Quan, Tai Ji or Taiji or Taijiquan or T'ai Chi or Tai Chi Chuan #6 #4 or #5 #7 #3 AND #6
EMBASE	'rheumatoid arthritis'/exp AND 'tai chi'/exp AND [embase]/lim

selection of studies. In cases of disagreement between the reviewers regarding the inclusion of specific studies, a third reviewer (AI) was included for making a final decision.

Data extraction was performed by two independent reviewers (HP and EF), through accessing the full published texts. The authors were contacted directly if the full text was not available. Data compilation was performed using the Review Manager 5.3 (RevMan) software (Copenhagen: The Nordic Cochrane Centre, Cochrane Collaboration, 2014).

The risks of bias and quality of evidence assessed per outcome were extracted from the analyses that had been made in the original systematic reviews, when available. Methodological quality was assessed by two independent reviewers (SP and EF) using the tool "Assessing the Methodological Quality of Systematic Reviews 2" (AMSTAR 2). Quantitative analyses using continuous variables were grouped as those expressed as a mean difference (MD) or as those expressed as a standardized mean difference (SMD), with 95% confidence intervals (CI). Analyses involving dichotomous outcomes were grouped according to the relative risk (RR) with the respective 95% confidence interval, when available in the original review. The I^2 value was calculated and was found to present heterogeneity.

RESULTS

The search strategy found 182 studies **(Figure 1)**, out of which 134 were excluded because they did not meet the inclusion criteria. Initially, seven studies were included for qualitative synthesis. However, full-text analysis showed that three of them were incompatible with the interventions mentioned in their abstracts and these were therefore excluded from the final analysis. Among the remaining studies, it was not possible to obtain the full text of one of them. An e-mail was sent to the authors, to request this article, but without any response. Therefore, we were left with three studies for the final analysis.[22-24]

These systematic reviews were divided into different groups according to the intervention that was used.

Tai Chi in association with education and stretching exercises, versus education and stretching alone

The systematic review by Lee et al.[24] included two randomized clinical trials that investigated the effectiveness of the Tai Chi technique among people diagnosed with rheumatoid arthritis. In one of these randomized clinical trials, Tai Chi was applied in association with education for the patients combined with stretching exercises. The outcomes of pain, disability index and quality of life were assessed. The control group was formed by 10 volunteers who received educational instructions relating to the symptoms of rheumatoid arthritis and nutrition focused on this disease (40 minutes) plus stretching exercises (20 minutes), twice a week for 12 weeks. The intervention group participated in Tai Chi classes lasting 60 minutes, twice a week for 12 weeks. The group that practiced Tai Chi presented improvements in their disability index ($P = 0.01$) and quality of life ($P = 0.01$). However, no significant difference regarding pain was observed.

Regarding the pain outcome, neither of the studies showed any significant change in comparison with the control.[25,26] In one randomized clinical trial, there was a significant difference between the groups regarding the depression and mood assessments,[25] in comparison with the control, while in the other randomized clinical trial there was an improvement in the assessment through the profile of the mood state inventory.[26] This latter randomized clinical trial showed improvement in the intervention group regarding the functional index.[26] In relation to quality of life, the assessment in this second randomized clinical trial showed that Tai Chi was favorable for the aspect of vitality, compared with the control.[26]

In the systematic review by Macfarlane et al.,[22] the effectiveness of several complementary and alternative therapies for treating rheumatoid arthritis, including Tai Chi, was ascertained. One randomized clinical trial was included in their review, which was the same study as above, in which Tai Chi exercises were applied for 60 minutes, twice a week for 12 weeks. The control group was composed of 20 people who received guidance on nutrition and information regarding the disease for 40 minutes plus stretching exercises for 20 minutes, twice a week. Among the 13 outcomes assessed, 10 did not show any statistically significant change between the groups, including pain, change in the overall assessment, joint swelling, sore spots, fatigue and functional capacity. There were considerable improvements in vitality, mood and skills in the intervention group. No significant differences in laboratory tests such as erythrocyte sedimentation rate (ESR) and C-reactive protein (CRP) were found.

Tai Chi versus control (not practicing Tai Chi)

In the systematic review published by Mudano et al.,[20] the effect of Tai Chi for treating rheumatoid arthritis treatment was analyzed. Out of all the studies assessed in this review, seven studies with 345 participants were selected, comprising 180 individuals who received Tai Chi intervention and 165, other treatments. The following outcomes were analyzed: pain, disease activity using a disease activity score, function, joint sensitivity, swelling, range of motion, handgrip strength, 50-foot walking test and ACR20. The ACR20 measurement of clinical improvement is defined as a 20% improvement in three out of the following five criteria: patient overall assessment; physician overall assessment; functional ability measurement, visual analogue pain scale (VAS); and erythrocyte sedimentation or C-reactive protein rate.

Based on the studies used in this review, which were of low quality, the authors indicated that was not possible to affirm that use of Tai Chi resulted in an improvement in pain, as measured using a visual analogue pain scale. This was despite a mean difference

(MD) in VAS score of −2.15 (95% CI −3.19 to −1.11) through its use, which may have been clinically relevant. The results regarding disease activity and functional ability, measured using the Health Assessment Questionnaire (HAQ) (MD −0.33; 95% CI −0.79 to 0.12), were also inconclusive. Regarding the disease pattern assessed using ACR20, there was no statistically significant result, but the difference may have been clinically relevant. Thus, the result for this outcome was also inconclusive: Tai Chi group (RR = 11.0; 95% CI 0.69 to 175.86); with 50% absolute difference (95% CI 18% to 82%). Likewise, the results regarding the outcomes of sensitivity, swelling, range of motion, handgrip strength and walking test were inconclusive. The intervention program duration ranged from 8 to 12 weeks.

Methodological quality assessment

The methodological quality assessment showed that among the three systematic reviews (Lee et al.,[24] Macfarlane et al.[22] and Mudano et al.[20]), only one (Mudano et al.[20]) presented high methodological quality (**Table 2**). According to AMSTAR 2, a systematic review has high quality in a situation of absence or presence of only one non-critical item. Thus, AMSTAR 2 provided an accurate understanding of the results from the studies included.

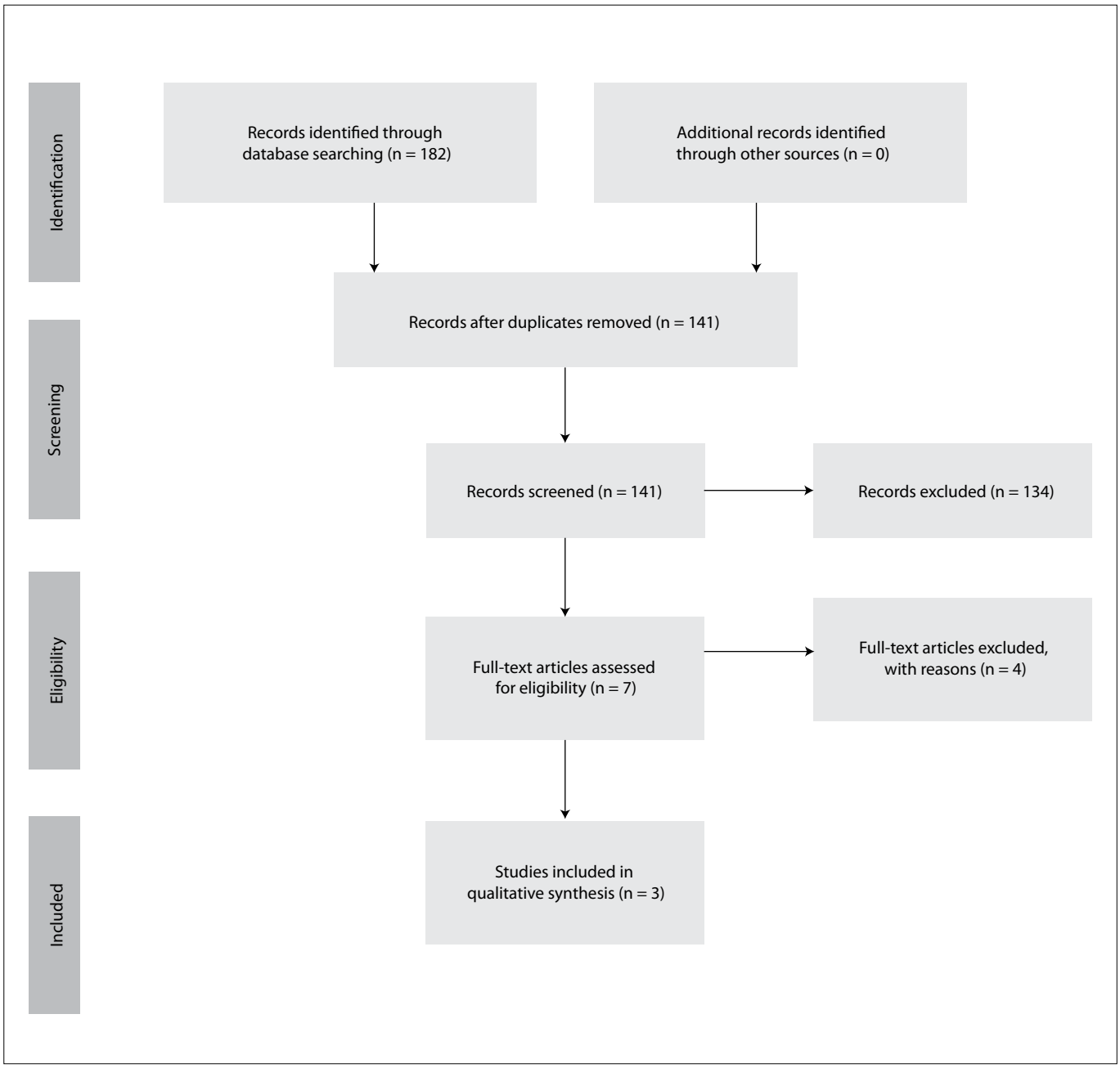

Figure 1. Flow diagram of literature searched and selection criteria.

The other two systematic reviews were considered to be of low methodological quality. According to Shea et al.,[27] studies of low quality do not present sufficient reliability to provide an accurate and complete summary of the data. AMSTAR 2 defines the following as critical domains: protocol registered before commencement of the review; adequacy of the literature search; justification for excluding individual studies; risk of bias from the individual studies included; appropriateness of meta-analysis methods; consideration of risk of bias in interpreting the results from the review; and assessment of the presence and likely impact of publication bias. The studies included are described in **Table 3**.

Table 2. AMSTAR 2 assessment of the studies included

Questions AMSTAR 2	1	2	3	4	5	6	7	8	9	10	11	12	13	14	15	16
Mudano et al.[20]	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	No	Yes	No	Yes	Yes	Yes	Yes
Lee et al.[23]	Yes	No	Yes	No	No	Yes	No	No	No	No	*	*	Yes	No	*	Yes
Macfarlane et al.[21]	Yes	No	Yes	Yes	Yes	No	No	Yes	No	No	*	*	No	No	*	Yes

*No meta-analysis conducted

Table 3. Description of the studies included

Study ID	Objective of the study	Number of articles included	Outcomes and results
Mudano et al.[20]	To assess the benefits and harm of Tai Chi as a treatment for people with rheumatoid arthritis.	Seven RCTs with 345 participants	The majority of the trials presented high risk of performance bias and detection bias, due to the lack of blinding of participants or assessors. The duration of the Tai Chi programs ranged from 8 to 12 weeks. It was uncertain whether Tai Chi-based exercise programs provided any clinically important improvement in pain among Tai Chi participants, compared with no therapy or alternate therapy. There was very low-quality evidence, which was downgraded in relation to blinding and attrition. The evidence was inconclusive with regard to any significant difference in disease activity. Regarding assessment of function, the change in mean score in the Health Assessment Questionnaire for the Tai Chi group was an 11% absolute improvement, but with very low-quality evidence. The authors were unsure whether there had been any significant improvement, given that the results were inconclusive.
Lee et al.[23]	To update and evaluate the clinical trial evidence for the effectiveness of Tai Chi for patients with rheumatoid arthritis.	Five studies: 2 RCTs and 3 CCTs	Pain: Two RCTs suggested that there was no significant reduction in pain, compared with education plus stretching exercise and usual activity. One CCT suggested that there was significant pain reduction, compared with the usual activity control group. Fatigue: One RCT showed that there was no improvement, compared with usual activity. One CCT compared use of Tai Chi with usual activity and suggested that use of Tai Chi was effective in relation to fatigue. Range of motion and joint functions: Two CCTs did not show any intergroup differences with regard to joint tenderness and the number of swollen joints, compared with usual activity. Depression and mood: One RCT reported that there was a significant intergroup difference in depression, compared with education plus stretching exercise. One RCT compared use of Tai Chi with usual activity and suggested that its use led to improvement of mood in the profile of mood state inventory. Functional index: One RCT compared use of Tai Chi with education plus stretching exercise and reported that its use was favorable regarding the disability index. One CCT reported that there was no improvement regarding the ability to perform activities of daily life. Quality of life: One RCT tested the effectiveness of Tai Chi regarding quality of life and reported that its use led to an intergroup difference on the vitality subscale of the SF36 questionnaire, compared with education plus stretching exercise.
Macfarlane et al.[21]	To review the evidence from RCTs relating to management of rheumatoid arthritis with complementary therapy (not taken orally or applied topically).	11 RCTs included, but only one study about Tai Chi	Use of Tai Chi led to significantly greater improvement in terms of disability, vitality and mood. There were no significant differences between the groups regarding 10 of the 13 outcomes measured, including pain (past week and current), patient's overall assessment of change, swollen joints, tender points, fatigue and functional capacity.

RCT = randomized clinical trial; CCT = controlled clinical trial.

DISCUSSION

The purpose of this overview was to ascertain the effectiveness of the Tai Chi method used among people who had been diagnosed with rheumatoid arthritis. Through the systematic search and application of the inclusion and exclusion criteria, three systematic reviews on the use of the Tai Chi method for treating rheumatoid arthritis were included.

Lee et al.[24] showed that use of Tai Chi was beneficial regarding the outcomes of disability and quality of life. However, there was no difference in the pain outcome. In the study by Mudano et al.,[20] which was a Cochrane systematic review, use of the Tai Chi method improved the parameters of pain and disease pattern, as assessed using ACR20. There was no statistical difference; however, because the outcome levels were lower, the difference may have been clinically relevant. Other results were also considered inconclusive, such as sensitivity, swelling, range of motion, handgrip strength and walking test. The review authors reported that the articles were of poor quality. Thus, the effects of the Tai Chi method with regard to improvement of rheumatoid arthritis patients' condition remain inconclusive.

Slight increases in parameters such as pain and disease activity may have been due to the condition of the patients included in the study. Given that Tai Chi requires balanced and controlled movements, patients who can practice this type of exercise often do not present pain as the main symptom.[28] This may have been the reason why there was no statistically significant difference in the pain outcome after Tai Chi programs. The same explanation can be put forward in relation to inconclusive outcomes such as the number of painful and edematous joints.

Regarding improvements in disability and quality of life, authors like Wang[28] have reported that Tai Chi is associated with reduced stress, anxiety and depression, as well as improved quality of life.

The methodological quality assessment demonstrated that the review by Mudano et al.,[20] published by the Cochrane Collaboration, was superior regarding most of the AMSTAR 2 methodological aspects. It is important to highlight critical points that were not addressed by Lee et al.[24] and Macfarlane et al.,[22] in the other systematic reviews included, such as the lack of protocol registration before the commencement of the review and the lack of risk-of-bias assessment regarding the individual studies included. Following the previously published protocol reduces the risk of bias, while a risk-of-bias assessment is extremely relevant, because bias may be present in the design, planning, conduction and analysis of clinical trials.

In the studies included, practicing Tai Chi led to positive results regarding improvement of disability, quality of life, depression, mood and vitality. Regarding pain, one of the main symptoms of rheumatoid arthritis, these studies did not show any clear benefits.

Based on this overview, in analyzing the use of Tai Chi for treating conditions such as dementia in a population that was considered to be of senior age, its use gave rise to improvement in cognitive functions, visuospatial skills, semantic memory and verbal learning, thus leading to improvement of mood, quality of life and, consequently, vitality.

Limitations such as difficulty in standardizing the methods used in Tai Chi practice and the diagnostic model for primary study samples made it impossible to include some studies in the qualitative result analysis of this overview.

The low number of systematic reviews included in the present overview and the low methodological quality of two out of these three systematic reviews further exemplify the limitations found. Based on the findings from the present overview, healthcare professionals should consider using this overview to improve possible symptoms in people diagnosed with rheumatoid arthritis, either in a rehabilitative or in a preventive manner, according to whether any symptoms have yet been exhibited.

The implication from the present overview is that studies with longer follow-up periods (more than six months) should be conducted. Furthermore, qualitative studies should be conducted to assess other aspects of the effect of Tai Chi on disorders such as anxiety, depression and stress.

CONCLUSION

The present review identified three studies regarding use of Tai Chi among patients who had been diagnosed with rheumatoid arthritis. The findings suggest that its use led to clinical improvement, though not statistically significant regarding pain and disease pattern, as assessed using the ACR20 measurement. Moreover, there were improvements relating to disability and quality of life. Other outcomes, such as sensitivity, swelling, range of motion, handgrip strength and walking test, were inconclusive. Considering that among the three studies included only one presented high methodological quality, while the other two were of low quality, caution is needed in evaluating these data. The three studies included present poor reliability for providing an accurate and complete summary of use of the practice of Tai Chi among people diagnosed with rheumatoid arthritis.

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Adherence to antiretroviral therapy among women living with HIV/AIDS in the interior of the Brazilian state of Pará: cross-sectional study

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ABSTRACT

BACKGROUND: High prevalence of human immunodeficiency virus (HIV) infection and occurrence of drug-resistant strains have been recorded in northern Brazil. Abandonment of treatment and insufficient and inadequate adherence to antiretroviral therapy (ART) among people living with HIV/AIDS (PLWHA) have been recorded in the metropolitan area of Belém, the capital of the state of Pará.

OBJECTIVES: To identify the sociodemographic profile and level of adherence to ART among women seen at a referral unit in the interior of Pará, northern Brazil.

DESIGN AND SETTING: Cross-sectional study at a referral unit for care for PLWHA.

METHODS: We included 86 women living with HIV/AIDS (WLWHA) in the Rio Caeté integrated region, northeastern Pará. Social, demographic and behavioral information, as well as the ART level, were obtained using forms that have been described in the scientific literature. Logistic regression models were used to assess associations of variables with ART.

RESULTS: Most WLWHA were single (52.4%), young (47.7%) and heterosexual (97.7%), had low levels of education (63.0%), were unemployed (69.8%), had one sexual partner (75.7%), used condoms (46.7%) and were not using either licit drugs (68.7%) or illicit drugs (89.6%). Their adherence level was classified as insufficient , and only their viral load showed an association with ART.

CONCLUSIONS: The participants' low level of education and poor socioeconomic conditions may have been interfering with their adherence to ART. Such influences can be minimized through multiprofessional interventions that take the individuality of women served by the healthcare service into consideration.

INTRODUCTION

In Brazil, the epidemic scenario of infection by the human immunodeficiency virus (HIV) and the acquired immunodeficiency syndrome (AIDS) has undergone several changes over time.[1] Currently, involvement of socially more vulnerable populations, non-homogeneous distribution of the disease among Brazilian regions, especially with increased numbers of notifications in small and medium-sized municipalities, and the growing number of HIV-infected women are hallmarks of this epidemic.[2-4] These characteristics indicate that the Brazilian healthcare system presents deficiencies with regard to prevention and treatment of HIV infection, especially in municipalities and population groups located in more distant and difficult-to-access areas, as occurs in northern Brazil.[1,2,5-7]

Over the last ten years, the northern region of Brazil has shown an upward trend in the rate of HIV/AIDS detection: 16.4 cases per 100,000 inhabitants were registered in 2007 and 23.6 cases per 100,000 inhabitants were registered in 2017 (an increase of 44.2%), with the state of Pará contributing an increase of 55%.[2] In this Brazilian state, high prevalences of HIV infection and occurrences of drug-resistant strains have been recorded among people living with HIV/AIDS (PLWHA) in the cities of Belém and Bragança.[7-10] Abandonment of treatment and insufficient and inadequate adherence to antiretroviral therapy among PLWHA has also been recorded in the city of Belém.[11]

In northern Brazil, there are few studies on adherence to antiretroviral therapy (ART) among PLWHA. Proper use of ART enables reductions in morbidity and mortality rates and significant improvements in quality of life and life expectancy among PLWHA.[12-14] Multiple factors have been

correlated with abandonment of treatment and with insufficient or inadequate adherence to ART, such as: complexity of therapeutic methods and their respective effects, socioeconomic status, low level of education, family beliefs and values, affective social support, PLWHA's relationships with doctors and other professionals in healthcare services, use of psychotropic drugs and mental disorders.[1,12,14,15] Non-adherence or low adherence to treatment and incorrect use of ART are considered to be strong threats to the effectiveness of treatment among PLWHA. These situations have been directly correlated with therapeutic failure. They facilitate proliferation of HIV strains that are resistant to existing drugs, which gives rise to a need for combined use of other drugs.[14,16] Accurate assessment of adherence and other aspects of this process is essential for proper planning of care for PLWHA and for development of effective strategies for adherence to ART.

OBJECTIVES

The objectives of the present study were to identify the sociodemographic profile of women attended at a referral unit for specialized HIV/AIDS care in the Rio Caeté integrated region, Pará, northern Brazil, and their level of adherence to ART.

METHODS

Study area

This study was conducted among women assisted at a specialized care service (SCS) in the city of Bragança. This SCS formed a reference unit for specialized care relating to HIV/AIDS in the Rio Caeté integrated region, which is located in the northeast of the state of Pará, northern Brazil.[17] This region has the second highest demographic density in the state of Pará, with a population of around 495,000 inhabitants, distributed in 16 municipalities: Augusto Correa, Bonito, Bragança, Cachoeira do Piriá, Capanema, Nova Timboteua, Ourém, Peixe-Boi, Primavera, Quatipuru, Salinópolis, Santa Luzia do Pará, Santarém Novo, São João de Pirabas, Tracuateua and Viseu (**Figure 1**). Fishing, agriculture and extraction of natural resources, such as crabs, shrimps, wood and minerals, are the main economic activities developed in this region. Most of these municipalities have low human development indexes (HDI) and a variety of socioeconomic problems, such as high illiteracy rates, informal work and crack use, and more than half of the population is below the poverty line.[7,17,18]

Study design and sampling

This cross-sectional study consisted of a convenience sample (non-probabilistic). Hence, participants living with HIV/AIDS were selected when they attended the SCS for medical consultations or medication withdrawal. Specifically, all women aged 18 years or over who had previously been diagnosed with HIV/AIDS, had been receiving ART for more than three months and were being attended at the SCS of the Rio Caeté integrated region were invited to participate in this study. Women who refused to complete the data-gathering questionnaires, pregnant women

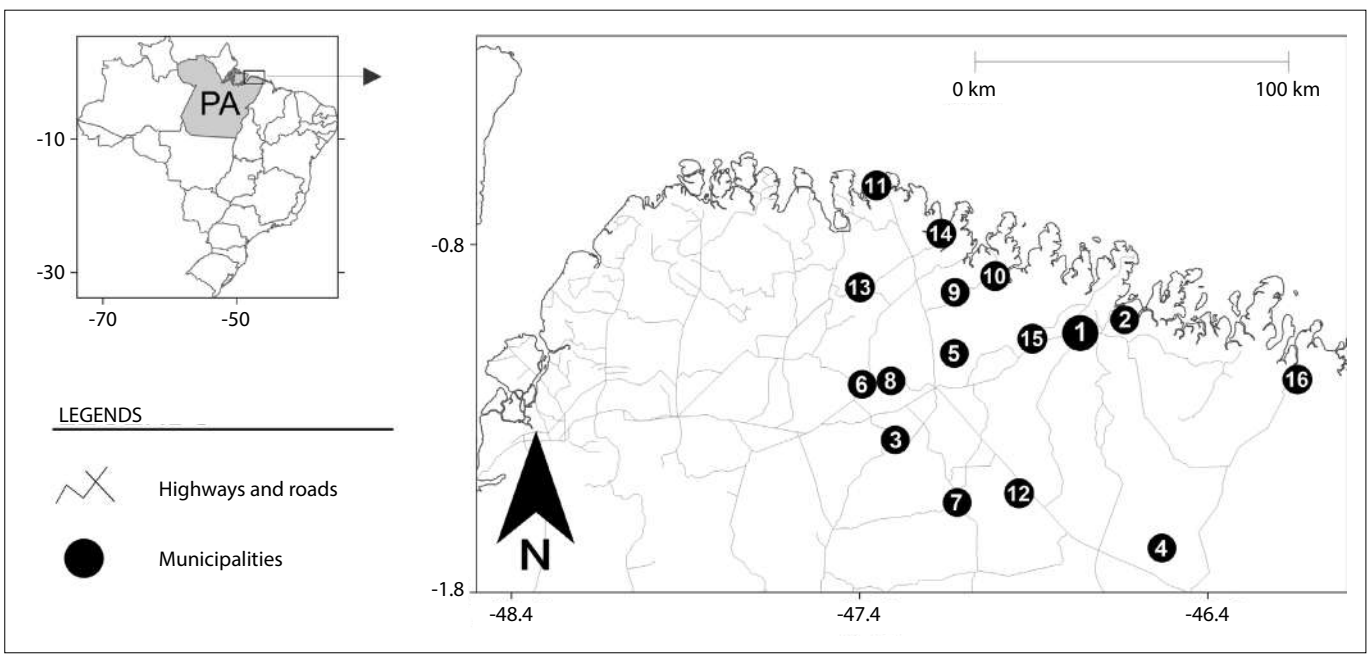

Figure 1. Geographical locations of the 16 municipalities in the Rio Caeté integrated region, Pará (PA), northern Brazil. Points = municipalities: Bragança (1), Augusto Corrêa (2), Bonito (3), Cachoeira do Piriá (4), Capanema (5), Nova Timboteua (6), Ourém (7), Peixe Boi (8), Primavera (9), Quatipuru (10), Salinópolis (11), Santa Luzia do Pará (12), Santarém Novo (13), São João de Pirabas (14), Tracuateua (15) and Viseu (16).

and women with cognitive impairment and/or with some debilitating infection that would make it impossible to answer the questionnaires were excluded.

Thus, between October and December 2018, 110 women living with HIV/AIDS (WLWHA) were attended at the SCS of the Rio Caeté integrated region, Pará. All of these women were invited to participate in this study. However, 24 women were not included: nine were just starting ART and 15 did not agree to answer the questions of the data-gathering instruments. Therefore, the sample was composed of 86 WLWHA, i.e. 78.2% of the WLWHA attended at the SCS of the Rio Caeté integrated region during the study period.

Data-gathering

Data on the participants were gathered by asking them to answer two questionnaires. The first of these had been adapted from a previous study[19] and was used to obtain sociodemographic, clinical and behavioral information. It contained questions relating to the following variables: age, marital status, place of residence, education level, family income, religion, time of HIV infection, co-infections, time on ART, sexual orientation, condom use, number of sexual partners in the last 12 months, use of licit drugs in the last six months and use of illicit drugs during life. Information on $CD4^+$ T-lymphocyte ($CD4^+$TL) levels and plasma viral load (VL) were obtained from the participants' medical records.

The second instrument was the online version in Portuguese of a multidimensional questionnaire assessing adherence to antiretroviral treatment ("Cuestionario para la Evaluación de la Adhesión al Tratamiento Antiretroviral", iCEAT-VIH).[13] The main issues addressed in iCEAT-VIH comprised the patient's compliance with medication intake, antecedents of non-adherence, doctor-patient communication, beliefs about ART, beliefs and expectations about therapeutic efficacy, efforts to follow the treatment, assessment of side effects and level of satisfaction. This questionnaire was completed by the participants in a place in the SCS that had been set aside for this purpose. Both the participant and the researcher were left with copies of the answers placed in the questionnaire.

From the responses given in the online version of this questionnaire (http://www.ceat-vih.info), the ART adherence profile was calculated. At the end of completion of each online questionnaire, a graph with five domains (compliance, history of non-adherence, doctor-patient communication, beliefs and expectations about treatment and satisfaction with treatment) and an overall adherence index, in which scores are transformed onto a scale from 0 to 100, was generated and registered by the participant and, subsequently, by the researcher. To interpret this information, the classification devised by the authors of this questionnaire was used: scores from 0 to 50 = inadequate adherence; scores from 51 to 85 = insufficient adherence; and scores from 86 to 100 = adequate adherence.[13]

Statistical analysis

All the study data were entered into an Excel database (Microsoft Corporation, Redmond, WA, United States, 2010) and then exported into the SPSS software (IBM, Armonk, NY, United States). Absolute (N) and relative (%) frequencies of the variables were used for descriptions. Odds ratios (OR) and 95% confidence intervals (CI) were used as measurements of the strength of association between low adherence to antiretroviral therapy (outcome), as indicated by inadequate and insufficient levels, and the independent variables. Variables associated with the outcome, with P-value (P) < 0.30 using bivariate analysis, were entered into a backward stepwise logistic regression model (multivariate analysis). P-values < 0.05 were taken to be significant in all analyses. Lastly, statistical analyses were conducted using the SPSS 23.0 software (IBM, Armonk, NY, United States).

Ethics approval and consent to participate

All participants were included only after providing informed written consent. All procedures were performed in accordance with the relevant guidelines and regulations. This study was approved by the Research Ethics Committee of the Tropical Medicine Center of the Federal University of Pará (Universidade Federal do Pará) in Belém, Brazil (approved on September 13, 2020; CAAE 87450718.0.0000.5172).

RESULTS

The women's average age was 37 years. The largest proportions of these subjects were married (47.7%), heterosexual (97.7%), aged between 18 to 35 years (47.7%) and living in the urban area of one of the municipalities in the Rio Caeté integrated region (55.9%); had some religion (94.2%), had low levels of education (illiterate or incomplete elementary school) (63.0%) and were unemployed (69.8%). In addition, many of these women reported that they only had one sexual partner (75.7%), that their partner used a condom during sexual intercourse (46.7%) and that they were not using either licit drugs (68.7%) or illicit drugs (89.6%) (**Table 1**). More details on the subjects' socioeconomic, demographic and behavioral characteristics can be seen in the supplementary material (**Table S1**).

A general profile of the responses relating to ART that the participants provided in the iCEAT-VIH questionnaire can be seen in **Table 2**. Most of the women (79.0%) had insufficient adherence to antiretroviral treatment and obtained scores between 51 and 85 points (average = 75.4) in the iCEAT-VIH. On the other hand, 17 women (19.8%) obtained scores above 85 points (average = 91.0) and were therefore classified as presenting adequate adherence. Only one woman (1.2%) was classified as presenting inadequate adherence, with a score of 28 points.

In addition, for the majority of the women (53.5%), their VL in their last laboratory test had been undetectable (< 40 copies/ml). The highest VL recorded for any of the participants was 163 copies/ml. Regarding $CD4^+$TL levels, the range observed was from 44 to 2,041 cells/mm^3. The majority of the women (65.1%) had levels of at least 350 cells/mm^3 (**Table 1**). The average length of time since receiving the diagnosis of HIV infection was five years, with a range from 1 to 18 years. A majority of the women (45.3%) used

Table 1. Sociodemographic, behavioral and therapeutic characteristics of women with human immunodeficiency virus/acquired immunodeficiency syndrome who were treated at the reference unit of the Rio Caeté integrated region (Pará, northern Brazil), in relation to the level of adherence to antiretroviral therapy (ART)

Characteristics	N	ART level	
		Inadequate + Insufficient n (%)	Adequate n (%)
Total	**86**	**69 (80.2)**	**17 (19.8)**
Age (years)			
18-40	55	42 (76.4)	13 (23.6)
More than 40	31	27 (87.1)	4 (12.9)
Marital status			
Not married	45	37 (82.2)	8 (17.8)
Married	41	32 (78.0)	9 (22.0)
Area of residence			
Rural	38	31 (81.6)	7 (18.4)
Urban	48	38 (79.2)	10 (20.8)
Education level			
Up to complete elementary school	61	51 (83.6)	10 (16.4)
High school + university	25	18 (72.0)	7 (28.0)
Work status			
Without job	60	49 (81.7)	11 (18.3)
With job (including retired)	26	20 (76.9)	6 (23.1)
Has a sexual partner			
Yes	71	59 (83.1)	12 (16.9)
No	15	10 (66.7)	5 (33.3)
Number of sexual partners in the last 12 months			
More than one	6	6 (100.0)	0
Up to one	80	63 (78.8)	17 (21.2)
Use of alcohol in the last 12 months			
Yes	23	17 (73.9)	6 (26.1)
No	63	52 (82.5)	11 (17.5)
Use of illicit drugs in life			
Yes	77	61 (79.2)	16 (20.8)
No	9	8 (889)	1 (11.1)
Plasma viral load (copies/ml)			
Detected (≥ 40 copies)	40	37 (92.5)	3 (7.5)
Not detected (< 40 copies)	46	32 (69.6)	14 (30.4)
$CD4^+$ T lymphocyte count (cells/mm^3)			
Up to 350	30	27 (90.0)	3 (10.0)
More than 350	56	42 (75.0)	14 (25.0)
Number of pills a day			
More than one	47	37 (78.7)	10 (21.3)
Only one	39	32 (82.1)	7 (17.9)
Length of time with HIV diagnosis			
Up to 5 years	51	39 (76.5)	12 (23.5)
More than 5 years	35	30 (85.7)	5 (14.3)
Length of time on ART			
Up to 5 years	59	45 (76.3)	14 (23.7)
More than 5 years	27	24 (88.9)	3 (12.5)
Level of satisfaction with ART			
Dissatisfied	15	14 (93.3)	1 (6.7)
Satisfied	71	55 (74.5)	16 (22.5)

only one pill and only 15 participants (17.4%) had had any opportunistic infections in the last 12 months.

The bivariate analysis indicated that only the variable "plasma viral load" was associated with low adherence to ART (**Table 3**). In addition, a multivariate analysis was performed using age, educational level, having a sexual partner, plasma viral load, CD_4^+ T-lymphocyte count, time since diagnosis of HIV infection and length of ART use. Again, only the variable "plasma viral load" was associated with low adherence to ART among these women in the Rio Caeté integrated region (supplementary material; **Table S2**).

DISCUSSION

This was one of the first scientific reports on the sociodemographic characteristics and the level of adherence to ART among WLWHA in an area located far from the Brazilian metropolitan regions. It was also the first report from an area in the interior of northern Brazil.

Most of the WLWHA of this study were young (in the reproductive phase) and unmarried, with low levels of education, and had had their diagnoses of HIV/AIDS for approximately five years. These characteristics had already been reported in studies developed in the states of Ceará (northeastern Brazil) and Rio de Janeiro (southeastern Brazil).[20,21] According to Silva et al.,[20] a positive diagnosis of HIV/AIDS can generate a depressed mood and make it difficult to build and maintain affective relationships. This scenario can have a negative impact on women's lives that may even interfere with their acceptance of the diagnosis and adequate adherence to treatment. This might be even more intense in the context of people with low levels of education and low monthly income, given that these factors could impair their understanding of ART.[14,15]

Most of the participants in this study lived in the urban areas of municipalities in the Rio Caeté integrated region. This finding (that they mostly lived in urban areas) corroborates what was observed in a study conducted in the municipality of Caxias, state of Maranhão (northeastern Brazil).[1] Interestingly, a considerable proportion of the women (44.1%) attended at the referral unit lived in the rural areas of these municipalities. This proportion was much higher than the proportion from the rural area that was attended in the municipality of Caxias (10.8%).[1] This indicates that PLWHA in the interior of Pará are indeed being served by healthcare services. However, the reasons for this difference (in relation to the municipality of Caxias) need to be investigated in the future, in order to provide consistent information for improving healthcare services in the northern and northeastern regions of Brazil, such that more women living in remote areas can be served.

Regarding the sexual behavior of these WLWHA in the interior of Pará, most of them were heterosexual and had only one sexual partner, and their partner used a condom during sexual intercourse. These characteristics are relevant at both the individual and the collective level, since they function as factors for limiting HIV transmission to the sexual partner and, consequently, to the population in general.

At the beginning of the HIV/AIDS pandemic, transmission of the retrovirus was marked by unprotected sex in homosexual relationships and among people with multiple partners.[22] According to Bertagnoli and Figueiredo,[23] HIV transmission now occurs more

Table 2. Description of data collected regarding adherence to antiretroviral therapy, highlighting the most frequent option among the responses to each of the questions answered by women living with the human immunodeficiency virus/acquired immunodeficiency syndrome (HIV/AIDS) in the Rio Caeté integrated region, Pará, northern Brazil

Questions	Highest frequency response	N (%)
Have you ever stopped taking your medication?*	Not once	57 (66.3)
Have you ever felt better and stopped taking your medication?*	Not once	74 (86.0)
Have you ever felt worse after taking your medication and stopped taking it?*	Not once	73 (84.9)
Have you ever felt sad or depressed and stopped taking your medication?*	Not once	75 (87.2)
How is the relationship you have with your doctor?	Good	72 (83.7)
How much effort do you make to follow (comply) with your treatment?	Much	35 (40.7)
How much information do you have about the medicines you take for HIV/AIDS?	Little	32 (37.2)
How much benefit can the use of these medicines bring you?	Much	45 (52.3)
Do you think your health has improved since you started taking HIV/AIDS medications?	Quite	29 (33.7)
To what extent do you feel able to continue with the treatment?	Much	59 (68.6)
Do you usually take medication on time?	Yes	48 (55.8)
When the test results are good, does your doctor usually use them to give you encouragement and motivation to continue with the treatment?	Yes	74 (86.0)
How do you feel in general about your treatment since you started taking your medication?	Satisfied	47 (54.7)
How do you rate the intensity of side effects relating to the use of HIV/AIDS drugs?	Nothing intense	43 (50.0)
How much time do you think you spend taking your medication?	Short time	46 (53.5)
What assessment do you have of yourself regarding taking HIV/AIDS medications?	Very respectful	44 (51.2)
How much difficulty do you have in taking medication?	Little difficulty	64 (74.4)

*In the last seven days.

Table 3. Results from bivariate analysis on factors relating to low adherence to antiretroviral therapy (inadequate + insufficient) among women living with human immunodeficiency virus/acquired immunodeficiency syndrome (HIV/AIDS) in the Rio Caeté integrated region, Pará, northern Brazil

Factors	Low adherence to antiretroviral therapy	
	OR (95% CI)	P-value
Age (years)		
More than 40	2.1 (0.6-7.1)	0.24
Up to 40	1.0	
Marital status		
Not married	1.3 (0.5-3.8)	0.63
Married	1.0	
Area of residence		
Rural	1.2 (0.4-3.4)	0.78
Urban	1.0	
Education level		
Up to complete elementary school	2.0 (0.7-6.0)	0.22
High school + university	1.0	
Work status		
Without job	1.3 (0.4 - 4.1)	0.61
With job or retired	1.0	
Has a sexual partner		
Yes	2.5 (0.7-8.5)	0.16
No	1.0	
Number of sexual partners in the last 12 months		
More than one	197.39 (0.0 - ∞)	0.88
Up to one	1.0	
Use of alcohol in the last 12 months		
Yes	0.6 (0.2-1.9)	0.38
No	1.0	
Use of illicit drugs in life		
Yes	2.1 (0.2-18.0)	0.50
No	1.0	
Plasma viral load (copies/ml)		
Detected (≥ 40 copies)	5.4 (1.4-20.5)	0.01
Not detected (< 40 copies)	1.0	
$CD4^+$ T lymphocyte count (cells/mm^3)		
Up to 350	3.0 (0.8-11.4)	0.10
More than 350	1.0	
Number of pills a day		
More than one	0.8 (0.3-2.4)	0.70
Only one	1.0	
Length of time with HIV diagnosis		
Up to 5 years	0.6 (0.2-1.7)	0.29
More than 5 years	1.0	
Length of time on ART		
Up to 5 years	0.4 (0.1-1.5)	0.18
More than 5 years	1.0	
Level of satisfaction with ART		
Dissatisfied	230.9 (0.0 - ∞)	0.81
Satisfied	1.0	

OR = odds ratio; CI = confidence interval; ART = antiretroviral therapy

frequently in heterosexual relationships than in homosexual relationships. In the states of Ceará (northeastern Brazil) and São Paulo (southeastern Brazil), WLWHA reported having acquired HIV through heterosexual intercourse with a long-term unprotected partner who they had believed to be faithful, and they used other contraceptive methods.[22,24] Another notable behavioral trait among these women in the Rio Caeté integrated region was that they were not using any psychotropic drugs (licit or illicit). Studies have indicated that such behavior is associated with consistent condom use and assists in adherence to ART.[2,25,26]

Nonetheless, most of the women in this study were classified as having insufficient adherence to ART. This indicates that there is a need for greater attention from healthcare professionals and institutions that directly care for PLWHA in the interior of Pará. This result is similar to the findings in studies conducted in northeastern, central-western, southeastern and southern Brazil.[14,27-29] In addition, the rate of adequate adherence to ART in this study was lower than what was reported in Equatorial Guinea (42.86%), an African country with a low HDI that is similar to the Rio Caeté integrated region in the Brazilian state of Pará.[29] Adequate adherence to ART can inhibit HIV replication, thereby resulting in increased CD4+TL counts, which are an important part of the organism's defenses and also enable improvement of physical resistance to perform work tasks.[5]

Among the variables analyzed in this study, only low plasma viral load was associated with adherence to ART. Thus, care strategies need to be created or improved in order to promote acceptance of and satisfaction with adherence to ART among WLWHA. Concern regarding adherence to ART is a reality in healthcare services and requires multiprofessional intervention. According to Carvalho et al.,[16] healthcare services need to identify the profile of PLWHA, systematize compliance measures and assess the factors associated with adherence, at regional and even local level, so as to enable early detection of non-adherence to ART and establish the necessary interventions. Low economic status, poverty, illiteracy and low levels of education have been registered as important factors associated with reduced adherence to ART.[1,15,29] These characteristics were observed in the sample of the present study.

Thus, we recommend that the healthcare team's actions should go beyond care centered on use of drugs and their effects. Healthcare for WLWHA in the interior of Pará needs to include individuals' characteristics, taking into account their sociodemographic and behavioral profiles in relation to treatments. Through health education, actions that expand people's knowledge and encourage behaviors that can enhance adherence to ART need to be promoted.

This study had limitations that should be considered. Firstly, the sample size was small and restricted to a single healthcare service, although this data-gathering site is a reference point in assistance

for PLWHA in the interior of Pará. In addition, the data-gathering was limited to use of questionnaires. The responses to the questions were statements that were not further investigated, which may have given rise to bias in the information collected. Lastly, scenarios and questions that were misinterpreted by some of the potential participants may have led to their refusal to participate in the study.

CONCLUSIONS

This study was unique and is very important for the epidemiological scenario of HIV infection in northern Brazil. It identified the sociodemographic, behavioral and clinical characteristics of WLWHA who were seen at a reference unit for HIV/AIDS in the interior of the state of Pará. The characteristics found were similar to those reported in some other Brazilian locations. The participants' adherence to ART was mostly classified as insufficient. Low plasma viral load was the only variable associated with adherence to ART. It is likely that the participants' low levels of education and poor socioeconomic conditions interfered with their adherence to ART. This influence may be minimized through multiprofessional interventions that take into account the individuality of the women served by this healthcare service.

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Physician and patient-related factors associated with inappropriate prescribing to older patients within primary care: a cross-sectional study in Brazil

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ABSTRACT

BACKGROUND: Physician and patient-related characteristics can influence prescription of medications to older patients within primary healthcare. Use of Brazilian criteria may indicate the real prevalence of prescription of potentially inappropriate medications to this population.

OBJECTIVES: To evaluate prescription of potentially inappropriate medications to older patients within primary care and identify patient-related and prescribing physician-related factors.

DESIGN AND SETTING: This cross-sectional study was conducted in 22 public primary care facilities in Brazil, among older people (≥ 60 years) who were waiting for medical consultations.

METHODS: Interviews were conducted before and after the medical consultations. If the patient received a medical prescription at the consultation, all the drugs prescribed and the physician's medical council registration number were recorded. Prevalence ratios were estimated to ascertain the magnitude of prescription of potentially inappropriate medications, along with patient and physician-related factors associated with such prescription.

RESULTS: In total, 417 older patients were included; 45.3% had received ≥ 1 potentially inappropriate medication, and 86.8% out of 53 physicians involved had prescribed ≥ 1 potentially inappropriate medication. The strongest patient-related factor associated with higher prevalence of prescription of potentially inappropriate medications was polypharmacy. Among physician-related factors, the number of patients attended, number of prescriptions and length of medical practice < 10 years were positively associated with prescription of potentially inappropriate medications.

CONCLUSIONS: High prevalence of prescription of potentially inappropriate medications was observed. Physician-related characteristics can influence prescription of medications to older people within primary healthcare. This suggests that there is a need for interventions among all physicians, especially younger physicians.

INTRODUCTION

Prescription of potentially inappropriate medications (PIMs) to older adults refers to the prescribing of medications that can potentially increase the risk of adverse health outcomes, given that safer and more effective treatment options are available for a particular indication. Prescription of PIMs may even refer to a situation in which the risks of therapy outweigh the benefits.[1-4] Thus, prescribing practices have the biggest impact on occurrences of preventable adverse reactions due to the drug.[3,5-9] Such occurrences impose significant burdens, like functional decline, falls, delirium and other geriatric syndromes,[5,10,11] and lead to greater numbers of emergency department visits and hospital admissions, and higher mortality rate.[9,12,13]

In addition, the high cost of prescribing PIMs to older adults places a great economic burden on healthcare systems.[3,5,8,14-16] Therefore, PIM prescription has become an important worldwide public health issue.[2,3,17] In 2013, 37% of non-hospitalized older people in Canada received ≥ 1 prescription of PIM, equivalent to an estimated cost of US$ 75 per older person or a total cost of US$ 419 million in that year.[15] Similarly, after starting to use at least one PIM, a quarter of older adults continued to use them beyond one year,[18] thereby potentially increasing the risk of adverse events and raising healthcare costs.

Both, clinical and nonclinical factors may influence the prescription of medications. However, it is necessary to recognize factors that may influence clinical decisions, such as physician and

patient-related characteristics. These can include the physician's length of medical practice and time in the specialty; and the patient's age, sex, income and comorbidities.[19] In a systematic review of European studies, polypharmacy, advanced age and female sex were the patient-related factors that were most frequently associated with PIM prescription. Other factors that were less frequently associated with PIM prescription included depression, moderate self-rated health quality and poor functional and economic status.[17]

In Brazil, a previous study among community-dwelling older adults was conducted to assess the use of PIMs. It was noted that 34.5% of those older people used ≥ 1 PIM and that certain patient factors were associated with the use of inappropriate medication. These factors included drug use by illiterate older adults, black race, daily use of ≥ 4 medications, use of prescription drugs and acquisition of the drug through the Brazilian public healthcare system as opposed to acquisition in drug stores.[20] However, only a few studies have hitherto evaluated associations of physician-related factors with PIM prescription.[19,21-23] In some of those studies, it was noted that less time spent with patients and certain medical specialties were associated with higher likelihood of PIM prescription.[19,21]

Therefore, it is essential to understand the drivers of PIM prescription in order to be able to target specific interventions that might improve prescribing practices for the older adult population.

OBJECTIVE

The aims of this study were to evaluate the frequency of prescription of potentially inappropriate medications to older patients within primary care, in accordance with Brazilian criteria, and to identify the factors associated with such prescriptions, among patients and their prescribing physicians.

METHODS

Study design

This cross-sectional study constituted the baseline component of a randomized clinical trial named "Development and evaluation of a mobile application for supporting prescription of appropriate medications to the elderly."

Setting

This study was conducted in all the public primary care facilities in the urban area of Vitória da Conquista (BA), Brazil, which included 15 family health units (FHUs) and 7 primary healthcare units (PHUs). These units belong to the Brazilian public healthcare system (Sistema Único de Saúde, SUS), which provides public healthcare at primary, secondary and tertiary levels to the entire population. Despite the availability of a complementary healthcare system that provides health insurance and private health care for individuals who can afford it, most Brazilian people are assisted only through SUS. The Family Health Strategy is a major program that delivers public primary healthcare to families in areas covered by FHUs. Each FHU has at least one multidisciplinary team that comprises general practitioner physicians, nurses, dentists, nursing technicians and community health workers. The PHUs in the city of Vitória da Conquista provides primary healthcare without the coverage of the Family Health Strategy.

Data collection

Data were collected from all the public primary care facilities in the urban area of the city between September 2016 and December 2017. This was done using a multidimensional questionnaire adapted from the instrument used in the Health, Wellbeing and Aging in Latin America and the Caribbean (SABE) project.[24] This questionnaire was then created in a digital data collection platform (KoBoToolbox, Cambridge, MA, United States). Participant interviews were conducted both before and after their medical consultations at the 22 primary care facilities mentioned above, and all these medical consultations were timed. After the consultations, if the patient had received a medical prescription, we recorded all drugs that had been prescribed and the physician's registration number in the regional medical council's registry. If the patient had any health-related interview impediments such as deafness or moderate-to-severe cognitive deficit, all the information was obtained from the person accompanying the patient.

Study population

The patients eligible for inclusion were older people aged ≥ 60 years who were waiting for medical consultations in the facilities. They were invited to participate in the study and were included only after agreeing to this and signing an informed consent form. We excluded individuals who did not receive a medical prescription and those who had hearing impairments and/or severe cognitive deficits and were unaccompanied by a person with whom the interview could be conducted on the patient's behalf.

Sample description

This study used a non-probabilistic sampling method and the participants were selected through consecutive sampling. The sample size was estimated at 513 participants, considering a confidence level of 95%, an acceptable difference of 0.05, an assumed proportion of PIM prescription (the event of interest) of 50% and an expected loss rate of 25%.

Variables

The main outcome from the study (dependent variable) was a PIM prescription. The independent variables relating to patients included the following: 1) sociodemographic characteristics (i.e.

sex, age, marital status, schooling, income, ethnicity and health insurance); 2) clinical characteristics (i.e. cognitive deficit, sensory deficits [auditory/visual], chronic pain, insomnia, multimorbidity, fall history, functional status and hospitalization); and 3) characteristics relating to medical care (i.e. having a companion attending consultations, consultation length ≤ 10 minutes and prescription of polypharmacy). The independent variables relating to physicians comprised sex, length of time in medical practice, specialty, type of primary care unit, number of patients attended per physician, number of prescriptions per physician and number of PIM prescriptions per physician.

Measurement tools

The prescribed medications were analyzed in terms of the composition of their active ingredients. Prescriptions were considered to be PIMs based on the Brazilian consensus on potentially inappropriate medications for elderly people,[4] with regard to rationale, clinical condition and exceptions.

The patient-related variables included the following:

1. Personal monthly income (the Brazilian minimum monthly wage corresponded to US$ 283.00 at the time of our current study).
2. Cognitive impairment, which was assessed using the Mini-Mental State Examination,[25,26] considering different cutoff points according to educational level.[27]
3. Functional status, using the Katz Index of Activities of Daily Living[28,29] and Pfeffer's Functional Assessment Questionnaire[30,31] (the latter was applied only to the person accompanying the patient). These instruments were used to assess functional status in the form of the ability to perform activities of daily living (ADLs) and instrumental activities of daily living (IADLs), respectively.
4. Self-perceived visual impairment and auditory impairment.
5. History of falls: falls after reaching the age of 60 years.
6. Chronic pain, i.e. pain that lasted longer than 12 weeks.
7. Multimorbidity, defined as the presence of two or more self-reported chronic diseases.
8. Attending the consultation together with a companion, i.e. the presence of a person who accompanied the patient to the consultation.
9. Hospitalization, defined as hospital admission within the past 12 months.
10. Insomnia, i.e. difficulty in falling asleep or staying asleep.
11. Polypharmacy, defined as prescription of ≥ 5 medications.[32]

To determine the physician-related variables, the prescribing physicians were firstly identified through their registration numbers in the regional medical council's registry, which was available from the prescription forms that had been issued to the patients. From these registration numbers, we searched for the following data on the website of the medical council: sex, specialty and year in which the physician issued his or her first prescription. The latter was used to calculate the length of time for which the physician had been in medical practice, in years. The primary care units were classified as FHU or PHU.

Statistical analysis

Descriptive analyses were performed on the variables. Associations between categorical variables were assessed using the chi-square test, and the prevalence ratio (PR) was measured to estimate the strength of the association. Means of the continuous variables were compared by means of the t test if the statistical assumptions were satisfied, or the Mann-Whitney U test if otherwise.

Multivariable analysis (Poisson regression) was used to adjust for potential confounders. Statistical significance was determined in terms of a 95% confidence interval (CI) or a P-value < 0.05. Data were considered to be missing from the analyses in the following cases: 1) the interviewer marked the option "unknown" in the questionnaire; 2) the physician did not have a registration number in the regional medical council's registry (e.g. if the physician was working in the "More Doctors" program); or 3) certain words and numbers were illegible (e.g. drug name in the prescription and regional medical council registration number). The R statistical software package was used to calculate the prevalence ratio, while all other analyses were undertaken using the SPSS software, version 25 (IBM Corp., Armonk, NY, United States).

Ethics approval

This study was approved by the Research Ethics Committee of the Multidisciplinary Health Institute, Federal University of Bahia (technical opinion number 378.198; on August 30, 2013). All participants signed an informed consent statement at the time of their participation in the study.

RESULTS

Out of the 522 eligible older people who were waiting for medical consultations in the primary care units, we included 417 cases who received medical prescriptions at their consultations. Among these 417 prescriptions, 189 had at least one PIM. The older people in this study had a median age of 69 years (**Table 1**); 67.4% of them were women; and 62.4% had a monthly income < 1 minimum wage. Regarding medical conditions, 50.2% had cognitive impairment, 67.9% suffered from chronic pain and 62.8% reported multimorbidity. Older people who received polypharmacy prescriptions and prescriptions with ≥ 1 PIM accounted for 16.8% and 45.3%, respectively.

Table 1. Sociodemographic and clinical characteristics of the study participants

Characteristics	Percentage (n/N)
Sex	
Female	67.4 (281/417)
Male	32.6 (136/417)
Age in years, median (IQR)	69.0 (64.0-75.0)
Schooling	
Illiterate	43.1 (179/415)*
Literate	56.9 (236/415)*
Marital status	
Single, widowed or divorced	52.0 (217/417)
Married	48.0 (200/417)
Ethnicity	
White	24.9 (102/409)*
Mixed	75.1 (307/409)*
Personal income	
< 1 minimum monthly wage	62.4 (260/417)
1 minimum monthly wage	37.6 (157/417)
Health plan	
Yes	3.4 (14/417)
No	96.6 (403/417)
Cognitive impairment	
Yes	50.2 (209/416)*
No	49.6 (207/416)*
ADL impairment	
Yes	35.5 (148/417)
No	64.5 (269/417)
IADL impairment	
Yes	60.2 (50/83)*
No	39.8 (33/83)*
Visual impairment	
Yes	58.5 (245/417)
No	41.2 (172/417)
Hearing impairment	
Yes	34.5 (144/417)
No	65.5 (273/417)
Insomnia	
Yes	48.4 (201/415)*
No	51.6 (214/415)*
Chronic pain	
Yes	67.9 (83/4117)
No	32.1 (134/417)
Fall history	
No	41.3 (169/409)*
Yes	58.7 (240/409)*
Hospitalization	
Yes	12.2 (51/417)
No	87.8 (366/417)
Companion attending consultation	
Yes	20.0 (83/416)*
No	80.0 (333/416)*
Multimorbidity	
Yes	62.8 (262/417)
No	37.2 (155/417)
Polypharmacy	
Yes	16.8 (70/417)
No	83.2 (347/417)
PIM prescription	
Yes	45.3 (189/417)
No	54.7 (228/417)
Length of consultation ≤ 10 minutes	
Yes	52.8 (220/417)
No	47.2 (197/417)

*Data missing. One minimum monthly wage was equivalent to US$ 283.00.
ADL = activity of daily living; IADL = instrumental activity of daily living; PIM = potentially inappropriate medication; IQR = interquartile range.

Prescriptions provided by 53 physicians were analyzed in this study (**Table 2**). Older men accounted for 51% of the physicians; those without a specialty constituted 75.5%; and the median length of medical practice was eight years. A total of 86.8% of the physicians prescribed at least one PIM, with a median of four PIMs prescriptions per physician.

In this study, a total of 1,281 drugs were analyzed, within 417 prescriptions. Forty-two per cent (538/1,281) of the medications prescribed were considered to be PIM-suspect medications. After analysis on the rationale, clinical condition and exceptions, 44.6% (240/538) of them were confirmed as PIMs (**Table 3**). The five most frequently prescribed pharmacological classes of PIMs were anti-inflammatory agents (22.5%), oral hypoglycemic agents (12.1%), systemic corticosteroids (10.0%), proton pump inhibitors (9.6%) and benzodiazepines (8.3%).

According to the univariate analysis in **Table 4**, the patient factors associated with PIM prescription were female sex (PR: 1.56; 95% confidence interval, CI: 1.20-2.03); being single, widowed or divorced (PR: 1.31; 95% CI: 1.06-1.62); reporting insomnia (PR: 1.36; 95% CI: 1.10-1.68); having an allotted consultation length < 10 minutes (PR: 0.72; 95% CI: 0.59-0.90); and receiving

Table 2. General characteristics of the prescribing physicians

Characteristics	Percentage (n/N)
Sex	
Female	49.0 (25/51)*
Male	51.0 (26/51)*
Length of time in practice in years, median (IQR)	9.0 (5.0-26.5)
Specialty	
Yes	24.5 (12/49)**
No	75.5 (37/49)**
Type of primary care unit	
FHU	64.2 (34/53)
PHU	35.8 (19/53)
Number of patients attended per physician, median (IQR)	11.0 (6.0-14.5)
Number of prescriptions per physician, median (IQR)	10.0 (5.0-12.0)
PIM prescriptions	
Yes	86.8 (46/53)
No	13.2 (7/53)
Number of PIM prescriptions per physician, median (IQR)	4.0 (2.0-5.0)
Length of time in practice < 10 years	
Yes	47.2 (25/53)
No	52.8 (28/53)

*Data missing due to illegibility of the physician's registration number in the medical council's registry, thus making it impossible to identify the physician's sex; **Data missing due to unavailability of the physician's registration number in the medical council's registry (for example, because of working in the "More Doctors" program).
IQR = interquartile range; PHU = primary healthcare unit; FHU = family health unit; PIM = potentially inappropriate medication.

a prescription of polypharmacy (PR: 1.68; 95% CI: 1.37-2.05). However, after adjusting for potential confounders in the multivariate analysis, only the association with receiving polypharmacy remained statistically significant (PR: 1.50; 95% CI: 1.06-2.12).

Regarding physician-related factors (**Table 5**), the univariate analysis showed that prescription of PIMs showed positive associations with the number of patients attended (P < 0.001) and the number of prescriptions per physician (P < 0.001). Furthermore, younger physicians (length of time in medical practice < 10 years) prescribed more PIMs than older physicians (PR: 1.22; 95% CI: 0.99-1.51).

DISCUSSION

In this study, a total of 45.3% of the patients received a prescription of ≥ 1 PIM, as determined using the Brazilian criteria.[4] In addition, 86.8% out of 53 physicians prescribed ≥ 1 PIM. The strongest patient-related factor was polypharmacy, while the number of patients attended, number of prescriptions per physician and length of time in medical practice < 10 years were significant physician-related factors. To the best of our knowledge, this study is so far one of the largest studies to examine PIM prescriptions among older adults in Brazil, and the first study to evaluate physician-related factors associated with PIM prescriptions in Brazil.

A systematic review of 19 studies conducted in different countries reported that one in five medications prescribed to older people within primary care was inappropriate.[23] The prevalence of PIM prescription within primary care varied between countries and according to the criteria used: totals of 41% in the United States (Beers 2003 criteria);[5] 36% in Ireland (Screening Tool for Older Persons' potentially inappropriate Prescriptions [STOPP] criteria, 2008 version);[14] 34.8% in Norway (Norwegian General Practice criteria, [NORGEP]);[33] 27.3% in Serbia (STOPP criteria, 2008 version);[34] 37% in Canada (Beers 2012 criteria);[15] 34.7% in the Netherlands (Dutch version of the STOPP criteria);[35] 26.4%, 37.4% and 13.7% in Germany, defined by the 2015 Beers criteria, the European Union (EU) (7)-PIM list [EU(7)-PIM] and the PRISCUS list, respectively;[10] and 48.5% in Spain (STOPP criteria, version 2015).[36] These data show that, in several countries, the criteria specified and local prescription habits influenced the prevalence of PIM prescription.

Like in several other studies, it was found in the present study that the pharmacological classes of PIM that were most prescribed were benzodiazepines,[2,5,10,14,15,18,33,34,37] nonsteroidal anti-inflammatory drugs (NSAIDs),[2,5,11,14,17,18,21,34] proton pump inhibitors,[11,14,18] first-generation antihistamines,[2,5,11,14,18,21,33] muscle relaxants,[2,5,15,18,33] tricyclic antidepressants,[2,5,11,14,15,33] antihypertensives,[2,14,18,33] and oral antihyperglycemics.[5,14,15,18,33,34] However, in contrast to previous research, we observed large numbers of prescriptions of systemic corticosteroids, particularly injectables. In our study, approximately 70% of the older patients suffered from chronic pain. They probably received a prescription of systemic corticosteroids to manage chronic pain, even though this prescriptive approach for older adults is not supported by any data in the literature.[38-40] Similarly, although systemic corticosteroids are not recommended for low back pain management,[41,42] a survey reported that nearly 25% out of 720 American physicians opted for systemic corticosteroids as their initial approach for managing acute low back pain-related sciatica.[43]

As reported in the literature, the most important predictor of inappropriate prescribing to older individuals is prescription of polypharmacy.[14,17,32] Depending on the circumstances, including why and how medications are being administered, polypharmacy may be either appropriate (the potential benefits outweigh the potential harm) or inappropriate (the potential harm outweighs the potential benefits). Therefore, the main anti-PIM intervention might consist of avoidance of inappropriate polypharmacy through applying the principles of rational and appropriate prescription and deprescribing medications that are no longer needed.[44,45]

Table 3. Classes of potentially inappropriate medications most frequently prescribed to older people

Ranking	Pharmacological class	Specification	Percentage of potentially inappropriate prescriptions % (n/N)
1	Non-steroidal anti-inflammatory agent	Ibuprofen, meloxicam, ketoprofen	22.5 (54/240)
2	Hypoglycemic	Glyburide	12.1 (29/240)
3	Systemic corticosteroid	Betamethasone (injectable), dexamethasone (injectable), prednisone (oral)	10.0 (24/240)
4	Proton pump inhibitor	Omeprazole, pantoprazole	9.6 (23/240)
5	Benzodiazepines	Alprazolam, clonazepam, diazepam	8.3 (20/240)
6	Muscle relaxant	Cyclobenzaprine, carisoprodol	5.8 (14/240)
7	First-generation antihistamine	Dexchlorpheniramine, promethazine	5.4 (13/240)
8	Antispasmodic	Scopolamine	3.8 (9/240)
9	Antihypertensive	Methyldopa, clonidine, nifedipine	3.8 (9/240)
10	Tricyclic antidepressants	Amitriptyline, clomipramine, imipramine	3.8 (9/240)

Table 4. Patient-related factors associated with prescription of potentially inappropriate medications

Characteristics	PIM		Univariate analysis		Multivariate analysis*	
	Yes % (n/N)	No % (n/N)	PR (95% CI)	P-value	Adjusted PR (95% CI)	P-value
Sex						
Male	33.1 (45/136)	66.9 (91/136)	1.0 1		1	
Female	51.6 (145/281)	48.4 (136/281)	1.56 (1.20-2.03)	< 0.001	1.32 (0.90-1.94)	0.154
Age in years, median (IQR)	68.0 (64.0-74.25)	69.0 (65.0-75.0)		0.337**		
Schooling						
Literate	47.9 (113/236)	52.1 (123/236)	1		1	
Illiterate	43.0 (77/179)	57.0 (102/179)	1.11 (0.90-1.38)	0.325		
Marital status						
Married	39.6 (86/217)	60.4 (131/217)	1		1	
Single, widowed or divorced	52.0 (104/200)	48.0 (96/200)	1.31 (1.06-1.62)	0.011	1.12 (0.82-1.54)	0.463
Ethnicity						
White	39.2 (40/102)	60.8 (62/102)	1			
Mixed	48.5 (149/307)	51.5 (158/245)	1.24 (0.95-1.62)	0.102		
Personal income						
1 minimum salary	43.3 (68/157)	56.7 (89/157)	1			
< 1 minimum salary	46.9 (122/260)	53.1 (139/260)	1.07 (0.58-1.97)	0.473		
Health plan						
Yes	42.9 (6/14)	57.1 (8/14)	1			
No	45.7 (184/403)	54.3 (219/403)	1.07 (0.58-1.97)	0.836		
Cognitive impairment						
No	44.0 (91/207)	56.0 (116//207)	1			
Yes	47.4 (99/209)	52.6 (110/209)	1.08 (0.87-1.33)	0.485		
ADL impairment						
No	43.1 (116/269)	56.9 (153/269)	1			
Yes	50.0 (74/148)	50.0 (74/148)	1.16 (0.94-1.43)	0.224		
IADL impairment						
No	45.5 (15/33)	54.5 (18/33)	1			
Yes	38.0 (19/50)	62.0(31/50)	0.84 (0.50-1.40)	0.499		
Visual impairment						
No	44.8 (77/172)	55.2 (95/172)	1			
Yes	46.1 (113/245)	53.9 (132/245)	1.03 (0.83-1.28)	0.848		
Hearing impairment						
No	45.8 (125/273)	54.2 (148/273)	1			
Yes	45.1 (65/144)	54.9 (79/144)	0.99 (0.79-1.23)	0.899		
Insomnia						
No	38.8 (83/214)	61.2 (131/214)	1			
Yes	52.7 (106/201)	47.3 (95/201)	1.36 (1.10-1.68)	0.004	1.29 (0.95-1.75)	0.105
Chronic pain						
No	41.0 (55/134)	59.0 (79/134)	1			
Yes	47.7 (135/283)	52,3 (148/283)	1.16 (0.92-1.47)	0.227		
Fall history						
No	41.4 (70/169)	58.6 (99/169)	1			
Yes	49.2 (118/240)	50.8 (122/240)	1.19 (0.95-1.48)	0.122		
Hospitalization						
No	45.4 (165/366)	54.6 (200/366)	1			
Yes	47.1 (24/51)	52.9 (27/51)	1.04 (0.76-1.42)	0.790		
Multimorbidity						
No	59.3 (16/27)	40.7 (11/27)	1			
Yes	44.6 (174/390)	55.4 (216/390)	1.16 (0.93-1.46)	0.178		
Polypharmacy						
No	40.9 (142/347)	59.1 (205/347)	1		1	
Yes	68.6 (48/70)	31.4 (22/70)	1.68 (1.37-2.05)	< 0.001	1.50 (1.06-2.12)	0.022
Companion attending consultations						
Yes	41.0 (34/83)	59.0 (49/83)	1			
No	46.5 (155/333)	53.5 (178/333)	1.14 (0.86-1.51)	0.361		
Length of consultation ≤ 10 minutes						
No	53.3(105/197)	46.7 (92/197)	1			
Yes	38.6(85/220)	61.4 (135/220)	0.72 (0.59-0.90)	0.003	0.77 (0.57-1.05)	0.095

*Dependent variable was PIM; model: (intercept), sex, marital status, insomnia, multimorbidity, polypharmacy and consultation length < 10 minutes; **Mann-Whitney U test. One minimum monthly wage was equivalent to US$ 283.00.

ADL = activity of daily living; CI = confidence interval; IADL = instrumental activity of daily living; PIM = potentially inappropriate medication; PR = prevalence ratio; IQR = interquartile range.

Table 5. Physician-related factors associated with prescription of potentially inappropriate medications

Characteristics	Prescription of PIMs		Univariate analysis	
	Yes % (n/N)	No % (n/N)	PR (95% CI)	P-value
Number of physicians	86.8 (46/53)	13.2 (7/53)		
Sex				
Male	84.6 (22/26)	15.4 (4/6)	1	
Female	92.0 (23/25)	8.9 (2/6)	1.09 (0.89-1.33)	0.413
Length of time in medical practice < 10 years				
No	78.6 (22/28)	21.4 (6/28)	1	
Yes	96.0(24/25)	4.0(1/25)	1.22 (0.99-1.51)	0.060
Specialty				
Yes	91.7 (11/12)	8.3 (1/12)	1	
No	89.2 (33/37)	10.8 (4/37)	1.03 (0.84-1.26)	0.805
Type of primary care unit				
FHU	88.2 (30/34)	11.8 (4/34)	1	
PHU	84.2 (16/19)	15.8 (3/19)	1.05 (0.83-1.32)	0.678
Number of patients attended per physician, median (IQR)	11.5 (7.25-15.0)	1.0 (1.0-1.0)	-	< 0.001*
Number of prescriptions per physician, median (IQR)	10.0 (6.25-12.0)	1.0 ± 0 (1.0-1.0)	-	< 0.001*

*Mann-Whitney U test.

PHU = primary healthcare unit; CI = confidence interval; FHU = family health unit; PIM = potentially inappropriate medication; PR = prevalence ratio; IQR = interquartile range.

With regard to the physicians in the present study, almost all of them (90%) prescribed ≥ 1 PIM. In addition, physicians who attended to more patients and wrote more prescriptions were more likely to prescribe ≥ 1 PIM. Furthermore, PIM prescription was 22% more prevalent among younger physicians. According to a German study, the reasons for PIM prescription by family physicians included the following: their limited knowledge of PIMs; limited applicability of detecting PIM lists (like the Beers and STOPP criteria) in daily practice; shortages of time; lack of alternative medications; and bad experiences relating to medication changes.[46]

The findings from this cross-sectional study warrant future studies to assess interventions that can help improve the appropriateness of drug prescriptions to elderly people. The topics that need to be addressed include education programs targeted to family physicians and the use of decision support systems in primary care settings.

LIMITATIONS

The findings of the present study might be explained by the primary care doctors' unfamiliarity with PIMs and the limited availability of safer therapeutic alternatives for older people through SUS.[47] However, our study was not designed primarily to investigate factors relating to the prescribing physician and, therefore, our sample was not calculated to address these factors. Moreover, the variables relating to physicians were limited to data held by the Federal Council of Medicine, which therefore left some gaps that future investigations should address.

CONCLUSION

Half of the patients in our current study received ≥ 1 PIM prescription and nine in every ten primary care physicians prescribed ≥ 1 PIM. Regarding the patient-related factors, polypharmacy was the strongest factor associated with higher prevalence of PIM prescriptions. Among the physician-related factors, we found that the number of patients attended per physician, the number of PIM prescriptions per physician and length of time in medical practice < 10 years were positively associated with prescription of PIMs. Moreover, NSAIDs, oral hypoglycemic agents and injectable systemic corticosteroids were more commonly prescribed than the other pharmacological classes of PIMs. Future interventions targeting all physicians, especially the younger ones, are required in order to promote prescription of appropriate medications to older patients.

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Popular knowledge of stroke in São Paulo: a cross-sectional study within the World Stroke Campaign

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ABSTRACT

BACKGROUND: Stroke is the second leading cause of death in Brazil and the main cause of disability. Inability to identify alarm signals causes delays in seeking emergency services, thereby leading to a worse prognosis.

OBJECTIVES: To assess the population's knowledge of how to recognize and prevent stroke.

DESIGN AND SETTING: Prospective cross-sectional study on data derived from a questionnaire that was administered during the 2016 World Stroke Campaign, launched in the city of São Paulo, Brazil.

METHODS: Data on 806 interviewees were evaluated using descriptive statistics and univariate and multivariate analyses.

RESULTS: Among all the interviewees, 52.1% knew how to conceptualize stroke; 70.07% knew someone who had suffered a stroke; and 29.03% listed three or more risk factors. Only 27.5% mentioned controlling high blood pressure as a preventive measure. In the event of witnessing a stroke, 57.8% would call the emergency service and 2.9% would check the timing. Less educated individuals were 5.6 times more likely (95% confidence interval, CI 3.45-9.02) to have poor knowledge of stroke, compared with the more educated group. Knowing someone who had had a stroke reduced the chances of not knowing the terms relating to the disease (odds ratio, OR = 0.56; 95% CI 0.4-0.78).

CONCLUSIONS: Despite the severity and prevalence of stroke, the population still has little information on this disease. In this context, the importance of mounting campaigns to improve prevention and treatment and to contribute to healthcare policies becomes evident.

INTRODUCTION

Stroke is the second most impactful condition that leads to mortality, accounting for 5.7 million deaths worldwide in 2016.[1,2] According to the Health Informatics Department of the Brazilian Ministry of Health, stroke is also the second leading cause of mortality in Brazil, accounting for 102,965 deaths in 2016,[3] and is the leading cause of disability among adults.[1] According to a national home-based epidemiological survey on health conducted in Brazil, an estimated 2,223,000 people had suffered a stroke and 568,000 had been left with a severe disability (absolute figures). The prevalence was higher among individuals of more advanced age, those with less education and those living in urban areas.[4]

Among the factors leading to worse outcomes from stroke in Brazil is a lack knowledge of the disease. This causes delays in seeking medical care and impairs prevention, thereby resulting in a worse prognosis.[5]

The neurology team at the institution where the present study was developed has joined forces with the World Stroke Campaign. Through this partnership, an awareness campaign on stroke has been under development since 2000. The key points emphasized within this awareness campaign have been how to prevent, identify and react to stroke through knowing its warning signs.

OBJECTIVE

To assess the population's knowledge of how to prevent and recognize stroke.

METHOD

This was a prospective cross-sectional study on data from a questionnaire administered within the context of the World Stroke Campaign in Brazil, on October 29, 2016.

The sample evaluated was composed of random passers-by assessed within the campaign who voluntarily showed interest in participating. People who were less than 18 years of age were excluded from the sample. Demographically, the interviewees were characterized according to their gender, age group and education level, and according to the interview site.

The passers-by were asked whether they knew something about stroke, firstly using the term "acidente vascular cerebral" (AVC) and then using the most popular colloquial term used in our region, "derrame". People were asked what the symptoms of stroke were, and what could be done to avoid stroke. Afterwards, the interviewer would explain the definition and symptoms for people who had not answered the first question correctly. They were then asked what they would do if they identified an acute onset of those symptoms. The interviewer explained the importance of seeking medical help quickly and introduced the concept of stroke as a medical emergency, with a thrombolytic time window and high levels of morbimortality. After the interviewer had explained the potential disabilities relating to stroke, he asked whether the interviewees knew anyone who had suffered a stroke. The questions were open and responses were not induced. **Table 1** presents the questions and the answers that were considered correct.

The questionnaire was administered by students enrolled at 14 medical schools in the state of São Paulo. A training course focusing on the main risk factors, preventive measures and key signs and symptoms of stroke had previously been provided by professors to these students. The students were divided into groups, which were then sent to four different subway stations (República, Sé, Barra Funda and Tatuapé) and a public square (Parque da Água Branca), which are in different zones of the city of São Paulo, during one Saturday (October 29, 2016).

This survey had previously been granted approval by the Research Ethics Committee of Irmandade da Santa Casa de Misericórdia de São Paulo, São Paulo (SP), Brazil, under Certificate of Submission for Ethical Appraisal number 60023316.9.0000.5479, on September 16, 2016.

The data were analyzed using descriptive statistics and univariate and multivariate analyses. The univariate analysis characterized interviewees as either knowing or not knowing three or more symptoms, risk factors and protective factors. To evaluate lack of knowledge about stroke in the multivariate analysis, the interviewees were assessed on whether or not they knew the Portuguese-language terms for "stroke" (acidente vascular cerebral or "derrame").

The multivariate analysis was performed by means of logistic regression, using the stepwise forward strategy to construct the model and considering P = 0.05 for variable input and P = 0.10 for keeping a variable in the model.

RESULTS

A total of 825 people were interviewed and 806 questionnaires were analyzed (19 needed to be excluded because they had been poorly filled out or the interviewee's age was less than 18 years).

The demographic profile is shown in **Table 2**. In this population, 70.07% knew someone who had had a stroke.

With regard to knowledge of stroke, 47.9% did not know how to define stroke or "derrame". This trend was seen to decrease with increasing education level in a statistically significant manner: from 73.48% in the least educated group to 32.23% in the group that

Table 1. Questionnaire

Open question	Answers considered correct
What is stroke (in Portuguese, acidente vascular cerebral)? What is "derrame"?	Interruption of blood circulation in the brain or encephalic bleeding "A brain infarction"
How do you identify a person *who is having* a stroke? What are the symptoms?	Weakness Mental confusion or aphasia Visual impairment Dizziness or coordination impairment Paresthesia Sudden intense headache
How can strokes be avoided?	Hypertension control Dyslipidemia control Physical activity Healthy diet Obesity treatment Avoidance of smoking, excessive drinking and stress
What should you do if you identify someone *who is having* a stroke?	Seek immediate medical attention (by calling 192, which is the emergency number in Brazil) Pay attention to the time of symptom onset

Table 2. Demographic profile of the population sample, compared with data for the state of São Paulo

	n = 806 (%)		State of São Paulo
Gender*			
Male	390	49%	47.9%
Female	413	51%	52.1%
Age groups, in years			
20-39	170**	21%**	35.7%
40-59	315	39%	25.6%
60-79	294	36%	06.5%
> 79	23	3%	01.4%
Level of education			
Incomplete elementary school	135	17%	41.9%
Completed elementary school	151	19%	18.8%
Completed high school	316	39%	27.5%
Completed tertiary education	203	25%	11.0%

*Three individuals were excluded from this analysis due to data missing from their questionnaires; **Four individuals were excluded from this analysis because they were between 18 and 19 years of age, since there are no data relating to the state of São Paulo for comparison.

had completed tertiary education. In a stratified analysis, those who knew someone who had suffered a stroke showed statistically significant better knowledge of the disease (P = 0.001) (**Table 3**).

Regarding the other questions, 29.03% listed three or more risk factors, 18.1% listed three or more symptoms and 67.8% cited at least one preventive measure; 57.8% would call the emergency service, but only 2.9% would check the timing of onset of the signs and symptoms of stroke. The most frequently mentioned symptom was paresthesia (33.6%), followed by dizziness/motor coordination impairment (24.06%), weakness (23.8%), headache (23.2%), mental confusion/aphasia (19.4%) and visual impairment (7.3%).

Among the risk factors, the one that was most cited was obesity (48.2%), followed by sedentary lifestyle (40.5%), systemic arterial hypertension (27.5%), smoking (16.3%), alcoholism (14.01%), dyslipidemia (12.15%) and diabetes mellitus (8%). Among all the interviewees, 29.03% listed three or more risk factors. In a stratified analysis according to education level, this rate rose to 34.19% among those with the highest education level, while among those with the lowest education level it was only 7.69%. This difference was statistically significant (P = 0.01).

The preventive measure most frequently mentioned by the interviewees was avoidance of obesity (48.51%), followed by physical activity (40.5%), high blood pressure control (27.5%), smoking cessation (16.5%), avoidance of alcoholism (14.01%), controlling dyslipidemia (12.15%) and control over diabetes mellitus (8%). Altogether, 25.06% of the interviewees mentioned three or more preventive measures, with a statistically significant difference (P < 0.05) in the analysis stratified according to education level: 32.67% of the individuals who had completed tertiary education and 7.93% of those with incomplete elementary education.

When participants were asked how they would proceed if they witnessed a stroke episode, 57.8% responded that they would call the emergency service, while only 2.9% would check the timing of onset of signs and symptoms and 2.3% would do both. Among this minority that would proceed correctly, 84.2% knew someone who had had a stroke (**Table 3**).

Accepting P < 0.05 as significant, a multivariate analysis was performed to investigate the relationship between the variables and lack of knowledge about stroke.

Education level was a statistically significant factor, since the group with the lowest education level (incomplete elementary school) was 6.1 times more likely (95% confidence interval, CI 3.73-9.96) to have poor knowledge, compared with the group with the highest education level (completed tertiary education) (**Table 4**).

Knowing someone who had had a stroke reduced the chances of not knowing the terms relating to the disease (odds ratio, OR = 0.56; 95% CI 0.4-0.78). Among those who knew someone who had had a stroke, there were no statistically significant differences regarding sex, age or education level.

DISCUSSION

Because of the impact of vascular diseases in Brazil and around the world, especially stroke, interventions involving education and preventive measures should be encouraged. Improving the population's knowledge about this subject can positively impact the mortality and complication rates associated with this disease.[5]

As a potentially treatable condition, albeit with a limited therapeutic window, the prognosis for stroke depends on the population's education and knowledge levels. Better education and

Table 3. Univariate analysis on not knowing the meaning of the Portuguese-language terms for stroke ("AVC" or "derrame") and on calling an emergency service when a stroke is identified

Age group (years)	Did not know the meaning of either term					
	20-59		60 and over		Total	
	Freq	%	Freq	%	Freq	%
Gender						
Female	110	43.1	77	48.7	187	45.3
Male	108	46.6	99	62.7	197	50.5
Level of education						
Incomplete elementary school	54	**76.1***	43	**70.5***	97	**73.5***
Completed elementary school	52	**58.4**	39	**65.0**	91	**61.1**
Completed high school	77	**37.7**	53	**48.2**	130	**41.4**
Completed tertiary education	34	**28.3**	31	**37.3**	65	**32.0**
Do you know anyone who had suffered a stroke?						
No	76	**56.7***	49	59.0	125	**57.6***
Yes	144	**40.6**	117	50.0	261	**44.3**
Age group (years)	**Would call an emergency service**					
	20-59		60 and over		Total	
	Freq	%	Freq	%	Freq	%
Gender						
Female	155	60.8	100	63.3*	255	61.7*
Male	128	55.2	81	51.3	209	53.6
Level of education						
Incomplete elementary school	28	**39.4***	23	**37.7***	51	**38.6***
Completed elementary school	47	**52.8**	31	**51.7**	78	**52.3**
Completed high school	128	**62.7**	75	**68.2**	203	**64.6**
Completed tertiary education	80	**66.7**	51	**61.4**	131	**64.5**
Do you know anyone who has suffered a stroke?						
No	68	**50.7***	42	50.6	110	**50.7***
Yes	216	**60.8**	140	59.8	356	**60.4**

*P < 0.05; Freq = frequency.

Table 4. Multivariate analysis on interviewees who did not know the Portuguese-language terms for stroke ("AVC" or "derrame")

	Univariate		Multivariate	
	OR	95% CI	OR	95% CI
Level of education				
Incomplete elementary school	5.88	3.61-9.57	6.10	3.73-9.96
Completed elementary school	3.33	2.14-5.18	3.29	2.10-5.14
Completed high school	1.50	1.03-2.17	1.51	1.04-2.20
Completed tertiary education	1.00		1.00	
Do you know anyone who has suffered a stroke?				
Yes	1.00		1.00	
No	1.71	1.25-2.34	1.79	1.28-2.48
Gender				
Female	1.00		-	
Male	1.23	0.93-1.63		
Age				
20-59 years	1.00		-	
60 years and over	0.74	0.56-0.99		

OR = odds ratio; CI = confidence interval.

knowledge enables people to quickly recognize a stroke episode and call the emergency service.[2,4,5] In this context, medical entities have been investing in educational programs with the aim of achieving better results with regard to controlling cardiovascular and cerebrovascular diseases.[6-8]

This study revealed alarming data regarding the population's knowledge on preventing, recognizing and reacting to stroke. Although the sample studied had a significantly higher education level than the average for the state of São Paulo, its knowledge of stroke was unsatisfactory.

Knowledge of stroke directly correlates with the level of education, as already observed in studies conducted in developed countries.[9] The same correlation was found in the present study (60.8% among the individuals with the highest education level versus 22% among those with the lowest level). Those in the subgroup with the highest education level were better able to recognize the signs and symptoms (19.3% versus 9.9%), risk factors (42.2% versus 19.8%) and preventive measures (34.6% versus 15.4%). This group was also better aware of the immediate steps to be taken when a stroke episode is recognized, such as seeking an emergency service (64.5% versus 38.6%).

These data contrast with what was found in a previous study,[10] in which, irrespective of the level of education, 70% would call an emergency service, whereas in the present sample, only 57.8% would do so. Our study showed that only 2.9% of all the participants knew the importance of taking note of the timing of the onset of symptoms. Among those who know someone who had had a stroke, 44.31% and 31.78% did not know how to define stroke or list the appropriate measures to be taken if faced with a stroke episode, respectively.

The above scenario may reflect a lack of investment by the government in policies to educate the population and provide training in recognizing medical emergencies. In a systematic review, Saver reported that delayed access to emergency services was directly related to neuronal loss.[11] In addition, rapid access to emergency services correlates with the likelihood of better treatment, such as thrombolysis. In a meta-analysis also published by Saver in 2016, the efficacy of administering endovascular therapy within seven hours of the onset of symptoms became evident.[12] The 2018 guidelines of the American Heart Association (AHA) support the recommendation of thrombectomy for patients eligible for the procedure, for up to 24 hours after stroke onset in selected cases; the prognosis is better when the procedure is performed early.[13] Investing in minimizing the delay in seeking an emergency service would substantially reduce morbidity, mortality and stroke-related costs.

A Brazilian study by Pontes-Neto et al.,[8] with 814 participants who were interviewed in five major cities including São Paulo in 2007, generated results concerning the lack of information. One of its findings was that less than half of the population studied (38.7%) would seek an emergency service in the event of a stroke episode**.** In a study carried out by the team from São Paulo during a stroke campaign in 2011, similar data were found: less than half of the participants reported that they would seek an emergency service (33.6%).[6] In contrast, more than half of the people interviewed in a study conducted in Belo Horizonte in 2014 said that they would take this measure (66.8%).[14] In the present study in 2016, more than half of the interviewees said that they would react by seeking an emergency service (57.8%). These data suggest that a progressive improvement in the level of knowledge about this subject may have occurred.

Regarding preventive measures, the most frequent response was that obesity needed to be controlled (48.51%), whereas only 27.5% mentioned controlling high blood pressure as an important measure. According to the AHA, there is a consensus across multiple meta-analyses that controlling high blood pressure is the most beneficial measure for reducing the risk of stroke.[15] The results from the present study contrast with findings reported in other studies, in which high blood pressure was referred to as the main risk factor: Nordhorn et al.[7] in Berlin (43%) and a study previously conducted in São Paulo in 2011 (41.8%).[6] There is a need to raise the awareness of the population about the impact of controlling high blood pressure upon prevention of cerebrovascular events.[14]

Thus, there is a need to disseminate information on stroke to the general population. This information remains scarce across all levels of education, especially regarding preventive measures. There is a notable disparity in the knowledge about the disease, as became evident from our multivariate analysis, with a greater lack of knowledge in the less educated population, which is precisely the population with the highest incidence of the disease.

LIMITATIONS

The main limitation of this study related to its use of a convenience sample. This failed to represent the population of the state of São Paulo. The same limitation was observed in other studies conducted on this same subject. There was a selection bias in the present study, as shown in **Table 1**, since the interviewees' mean age and level of education differed from the state averages. In our sample, the population was older than the state average, although it was younger than the population at greatest risk of stroke. This is not necessarily a limitation, since the concept of stroke prevention should be taught to the entire population, irrespective of age.

Because the population studied was composed of people with a higher level of education than the general population, our results may have underestimated the lack of knowledge about the subject. In addition, the symptoms mentioned by the participants were not specific to stroke. Furthermore, correct responses do not necessarily mean that the participants would know how to identify a stroke.

Another limitation was the lack of information on the number of people who refused to respond to the questionnaire. It is possible that the participants who agreed to respond were ones who were most interested in this matter and, accordingly, already had some knowledge of the subject.

The source of knowledge among these passers-by was not evaluated. This can be considered to be a limitation, since this could have provided an opportunity to understand what types of campaigns in the media would have the best reach regarding this disease.

CONCLUSIONS

Despite the severity and prevalence of stroke, the population still has little information on this disease. In this context, the importance of mounting campaigns to improve prevention and treatment of stroke and contribute to healthcare policies becomes evident.

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Prediction of all-cause and cardiovascular mortality using central hemodynamic indices among elderly people: systematic review and meta-analysis

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ABSTRACT

BACKGROUND: Despite widespread usage of central blood pressure assessment its predictive value among elderly people remains unclear.

OBJECTIVE: To ascertain the capacity of central hemodynamic indices for predicting future all-cause and cardiovascular hard outcomes among elderly people.

DESIGN AND SETTING: Systematic review and meta-analysis developed at the Del Cuore cardiology clinic, in Antonio Prado, Rio Grande do Sul, Brazil.

METHODS: 312 full-text articles were analyzed, from which 35 studies were included for systematic review. The studies included needed to report at least one central hemodynamic index among patients aged 60 years or over.

RESULTS: For all-cause mortality, aortic pulse wave velocity (aPWV) and central systolic blood pressure (SBP) were significant, respectively with standardized mean difference (SMD) 0.85 (95% confidence interval, CI 0.69-1.01; I^2 96%; P < 0.001); and SMD 0.27 (95% CI 0.15-0.39; I^2 77%; P 0.012). For cardiovascular mortality brachial-ankle PWV (baPWV), central SBP and carotid-femoral PWV (cfPWV) were significant, respectively SMD 0.67 (95% CI 0.40-0.93; I^2 0%; P 0.610); SMD 0.65 (95% CI 0.48- 0.82; I^2 80%; P 0.023); and SMD 0.51 (95% CI 0.32-0.69; I^2 85%; P 0.010).

CONCLUSIONS: The meta-analysis results showed that aPWV was promising for predicting all-cause mortality, while baPWV and central SBP demonstrated consistent results in evaluating cardiovascular mortality outcomes. Thus, the findings support usage of central blood pressure as a risk predictor for hard outcomes among elderly people.

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INTRODUCTION

Brachial arterial blood pressure is still widely used as a predictive parameter for cardiovascular damage, morbidity and mortality, in assessing cardiovascular risk within clinical practice. However, this does not correspond to central blood pressure measured through the carotids and ascending aorta.[1,2] Previous studies have demonstrated that central blood pressure measurements are better predictors of vascular disease and cardiovascular events than brachial pressure.[3-5]

Central blood pressure relates to arterial stiffening and the aging process, and it is an independent predictor for cardiovascular clinical events.[6] Furthermore, the pharmacological superiority of vasodilating drugs with regard to cardiovascular outcomes may be due to their different effects on central blood pressure, rather than similar effects on brachial blood pressure.[7] Thus, peripheral blood pressure measurements may not be a proper substitute for assessing the antihypertensive effects of arterial hemodynamics.[8]

Despite the relevance of central hemodynamic measurement in making diagnoses, determining therapies and making prognoses, many aspects of these measurements remain unclear. This lack of clarity is reflected in low usage of this method in clinical practice. The definition of cutoff values for central blood pressure varies between different ages and populations,[9] especially in older populations, whose distinct aging and pathological stiffening of arteries may constitute confounding factors with regard to central arterial hypertension. One confounding factor is that either indications for central blood pressure assessment are absent from guidelines[10] or, when present, their use

has been shown to only have questionable incremental value for diagnosing hypertension, compared with standard arterial pressure, except in assessing systolic arterial pressure in young adults.[2]

It has been shown that central blood pressure assessment is widely used as a substitute marker for predicting future cardiovascular events.[7] Nonetheless, the predictive value of this marker in populations that are known to be susceptible, like the elderly, remains unclear in the data in the literature.

OBJECTIVE

Thus, the present systematic review and meta-analysis was conducted with the aim of providing a quantitative estimate of the capacity of central blood pressure for predicting future cardiovascular events in older populations. In addition, the aim was to assess the current pending issues regarding the applicability of this method. Through this, it was sought to glean evidence to support usage of indirect central blood pressure assessment within daily clinical practice.

METHODS

Protocol and registration

This systematic review was reported in accordance with the MOOSE guidelines (Meta-analysis Of Observational Studies in Epidemiology).[11] Additionally, we took into account the guidelines of PRISMA (Preferred Reporting Items for Systematic Reviews and Meta-Analysis)[12] and AMSTAR 2 (A MeaSurement Tool to Assess Reviews).[13] The protocol for this study was registered in the Prospero database (International Prospective Register of Systematic Reviews),[14] under the code CRD42018085264, and this protocol was previously published in a scientific journal.[15]

Eligibility criteria

We included full peer-reviewed articles that reported on longitudinal studies that had included samples of patients with a mean age of 60 years or over. The studies included needed to have reported at least one of the following central hemodynamic indexes: central systolic blood pressure (SBP), central pulse pressure (PP), central augmentation index (AIX), aortic pressure, wave reflection (WR) and pulse wave velocity (PWV). Additionally, the studies included needed to have reported all-cause mortality and/or cardiovascular mortality as the outcome. We excluded studies if they had reported results from duplicate populations.

Information sources

We searched the following electronic databases: PubMed, EMBASE and Virtual Health Library (VHL), which contained citations from LILACS, IBECS, MEDLINE, Cochrane Library and SciELO. In addition, we manually searched the reference lists of the articles included and performed citation analysis on the studies included, using Google Scholar. We also sought experts' suggestions through e-mail communications.

Search

The initial search comprised the MeSH terms "Aged", "Aged, 60 and over", "Pulse wave analysis" and related entry terms, along with other terms relating to central hemodynamics such as "Central systolic blood pressure", "Central pulse pressure", "Central augmentation index", "Central pressures", "Aortic pressure", "Wave reflections". A sensitive search strategy for observational studies was also used. The complete search strategy used for the PubMed database is shown in **Appendix 1.** We did not impose any limits for language.

Study selection

The titles and abstracts of the articles retrieved were independently evaluated by two reviewers (GC, TV). Abstracts that did not provide enough information regarding the eligibility criteria were kept for full-text evaluation. The reviewers independently evaluated the full-text articles and determined study eligibility. Any disagreements were resolved through reaching a consensus among three other researchers (GBG, ATS, CR).

Risk of bias

Risk of bias was evaluated by ranking each study in accordance with the ROBINS-I tool (Risk Of Bias in Non-randomized Studies - of Intervention).[16] The following types of bias were considered: bias due to confounding, bias in selection of participants into the study, bias in classification of interventions, bias due to deviations from intended interventions, bias due to missing data, bias in measuring of outcomes, bias in selection of the reported result and overall bias. Each item was classified as presenting low, moderate, serious or critical risk of bias, or as "no information" when the article did not provide any information on which to base a judgement about risk of bias for this domain. This evaluation was performed independently by two reviewers (GC, TV).

Any disagreements were resolved through reaching a consensus with two other researchers (GBG, ATS).

Data extraction

Four reviewers independently conducted data extraction, and any disagreements were resolved through reaching a consensus among three other researchers. Data on the general characteristics of the studies were collected, such as: study title, author, journal and year of publication, study design, inclusion and exclusion criteria, outcomes definitions, outcome measurements and follow-up. In addition, we extracted specific information about central hemodynamic indexes and their predictive values (when available).

Data analysis

The data collected were extracted to the Microsoft Excel software v16.42 (Microsoft, Redmond, United States) for tabulation. The meta-analyses were performed using the STATA software v11.0 (STATA Corp., College Station, United States).

The meta-analyses was made using a fixed model. To analyze the methods used for measuring central pressure hemodynamics, we used the standardized mean difference (SMD) for quantitative variables. We used P (Peeta) and I^2 to assess heterogeneity, Egger's test and Begg's test for small study biases and funnel plot graphs for publication biases. Trim-and fill analyses were performed to validate the data. The final results were presented using a forest plot graph. Meta-regression and sensitive analyses were evaluated for confounding biases.

RESULTS

Our search strategy yielded a total of 5,145 citations from electronic databases. After the keyword and medical term search, we included 5,145 abstracts for review. After removing duplicates and excluding records based on analysis of their titles, 312 full-text articles were analyzed, from which 35 studies were included for systematic review. **Figure 1** presents the study selection flow diagram.

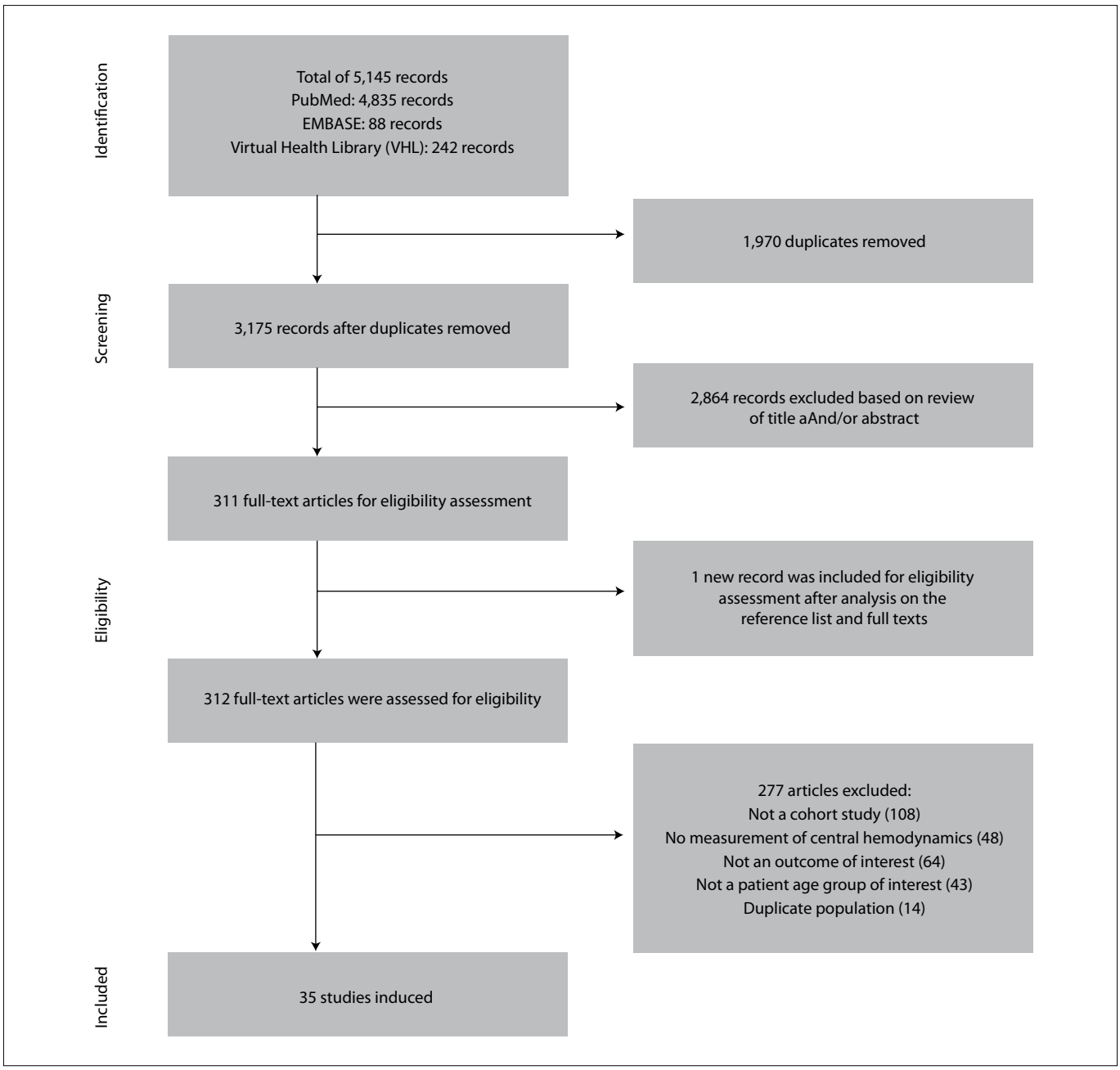


Figure 1. Study selection flow diagram.

The studies included were published between 2001 and 2016. Out of these 35 studies, 32 (91%) were prospective cohorts and three (9%) were retrospective cohorts. The total participants comprised patients with diabetes (3.9%), hemodialysis patients (10.29%), and patients receiving coronary interventions (2.6%). The participants' mean ages ranged from 60 ± 11 years to 86.8 ± 6.9 years. The prevalences of hypertension and diabetes ranged from 19% to 100% and from 7.1% to 100%, respectively. The prevalence of histories of cardiovascular disease ranged from 3.1% to 60.2%; the most prevalent events were stroke and myocardial infarction. A more detailed overview of the study characteristics is available in **Table 1**. All the studies were assessed for methodological quality in accordance with the ROBINS-I tool (Risk Of Bias in Non-randomized Studies - of Interventions), and these assessments are presented in **Figure 2**. The risk-of-bias evaluation on each study included is shown in further detail in **Table 2** and is summarized in **Figure 2.**

All-cause mortality

Augmentation index

Five studies used the augmentation index (AIX). In two of these studies, the population consisted of patients who had undergone coronary angiography[17,18] (the increase in AIX@75 was correlated with the mortality events). In one study,[17] the population was formed only by male patients. The populations of the remaining studies comprised one population-based cohort[19] (AIX@75 was not correlated with the mortality events), one group of patients experiencing acute ischemic stroke[20] (which was associated with intra-hospital mortality) and one group of patients with heart failure[21] (which was shown to have significant predictive value regarding mortality post-hospital discharge).

Augmented pressure

One study[21] evaluated carotid augmented pressure (cAP) in patients hospitalized due to heart failure and found that cAP showed a significant association with all-cause mortality. Additionally, a higher risk of all-cause mortality was observed in another study, among patients who underwent coronary angiography.[17]

Central systolic blood pressure

Central systolic blood pressure assessment was used in three studies.[6,20,22] In a cohort studied by Tziomalos et al.,[20] central SBP did not present any association with the outcome, compared with patients who received hospital discharge. A study on a population with previous histories of cardiovascular disease[22] did not demonstrate any association with the outcome. However, in a study on decompensated heart failure patients who had been admitted to the emergency ward,[21] the findings were significant as a predictive value regarding post-hospital discharge.

Central pulse pressure

Central pulse pressure (cPP) was evaluated as a marker of arterial stiffness in three studies.[20-22] In a study on patients with acute ischemic stroke (AIS), the lowest cPP values were associated with intra-hospital mortality.[20] In patients with decompensated heart failure,[21] cPP presented significant predictive values for all-cause mortality post-hospital discharge. In a study on hospitalized elderly patients with histories of cardiovascular disease,[22] increased cPP was not associated with mortality.

Carotid-femoral pulse wave velocity (cfPWV) and aortic pulse wave velocity (aPWV)

Carotid-femoral PWV (cfPWV) was used to measure central arterial stiffness in 12 studies. In one study, higher baseline cfPWV levels were associated with all-cause mortality for patients with estimated glomerular filtration rate (eGRF) < 90 ml/min/1.73 cm^2.[23] In a study on subjects undergoing hemodialysis,[24] cfPWV was a significant predictor of events within six months after discharge. However, in a study by Hoom et al., higher cfPWV in patients with higher risk of cardiovascular events was not predictive for all-cause mortality.[19] In a cohort of inpatients, there was no association with mortality.[22] In the Rio de Janeiro Type 2 Diabetes Cohort Study, separate analyses for cardiovascular and non-cardiovascular mortality did not show any association.[25]

In a cohort of very old frail subjects with histories of cardiovascular diseases,[26] a positive nonsignificant trend was observed between PWV and mortality risk. In a study that also evaluated hemodialysis patients,[27] the odds ratios were 1.3 for PWV-high/low and 3.2 for PWV high/high, compared with the PWV-low/low reference group.

In a population with decompensated heart failure, cfPWV had significant predictive values for adverse post-discharge outcomes.[21] In a cohort of Japanese patients, the Kaplan-Meier time-to-event curves for death from all causes differed significantly among the four groups over the entire follow-up period ($P < 0.0001$).[28]

In the Rotterdam Study, a trend in relation to all-cause mortality was observed after data adjustment.[29] In well-functioning community-dwelling subjects, the association between all-cause mortality and PWV was not independent of heart rate.[30] Lastly, in a prospective cohort of Japanese-Americans, higher PWV values were significantly associated with all-cause mortality. However, multivariate analysis revealed that there was only a higher tendency towards all-cause mortality, which was not statistically significant.[31]

The parameter of aortic PWV measurement was used in four cohort studies to estimate central arterial stiffness.[20,32-34] In patients with type 2 diabetes (DM2), PWV was an independent predictor of later mortality across the entire spectrum of glucose tolerance.[32] In a population undertaking regular hemodialysis, the baseline PWV was lower for survivors than for

dead patients.[33] In a study on a nondiabetic population, PWV had a significant independent impact on all-cause mortality.[34] In a cohort of AIS patients, on the other hand, aortic PWV did not show any predictive value for the all-cause mortality outcome. **Table 1** summarizes all the studies reporting all-cause and cardiovascular mortality.[20]

Table 1. Studies included in the meta-analysis

Study, year	Method evaluated	Outcome	Population	Mean age (mean ± SD)	Male gender (%)	Hypertension (%)	Diabetes (%)	BMI (mean ± SD)	History of CVD (%)
Anderson, 2009[34]	aPWV	All-cause	Nondiabetic participants aged 45 to 74 years	Arm 1: 58.7 (57-59) Arm 2: 63.6 (62.1-65.1)*	Arm 1: 49.1 Arm 2: 55.1	Arm 1: 19 Arm 2: 16&	NA	Arm 1: 26.6 (25.9-27.4) Arm 2: 25.7 (24.7-26.7)*	NA
Cruickshank, 2002[32]	aPWV	All-cause	Patients with DM2	60 (59-71)*	57.6	NA	100	NA	NA
Huang, 2011[6]	CSBP	All-cause, CV	Patients receiving PCI	70 ± 12	88	66	34	NA	MI: 17 CABG/PCI: 30
Kato, 2010[43]	baPWV	CV	Patients who had been undergoing regular HD	64 ± 12	65.4	NA	20.1	NA	20.1
Kato, 2012[36]	baPWV	CV	Patients undertaking regular HD	60 ± 11	67		36.4		12.5
Meaume, 2001[48]	cfPWV	CV	Patients hospitalized for rehabilitation after infectious disease, CHF, recent surgery, recent stroke, or end-stage Parkinson's disease.	87.1 ± 6.6	27	NA	NA	22.03 ± 3.97	Atherosclerosis of the lower limbs: 16 Previous stroke: 21 Previous MI: 12
Onuigbo, 2013[33]	aPWV	All-cause	Patients undergoing regular HD	NA	Arm 1: 45.8 Arm 2: 57.8	NA	NA	NA	NA
Pini, 2008[5]	CSBP	CV	Community-dwelling individuals ≥ 65 years of age	73 ± 6	45		9	26.7 ± 4.3	Stroke, TIA: 5 PVD: 10 CAD: 9
Sung, 2011[21]	AIX	All-cause	Patients with acute heart failure syndrome	Arm 1: 72.2 ± 14.9 Arm 2: 75.0 ± 12.5	Arm 1: 82.4 Arm 2: 82.8	Arm 1: 74.5 Arm 2: 82.8	Arm 1: 39.2 Arm 2: 58.6	Arm 1: 25.6 ± 5.1 Arm 2: 24.1 ± 4.2	Arm 1: 51 Arm 2: 62.1
Tziomalos, 2014[20]	aPWV, CSBP, AIX, cPP	All-cause	Patients who were admitted with acute ischemic stroke	Arm 1: 81.9 ± 7.6 Arm 2: 78.5 ± 6.5	Arm 1: 47.2 Arm 2: 38.5	Arm 1: 72.2 Arm 2: 83.9	Arm 1: 30.5 Arm 2: 32.7	Arm 1: 27.1 ± 6.4 Arm 2: 27.3 ± 4.9	CAD: Arm 1 27.7; Arm 2 27.9. Previous stroke: Arm 1 44.4; Arm 2 41.2
Van Sloten, 2014[19]	AIX, cfPWV	All-cause, CV	Population- based cohort in the Netherlands	Arm 1: 69.0 ± 6.4 Arm 2: 71.9 ± 6.2	50 overall Arm 1: 45.2 Arm 2: 64.6	Arm 1: 62.9 Arm 2: 80.6	23 overall Arm 1: 22.1 Arm 2: 25.8	Arm 1: 27.0 ± 3.6 Arm 2: 27.0 ± 3.4	Arm 1: 47 Arm 2: 63.8
Zhang, 2013[22]	CSBP, cPP	All-cause	Hospitalized elderly patients	86.8 ± 6.9	25.98	75.2	20.9	27.2 ± 5.7	CHD: 33 HF: 22.2 AF: 17.2

*Data are presented as mean (range); % - data only available for men and women separately; &Only patients receiving anti-hypertensive drug therapy were considered hypertensive.

NA = data not available; MI = myocardial infarction; PCI = percutaneous coronary intervention; CABG = coronary artery bypass grafting; SBP = systolic blood pressure; DBP = diastolic blood pressure; aPWV = aortic pulse wave velocity; CSBP = central systolic blood pressure; AIX = augmentation index; cPP = central pulse pressure; baPWV = brachial-ankle pulse wave velocity; cfPWV = carotid-femoral pulse wave velocity; PWV = pulse wave velocity; CV = cardiovascular; DM2 = type 2 diabetes mellitus; CHF = chronic heart failure; HF = heart failure; HD = hemodialysis; CAD = coronary artery disease; AF = atrial fibrillation; TIA = transient ischemic attack; PVD = peripheral vascular disease.

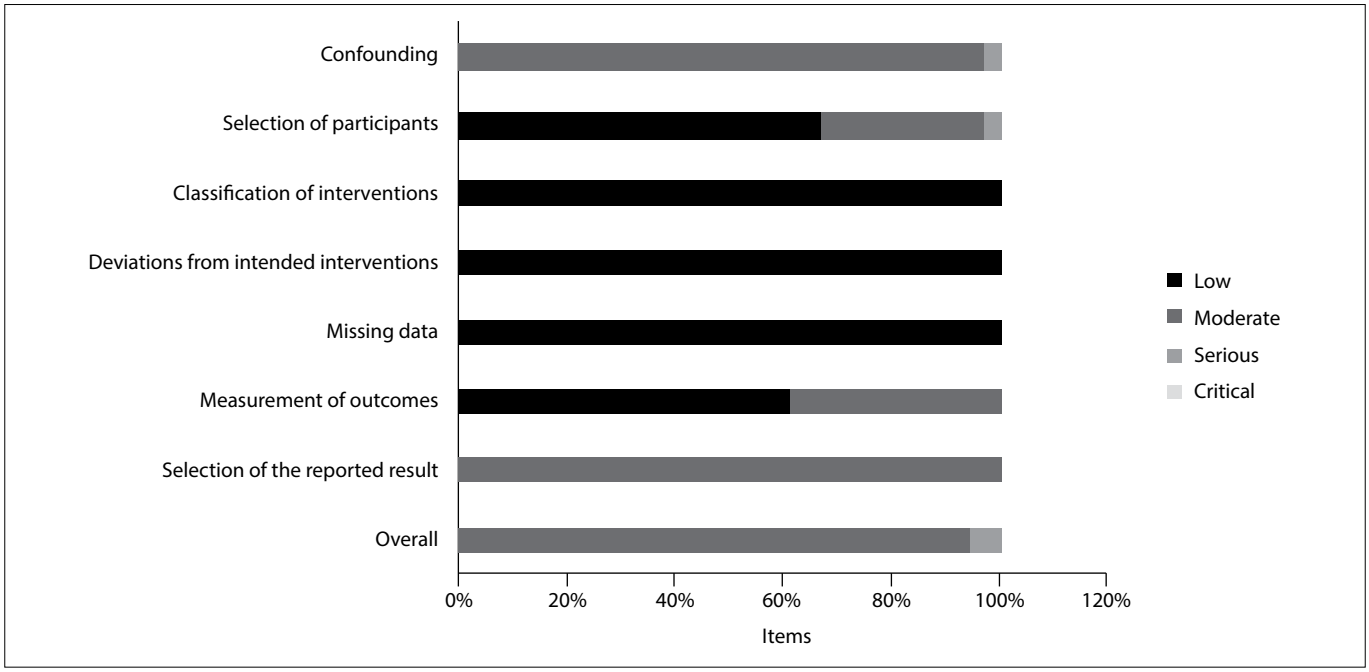


Figure 2. Risk-of-bias evaluation of methodological quality, in accordance with the ROBINS-I tool (Risk Of Bias In Non-randomized Studies - of Interventions).

Table 2. Meta-analysis results

All-cause mortality						
Method	**Studies**	**Year**	**Cases**	**Controls**	**SMD (±95% CI)**	**Weight (%)**
aPWV	Anderson et al.[34]	2009	60	114	2.34 (1.94 to 2.74)	16.25
	Cruickshank et al.[32]	2002	22	97	1.83 (1.32 to 2,35)	9.58
	Onuigbo et al.[33]	2013	106	308	0.40 (0.17 to 0.62)	52.22
	Tziomalos et al.[20]	2014	36	379	0.41 (0.07 to 0.76)	21.95
	Overall (I-squared = 96.7%; P = 0.000)				0.85 (0.69 to 1.01)	100
CSBP	Huang et al.[6]	2010	201	813	0.42 (0.27 to 0.58)	59.92
	Tziomalos et al.[20]	2014	36	379	0.09 (-0.25 to 0.43)	12.39
	Zhang et al.[22]	2013	110	221	0.03 (-0.19 to 0.26)	27.69
	Overall (I-squared = 77.4%; P = 0.012)				0.27 (0.15 to 0.39)	100
AIX	Sung et al.[21]	2011	29	51	0.26 (-0.19 to 0.72)	14.08
	Tziomalos et al.[20]	2014	36	379	-0.90 (-1.25 to -0.55)	24.46
	Van Sloten et al.[19]	2014	96	483	0.11 (-0.11 to 0.33)	61.46
	Overall (I-squared = 92.4%; P = 0.000)				-0.11 (-0.29 to 0.06)	100
cPP	Tziomalos et al.[20]	2014	36	379	-0.57 (-0.91 to -0.22)	30.66
	Zhang et al.[22]	2013	110	221	0.06 (-0.17 to 0.29)	69.34
	Overall (I-squared = 88.6%; P = 0.003)				-0.13 (-0.33 to 0.06)	100
Cardiovascular mortality						
Method	**Studies**	**Year**	**Cases**	**Controls**	**SMD (± 95% CI)**	**Weight (%)**
baPWV	Kato et al.[43]	2010	39	156	0.61 (0.25 to 0.96)	56.11
	Kato et al.[36]	2012	33	102	0.75 (0.34 to 1.15)	43.89
	Overall (I-squared = 0.0%; P = 0.611)				0.67 (0.40 to -0.93)	100
CSBP	Pini et al.[5]	2008	122	276	0.50 (0.28 to 0.72)	62.10
	Huang et al.[6]	2011	55	813	0.91 (0.63 to 1.18)	37.90
	Overall (I-squared = 80.6%; P = 0.023)				0.65 (0.48 to 0.82)	100
cfPWV	Meaume et al.[48]	2001	73	68	0.15 (-0.18 to 0.48)	31.14
	Van Sloten et al.[19]	2014	96	483	0.67 (0.45 to 0.89)	68.86
	Overall (I-squared = 85%; P = 0.010)				0.51 (0.32 to 0,69)	100

aPWV = aortic pulse wave velocity; CSBP = central systolic blood pressure; AIX = augmentation index; cPP = central pulse pressure; baPWV = brachial-ankle pulse wave velocity; cfPWV = carotid-femoral pulse wave velocity; SMD = standardized mean difference; CI = interval confidence.

Brachial-ankle pulse wave velocity (baPWV)

Ten studies used baPWV to evaluate arterial stiffness in patients older than 60 years.[35-44] In a cohort of diabetic patients, baPWV values were a significant predictor of the mortality endpoint.[39] In a study on patients with lacunar stroke syndrome, those with high baPWV values were at higher risk of all-cause mortality.[40] In an Asian study on patients in the acute phase of stroke, patients with higher baPWV were at higher risk of all-cause mortality.[41] In a review study that included patients with DM2, the combination of ankle brachial index (ABI) and baPWV showed significantly higher all-cause mortality rates.[42] In another cohort, after multivariate hazard ratio (HR) analysis, the results showed a significant difference between the top decile of baPWV and the whole study population for all-cause mortality outcomes.[35]

In four studies, patients were undergoing hemodialysis were evaluated.[36,38,43,44] In a study by Kato et al.,[43] patients with baPWV values in the highest tercile had a significantly lower survival rate than those in the middle and lowest terciles.[43] In a later study, the total survival rate was significantly lower among patients with higher baPWV.[36] In a retrospective cohort study, baPWV was a significant predictor of the all-cause mortality outcome.[44] Additionally, in the Kahoku longitudinal study, higher baPWV levels were significantly associated with all-cause mortality.[38]

Cardiovascular mortality

Brachial-ankle pulse wave velocity (baPWV)

In six studies, baPWV was used to evaluate arterial stiffness and the corresponding predictive value for cardiovascular mortality. In a Chinese population, baPWV was significantly associated with cardiovascular mortality.[35] In a cohort of hemodialysis patients, no increase in baPWV was observed.[45] In another study on a population undergoing hemodialysis, patients with higher baPWV presented higher cardiovascular mortality risk than those in the lower terciles.[36] In a longitudinal study, high baPWV levels were significantly associated with higher risk of three-year cardiovascular mortality.[37] In a Japanese cohort that observed 85 endpoints, cardiovascular mortality was progressively and significantly greater from the second quartile of baPWV onwards.[38] Lastly, in the LILAC study, the increase in baPWV was associated with an increased risk of cardiovascular mortality.[46]

Carotid-femoral pulse wave velocity (cfPWV)

Four studies used cfPWV.[30,31,47,48] In a hemodialysis patient cohort,[47] increasing terciles of PWV1 but not those of PWV2 or PWV3 were significantly correlated with cardiovascular mortality. A prospective study on Japanese-Americans showed that higher PWV values correlated with higher risk of cardiovascular mortality.[31] Another study showed significant associations with cardiovascular mortality.[30] A further study was conducted on subjects over 70 years of age and it was found that increased PWV was associated with cardiovascular mortality.[48]

Diverse parameters for pulse wave velocity evaluation

In a cohort study on patients undergoing hemodialysis, the prognostic value of cfPWV, carotid AI, CPP and carotid-brachial pulse pressure amplification (AMP) were measured. The AI, CPP and AMP parameters after dialysis did not show any association with cardiovascular mortality.[49] In another cohort, the carotid SBP was an independent predictor of cardiovascular mortality after eight years of follow-up.[5] In a study on patients who underwent percutaneous coronary intervention, CPP itself was independently associated with the risk of cardiovascular events after this procedure.[50]

Meta-analysis

Table 1 provides a description of all the studies used in the meta-analysis, grouped according to the methods used: PWV, central SBP, AIX and cPP. The results regarding all-cause mortality and cardiovascular mortality are presented in **Table 2**.

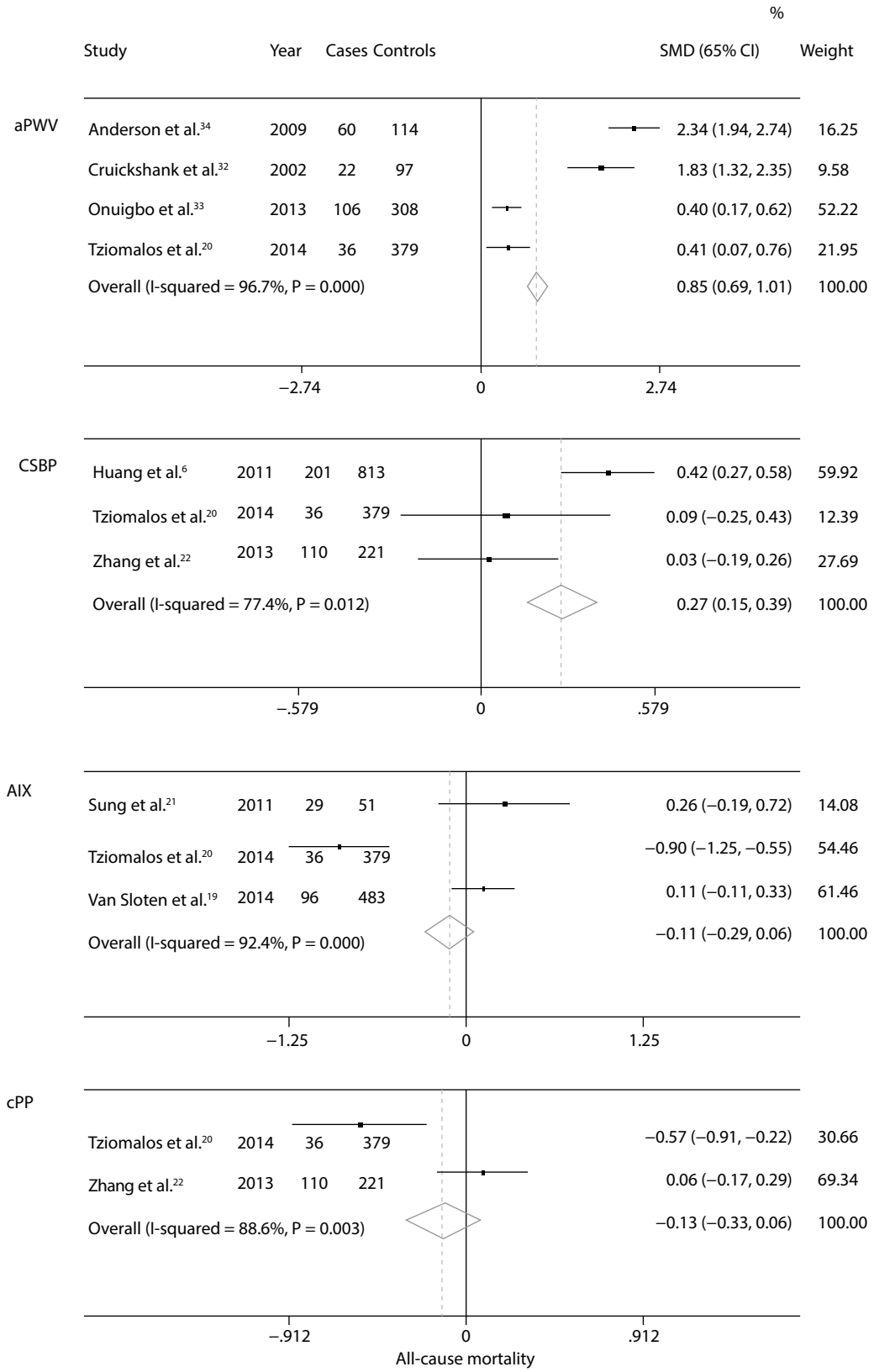
For all-cause mortality, we found 28 studies, among which eight were included in the meta-analysis. Three of these evaluated AIX, three evaluated central SBP, two evaluated cPP and four evaluated aPWV. There were 878 cases in total, and 3,824 controls. Among the remaining studies, either the data were not shown or it was not feasible to extract the data.

For cardiovascular mortality we found 20 studies, among which six were included in the meta-analysis. These comprised two evaluating central SBP, two evaluating baPWV and two evaluating cfPWV, with a total of 418 cases and 1898 controls. Among the remaining studies, either the data were not shown or it was not feasible to extract the data.

For all-cause mortality, aPWV and central SBP were significant, respectively with SMD 0.85 (95% CI 0.69-1.01; I^2 96%; P < 0.001) and SMD 0.27 (95% CI 0.15-0.39; I^2 77%; P 0.012). Also for all-cause mortality, AIX and cPP were not significant, respectively with SMD -0.11 (95% CI -0.29-0.06; I^2 92%; P < 0.001) and SMD -0.13 (95% CI -0.33-0.06; I^2 88%; P 0.003) (**Figure 3**).[6,19-22,32-34]

For cardiovascular mortality, baPWV, central SBP and cfPWV were significant, respectively with SMD 0.67 (95% CI 0.40-0.93; I^2 0%; P 0.610), SMD 0.65 (95% CI 0.48-0.82; I^2 80%; P 0.023) and SMD 0.51 (95% CI 0.32-0.69; I^2 85%; P 0.010) (**Figure 4**).

The evaluation on biases is shown in **Figure 5**, as funnel plots for all-cause mortality and cardiovascular mortality. Begg's test and Egger's teste were performed. Fill-and-trim analyses were performed for aPWV in relation to all-cause mortality, and for central SBP and baPWV in relation to cardiovascular mortality, and these showed that there was no modification of the results,



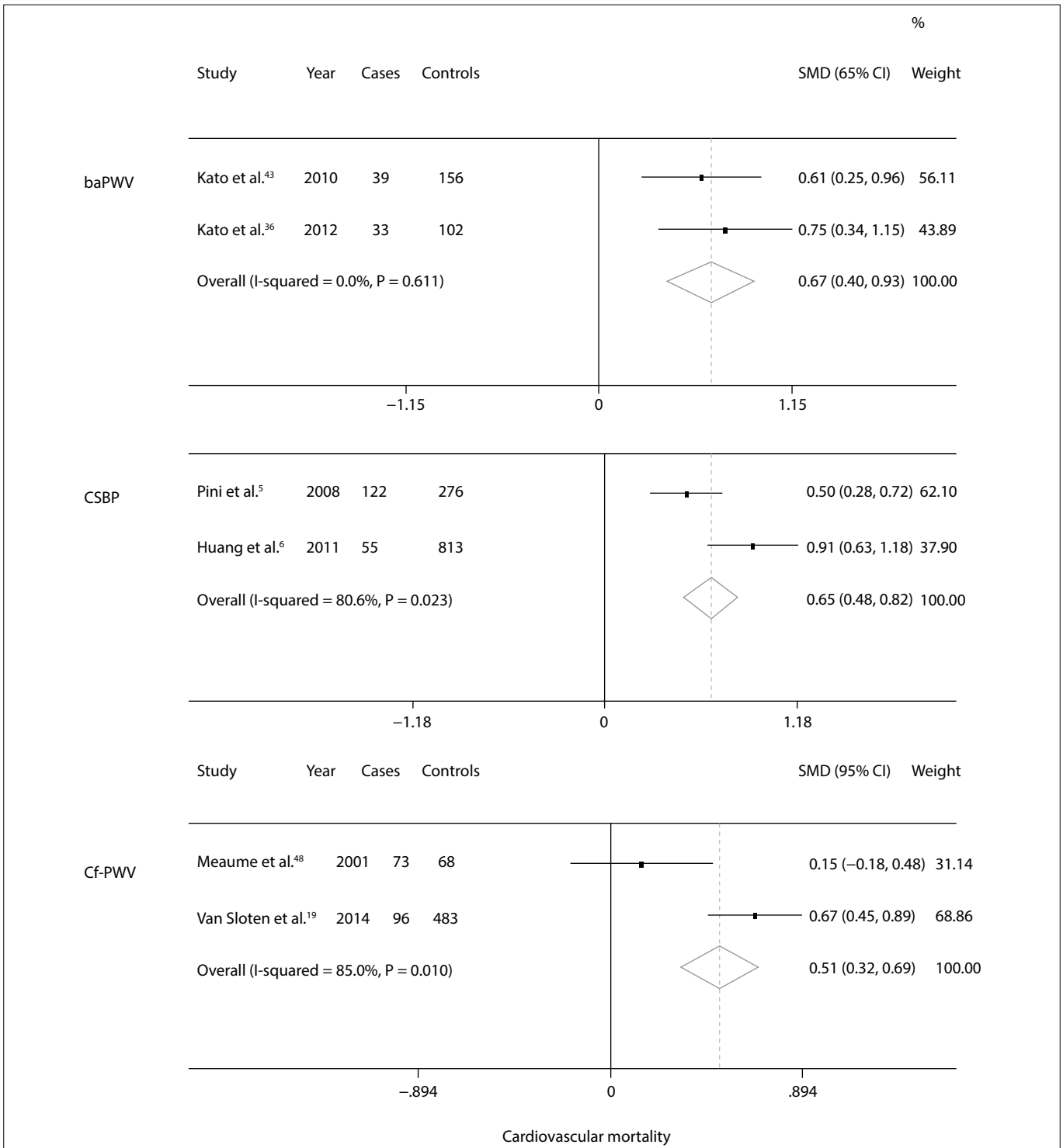
aPWV = aortic pulse wave velocity; CSBP = central systolic blood pressure; AIX = augmentation index; cPP = central pulse pressure; SMD = standardized mean difference; CI = confidence interval.

Figure 3. Forest plot for all-cause mortality and indirect central blood pressure assessment method.

with P < 0.001 for all of these analyses. In relation to age and sex prevalence, we performed a meta-regression that showed that the variable aPWV did not make any contribution to all-cause mortality. **Table 2** summarizes the bias evaluations.

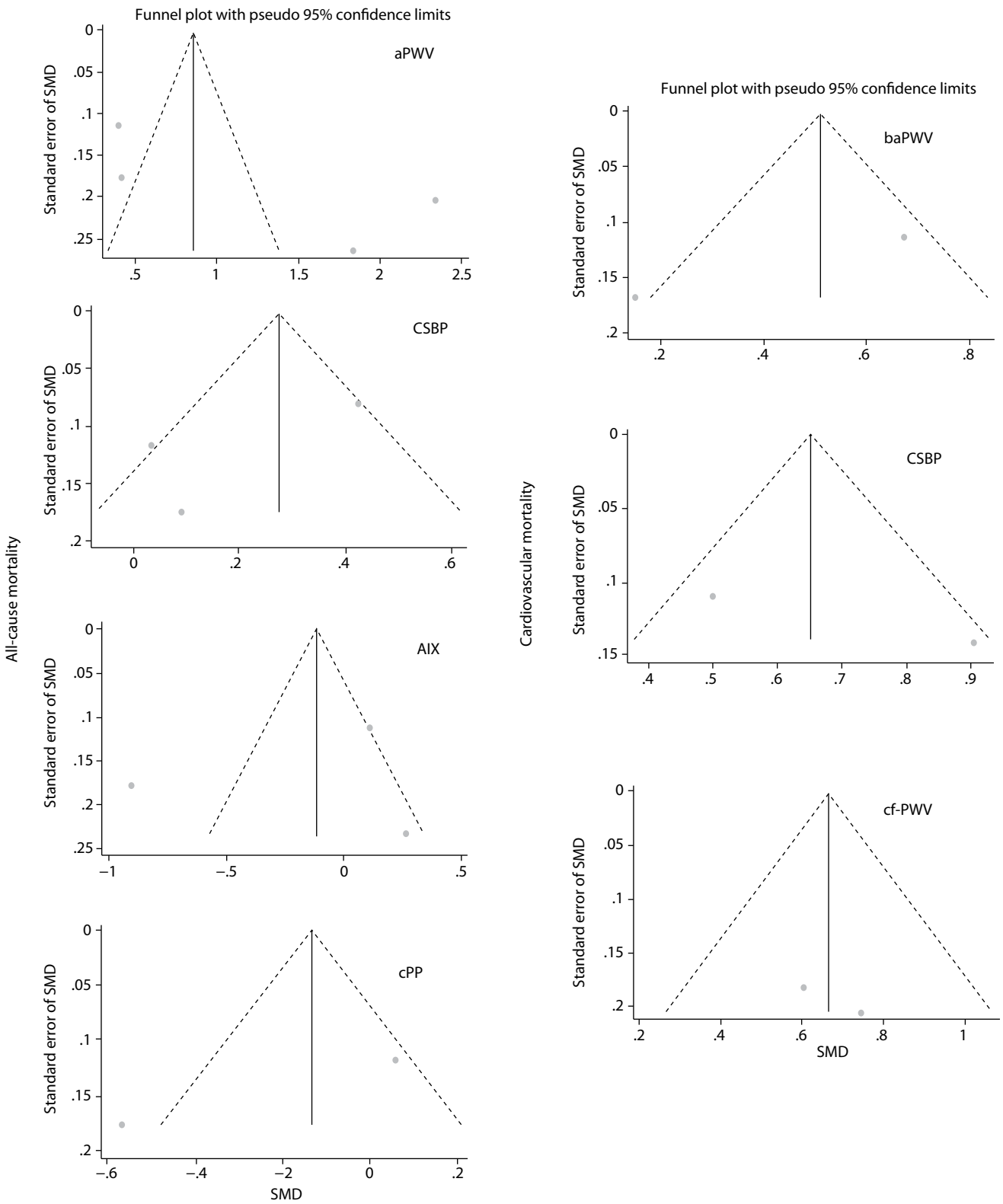
DISCUSSION

In our study, increased aortic PWV and central SBP were associated with all-cause mortality. Higher baPWV, central SBP and cfPWV were associated with cardiovascular mortality, with



baPWV = brachial-ankle pulse wave velocity; CSBP = central systolic blood pressure); cfPWV = carotid-femoral pulse wave velocity; SMD = standardized mean difference; CI = confidence interval.

Figure 4. Forest plot for cardiovascular mortality and indirect central blood pressure assessment method.



aPWV = aortic pulse wave velocity; CSBP = central systolic blood pressure; AIX = augmentation index; cPP = central pulse pressure; baPWV = brachial-ankle pulse wave velocity; cfPWV = carotid-femoral pulse wave velocity; SMD = standardized mean difference.

Figure 5. Funnel plot for all-cause mortality and cardiovascular mortality for each indirect central blood pressure assessment method.

higher accuracy for prediction, compared with the parameters for peripheral arterial pressure evaluation. Central blood pressure was found to reflect arterial stiffness and hemodynamic pressure in the heart and great vessels more accurately for predicting intermediate and surrogate endpoints, compared with brachial arterial pressure.[25]

Arterial stiffness increases with aging, and it has been suggested that this is a modulator of atherosclerosis progression and hypertension.[41] Although central blood pressure is used as a marker for clinical outcomes, few studies have evaluated the possibility of validating this prognostic tool for older populations.[26] Therefore, it was sought through the present systematic review and meta-analysis to evaluate the evidence regarding usage of central pressure data, in various assessment techniques, as a predictor of hard clinical outcomes in older populations. The main conclusion reached was that in all the studies eligible for the meta-analysis, central pressure data presented predictive value for mortality and cardiovascular outcomes. Moreover, among these studies, two studies showed that central blood pressure was predictive of all-cause mortality, regardless of the non-invasive technique used for its measurement. These results give rise to the possibility of differentiating physiological vascular aging in older patients according to their biological alterations and the chronic structures that unleash the pathological process of arterial stiffness and its consequent clinical implications.

This strong relationship between central blood pressure findings and cardiovascular mortality suggest that there is a close relationship between arterial stiffness and traditional cardiovascular risk factors. Alterations to homeostasis, with reduction of coronary diastolic filling, plus elastic abnormalities of the aorta due to arterial stiffness, as observed through raised PWV,[26] is a plausible mechanism that would contribute to the observed outcomes. The studies reviewed here show that it is feasible to make fast non-invasive PWV measurements with reliable results and that these could become part of routine outpatient clinical care.

The two techniques for estimating central arterial stiffness that demonstrated predictive value both for all-cause mortality and for cardiovascular mortality were aortic PWV (aPWV) and central SBP. aPWV was an independent predictor of subsequent all-cause and cardiovascular mortality among patients with or without DM2 and among patients with chronic kidney failure. However, in a cohort of patients with acute ischemic stroke,[20] aPWV did not present any predictive value for all-cause mortality. Central SBP was also a predictor of all-cause mortality among patients with heart failure after hospital discharge.[21] This observation raises the possibility of using central blood pressure measurement as a therapeutic orientation within this clinical context, considering that a larger clinical benefit seems to be achieved through a large decline in central blood pressure.[20] Studies that used baPWV were also selected in this review. baPWV is an indicator of the combination of central and peripheral arterial stiffness, and previous longitudinal studies and a meta-analysis have demonstrated that the prognostic value of baPWV is as significant as the value of cfPWV.[51]

The population in the studies selected here (i.e. older patients) was theoretically less susceptible to the effects of arterial stiffness with later clinical manifestation. However, one of the factors that may have contributed to the findings in the present study was the presence of high numbers of patients with chronic Kidney failure and DM2 in the cohorts included in this study. These populations have greater numbers of risk factors associated with death and cardiovascular events,[52] among the non-invasive techniques used to evaluate arterial stiffness, which may have contributed to the number of events observed. Differences in the equipment used to estimate central pressure between studies may have allowed measurement bias. The different populations studied may also have contributed to the heterogeneity that was observed. However, these limitations do not invalidate the strong association observed in the present meta-analysis, in predicting future cardiovascular events and all-cause mortality in a strong and independent manner.

This systematic review and meta-analysis examined the relationship between central blood pressure measurements using different non-invasive techniques and occurrences of hard outcomes such as cardiovascular and all-cause mortality in a population over the age of 60 years. Most previous studies focused on younger populations and used intermediary outcomes. The present meta-analysis results point to more promising results from aPWV for predicting all-cause mortality, while baPWV and central SBP demonstrated more consistent results for evaluating cardiovascular mortality outcomes. Thus, the findings support the usage of central blood pressure as a risk predictor for hard outcomes in an older population. The data extracted originated from wide-ranging cohort studies in quality was evaluated, and give grounds for the idea that wider usage of central blood pressure measurement without limitation through patient age is important.

CONCLUSIONS

This study revealed that there was a strong association between central blood pressure and both cardiovascular and all-cause mortality outcomes in an older population. These findings support the idea that hemodynamic overload and the consequent physiopathology of arterial stiffness involve central vessels. From this perspective, the findings of this study support the idea of wider usage of tools for central blood pressure measurement in various clinical scenarios, as an independent prognostic marker. This study also provides a stimulus towards production of further studies on the clinical impact of these findings.

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Use of healthcare services and therapeutic measures associated with new episodes of acute low back pain-related disability among elderly people: a cross-sectional study on the Back Complaints in the Elders - Brazil cohort

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ABSTRACT

BACKGROUND: Patients with low back pain frequently undergo a variety of diagnostic and therapeutic interventions, but some of these have uncertain effectiveness. This highlights the importance of the association of healthcare services and therapeutic measures relating to disability.

OBJECTIVE: To analyze the use of healthcare services and therapeutic measures among Brazilian older adults with disability-related low back pain.

DESIGN AND SETTING: Observational cross-sectional study on baseline assessment data from the Back Complaints in the Elders - Brazil (BACE-B) cohort.

METHODS: The main analyses were based on a consecutive sample of 602 older adult participants in BACE-B (60 years of age and over). The main outcome measurement for disability-related low back pain was defined as a score of 14 points or more in the Roland Morris Questionnaire.

RESULTS: Visits to doctors in the previous six weeks (odds ratio, OR = 1.82; 95% confidence interval, CI 1.22-2.71) and use of analgesics in the previous three months (OR = 1.57; 95% CI 1.07-2.31) showed statistically significant associations with disability-related low back pain. The probability of disability-related low back pain had an additive effect to the combination of use of healthcare services and therapeutic measures (OR = 2.57; 95% CI 1.52-4.36). The analyses showed that this association was significant among women, but not among men.

CONCLUSIONS: Occurrence of the combined of consultations and medication use was correlated with higher chance of severe disability among these elderly people with nonspecific low back pain. This suggested that overuse and "crowding-in" effects were present in medical services for elderly people.

INTRODUCTION

Disabilities caused by chronic-degenerative diseases and their symptoms, such as spinal problems, combined with the aging population, are a major challenge to healthcare systems around the world.[1,2] Low back pain is the single biggest cause of years lived with disability worldwide and is the condition that most contributes to overall disability and life years with disability.[3,4]

In Brazil's National Household Sampling Survey (Pesquisa Nacional por Amostra de Domicílio), performed in 2003, back pain was identified as the most prevalent chronic disease. Its incidence increased with increasing age, to reach 40% among older adults between 69 and 79 years of age.[5] The point-prevalence of low back pain was found to be 25.0% among elderly Brazilians in a systematic review, and other studies indicated its potential to affect the functions, activities and social participation of older adults, with concomitant impacts on quality of life and independence.[4,6-8]

Longitudinal analyses have shown that after one year, 60.3% of older adults with low back pain continue to present disability. After two years, the disability-related low back pain of only 36% of older adults has halved, which demonstrates the long-term latency of such complaints.[9,10] It has consequently been observed that the high prevalence of low back pain, its related disability and the poor long-term prognosis induces older adults to request specific interventions.[11] Among community-dwelling elderly people, about 58% seek healthcare due to low back pain.[12] Patients with back pain frequently undergo a variety of diagnostic and therapeutic interventions (imaging tests, injections, pain medications, physical therapy, surgery, braces, etc.), and some of these have uncertain effectiveness.[13-17] Elderly people with severe disability have been found to

be 3.8 times more likely to be seeking care, and factors like gender, histories of previous low back pain and general health also influence care-seeking behavior.[12]

Recent reports have shown that people with the poorest physical and mental health are significantly more likely to present associated low back pain-related disability.[18,19] The causes of use of healthcare services and therapeutic measures are related to context (types of healthcare systems and their organization, for example) and individual factors (age, sex, education and income).[20,21] According to the classical model of Andersen and Newman, individual factors include predisposing factors (age and sex),[21] enabling characteristics (like education level and income) and healthcare needs from the perspectives of professionals and users. Thus, the findings from the existing studies cannot be extrapolated to populations in low and middle-income countries, such as Brazil, due to differences in the setup and planning of their healthcare systems.

Studies on the utilization of healthcare services and therapeutic measures among older adults with disability-related low back pain remain at an initial stage. Therefore, it was sought through the present study to investigate the healthcare services and therapeutic measures that are used in relation to complaints of acute low back pain-related disability among community-dwelling elderly people. We hypothesized that the associations between the characteristics of use of healthcare and therapeutic measures and occurrences of disability would differ between the sexes.

OBJECTIVE

In this study, data from the Back Complaints in the Elders - Brazil (BACE-B) cohort were used. The aim was to analyze associations between the use of healthcare services and therapeutic measures and occurrences of disability reported by elderly people.

METHODS

Study design and ethics

This study forms part of an international consortium of epidemiological studies named Back Complaints in the Elders, which includes researchers in Australia, Brazil and the Netherlands.[22] The Back Complaints in the Elders - Brazil project is a prospective cohort study with data collected between October 2011 and September 2015. The present analysis was an observational cross-sectional study on baseline assessment data from the Back Complaints in the Elders - Brazil cohort. Ethical approval for this study was obtained from the Ethics Committee of the Federal University of Minas Gerais (Universidade Federal de Minas Gerais, UFMG), under the number ETIC 0100.0.203.000-11, on February 24, 2016.

Study population

The sample for this study comprised consecutive participants in the baseline survey for the Back Complaints in the Elders – Brazil cohort. They were aged ≥ 60 years, with acute complaints of low back pain, and were residents in the metropolitan region of Belo Horizonte, Minas Gerais, Brazil. Elderly people with low back pain symptoms were identified by healthcare professionals (physicians, physiotherapists and occupational therapists, among others) working in either the public or the private healthcare sector, and were directed to the BACE-B research team.

Only elderly people presenting criteria for a new episode of acute low back pain were included in the Back Complaints in the Elders - Brazil study. Low back pain was defined as complaints of pain, tension or stiffness in the region between the last ribs and the gluteal line, with or without irradiation of pain to the lower limbs.[23] A new episode of low back pain was defined as a situation in which the individual had not sought treatment for low back pain over a six-month period immediately preceding participation in the study.[22] Acute symptoms were defined as an occurrence of a low back pain crisis not more than six weeks before the baseline assessment.[24]

Participants with visual, motor, hearing or cognitive impairment that could influence their responses to questionnaires or prevent adequate performance in physical and functional tests were excluded.[25]

Outcome variable

The outcome measurement of this study was disability-related low back pain, as assessed using the Roland Morris Disability Questionnaire (RMDQ), which consists of 24 items relating to the influence of back pain on daily activities and measures the level of disability associated with low back pain. The questionnaire scores range from 0 to 24, with higher scores indicating a worse level of disability.[26,27] Scores over 14 were taken to indicate severe disability.[27]

Exposure variable

Five indicators of use of healthcare services were considered: doctor visits made over the preceding six weeks, including generalist, specialist and occupational doctors; physiotherapy consultations over the preceding six weeks; diagnostic tests made during the preceding three months, including blood tests, X-rays, computed tomography and magnetic resonance imaging; and use of analgesics and complementary noninvasive therapies (orthoses, braces, acupuncture, yoga, Pilates, overall postural re-education or other types).

Sociodemographic and back pain variables

Potential confounding variables were selected for this analysis based on the theoretical model of Andersen and Newman,[21] in

which predisposing and enabling factors for the use of healthcare services were considered. Among the predisposing factors, sex and age (continuous variable) were considered. Among the enabling factors, living with a spouse/partner (yes or no), educational level/schooling years (less than four; or four or more) and own income (up to one minimum monthly wage, two to four, or five or more) were considered.

The low back pain intensity in the last week was evaluated by means of a numerical rating scale (NRS), on which the scores could range from 0 (no pain) to 10 (maximum pain).

Statistical analysis

Descriptive analyses were performed on the outcomes investigated, both for the total population and with stratification according to sex, using proportions and means (with standard deviation). Comparisons between groups were made using Pearson's chi-square or Fisher's exact test (for proportions), or using Student's t test (for means).

Multivariate analysis was done to investigate associations between disability and indicators of use of healthcare services and therapeutic measures and was based on odds ratio (OR) estimates, by means of binary logistic regression. The multivariate models were adjusted for age, sex, living with spouse/partner, education level and income. Binary logistic regression was used to estimate the predicted probability of occurrences of doctor visits over the preceding six weeks and use of analgesic medications over the preceding three months, according to disability.

All the analyses were performed using the procedures for complex samples in the Stata statistical package, version 13.0 (StataCorp LLC, College Station, TX, United States), with a significance level of 5%.

RESULTS

The sample consisted of 602 elderly people with complaints of acute nonspecific low back pain. **Figure 1** illustrates the selection process for the participants in this study.

The participants' mean age was 67.7 ± 7.0 years. They were mostly female (84.9%), with an education level of more than four years of schooling (38.5%) and had low income (86.5% had a mean income of not more than four minimum monthly wages). Their mean pain intensity was 7.2 (± 2.6) on the numerical rating scale. The prevalence of severe low back pain-related disability was 54.5% (95% CI 50.5-58.4) for all participants, 54.6% (95% CI 50.2-58.9) for woman and 53.8% (95% CI 43.4-64.0) for men. The prevalence of disability was significantly higher among the elderly people with higher education level: 54.7% in the sample overall; 56.8% among the women, but 42.9% among the men. More details on the sociodemographic characteristics of the survey participants can be seen in **Table 1**.

Table 2 presents the characteristics of usage of healthcare services and therapeutic measures among all the participants and stratified according to sex and disability. Just 3.0% of these elderly people had consulted a physical therapist during the preceding six weeks, while 74.1% had used at least one analgesic. The results from bivariate analysis on the association between disability and indicators of use of healthcare services showed that the proportion of disability was more significant among those who had visited doctors during the preceding six weeks (35.4%), but not for men alone (30.6%). Among the indicators of therapeutic measures, the proportion of disability was higher among the elderly people who had used analgesics (78.1%) and was even higher among the women (79.9%).

Table 3 shows odds ratios for indicators of use of healthcare services and therapeutic measures due to low back pain-related disability for the total sample, adjusted for sociodemographic characteristic. The elderly people who visited doctors were 1.82 times (95% CI 1.22-2.71) more likely to present severe disability. The subjects who used analgesics were 1.57 times (95% CI 1.07-2.31) more likely to present disability. Women who visited doctors and used analgesics were significantly more likely to present severe disability. However, no significant association was found between the indicators of use of healthcare services and therapeutic measures and occurrences of severe disability in men. An additive effect was observed with regard to the chances of disability, in analyzing the combination of doctor visits and use of analgesics, both for the total sample (OR = 2.57; 95% CI 1.52-4.36) and for women (OR = 2.80; 95% CI 1.58-4.94).

Figure 2 shows that the predicted probability of doctor visits and use of analgesics was clearly stratified between different ages, with more significant probability among elderly people with severe disability.

DISCUSSION

The results from this study showed that among elderly people, low back pain-related severe disability was associated with more significant chances of going to visit a doctor and using analgesics, even after taking into account potential confounding factors. Nevertheless, it should be noted this was more evident among women.

Doctor visits are a positive aspect of healthcare, since they provide opportunities for timely diagnosis, prevention, treatment and referral for rehabilitation.[19] Perception of the severity of pain and, consequently, disability, may form the trigger for seeking medical attention.[28,29] On the other hand, we expected that the elderly people who sought medical care and made use of analgesic medication would achieve relief from their pain symptoms and subsequently from the resulting disability. However, senescence and senility can cause higher demand for medical appointments, not

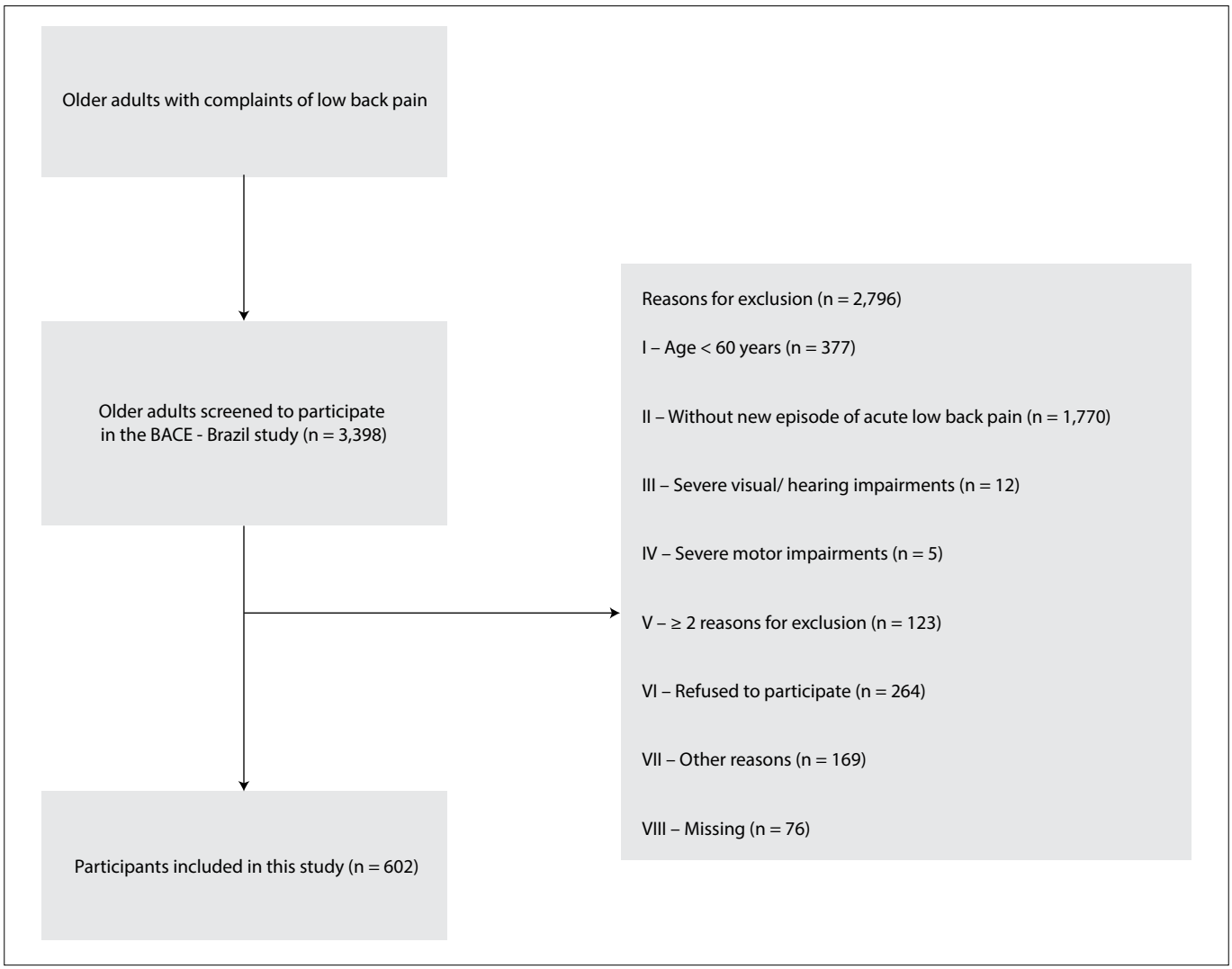


Figure 1. Flowchart of entry of participants into the study.

Table 1. Sociodemographic and pain intensity characteristics of the sample of older adults complaining of acute low back pain, according to presence of disability, and with stratify according to sex. Back Complaints in the Elders - Brazil, 2016

Characteristic	Total sample (n = 602)	Disability*								
		All participants			Women			Men		
		Not severe (45.5%; n = 274)	Severe (54.5%; n = 328)	P-value	Not severe (38.5%; n = 232)	Severe (46.3%; n = 279)	P-value	Not severe (7.0%; n = 42)	Severe (8.1%; n = 49)	P-value
Age, median (SD)	67.7 (7.0)	68.1 (6.9)	67.3 (7.1)	0.157	67.9 (6.6)	67.5 (7.2)	0.483	69.4 (8.4)	66.4 (6.5)	0.060
Living, %										
With spouse/partner	44.9	43.6	46.0	0.548	35.6	39.8	0.466	82.9	81.6	0.873
Alone	55.1	56.4	54.0		63.4	60.2		17.1	18.4	
Education level, %										
< 4 years	38.5	30.3	45.3	< 0.001	30.4	43.2	0.003	29.3	57.1	0.008
4 or more years	61.5	69.7	54.7		69.6	56.8		70.7	42.9	
Income in minimum monthly wages, %										
Up to 1	39.7	34.7	44.0	0.070	35.1	45.3	0.061	32.5	36.2	0.806
2 to 4	46.8	50.9	43.3		52.0	42.8		45.0	46.8	
5 or more	13.5	14.4	12.7		13.0	12.0		22.5	17.0	
Pain intensity – NRS (0-10)	7.2 (2.6)	7.2 (2.5)	7.1 (2.7)	0.608	7.3 (2.6)	7.2 (2.7)	0.463	6.9 (2.3)	7.1 (2.6)	0.601

*Low back pain-related disability assessed using the Roland Morris Disability Questionnaire (RMDQ); SD = standard deviation; NRS = numerical rating scale.

Table 2. Bivariate analysis on the association between disability, indicators of use of healthcare services and indicators of therapeutic measures in the sample of older adults aged 60 years or over with complaints of acute low back pain. Back Complaints in the Elders – Brazil, 2016

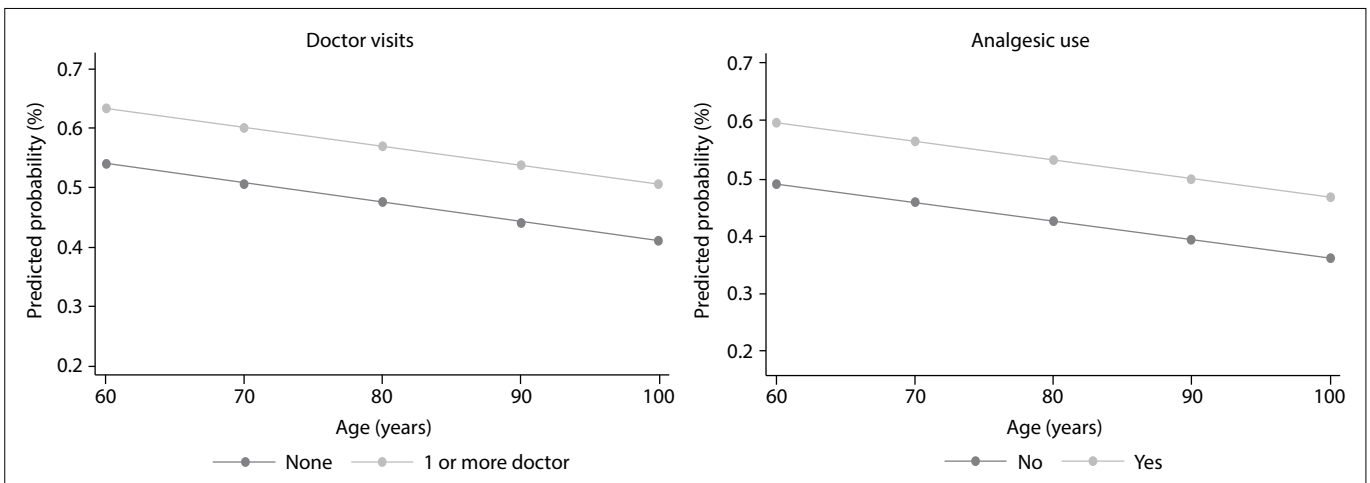
Indicator	Total sample (n = 602)	Disability*								
		All participants*			Women			Men		
		Not severe (n = 274)	Severe (n = 328)	P-value	Not severe (38.5%; n = 232)	Severe (46.3%; n = 279)	P-value	Not severe (7.0%; n = 42)	Severe (8.1%; n = 49)	P-value
Use of healthcare services										
Doctor visits in the past 6 weeks**, %	31.2	26.3	35.4	0.017	25.9	35.2	0.012	28.6	30.6	0.832
Physiotherapy consultations in the past 6 weeks, %	3.0	2.6	3.4	0.567	2.6	3.2	0.670	2.4	4.1	0.658[a]
Diagnostic tests in the past 3 months, %	13.8	14.2	13.4	0.772	15.5	12.9	0.398	7.1	16.3	0.213[a]
Therapeutic measures										
Analgesic use, %	74.1	69.3	78.1	0.015	69.8	79.9	0.008	66.7	67.4	0.945
Complementary noninvasive therapy use***, %	13.6	13.1	14.0	0.752	11.6	15.4	0.217	21.4	6.12	0.059[a]

*Low back pain-related disability assessed using the Roland Morris Disability Questionnaire (RMDQ); **Doctor visits included general practitioner, specialist and occupational doctors; ***Complementary noninvasive therapies included use of orthoses, braces, acupuncture, yoga, Pilates, overall postural re-education or other types; [a]Fisher's exact test.

Table 3. Multivariate logistic regression between indicators of use of healthcare services and therapeutic measures and occurrences of disability among older adults with complaints of acute low back pain. Back Complaints in the Elders - Brazil, 2016

Indicator	All participants*		Women*		Men*	
	OR (95% CI)	P-value	OR (95% CI)	P-value	OR (95% CI)	P-value
Doctor visits in the past 6 weeks**	1.82 (1.22-2.71)	0.003	2.00 (1.30-3.06)	0.002	0.77 (0.23-2.63)	0.681
Physiotherapy consultations in the past 6 weeks	1.07 (0.38-2.96)	0.902	0.97 (0.32-2.94)	0.963	2.82 (0.17-47.32)	0.472
Diagnostic tests in the past 3 months	0.72 (0.42-1.21)	0.217	0.60 (0.34-1.06)	0.076	3.53 (0.60-20.87)	0.165
Analgesic use	1.57 (1.07-2.31)	0.021	1.64 (1.08-2.50)	0.021	1.07 (0.36-3.16)	0.908
Complementary noninvasive therapy use***	1.27 (0.76-2.11)	0.361	1.60 (0.92-2.77)	0.094	0.26 (0.05-1.39)	0.115

OR = odds ratio; CI = confidence interval; *Odds ratio and 95% confidence interval adjusted for age, living with spouse or partner, education level, income and pain intensity, as estimated through logistic regression; the exposure category was the low back pain-related disability and the response variables were the indicators of use of healthcare services and therapeutic measures; **Doctor visits included general practitioner, specialist and occupational doctors; ***Complementary noninvasive therapies included use of orthoses, braces, acupuncture, yoga, Pilates, overall postural re-education or other types.



*Model adjusted for age, living with spouse or partner, education level and income, as estimated using logistic regression.**Low back pain-related disability assessed using the Roland Morris Disability Questionnaire (RMDQ).

Figure 2. Predicted probability* of visits to one or more doctor in the past six weeks and use of analgesics in the past three months, along the age continuum, according to disability**. Back Complaints in the Elders - Brazil, 2016.

only because of associations between pains and/or disability, but also because of involvement of the psycho-affective profile inherent to this age group. Among elderly people, stress, anxiety and depression are manifestations linked to occurrences of nonspecific low back pain and seeking medical appointments.[30,31] Another reason for the more extensive use of healthcare services among elderly people with disabilities is their higher prevalence of chronic diseases and comorbidities, along with their complications, which lead to increased use of medications.[17,32] Occurrences of psycho-affective factors and polypharmacy or other health conditions among elderly people can obscure accurate definition of the legitimate causal mechanisms that trigger severe symptoms of low back pain. This, which gives rise to a complex multidirectional relationship, means that it is sometimes impossible to distinguish temporal relationships from each manifestation, its diagnosis and the appropriate therapeutic approach.[33] In addition, the overuse of healthcare services by elderly people has been shown to be a marker of care with only moderate resolution. Because of the complex nature of painful dysfunction, many elderly people are discharged from specialized rehabilitation services without any resolution for their pain symptoms and, thus, they continue to present disabilities.[34]

Medicines are widely prescribed at the beginning of the course of low back pain, although there is no consensus regarding recommendations for their use among elderly people.[11,35,36] Our results have added to those in the literature, through understanding that inadequate management of healthcare can cause greater disabilities. The first line drugs recommended in the literature for reducing pain are analgesics and nonsteroidal anti-inflammatory drugs (NSAIDs).[37,38] Nonetheless, even these drugs can result in side effects in elderly people. Their effectiveness remains unproven in relation to low back pain, compared with exercise, for example.[39] Corroborating our results, increased risk of disability through chronic use of opioids within healthcare has been shown in the literature.[40,41] Elderly people are more susceptible to the adverse effects of opioids, as has been shown through associations with falls and fractures,[42] worse health outcomes, including worsening pain,[43] increased likelihood of surgery and drug addiction after using painkillers for up to two years.[41,43] Especially in older adults, important side effects associated with opioid use have been reported, including higher hospitalization risks, cardiovascular events, instability and cognitive impairment.[44-46] Furthermore, common adverse effects such as bowel dysfunction, constipation, nausea and somnolence can put older adults at risk of injuries and losses of daily function.[47]

Our results showed that elderly users of analgesics were 1.57 times more likely to present low back pain-related disability. Furthermore, the combination analysis on medical consultations and analgesics demonstrated that these individuals presented 2.57 times higher chance of disability. Gold et al.[48] demonstrated that elderly people with low back pain who received opioid medication early were 1.6 times more likely to have a new medical consultation and greater low back pain-related disability. Overuse of interventions and a "crowding-in effect", defined as an additive combination of therapeutic and diagnostic measures,[49] occur frequently among elderly people with low back pain.[29] However, a more thorough understanding of perceived needs is necessary, to ensure effective results for patients and for the healthcare system. In a study on the use of healthcare services among 4,814 Italian elderly people, home and specialized care were used twice as often among those with disabilities.[49] Chou et al.[14] demonstrated that patients with nonspecific low back pain sought medical care in order to obtain a diagnosis and receive treatment options, but that they only showed concerns relating to pharmacotherapy. In the same study, the authors concluded that, so far, both non-pharmacological and pharmacological interventions have only been seen to have low to moderate effects in treatments for low back pain. Therefore, these issues need to be considered in developing approaches toward managing low back pain, to minimize negative effects like disability among elderly people.

Greater severity of disability was observed among women. In analyzing the associations with the interventions used, the results indicated that this stratification existed in relation both to doctor visits and to analgesic use. This hypothesis was confirmed in previous studies that demonstrated greater disability and worse prognosis for nonspecific low back pain among elderly women.[19,50] The elderly population becomes preponderantly female, with consequently greater demand for healthcare services, and this has already been described in Brazil.[51]

The clinical course of differentiated low back pain among women reveals that they are at a disadvantage in relation to disability. Our results indicated that the frequency of low back pain-related disability among women was higher, but there was in addition a significant difference in the associations for doctor visits and analgesic use, in relation to disability. This may lead to the idea that the greater longevity, higher prevalence of low back pain and differences in musculoskeletal constitution and activities of daily living among women may constitute the key reasons that would explain the higher prevalence of disability and use of medical services in this subgroup.[1,6,52]

It is an established practice for individuals with low back pain to be referred to healthcare services such as diagnostic imaging, rehabilitation and other therapies, after the first visit to a doctor. A study by primary care physicians in Germany showed that the decision to refer a patient to specialized care was influenced by the characteristics of the healthcare system and the low back pain-related disability.[50] In Brazil, the decision to refer patients for subsequent care apparently is made if treatment guidelines are not followed. Thus, no associations between disability and imaging diagnoses,

consultations with physiotherapists or use of other noninvasive therapeutic measures were found in the present study. Likewise, Jarvik et al.[53] showed that performing imaging examinations (radiography, magnetic resonance or computed tomography) did not produce differing results regarding low back pain-related disability among American elderly people. Therefore, the results from this study are consistent with the recommendation that performing these tests does not justify conclusions that lead to unnecessary interventions and harmful exposures.

Among the indicators of use of healthcare services, physical therapy consultations offer the potential to explain the incapacity. However, in the present investigation, as corroborated through the investigations of Loy et al.[54] and Freburger et al.,[55] there was no association between consultations with a physiotherapist and occurrences of low back pain-related disability. It is possible that this result was influenced by the low number of participants who had physical therapy consultation during the preceding six weeks (only 3%), which would demonstrate flaws in the medical referral system within public services and health plan services in Brazil and problems regarding timely access.[56] Therefore, it can be concluded that the structure and funding of the healthcare system may have influenced the low demand for physical therapy assistance observed here. Medical-centered healthcare and a model based on overmedicalization could also explain the low frequency of use of non-invasive therapies as an alternative for treating low back pain and the associated disability.[13,14,17,56] This information can be used by health promoters, policymakers and urban planners to support effective policies, programs and initiatives to promote effective access and therapeutic interventions.

Limitations

The results from this study need to be considered cautiously. The cross-sectional design does not allow a temporal relationship to be established between the variables and the sample was predominantly composed of women, which may have led to underestimation of the results from the analyses between the subgroups. On the other hand, the present analysis was conducted on information that had been collected by trained professional interviewers using standardized instruments, which guaranteed the quality of the data. In addition, a careful analysis was carried out, considering potential confounding factors, according to the theoretical model. Thus, this study adds to the knowledge hitherto produced regarding the evidence from indicators of interventions associated with low back pain-related disability.

CONCLUSIONS

In summary, the present study demonstrated that the combined effect of consultations and medication use was associated with higher chances of low back pain-related severe disability among elderly people. This suggested that overuse of medical services and "crowding-in" effects at these services were occurring among elderly people. This knowledge can contribute towards enabling more thorough understanding of occurrences of this disease. This favors planning of actions aimed at individual and collective monitoring of the population that is most vulnerable to this outcome, at least with regard to the indicators for the use of healthcare services and therapeutic measures in this population segment.

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The Brazilian version of the Health-Related Quality of Life Questionnaire for Nausea and Vomiting of Pregnancy: translation, cross-cultural adaptation and reliability – an observational cross-sectional study

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ABSTRACT

BACKGROUND: The Health-Related Quality of Life Questionnaire for Nausea and Vomiting of Pregnancy (NVPQOL) is a validated questionnaire assessing quality of life among pregnant women with nausea and vomiting.

OBJECTIVE: To translate, cross-culturally adapt and evaluate the reliability of the NVPQOL.

DESIGN AND SETTING: Observational cross-sectional study developed in a public university in Brazil.

METHODS: The translation, synthesis of translations, back-translation, expert committee, pre-testing and validation were carried out, resulting in a Portuguese-language version. The internal consistency, intra-rater and test-retest reliability and correlation between the total score of the Portuguese-language version of the NVPQOL and the domains of the World Health Organization Quality of Life-bref questionnaire were considered in the data analysis.

RESULTS: The instrument went through the process with testing on 104 pregnant women. Strong internal consistency (Cronbach's α: 0.95), strong intra-rater and test-retest reliability ($P < 0.0$; intraclass correlation coefficient: 0.89; confidence interval: 0.791-0.945) and strong correlation between the total score of the Portuguese-language version of the NVPQOL and the physical health domain of the World Health Organization Quality of Life-bref questionnaire ($P < 0.01$; $R = -0.8$) were observed.

CONCLUSION: The NVPQOL was translated, cross-culturally adapted and validated for the Portuguese language with satisfactory psychometric properties for assessing quality of life, especially in relation to physical health, among pregnant women with symptoms of nausea and vomiting in the first trimester of pregnancy.

INTRODUCTION

Nausea is defined as an uncomfortable sensation that is associated with the urge to vomit, while vomiting is characterized by oral expulsion of gastric contents.[1] These symptoms are common during the first gestational trimester, affecting 70-80% of pregnant women, and their cause is still uncertain.[2,3] They are responsible for physical and emotional impairment, which tends to trigger social isolation and compromise quality of life, given that, according to Hizli et al.,[4] 8 to 12% of pregnant women with these symptoms isolate themselves socially. Pregnant women's common complaints include uncomfortable symptoms of physical discomfort that prevent them from successfully performing their daily activities. These involve negative feelings about pregnancy, which can give rise to emotional conflicts in these women's relationships with the baby and family.

These symptoms are more prevalent among young, multiparous and multiple gestation pregnant women.[5] They tend to soften after the 22nd gestational week,[6] although in some women they may continue until the end of the gestation,[6] thus characterizing pregnancy hyperemesis. In such cases, the symptoms of nausea and vomiting of pregnancy are persistent, excessively compromising and untreatable. They may lead to dehydration, ketosis, weight loss and electrolyte and nutritional disorders.[4,7,8]

Investigating the frequency of these symptoms and their impact on women's quality of life can help professionals to understand this condition, in order to minimize the impact of nausea and vomiting on this very special phase of women's lives. For this purpose, Lacasse et al.[9] created the

Modified Pregnancy – Unique Quantification of Emesis and Nausea questionnaire, which investigates the presence and severity of nausea and vomiting among pregnant women in the first trimester of pregnancy. Additionally, the same authors validated the Health-Related Quality of Life Questionnaire for Nausea and Vomiting of Pregnancy,[9] a questionnaire created by Magee et al.,[10] in order to measure the impact of specific nausea and vomiting of pregnancy on quality of life in the first trimester of pregnancy.

Currently, in Brazil, there is no instrument for measuring the impact of nausea and vomiting of pregnancy on pregnant women's quality of life, which therefore justified conducting the present study. Thus, we proposed to undertake the translation, cross-cultural adaptation and evaluation of the reliability of the Health-Related Quality of Life Questionnaire for Nausea and Vomiting of Pregnancy, in order to provide the Brazilian population with a reliable instrument for assessing the quality of life of pregnant women with symptoms of nausea and/or vomiting.

OBJECTIVE

To translate, cross-culturally adapt and evaluate the reliability of the Health-Related Quality of Life Questionnaire for Nausea and Vomiting of Pregnancy.

METHODS

Study type

This was an observational cross-sectional study.

Description of the Health-Related Quality of Life Questionnaire for Nausea and Vomiting of Pregnancy

The Health-Related Quality of Life Questionnaire for Nausea and Vomiting of Pregnancy is a self-administered questionnaire that was developed by Magee et al.[10] and validated by Lacasse et al.[9] in 2008. This instrument assesses quality of life among pregnant women with symptoms of nausea and vomiting of pregnancy and was originally validated among pregnant women in their first trimester of pregnancy. It is composed of 30 questions covering four main domains: physical symptoms and aggravating factors, fatigue, emotions and limitations.[10] For each question in the questionnaire, a range of possible responses is provided using a seven-point Likert scale, on which 1 represents "none of the time" and 7 represents "all of the time". The sum of the scores from these questions results in a total score ranging from 30 to 210. The lower the score is, the higher the quality of life is.[9]

Ethical issues

In order to begin the study, authorization was sought from the author Dr. Laura Magee, which was granted. Furthermore, approval was given by the Institutional Review Board of the study university, in accordance with the ethical and legal precepts (Institutional Review Board approval CAAE: 81392017.1.0000.5142; approval number: 2.543.785; approval date: March 14, 2018). All the study participants signed an informed consent statement.

Translation, cross-cultural adaptation and content validation processes of the Health-Related Quality of Life Questionnaire for Nausea and Vomiting of Pregnancy

The stages proposed by Beaton et al.[11] were used as a reference framework for developing the translation and cross-cultural adaptation stages of the Health-Related Quality of Life Questionnaire for Nausea and Vomiting of Pregnancy, in accordance with the COSMIN recommendations.[12]

Stage I: Initial translation

The original Health-Related Quality of Life Questionnaire for Nausea and Vomiting of Pregnancy went through the process of translation into Portuguese by two independent bilingual translators, who were Brazilians: one of them was lay and the other was a specialist in the field. Thus, two translations (T1 and T2) containing the instructions, questions and responses to the questionnaire were generated.

Stage II: Synthesis

The two versions generated in stage I (T1 and T2) were synthesized into a common version (T12) and all divergences were reported and agreed by the researchers responsible for this study.

Stage III: Back translation

The synthesized version (T12) was back-translated by two independent translators, who were native speakers of the English language and not healthcare professionals. Thus, two back-translated versions (BT1 and BT2) were generated. These presented content that was similar to that of the original version, thus ensuring consistency of the translation.

Stage IV: Expert committee

In order to verify equivalence, an expert committee composed of 12 healthcare professionals (seven physiotherapists, three nurses and two physicians) evaluated the translated versions (T1, T2, T12, BT1 and BT2) and approved the pre-final version of the questionnaire (Health-Related Quality of Life Questionnaire for Nausea and Vomiting of Pregnancy_pre-final_version).

Stage V: Pre-testing

The Health-Related Quality of Life Questionnaire for Nausea and Vomiting of Pregnancy_pre-final_version was applied to 104 pregnant women who had been selected from among attendees at a doctor's office and family health program in Alfenas (MG), Brazil. The aim in doing this was to identify any adaptations that might be necessary, ensure that the target population understood the questions and test the semantic, idiomatic, experimental

and conceptual equivalence. This sample was defined for convenience. Thus, after the pretest, the final version was generated (Health-Related Quality of Life Questionnaire for Nausea and Vomiting of Pregnancy_Portuguese), as shown in **Annex 1**.

Evaluation of the reliability of the Health-Related Quality of Life Questionnaire for Nausea and Vomiting of Pregnancy_Portuguese

After the translation, cross-cultural adaptation and content validation processes had ended, the reliability of the instrument was ascertained among another 36 pregnant women. These subjects were recruited from among the attendees at doctors' offices and the family health program of the municipality of Alfenas (MG), Brazil. These women attended two face-to-face interviews conducted by the same researcher, who had been trained and qualified to maintain an interview standard. There was a seven-day interval between the interviews.[13]

At both interviews, the subjects gave responses to two instruments: the Health-Related Quality of Life Questionnaire for Nausea and Vomiting of Pregnancy_Portuguese and the World Health Organization Quality of Life-bref questionnaire. The World Health Organization Quality of Life-bref questionnaire had previously been validated by Fleck et al.[14] It is composed of 26 questions, including two general questions and 24 questions divided into four domains: physical, psychological, social relations and environment.[15] This questionnaire was chosen for comparison purposes considering that no other gold standard that assessed the quality of life of individuals with symptoms of nausea and vomiting was found.

The inclusion criteria were that the participants needed to be over 18 years of age, with a pregnancy of gestational age less than 16 weeks. Women presenting neurological abnormalities, disorders and/or cognitive limitations that precluded participation in the study were excluded. Women who did not participate fully in the proposed activities, i.e. attendance at both interviews, were considered to have discontinued their participation.

Data analysis

The data analysis was carried out by two researchers and the following tests were performed: Cronbach's alpha coefficient test for internal consistency analysis (considering the first interview);[16] intraclass correlation coefficient (ICC) (model 2.1; two-way random; single measurement) for test-retest reliability analysis (considering instrument total scores at the first and second interviews);[16,17] Shapiro-Wilk test followed by the Spearman or Pearson correlation test to investigate the relationship between the total score of the Health-Related Quality of Life Questionnaire for Nausea and Vomiting of Pregnancy_Portuguese and the domain scores of the World Health Organization Quality of Life-bref questionnaire.

The Microsoft Excel 2010 software, version 14.4.9 (Microsoft Corporation, Redmond, WA, United States) and the R program software, version 3.3.3 (https://www.r-project.org/, Vienna, Austria) were used for data analysis. Coefficients below 0.5 were considered to present "poor reliability"; coefficients between 0.5 and 0.75, "moderate reliability"; and coefficients above 0.75, "strong reliability".[16] In all the analyses, a 95% confidence interval (CI) was used.

No inter-rater analysis was performed, given the self-applicable nature of the instrument, which does not require any intervention from the evaluator.

The Survio platform was used to make the questionnaires available and to collect answers in the different stages of the translation and expert committee analyses.

RESULTS

The whole process involved 140 pregnant women, who participated either in the pretesting process (n = 104) or in the reliability process (n = 36). **Table 1** presents the study population for the process of cross-cultural adaptation and evaluation of the reliability of the Health-Related Quality of Life Questionnaire for Nausea and Vomiting of Pregnancy_Portuguese.

Translation and cross-cultural adaptation

Table 2 presents the adaptations made during the process of translation and cross-cultural adaptation, through conformity analysis between the original and translated versions of the instrument.

Instrument validation

Internal consistency

The Health-Related Quality of Life Questionnaire for Nausea and Vomiting of Pregnancy_Portuguese showed strong internal consistency (Cronbach's α coefficient = 0.95).

Table 1. Demographic and clinical characteristics of the study population

Demographic data	Pretesting (n = 104)	Reliability (n = 36)
Age, years (standard deviation)[a]	26.5 (± 5.6)	27.1 (± 5.5)
Education level, n (%)[b]		
Elementary school	16 (15.4)	6 (16.7)
High school	66 (63.5)	12 (33.3)
University/college	22 (21.1)	18 (50)
Household income, n (%)[b]		
1-2 minimum monthly wages	74 (71.2)	22 (61.1)
3-4 minimum monthly wages	23 (22.1)	6 (16.7)
> 4 minimum monthly wages	7 (6.7)	8 (22.2)
Clinical data	**Pretesting (n = 104)**	**Reliability (n = 36)**
Gestational age, weeks (standard deviation)[a]	22.3 (± 10.4)	11.36 (± 3.67)
Nausea and vomiting presence, n (%)[b]		
No	56 (53.8)	11 (30.6)
Yes	48 (46.2)	25 (69.4)
Antiemetic use, n (%)[b]		
No	91 (87.5)	23 (63.9)
Yes	13 (12.5)	13 (36.1)

[a]Mean and standard deviation (±); [b]Absolute number (n) and relative frequency (%).

Instrument reliability

A strong correlation was observed in the test-retest analysis on the Health-Related Quality of Life Questionnaire for Nausea and Vomiting of Pregnancy_Portuguese (ICC = 0.89; 95% CI: 0.791-0.945; P < 0.0).

Instrument correlation

The total score of the Health-Related Quality of Life Questionnaire for Nausea and Vomiting of Pregnancy_Portuguese was correlated with the score for each domain of the World Health Organization Quality of Life-bref questionnaire. The presence of nausea and vomiting symptoms (high score in the Health-Related Quality of Life Questionnaire for Nausea and Vomiting of Pregnancy_Portuguese) was correlated with low quality of life scores, especially with regard to physical function (low domain scores in the World Health Organization Quality of Life-bref questionnaire) (**Table 3**). Clinically, an indirect relationship was observed between the nausea and vomiting symptoms and the physical health domain of the World Health Organization Quality of Life-bref questionnaire. This indicated that the greater the nausea and vomiting symptoms were, the greater the impairment of the quality of life of the pregnant women in the study also was.

DISCUSSION

Main findings

The Health-Related Quality of Life Questionnaire for Nausea and Vomiting of Pregnancy was translated[9,10] and cross-culturally adapted for the Portuguese language, and it presented good test-retest reliability and good correlation with the domains of the World Health Organization Quality of Life-bref questionnaire. The instrument showed satisfactory psychometric properties for assessing quality of life among pregnant women with symptoms of nausea and vomiting in the first gestational trimester.

The Portuguese-language version (Health-Related Quality of Life Questionnaire for Nausea and Vomiting of Pregnancy_Portuguese) presented strong internal consistency, strong intra-rater and test-retest reliability and strong correlation between the total score of the Health-Related Quality of Life Questionnaire for Nausea and Vomiting of Pregnancy Portuguese and the physical health domain of the World Health Organization Quality of Life-bref questionnaire. Thus, the translated questionnaire was reliable for measuring the impact of nausea and vomiting on the physical health aspect of quality of life among Brazilian pregnant women.

The Health-Related Quality of Life Questionnaire for Nausea and Vomiting of Pregnancy was originally created by Magee et al.[10] in 2002, using a sample of 500 women with nausea and vomiting of pregnancy. The methodology gave value to potential factors that correlate nausea and vomiting of pregnancy with quality of life. The validation study among women in the first trimester of pregnancy was conducted by Lacasse et al.[9] in 2008, using a sample of 288 pregnant women with symptoms of nausea and vomiting of pregnancy. Our study was designed in accordance with the same criteria used by Lacasse et al.,[9] in spite of adding the test-retest and intra-rater reliability analyses.

Our study found excellent internal reliability for the complete questionnaire, thus corroborating the results from the study by Lacasse et al.[9] In theory, reliability analyses follow the condition that the higher the test-retest reliability is, the higher the internal reliability also is, which was observed in the present study.[18]

Clinical and research implications

Health status is a factor relating to quality of life that is one of the essential components of health-related quality of life.[19] During the gestational period, there are important physiological changes and consequent emotional and physical changes that impact on women's health and quality of life, and these may negatively affect the mother-child binomial.

It is known that symptoms of nausea and vomiting of pregnancy affect up to 80% of women. They have greatest occurrence in the first trimester[20] and tend to decrease after this period. This justifies investigation of such symptoms during this period, through clinical research on the impact of nausea and vomiting of pregnancy on the quality of life of pregnant women.

Our study involved 140 women during the process of cross-cultural adaptation and validation, and we found that the questionnaire presented strong statistical validity, thus demonstrating its psychometric properties with regard to women in their first trimester of pregnancy.

According to the American College of Obstetricians and Gynecologists,[21] most cases of nausea and vomiting of pregnancy are self-limiting with a peak incidence around the 9th gestational week and symptom relief around the 20th gestational week. The present study was conducted with a limit on assessment and reassessment (test-retest) that was set at the 16th week of gestation, as was done in the validation study conducted by Lacasse et al.,[9] although the original study included women up to the 20th week.[10]

This approach was justified not only by the fact that the prevalence is highest in the first trimester, but also because complaints that tend to persist throughout the gestational process are already characterized as *hyperemesis gravidarum* and may involve other related factors, despite lack of full knowledge of the etiology so far.[22] In addition, the effect of memory and other characteristic symptoms of each gestational phase could influence the perception of health and consequently the quality of life in other gestational periods, such as the sensation of heartburn, which is a common characteristic of the last gestational trimester.[23]

Additionally, the emotional conflict experienced by these women, involving the mother-child relationship, needs to be considered, given that the impact of any distress after the acute phase of nausea and vomiting tends to be minimized. In this

Table 2. Process of translation and cross-cultural adaptation of the items of the Health-Related Quality of Life Questionnaire for Nausea and Vomiting of Pregnancy_Portuguese

Original version	T1	T2	T12	Pre-final version	Final version
Over the past week, how much have you been experiencing... (Please fill in one circle on the scale for each symptom)	*Durante a última semana, quantas vezes você teve os sintomas abaixo… (Colocar às vezes dentro do círculo para cada sintoma)*	*No período de uma semana, quantas vezes você sentiu… (Marque um círculo para cada sintoma)*	*Durante a última semana, quantas vezes você teve os sintomas abaixo... (Marque um círculo para cada sintoma)*	*Durante a última semana, quantas vezes você* ***apresentou os seguintes sintomas... (Por favor, marque um círculo na escala para cada sintoma)***	---
None of the time	*Nenhuma vez*	*Nunca*	*Nenhuma vez*	---	---
All of the time	*O tempo todo*	*Sempre*	*O tempo todo*	---	---
Nausea	*Náusea*	*Ânsia*	*Náusea*	***Enjoo***	---
Feeling sick to your stomach	*Estômago enjoado*	*Ânsia estomacal*	*Estômago enjoado*	***Dor no estômago***	---
Vomiting	*Vomitar*	*Vomitando*	*Vomitar*	*Vomitar*	***Vômito***
Dry-heaves (vomiting without bringing anything up)	*Ânsia de vômito*	*Ânsia de vômito*	*Ânsia de vômito*	---	---
Poor appetite	*Sem apetite*	*Pouco apetite*	*Pouco apetite*	***Perda de apetite***	---
Symptoms being worse in the evening	*Sintomas pioram à tarde*	*Sintomas pioram à tarde*	*Sintomas pioram à tarde*	***Piora dos sintomas no período da tarde***	---
Not eating for longer than you would like	*Não se alimentar mais do que queria*	*Não comer pelo tempo que quiser*	*Não comer o quanto gostaria*	*Não* ***posso*** *comer o quanto* ***desejaria***	---
Feeling worse when exposed to certain smells	*Sentir pior quando exposta a alguns cheiros*	*Sentir mal com cheiro forte*	*Se sente pior quando exposta a certos cheiros*	*Se sente pior quando* ***sente*** *certos cheiros*	---
Feeling worse when exposed to certain foods	*Sentir pior quando exposta a certos alimentos*	*Sentir mal com certas comidas*	*Se sente pior quando exposta a certas comidas*	*Se sente pior quando* ***come*** *certas comidas*	---
Fatigue	*Cansada*	*Cansada*	*Cansada*	***Fadiga***	---
Feeling worn-out and a loss of energy	*Sentir cansada e sem energia*	*Sentir esgotada e com pouca energia*	*Se sente esgotada e sem energia*	---	---
Feeling exhausted	*Se sentir exausta*	*Sentir exausta*	*Se sente exausta*	---	---
Feeling tired	*Se sentir cansada*	*Sentir cansada*	*Se sente cansada*	---	---
Feeling emotional	*Se sentir emotiva*	*Sentir emotiva*	*Se sente emotiva*	---	---
Being less interested in sex	*Sentir menos interesse em sexo*	*Ter menos interesse por sexo*	*Sente menos interessada em sexo*	*Sente menos* ***interesse*** *em sexo*	---
Feeling downhearted, blue, sad, unhappy, depressed, gloomy	*Sentir pra desanimada, triste, infeliz, deprimida e sem vontade*	*Sentir para baixo, triste, infeliz, deprimida sem vida*	*Se sente para baixo, desanimada, triste, infeliz, deprimida e sem vontade*	---	---
Feeling frustrated	*Se sentir frustrada*	*Sentir frustrada*	*Se sente frustrada*	---	---
Feeling fed up with being sick	*Ficar brava por estar doente*	*Sentir raiva de estar doente*	*Se sente brava por estar doente*	*Se sente* ***com raiva*** *por estar* ***enjoada***	---
Not feeling that your symptoms are all part of normal pregnancy	*Não perceber que os sintomas são partes da gravidez*	*Achar que os sintomas não fazem parte da gravidez*	*Não sente que todos os sintomas são de uma gravidez normal*	*Sente que todos seus sintomas não* ***correspondem*** *a uma gravidez normal*	*Sente que seus sintomas* ***não são de*** *uma gravidez normal*
Feeling that you can't enjoy your pregnancy	*Sentir que não irá aproveitar a gravidez*	*Sentir que não pode apreciar a gravidez*	*Sente que você não pode aproveitar a gravidez*	*Sente que você não pode* ***apreciar*** *a gravidez*	---
That everything is an effort	*Tudo é um esforço*	*Que tudo é um esforço*	*Que tudo é um esforço*	*Tudo é um esforço*	---
Feeling like you have accomplished less than you would like	*Sentir que fez menos do que poderia*	*Sentir que fez menos do que poderia*	*Sente que você fez menos do que gostaria*	*Sente que você* ***faz*** *menos do que* ***gostaria***	---
That it takes longer to get things done than usual	*Demorar mais para fazer algo era comum*	*Que demora mais para fazer algo*	*Demora mais para fazer algo do que o comum*	***Leva mais tempo*** *para fazer* ***as coisas do que normalmente***	---
Difficulty performing your work and activities	*Dificuldade para realizar um trabalho ou uma atividade*	*Dificuldade em completar alguma atividade*	*Dificuldade em realizar seu trabalho e atividades*	---	---
Difficulty maintaining your normal social activities	*Dificuldade para manter atividades sociais*	*Dificuldade de manter uma vida social*	*Dificuldade em manter suas atividades sociais*	---	---
Relying on your partner for doing things that you would normally	*Depender de seu companheiro para fazer as coisas que antes fazia normalmente*	*Depender de seu parceiro para fazer algo que fazia sozinha*	*Depende do seu parceiro para fazer coisas que você faria normalmente*	---	---
Difficulty looking after your home	*Dificuldade de cuidar da casa*	*Dificuldade de fazer trabalhos domésticos*	*Dificuldade em cuidar de sua casa*	---	---
Difficulty shopping for food	*Dificuldade em fazer compras*	*Dificuldade em fazer compras*	*Dificuldade em fazer compras*	---	---
Difficulty preparing or cooking meals	*Dificuldade em cozinhar*	*Dificuldade em cozinhar*	*Dificuldade em cozinhar*	---	---
Cutting down on amount of time you spend at work or other activities	*Diminuir o tempo de trabalho ou das tarefas normais*	*Diminuir o tempo de atividades*	*Redução do tempo de trabalho ou outras atividades*	---	---

This table presents the initial translation version, made by two Portuguese native speakers (T1 and T2); the synthesis version (T12); the pre-final version (Health-Related Quality of Life Questionnaire for Nausea and Vomiting of Pregnancy_pre-final_version) that was applied during the pre-test; and the final version named the Health-Related Quality of Life Questionnaire for Nausea and Vomiting of Pregnancy_Portuguese.
--- = unchanged.

regard, reliability studies have affirmed that the time interval between measurements may influence the interpretation of the test-retest reliability.[17] Therefore, we took care not only to always reapply the instrument after a seven-day interval, but also to ensure that the whole process was completed before reaching 16 weeks of gestation.

Improving the measurement quality of factors relating to the quality of life of pregnant women with symptoms of nausea and vomiting was one of the main contributions of the present study to clinical practice.

Quality of life implications

A strong correlation was found between the total score of the Health-Related Quality of Life Questionnaire for Nausea and Vomiting of Pregnancy_Portuguese and the physical health domain of the World Health Organization Quality of Life-bref questionnaire. In a study by Attard et al.,[24] it was found that pregnant women who had at least one of the symptoms of nausea, vomiting or fatigue also had significantly lower scores in assessments of quality of life specifically in the physical and mental domains, such that their health was negatively affected.

The presence of symptoms of nausea and vomiting of pregnancy is known to affect women's performance in their work and daily activities.[25] In this regard, these symptoms seem to have a negative impact when analyzed from the point of view of the international classification of functionality,[26] especially in terms of activity and participation. However, there are no studies linking women with nausea and vomiting of pregnancy to their functional capacity. This would be an important approach for future research, especially because this negative impact was observed by the present researchers in developing this study.

The World Health Organization Quality of Life-bref domains of overall perception of quality of life, overall perception of general health, psychological factors and social relationships showed moderate correlations with the total score of the Health-Related Quality of Life Questionnaire for Nausea and Vomiting of Pregnancy_Portuguese. This demonstrated that the symptoms of nausea and vomiting of pregnancy may also affect other matters that constitute quality of life overall. In a study by Chou et al.,[27] it was observed that symptoms of nausea and vomiting of pregnancy were associated with depressive symptoms, which may explain the correlation with the psychological domain.

However, there are inconsistencies between different studies that may reflect differences between populations. In interpreting the results from these studies in relation to quality of life, it is necessary to consider their environmental and cultural aspects.[28] In this regard, the present study showed a weak correlation with the symptoms of nausea and vomiting of pregnancy in the environment domain of the World Health Organization Quality of Life-bref questionnaire.

We observed that the strong correlation between the total score of the Health-Related Quality of Life Questionnaire for Nausea and Vomiting of Pregnancy_Portuguese and the physical health domain of the World Health Organization Quality of Life-bref questionnaire stood out in relation to comparisons with the general perception of quality of life and the health, psychological, social relationship and environment domains. This suggested, in interpreting the instrument, that there was a real relationship between the symptoms of nausea and vomiting of pregnancy and the physical health perceptions of pregnant women.

This finding also demonstrates the importance of thoroughness in interpreting the validation process of this study. We found greater correlations between certain domains of these two instruments, which have different scoring systems and ways of calculating them.

Strengths, limitations and suggestions for further studies

We suggest that future research should include use of the Health-Related Quality of Life Questionnaire for Nausea and Vomiting of Pregnancy_Portuguese in other gestational periods, i.e. in the second and third gestational trimesters. However, this does not mean that the questionnaire cannot already be used to access the symptoms of nausea and vomiting of pregnancy throughout the gestational period. What we want to point out is that we were unable to identify any studies investigating the validity, and no other instruments investigating nausea and vomiting of pregnancy, at these specific stages of pregnancy so far. This might be considered a limitation of our study. Follow-up pregnant women could provide enlightenment on whether nausea and vomiting of

Table 3. Reproducibility and instrument correlation analysis on the Health-Related Quality of Life Questionnaire for Nausea and Vomiting of Pregnancy_Portuguese

Domains of the World Health Organization Quality of Life-bref questionnaire	Health-Related Quality of Life Questionnaire for Nausea and Vomiting of Pregnancy_Portuguese (P-value)	Correlation coefficient (R)
Overall perception of quality of life	< 0.01[a*]	-0.55
Overall perception of general health	< 0.01[a*]	**-0.55**
Physical health	< 0.01[a*]	**-0.80**
Psychological	< 0.01[a*]	**-0.68**
Social relationships	< 0.01[a*]	-0.53
Environment	0.01[b*]	-0.42

[a]Spearman correlation test; [b]Pearson correlation test; [*]P-value < 0.05.

pregnancy in the first trimester of pregnancy really is a turning point in the quality of life of these women.

Furthermore, we suggest that future research should include adaptation and validation of the Health-Related Quality of Life Questionnaire for Nausea and Vomiting of Pregnancy_Portuguese for use in other populations suffering from nausea and vomiting, e.g. cancer patients undergoing chemotherapy. According to Wickham,[29] the mechanisms of nausea should be highly similar, regardless of its cause.

We also suggest that antiemetic treatment should be individualized and the effect of each intervention should be measured in terms of the patient's own reported outcome. This corroborates the idea that validated instruments should be indicated for investigating the presence, severity and impact of pregnancy nausea and vomiting on the quality of life among patients, who will evaluate for themselves the reported efficacy and effects, and their preferences. It is also important to consider that the impact of nausea and vomiting of pregnancy on quality of life may differ from individual to individual. Some individuals may even suffer continuously, with daily complaints that are secondary to nausea-triggering processes such as first-trimester gestation, a chemotherapy treatment period or a postoperative period. Others may suffer from sporadic nausea, such as symptoms that affect individuals during a trip, for example.

In a study by Dean et al.,[30] lack of attention towards addressing the symptoms of nausea and vomiting of pregnancy by healthcare professionals was reported. Thus, it is essential to emphasize the importance of using a validated assessment instrument that is available to Brazilian professionals and their patients.

CONCLUSION

The Health-Related Quality of Life Questionnaire for Nausea and Vomiting of Pregnancy was translated, adapted and validated for the Portuguese language with satisfactory psychometric properties for assessing quality of life, especially with regard to physical health among pregnant women up to their 16th week of gestation, with symptoms of nausea and vomiting. This generated the Health-Related Quality of Life Questionnaire for Nausea and Vomiting of Pregnancy_Portuguese version.

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Annex 1. Health-Related Quality of Life Questionnaire for Nausea and Vomiting of Pregnancy_Portuguese.

Health-Related Quality of Life for Nausea and Vomiting of Pregnancy_Portuguese							
Durante a última semana, quantas vezes você apresentou os seguintes sintomas... (Por favor, marque um círculo na escala para cada sintoma)							
	Nenhuma vez						**O tempo todo**
	1	2	3	4	5	6	7
1) Enjoo	☐	☐	☐	☐	☐	☐	☐
2) Dor de estômago	☐	☐	☐	☐	☐	☐	☐
3) Vômito	☐	☐	☐	☐	☐	☐	☐
4) Ânsia de vômito	☐	☐	☐	☐	☐	☐	☐
5) Perda de apetite	☐	☐	☐	☐	☐	☐	☐
6) Piora dos sintomas no período da tarde	☐	☐	☐	☐	☐	☐	☐
7) Não posso comer o quanto desejaria	☐	☐	☐	☐	☐	☐	☐
8) Se sente pior quando sente certos cheiros	☐	☐	☐	☐	☐	☐	☐
9) Se sente pior quando come certas comidas	☐	☐	☐	☐	☐	☐	☐
10) Fadiga	☐	☐	☐	☐	☐	☐	☐
11) Se sente esgotada e sem energia	☐	☐	☐	☐	☐	☐	☐
12) Se sente exausta	☐	☐	☐	☐	☐	☐	☐
13) Se sente cansada	☐	☐	☐	☐	☐	☐	☐
14) Se sente emotiva	☐	☐	☐	☐	☐	☐	☐
15) Sente menos interesse em sexo	☐	☐	☐	☐	☐	☐	☐
16) Se sente para baixo, desanimada, triste, infeliz, deprimida e sem vontade	☐	☐	☐	☐	☐	☐	☐
17) Se sente frustrada	☐	☐	☐	☐	☐	☐	☐
18) Se sente com raiva por estar enjoada	☐	☐	☐	☐	☐	☐	☐
19) Sente que seus sintomas não são de uma gravidez normal	☐	☐	☐	☐	☐	☐	☐
20) Sente que você não pode apreciar a gravidez	☐	☐	☐	☐	☐	☐	☐
21) Tudo é um esforço	☐	☐	☐	☐	☐	☐	☐
22) Sente que você faz menos do que gostaria	☐	☐	☐	☐	☐	☐	☐
23) Leva mais tempo para fazer as coisas do que normalmente	☐	☐	☐	☐	☐	☐	☐
24) Dificuldade em realizar seu trabalho e atividades	☐	☐	☐	☐	☐	☐	☐
25) Dificuldade em manter suas atividades sociais	☐	☐	☐	☐	☐	☐	☐
26) Depende do seu parceiro para fazer coisas que você faria normalmente	☐	☐	☐	☐	☐	☐	☐
27) Dificuldade em cuidar de sua casa	☐	☐	☐	☐	☐	☐	☐
28) Dificuldade em fazer compras	☐	☐	☐	☐	☐	☐	☐
29) Dificuldade em cozinhar	☐	☐	☐	☐	☐	☐	☐
30) Redução do tempo de trabalho ou outras atividades	☐	☐	☐	☐	☐	☐	☐
Se você trabalha fora de casa, você ainda continua trabalhando?	☐ Não		☐ Sim		☐ Não trabalho fora		
Escore: soma das respostas dos itens de 1 a 30, sendo que quanto menor o escore melhor a qualidade de vida.							

This is the Health-Related Quality of Life Questionnaire for Nausea and Vomiting of Pregnancy_Portuguese, which is the validated version for the Portuguese language. How to cite: Piccini A, Tulha AS, Silva SLA, et al. The Brazilian version of the Health-Related Quality of Life Questionnaire for Nausea and Vomiting of Pregnancy: translation, cross-cultural adaptation and reliability – an observational cross-sectional study. Sao Paulo Med J. 2021.

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Functional outcomes among stroke patients in Alagoas, Brazil: observational study

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KEY WORDS (MeSH terms):
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AUTHORS' KEY WORDS:
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ABSTRACT

BACKGROUND: Stroke is the principal cause of disability around the world and the ensuing functional dependence (FD) can be correlated with different factors.

OBJECTIVE: To determine how demographic factors and clinical characteristics after stroke distinguish patients who achieve functional independence from those who do not.

DESIGN AND SETTING: Observational study at specialized neurovascular clinic in Alagoas, Brazil.

METHODS: FD was classified according to the modified Rankin scale (mRs): 0 to 2 points were classified as independent (FD-), and 3 to 5 points were classified as dependent (FD+). Logistic regression analysis included age, sedentary lifestyle, the Center for Epidemiological Studies – Depression Scale (CES-D) and the National Institutes of Health Stroke Scale (NIHSS). The Mann-Whitney test and χ^2 test were used to compare groups.

RESULTS: We included 190 stroke patients with a mean age of 60.02 ± 14.22 years. We found that 34.8% of the patients were classified as FD+. Lower NIHSS and CES-D scores were more associated with achieving functional independence. Most of the patients had access to physical therapy, and the mean duration of rehabilitation therapy was 65.2 minutes per week. Females had higher prevalence of depressive symptoms (P = 0.005) and rehabilitation time was shorter for hemorrhagic stroke (P = 0.02).

CONCLUSION: We found a FD rate four times greater than in another Brazilian study. Lower stroke severity and fewer depressive symptoms were associated with achieving functional independence. Less than half of the patients were referred to a rehabilitation service at hospital discharge and few had access to multidisciplinary treatment.

INTRODUCTION

Stroke is an epidemic disease. Up to 2013, there had been more than 25 million stroke survivors and more than 6 million deaths worldwide.[1] In Brazil, more than 2 million cases of stroke were reported in 2013, with approximately 25% of these individuals remaining disabled.[2] Estimates from the Global Burden Disease Study showed prevalence of 170-339/100,000 for ischemic stroke and 0-39/100,000 for hemorrhagic stroke in Brazil.[3]

Despite these impactful numbers, reductions in the mortality rates due to stroke have been achieved in developing countries over the past two decades.[1] A study conducted in the city of Joinville, in southern Brazil, showed a significant reduction in incidence of 37%. These results can be explained by improvements in socioeconomic conditions and educational levels in this city.[4]

However, Brazil is a country of continental dimensions, and the reality is not the same throughout the national territory. Until now, little information about stroke in northeastern Brazil has been available. A study conducted in Fortaleza, in 2011, showed a prevalence of risk factors similar to what has been reported in the literature, including both high functional dependence (FD) after stroke and high in-hospital mortality.[5] A comparison among all the state capitals of northeastern Brazil showed that Maceio, state of Alagoas, had the highest mortality rate due to stroke and the lowest human development index (HDI).[6] Because of this, it is important to know more about the characteristics of stroke in this region.

In Brazil, information about the level of FD after stroke and the characteristics of these patients remains scarce. In the United States, stroke is the main cause of disability,[7] while in Brazil, 15%-20% of stroke patients have neurological deficits in the first year and 10% of ischemic stroke survivors

continue to have FD three years after stroke.[8] Thus, we hypothesize that stroke patients in Alagoas will have high levels of FD.

OBJECTIVE

The main objective of this study was to determine how demographic factors and clinical characteristics after stroke distinguish patients who achieve functional independence from those who do not, in a sample of patients attended at a specialized neurovascular clinic in Alagoas, Brazil. We also compared functionality in ischemic and hemorrhagic stroke patients and characterized the rehabilitation process of these patients.

METHODS

Design and ethical aspects

This was an observational study. The study procedures were approved by the research ethics committee of the local institution, in accordance with opinion report number 60717416.1.0000.5013 (October 27, 2016). Written informed consent was obtained from all of the participants.

Sample

We evaluated patients with ischemic and hemorrhagic stroke confirmed by neuroimaging who were consecutively attended at a specialized neurovascular clinic in Alagoas, Brazil. Patients were excluded if they were younger than 18 years old, had another neurological disease associated with stroke or had a severe concomitant systemic illness, such as cancer, severe kidney disease or severe hepatic disease.

Initial evaluation

The protocol assessment was composed of demographic and clinical data. To evaluate stroke severity, we used the National Institutes of Health Stroke Scale (NIHSS), which is composed of 11 items and has a maximum score of 42. Higher scores on this scale mean worse stroke severity.

To measure functional status, we used the Modified Rankin Scale (mRs) and the Functional Independence Measure (FIM). The mRs is often used to measure overall disability and primary outcomes in randomized clinical trials,[9] and its scale ranges from 0 (no symptom) to 6 (death). The FIM was developed to evaluate patients with different diagnostic and functional restrictions, and the main objective is to measure the burden of care demanded by a person in order to execute a series of motor and cognitive tasks.[10] The scale contains 18 items and is rated on a 7-point scale, ranging from 1 (total assistance needed) to 7 (complete independence).

The patients were also evaluated using the Center for Epidemiological Studies – Depression Scale (CES-D),[11] which is composed of 20 items. On this scale, higher scores suggest depressive symptoms. Furthermore, a structured questionnaire about implementation, frequency and duration of rehabilitation therapies was applied.

We classified functionality using the mRs. On this scale, patients with 0 to 2 points were classified as independent (FD-), and those with 3 to 5 points were classified as dependent (FD+).

Statistical analysis

All data were analyzed using the SPSS software (version 20.0; Chicago, IL, United States) at a significance level of 5%.

The distribution of the data was initially verified by means of histogram analysis. We used descriptive statistics to show the demographic and clinical characteristics of stroke patients and the proportion of FD based on the mRs and FIM scores.

Logistic regression analysis was performed using a dichotomous dependent variable (FD+ = 0 and FD- = 1), with the following admission variables to predict group associations: age, sedentary lifestyle, CES-D and NIHSS. The variables of age, CES-D and NIHSS were classified as continuous and the variable of sedentary lifestyle was classified as categorical. These were entered into the logistic regression to confirm the final variables in the model. The Hosmer and Lemeshow test confirmed that all the regression models adequately fitted the data ($P > 0.05$).

For descriptive purposes, the Mann Whitney test and χ^2 test were used to compare the groups (FD+ and FD-). The variables with statistical significance were chosen for the logistic regression. We also compared groups of ischemic versus hemorrhagic stroke and of female versus male patients, using the Mann-Whitney test and χ^2 test.

RESULTS

A total of 190 stroke patients with a mean age of 60.02 ± 14.22 years were evaluated. Among these patients, 61.6% were male and the mean schooling level was 5.8 ± 4.4 years. The mean time that had elapsed from the stroke to inclusion in the study was 27.2 ± 33.1 months. The demographic and clinical characteristics of these stroke patients are described in **Table 1**.

The mean CES-D score was 15.7 ± 11.6. Using the cutoff of 16 points, we found that 66 patients (40%) presented depressive symptoms. The mean FIM score was 99.1 ± 26.3. The median NIHSS score was 2 (interquartile range, IQR: 1-5), while the median score of the mRs was 2 (IQR: 1-3). We found that 34.8% of the patients were classified as FD+, according to the mRs. **Table 1** also compares the two groups (FD+ and FD-) and **Table 2** describes the results on the FIM scale, detailed according to item.

We also investigated the rehabilitation process. Only 30% of the patients reported having undergone some type of rehabilitation therapy during the period of their hospital stay, while 41% were referred to a rehabilitation service at hospital discharge. At

the time of the present evaluation, 41% had undergone rehabilitation therapy, including 40% receiving physical therapy, 11.6% speech therapy, 10% occupational therapy, 9.5% psychology and 7.4% nutritional monitoring. Of these patients, 44% underwent rehabilitation for more than 12 months, 25.3% for 3 to 12 months and 30.7% for less than 3 months. As many as 62.7% of the patients underwent rehabilitation twice a week, and the mean duration of their rehabilitation sessions was 65.2 minutes per week, with a range from 15 to 480 minutes.

Table 3 describes the comparison between patients with ischemic and hemorrhagic stroke. We also compared the same variables between males and females, and only found a significant difference in CES-D score (P = 0.005). Additionally, the results from the logistic regression analysis are shown in **Table 4**. The model was significant, categorizing 77.8% correctly. Lower NIHSS and CES-D scores were more associated with achieving functional independence.

Follow-ups on the patients were made using the mRs six months and one year after the patients had been included in the study. We were able to evaluate 82 patients after six months and 72 patients after one year. According to the mRs, after six months, 31.7% of the patients were classified as FD+, while after one year, 19.4% of patients were classified as FD+.

DISCUSSION

To the best of our knowledge, this is the first study to evaluate functional outcomes among stroke patients living in the community in the state of Alagoas, Brazil, and the relationship between demographic factors and clinical characteristics after stroke that leads to achievement of functional independence. A detailed analysis according to state and region is necessary in a country like Brazil with huge socioeconomic differences. Moreover, a recent study showed that Maceió has the highest stroke mortality rate and lowest human development index

Table 1. Demographic and clinical characteristics of all stroke patients and according to whether they were classified as presenting functional dependence or functional independence

Variables	All stroke patients (n = 190)	Patients with functional dependence* (n = 68)	Patients with functional independence* (n = 122)	P-value
Age (years)	60.02 ± 14.22	62.69 ± 1.71	58.56 ± 1.28	0.017#
Male (%)	117 (61.6%)	36 (52.9%)	81 (66.3%)	0.08
Schooling level	5.86 ± 4.44	5.22 ± 0.51	6.20 ± 0.41	0.14
Marital status (%)				
Married	116 (61.05%)	40 (58.8%)	76 (62.2%)	0.4
Single	37 (19.4%)	14 (20.5%)	23 (18.8%)	
Widowed	9 (4.7%)	1 (1.4%)	8 (6.5%)	
Divorced	28 (14.7%)	13 (19.1%)	15 (12.2%)	
Income (in minimum monthly wages)				
Up to 1	64 (33.7%)	19 (27.9%)	45 (36.8%)	0.3
2 to 3	84 (44.2%)	33 (48.5%)	51 (41.8%)	
> 3	17 (8.9%)	4 (5.8%)	13 (10.6%)	
Not declared	25 (13.2%)	12 (17.6%)	13 (10.6%)	
Stroke type				0.06
Ischemic	168 (88.4%)	66 (97%)	102 (83.6%)	
Hemorrhagic	16 (8.4%)	2 (2.9%)	14 (11.4%)	
Both	6 (3.1%)	0 (0%)	6 (4.9%)	
Risk factors				
Sedentary lifestyle (yes)	118 (62.1%)	48 (70.5%)	70 (57.3%)	0.004##
Smoking (yes)	40 (21.1%)	9 (13.2%)	31 (25.4%)	0.06
Alcohol consumption (yes)	59 (31.1%)	19 (27.9%)	40 (32.7%)	0.51
High blood pressure (yes)	150 (78.9%)	56 (82.3%)	95 (77.8%)	0.57
Diabetes mellitus (yes)	72 (37.9%)	25 (36.7%)	47 (38.5%)	0.87
Cardiopathy associated (yes)	48 (25.3%)	21 (30.8%)	27 (22.1%)	0.22
NIHSS	2 (IQR: 1-5)	5 (IQR: 1-7)	1 (IQR: 0-3)	0.0001#
CES-D	15.7 ± 11.6	18.88 ± 1.8	14.56 ± 1.05	0.008#
FIM total	99.1 ± 26.3	80.13 ± 3.22	113.8 ± 1.16	0.0001#

FIM = Functional Independence Measure; NIHSS = National Institutes of Health Stroke Scale; CES-D = Center for Epidemiological Studies – Depression Scale. *Functional dependence = patients with 3 to 5 points on modified Rankin scale; Functional independence = patients with 0 to 2 points on modified Rankin scale; IQR = interquartile range; #Mann-Whitney test: significance level < 0.05; ##χ^2 test: significance level < 0.05.

(HDI) of all the state capitals in northeastern Brazil,[6] which can directly influence the functional outcomes of stroke survivors.[12]

The mean time that had elapsed from the stroke to inclusion in the study was more than two years. This shows the difficulty that stroke patients have in accessing specialized neurovascular clinics after hospital discharge. This is largely because, in the whole state of Alagoas, there is only one center that specializes in monitoring stroke patients.

The CES-D is a screening tool for depression symptoms and its use in evaluating the emotional and cognitive status of stroke patients has been recommended by the National Institute of Neurological Disorders and Stroke (NINDS). A prevalence of depressive symptoms of 40% was found in our sample using the cutoff of 16 points, which was similar to findings from previous studies, in which prevalences of around 30%-40% were reported.[13-15] Post-stroke depression (PSD) is multifactorial,[16] and FD is one of its predictors.[15] Our sample was composed of chronic patients with higher levels of FD, which explains the high prevalence of PSD.

Two different scales for analyzing functionality were selected. The mRs is the primary outcome scale for almost all clinical trials[17,18] and is a validated instrument for assessing new stroke treatments.[9] Frequently, it is analyzed dichotomously (scores of 0-2 versus 3-6). However, some authors have argued in favor of using the entire range of the scale, which could improve its statistical power and enable a more detailed analysis of disability.[9,19,20] One negative point of the mRs is that it only has limited use in the field of rehabilitation, since this scale does not cover important aspects of rehabilitation, such as pain, communication and cognition.[21] Because of this, we also used the FIM to complement the mRs results.

We found high levels of FD (34.8%) in our sample. Another Brazilian study found FD of 33%, 30 days after the ictus; 12% after 1 year; 9% after 2 years; and 8% after 3 years.[8] Data from different countries have shown FD levels ranging from 20% to 52%.[22-24] Greater stroke severity at the initial presentation, cardioembolic and large strokes and absence of adequate treatment in the acute phase have previously been reported to be related to worse functional outcomes. In fact, few patients with ischemic stroke in Alagoas had access to thrombolysis or thrombectomy. In the public healthcare system of Alagoas, there is only one stroke center for acute-phase treatment, while in its private healthcare system, only a few hospitals have instituted a stroke protocol. Moreover, it is important to note that these hospitals are located in the state capital (city of Maceió), and patients from other cities in Alagoas need to come to the capital to have access to these treatments.

The lack of recommended treatments described in the literature, for the acute phase of stroke, partially explains the occurrences of FD. After hospital discharge, the rehabilitation process continues,

Table 2. Functional classification of stroke patients based on Functional Independence Measure (FIM) score*

Self-care	Functional dependence	Functional independence
Eating	76 (40%)	114 (60%)
Grooming	51 (26.8%)	139 (73.2%)
Bathing	58 (30.5%)	132 (69.5%)
Dressing – upper body	57 (30%)	133 (70%)
Dressing – lower body	60 (31.6%)	130 (68.4%)
Toileting	51 (26.8%)	139 (73.2%)
Sphincter control		
Bladder management	61 (32.1%)	129 (67.9%)
Bowel management	25 (13.2%)	165 (86.9%)
Transfers		
Bed/chair/wheelchair	57 (30%)	133 (70%)
Toilet	53 (28%)	137 (72%)
Tub/shower	53 (28%)	137 (72%)
Locomotion		
Walking/wheelchair	73 (38.4%)	117 (61.6%)
Stairs	102 (53.7%)	88 (46.3%)
Communication		
Comprehension	45 (23.7%)	145 (76.3%)
Expression	65 (34.2%)	125 (65.8%)
Social cognition		
Social interaction	61 (32.1%)	129 (67.9%)
Problem solving	96 (50.5%)	94 (49.5%)
Memory	87 (45.8%)	103 (51.2%)

*FIM score: 1 to 5 was classified as dependent, and 6 and 7 as independent.

Table 3. Comparison between patients with ischemic and hemorrhagic stroke

	Ischemic stroke (n = 168)	Hemorrhagic stroke (n = 16)	P-value
Age (years)	58.48 ± 2.08	52.75 ± 5.58	0.34
Schooling level	6.05 ± 0.58	9.25 ± 1.75	0.13
NIHSS	3 (1-5)	2 (1-4)	0.44
mRs	2 (1-3)	2 (1-2)	0.47
FIM	100.21 ± 3.07	115.5 ± 1.7	0.25
CES-D	15.4 ± 1.47	11 ± 4.34	0.32
Rehabilitation therapy (yes)	70 (41.6%)	4 (25%)	0.15
Duration of rehabilitation (min/per week)	69.57 ± 9.56	28.75 ± 7.73	0.02*

NIHSS = National Institutes of Health Stroke Scale; mRs = modified Rankin scale; FIM = Functional Independence Measure; CES-D = Center for Epidemiological Studies – Depression Scale.

*Mann-Whitney test: significance level < 0.05.

but less than half of these patients in Alagoas were referred to a rehabilitation service (41%). In the United States, more than two-thirds of stroke survivors receive rehabilitation after hospital discharge.[25] In Australia, a study investigated the hospitals that participated in the 2015 National Stroke Audit, and out of 3,462 patients, 39.2% receive post-acute rehabilitation, which was a proportion similar to that of our study. However, 71.3% of those patients were treated in a stroke unit, 6.1% received thrombolysis and 72.4% received rehabilitation during acute hospitalization, which may have influenced the functionality of these patients and may have explained why a smaller number of patients needed rehabilitation. In the city of João Pessoa, Paraiba, also in northeastern Brazil, 67.1% of the patients received rehabilitation after stroke.[26] Furthermore, in our study, few patients had access to speech therapy, occupational therapy or psychological care, which are fundamental for rehabilitation, since high levels of FD, in our sample, were related to poor levels of social cognition and poor levels of coping with activities of daily living.

In our study, we found that lower scores for NIHSS and CES-D were associated with functional independence after stroke. Higher stroke severity and greater numbers of depressive symptoms had already been pointed out in previous studies as potential barriers against achieving functional independence.[27-29] However, these results emphasize that there is a need for public policies in the state of Alagoas, for increasing access to treatment for the acute phase of stroke and rehabilitation.

Another important finding from our study was that the mean duration of rehabilitation sessions was 65.2 minutes per week, with a significant difference between ischemic and hemorrhagic stroke patients. Although hemorrhagic stroke has a worse prognosis, most patients in our sample were considered functionally independent (87.5%) and, at the time evaluated in our study, 25% of them underwent rehabilitation.

In comparing male and female patients, it was seen in our study that the females had higher prevalence of depressive symptoms (p = 0.005). In the literature, the relationship between sex and depression among stroke patients is not consistent. Some previous studies had already shown that female gender was an independent risk factor for PSD in the acute phase and subacute phase.[30,31] In addition, in the chronic phase, male gender was associated with depression.[32,33] However, in a meta-analysis, age at the time of the study and gender were not predictors of depression.[34]

The ideal amount of rehabilitation is still a matter for debate. The latest stroke rehabilitation guidelines recommend use of intensive and repetitive functional tasks for training gait and for diminishing upper-limb limitations (level 1A of evidence). However, the ideal dose and frequency have not been determined.[35] In the acute phase of stroke, high amounts (minutes per day) of mobilization have been shown to reduce positive functional outcomes, while increasing the daily frequency of out-of-bed sessions improved functional outcomes three months after stroke.[36] In the subacute and chronic phases of stroke, high intensities of rehabilitation were correlated with preventing recurrent stroke and mortality.[37] Also, increasing the total duration of physical therapy was associated with significant changes to motor FIM.[38] Other factors, such as socioeconomic factors, pre-existing comorbidities and the skill of the rehabilitation team, which were not investigated in the present study, may have had an influence on the functional outcomes of these patients and need to be better understood in samples of this nature.

CONCLUSION

We found a FD rate that was four times greater than what had been observed in another Brazilian study,[8] and this rate was associated with higher stroke severity and greater numbers of depressive symptoms. These results can be explained by the restricted access to treatment in the acute phase of stroke that is available in the state of Alagoas. Another important matter was the rehabilitation process, considering that less than half of the patients were referred to a rehabilitation service at hospital discharge and few had access to multidisciplinary treatment. Moreover, the time per week dedicated to the rehabilitation therapies was low. These results reflect the precarious organization of stroke care in Alagoas and raises

Table 4. Results from logistic regression analysis (dependent variable is mRs score of 0-2; FD-)

Independent variable	ß	SE	Wald	*df*	P	Odds ratio	95% CI
Age (years)	-0.12	0.016	0.53	1	0.46	0.98	0.95-1.02
Sedentary lifestyle (yes)	0.64	0.55	1.50	1	0.22	1.96	0.66-5.76
CES-D score	-0.38	0.019	4.17	1	0.04	0.96	0.92-0.99
NIHSS score	-0.52	0.10	25.68	1	0.0001	0.59	0.48-0.72
Constant	3.68	1.17	9.78	1	0.002	39.85	
Model X^2				54.25, *df* = 4, P = 0.0001			
Pseudo R^2				0.44			
N				144			
Hosmer and Lemeshow test (χ^2)				10.05, *df* = 8; P = 0.26			

mRs = modified Rankin scale; NIHSS = National Institutes of Health Stroke Scale; CES-D = Center for Epidemiological Studies – Depression Scale; SE = standard error, Wald = Wald statistics; Pseudo R^2 = Nagelkerke R square; *df* = degrees of freedom; CI = confidence interval.

questions about how this state's rehabilitation services are organized and whether treatments are being offered in accordance with international recommendations.

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Impact of super-spreaders on COVID-19: systematic review

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AUTHORS' KEY WORDS:
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ABSTRACT

BACKGROUND: Spreader and super-spreader are terms that refer to people who have greater potential for disease transmission, to infect other people.

OBJECTIVE: To present scientific evidence regarding the impact of COVID-19 spreaders.

DESIGN AND SETTING: Systematic review of the literature (using the PRISMA framework), performed at the Federal University of Santa Catarina (UFSC), Florianópolis (SC), Brazil.

METHODS: A search for articles was carried out in the SciELO, LILACS, PubMed, Scopus, Bireme and Web of Science databases. A search for gray literature was also conducted via Google Scholar. There was no restriction regarding place or language, and the search covered the period from January 2010 to August 2020. Studies were selected based on a combination of descriptors from the Medical Subject Headings (MeSH).

RESULTS: Isolated cases of people diagnosed with COVID-19 who were classified as super-spreaders were found. They had been classified thus because they may have had greater potential for infecting other individuals. However, greater numbers of interventions are needed in order to identify and manage COVID-19 cases. There is little evidence regarding this detection, which further hinders recognition and understanding of super-spreading events.

CONCLUSION: The scientific community needs greater depth of evaluation and understanding of how these patients physiologically develop the ability to propagate COVID-19 more intensely. A simpler way of tracking them is also necessary, given that many infected people are asymptomatic. Many patients also have mild symptoms, suggesting that these individuals could also be classified as possible COVID-19 spreaders.

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INTRODUCTION

The coronavirus is a zoonotic virus in the *Coronaviridae* family, a type of viruses that cause respiratory infections, first described in 1965. It is thus named due to its profile, which resembles a crown under a microscope.[1] People diagnosed with COVID-19 usually develop signs and symptoms that include mild respiratory problems and persistent fever, on average five to six days after infection.[1] The symptoms normally begin with fever in combination with a dry cough and fatigue, potentially leading to respiratory difficulties.[2]

Spreader and super-spreader are terms that refer to people with a propagation potential greater than the average (i.e. one person propagates to another three), to infect other people.[3] It is believed that about 10% of the cases of COVID-19 may be responsible for up to 80% of the propagation, which can be attributed to super-spreaders.[3]

The known characteristics of COVID-19 that cause concern in super-spreading events include the number of pneumonia cases relating to COVID-19, the existence of person-to-person transmission, the mean age of 61 years among individuals infected and the possibility that asymptomatic people may be an important source of infection.[4] Furthermore, the presence of super-spreaders was previously reported during the courses of the severe acute respiratory syndrome (SARS) and Middle East respiratory syndrome (MERS) pandemics.[5]

COVID-19 has been pronounced to be a pandemic global health emergency by the World Health Organization.[6,7] It has already killed more than 680,000 people, among the more than 17 million confirmed cases worldwide.[7] Hence, understanding the physiology of such spreaders and controlling over-propagation is essential, in order to be able to combat the pandemic and, especially, understand the mechanisms through which the numbers of cases in different populations are accelerated.[8]

OBJECTIVE

The main guiding objective of this study was to ascertain the impact of super-spreaders on COVID-19, so as to answer the following question: What is the impact of super-spreaders on the propagation of COVID-19?

METHODS

Protocol

This systematic review was carried out following the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) framework.[9] Scientific articles were searched by two independent researchers in the MEDLINE (PubMed), LILACS, SciELO, Scopus, Web of Science and BIREME databases, with no language or place restrictions. The search covered the period from January 2010 to August 2020. Additionally, a manual search was conducted on the references of the articles that had been included through the database search, along with a search for gray literature using Google Scholar.

The search was structured and organized based on the PICOS framework – an acronym for target Population, Intervention, Comparison, Outcomes and Study type. The population of interest or health problem (P) corresponds to the patients; intervention (I) concerns the intervention applied; comparison (C) refers to the spreaders; outcome (O) refers to COVID-19; and the study types (S) included in the review encompassed descriptive studies, cross-sectional studies, observational studies, case reports, case-control studies, controlled clinical trials and cohort studies (**Table 1**).

Search strategy

The descriptors were selected based on the Health Sciences Descriptors (DeCS) and Medical Subject Headings (MeSH), given their wide usage by the scientific community to index articles in the PubMed database. After the search for descriptors, the search in the other databases was adjusted. The following combination, with its Boolean operator, was firstly proposed for the search: [(covid 19) AND (spreaders)]. This search was concentrated on August 2020.

Table 1. Description of the PICOS components

Acronym	Definition
P	Spreaders
I	COVID-19
C	Transmission
O	Disease
S	Cross-sectional studies Observational studies Case reports Case-control studies Controlled clinical trials Cohort studies

Eligibility criteria

The study designs included in the search were descriptive studies, cross-sectional studies, observational studies, case reports, case-control studies, controlled clinical trials and cohort studies. They were included with no restriction of language or place, and the search covered articles published from January 2010 to August 2020. The inclusion and exclusion criteria for this search are shown in **Table 2**.

Risk of bias

The quality of the methodology used in the studies included in the review was independently assessed by the reviewers (APSR and LFG), as recommended by PRISMA.[9] The assessment gave priority to clearly described information. At this point, the review was blind, masking the authors' and journals' names to avoid any potential bias and conflict of interests.

Exclusion criteria

Studies published as letters to the editor, guidelines, literature reviews, narrative reviews, systematic reviews, meta-analyses and abstracts were excluded. Studies with unclear, unavailable or no descriptions were also excluded (**Table 2**).

Data analysis

The data for the eligibility process were extracted and collated in a spreadsheet designed for systematic reviews that had been developed in the Excel software, version 16.0 (Microsoft, Redmond, WA, United States). This was done by two researchers: the extracted data were initially entered by one of the researchers, and then checked by the other one.

Table 2. Summary of the inclusion and exclusion criteria

Inclusion criteria	
Design	Cross-sectional studies Observational studies Case reports Case-control studies Controlled clinical trials Cohort studies
Place	No restriction
Language	No restriction
Exclusion criteria	
Design	Letters to the editor Guidelines Reviews of the literature Systematic reviews Narrative reviews Meta-analyses
Studies	Unclear studies Poorly described or inadequate studies
Type of publication	Abstract only

Study selection method

Initially, the eligibility reviewers (APSR and LFG) were calibrated by PH, KMP and AIG to conduct the systematic review. After this process and after having any queries answered, the two eligibility reviewers (APSR and LFG) independently examined the titles and abstracts. Articles in which the title was on-topic but for which no abstract was available were also obtained and analyzed in full. Afterwards, the eligible studies were obtained and assessed in full. In specific cases, when a potentially eligible study presented incomplete data, it was envisaged that the authors of that study could be contacted via e-mail for further information. However, in the end, this measure was not necessary. When the reviewers disagreed, a third one (PH or KMP) was involved in the final decision.

Data collected

After the screening, the texts of the articles thus selected were reviewed and data were extracted by two authors (APSR and LFG) in a standardized manner under supervision by the other four (KMP, PH, AIG and CRH). The following information was identified: year of publication, place where the study was conducted, language of publication, type of study, sample, method, result and conclusion of the study.

Clinical result

The clinical result of interest consisted of ascertaining the impact of super-spreaders on COVID-19. Articles in which this approach was not used were not included in the sample for this review of the literature. The analysis of the present study was particularly limited by the rather small number of published articles addressing this topic that were retrieved. A limited number of patients were included in these articles. The fact that few articles had addressed this topic suggests that it is an innovative one that requires further studies with a larger sample size, in order to ascertain the real significance of super-spreaders.

RESULTS

Based on the descriptors that had been chosen, the scientific databases were consulted. The results thus obtained are presented in **Table 3**.

Initially, 41 articles were selected, which decreased to 37 after excluding the repeated ones. The titles and abstracts were then analyzed and 33 papers were excluded because they were not directly related to the topic proposed for investigation here. Hence, four articles were admitted for the final analysis, in which they were evaluated in full by the reviewers. These articles were designed as descriptive studies, cross-sectional studies and case reports (**Figure 1**).

The main characteristics extracted from each of the articles included in this review are described in **Table 4**.

Li et al.[10] analyzed the clinical and transmission characteristics of 25 cases of COVID-19 in a department of thoracic surgery, in order to better define these characteristics. Out of the 25 cases analyzed, 13 were men and 12 were women; these patients' mean age was 61 years. No information was obtained on how transmission occurred in that environment. Nevertheless, among the 25 cases observed, one individual proved to be a super-spreader who possibly infected another 11 people.

Zhang et al.[11] analyzed 135 cases in the city of Tianjin, among which 72 were men and 63 were women. They identified one case of a super-spreader who caused six infections. This analysis revealed heterogeneity in COVID-19 transmission.

Lin et al.[8] aimed specifically to understand super-spreading events (SSE) and identify the reasons behind the super-spreader's capacity for transmission. They analyzed a case in which one person infected another 28 people.

Xu et al.[12] stated that greater interventions would be necessary in order to identify and manage cases of COVID-19, given that the barriers preventing their detection reman large. This also makes it difficult to recognize super-spreading events. They reached this

Table 3. Classification of the references obtained from the PubMed, SciELO, LILACS, Web of Science and Scopus databases

Descriptors	Number of articles	References excluded	Reason	References selected	Database
[(covid 19) AND (spreaders)]	24	22	Excluded based on the title (15); excluded based on the abstract (4); duplicated (3).	2	PubMed
[(covid 19) AND (spreaders)]	17	15	Excluded based on the title (8); excluded based on the abstract (6); duplicated (1).	2	LILACS
[(covid 19) AND (spreaders)] [(covid 19) AND (espalhadores)]	-	-	-	0	SciELO
[(covid 19) AND (spreaders)]	-	-	-	0	Web of Science
[(covid 19) AND (spreaders)]	-	-	-	0	Bireme
[(covid 19) AND (spreaders)]	-	-	-	0	Scopus
Total	41	37		4	LILACS and PubMed

conclusion through an analysis on 643 transmission groups that were reconstructed from 9,120 cases of COVID-19 in China. Among these cases, 34 individuals were identified as super-spreaders.

Li et al.[10] also reported that it was important that measures to combat COVID-19 should encompass protective measures to avoid hospital infection, given that chronic obstructive pulmonary disease (COPD) has been found to be a risk factor for worsening the condition of people infected with COVID-19, with a likely scenario of poor prognoses and deaths.

Zhang et al.[11] stated that it was not possible to identify the underlying factors contributing to super-spreading. Studies going into greater detail would be required, considering that identifying these contributory factors was of immense importance in developing measures aimed at controlling the pandemic.

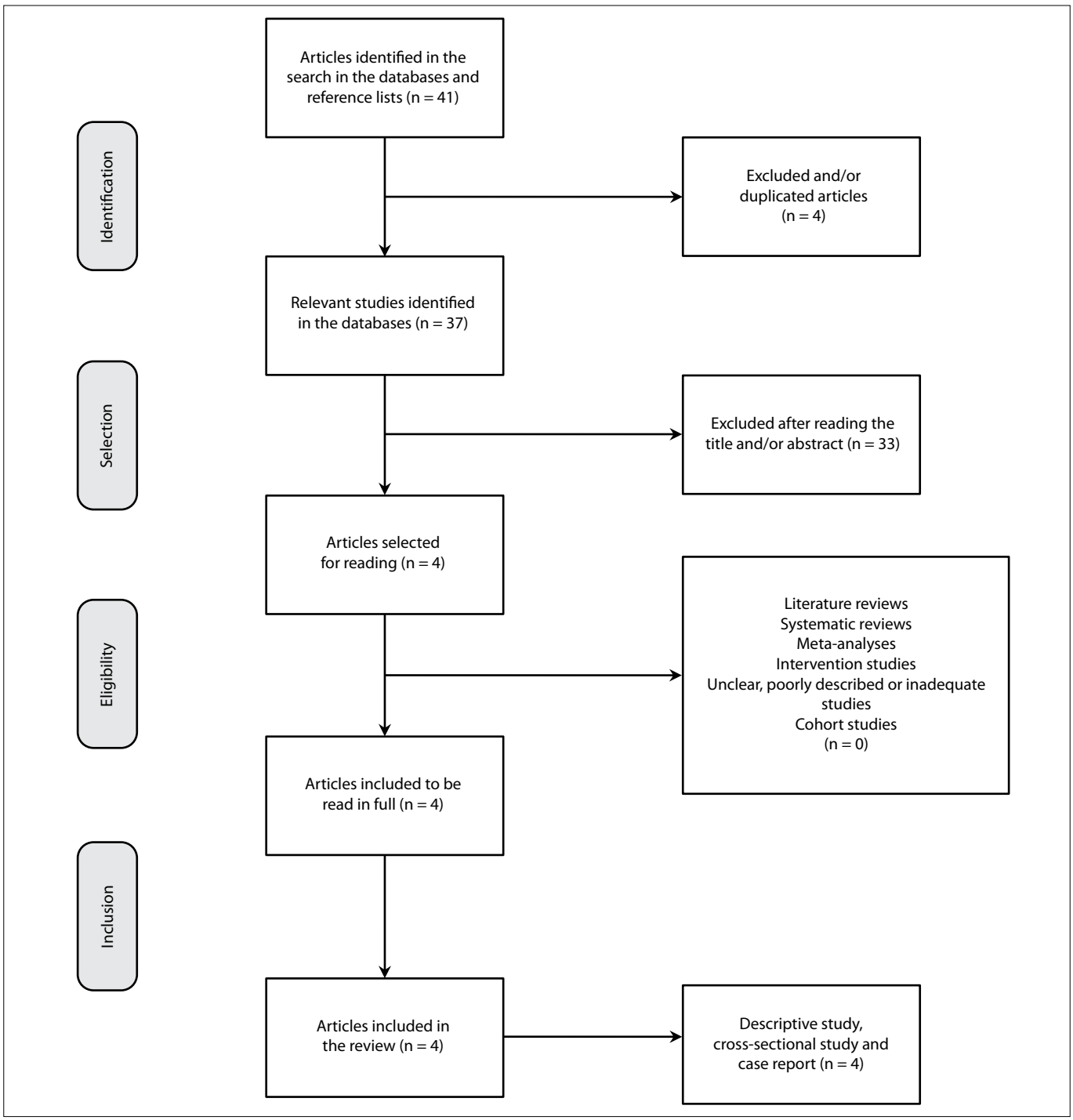

Figure 1. Flowchart of the search for articles and their analysis.

Lin et al.[8] reported with regard to super-spreaders that, although their case was an isolated one, they had managed to identify some general characteristics that are probably present among super-spreaders. These characteristics would include the following: 1) having a high viral load; 2) taking longer to eliminate the virus; 3) not necessarily having a serious condition; and 4) probably being active in social events, with greater chances of being in contact with many people within a short time.

DISCUSSION

Studies and research on the subject of super-spreading are still scarce due to the difficulty in isolating such findings. This review made it possible to see that there are various perceptions of the characteristics of a super-spreader. Some authors have stated that a super-spreader can be any person with a contamination power greater than the average (contaminating three people),[11] whereas others have stated that an individual can only be considered to be a super-spreader when he or she infects more than 10 other people.[12]

Several issues relating to the form of propagation can be highlighted. Firstly, this needs to be in contact with many people, which suggests that participation in a social event is required in order to give power to these contacts. Moreover, it can be supposed that this person has a high viral load, while not necessarily having a serious condition because of their COVID-19 contamination, and will take longer to eliminate the virus.

Table 4. Synthesis of the articles included

Author, year and country	Objective	n	Results	Conclusion
Li et al., 2020, China[10]	To analyze clinical and transmission characteristics of 25 cases of COVID-19 in a thoracic department.	25 people diagnosed with COVID-19.	76% of the cases of COVID-19 were confirmed through a positive COVID-19 nucleic acid test, and 6 cases (24%) were considered suspicious and were diagnosed as presenting clinical manifestations. Greater age and presence of chronic obstructive pulmonary disease (COPD) were significantly associated with the seriousness of the disease and deaths among patients with COVID-19. One possible super-spreader was found, given that 11 people who had been in contact with this person tested positive for COVID-19.	COVID-19 is associated with poor prognosis for patients undergoing thoracic surgery, especially those with COPD. Also, implementing comprehensive protective measures is important for controlling hospital infection.
Zhang et al., 2020, China[11]	To analyze COVID-19 transmission and its underlying causes.	135 inhabitants of the city of Tianjin who had been diagnosed with COVID-19.	135 cases in the city of Tianjin were included in the study. One super-spreader, who infected 6 people in the city, was identified. Based on simulations, the outbreak in Tianjin might have caused 165 infections, had control measures not been implemented in January.	The analysis suggests that heterogeneous COVID-19 transmission may result in a super-spreading event. Further study is necessary in order to verify the heterogeneity of this transmission in other populations and the contributing factors. These matters are crucial for development of measures to contain the pandemic.
Xu et al., 2020, China[12]	To obtain more detailed data involving domestic configurations, in order to have a better understanding of COVID-19 transmission dynamics, based on reconstruction of a database.	643 transmission groups, reconstructed based on 9,120 cases of COVID-19 in China. Out of these, 34 cases were identified as super-spreaders.	34 primary cases were identified as super-spreaders, with 5 super-spreading events within families. The risk of being infected outside the home was greater for people aged 18 to 64 years, whereas the risk of infection at home was greater for younger and older people.	Greater numbers of interventions in COVID-19 transmission are required, given the barriers against identifying and managing the cases, which are due to the non-negligible frequency of super-spreading events.
Lin et al., 2020, China[8]	To understand super-spreading events and the reasons behind the efficiency of their transmission capacity, based on a case report.	A specific case of one super-spreader.	The super-spreader reported in this case infected 28 people, among whom one was asymptomatic. These 28 people infected another 49, among whom 10 cases were asymptomatic.	It can be suggested that a super-spreader may have the following characteristics: 1) having a high viral load; 2) taking longer to eliminate the virus; 3) not necessarily being a seriously ill patient; and 4) being active in social activities and having the chance to be in contact with many people in a short time.

COVID-19 = coronavirus; COPD = chronic obstructive pulmonary disease.

Various cases of asymptomatic contaminated individuals who are less likely to transmit the virus have already been reported. However, it is still difficult to establish a process through which the contamination can be identified and controlled.[3] There have also been reports of people whose first test came out negative but who were diagnosed with COVID-19 in the retest.[3]

Cave[3] considered that use of the term super-spreader was problematic because it could put blame on the people who were supposedly causing this greater propagation, thus hindering identification of cases for scientific analysis. Furthermore, the term may have different meanings in given contexts. In the initial stage of a pandemic, it is mainly focused on people who have contact with many others, as stated in one of the studies examined in this analysis (Lin et al.[8]). At other stages of the pandemic, this may not make so much sense (for instance, in a situation of social isolation and distancing).

Early diagnosing of COVID-19 is essential for controlling its dissemination. Countries like New Zealand managed to control the pandemic, through eliminating community transmission with strategies such as large-scale testing to track and quickly detect cases and implementation of lockdowns, border controls and actions to promote health education. China also rapidly implemented measure for detection of COVID-19, which involved isolated of cases and tracking of all individuals with whom the cases had been in contact with, while always providing good clinical care for infected people.[13]

With regard to COVID-19 treatment, there is still no evidence to prove the effectiveness of some of the medications that have been considered for such treatments, such as hydroxychloroquine and azithromycin. According to Vieira et al.,[14] it has been hypothesized that these medications can change the course of the disease, through decreasing morbidity and more quickly diminishing the viral load. However, because there is no scientific proof, physicians should only use these treatments if patients explicitly agree to this, by signing an informed consent form.

Jayawardena et al.[15] published a clinical trial on viral diseases in which they sought to identify nutritional factors that might influence treatment and control of COVID-19. They identified potential benefits from use of vitamins (A and D), especially in populations that lacked them. In addition to vitamin supplementation, use of trace elements (selenium and zinc) was found to be effective for immunomodulation against respiratory viral infections. Some nutraceuticals and probiotics may also have a role in increased immunological functions, and micronutrients have been shown to be beneficial for older adults with nutritional deficiency. Hence, vitamins, trace elements, nutraceuticals and probiotics have been identified as beneficial for combating viral infections. They may therefore be useful in the effort to prevent and manage COVID-19.

On the other hand, Bomfim and Gonçalves[16] evaluated food supplements for controlling aggravated COVID-19 infection or its spread. They concluded that there was no scientific evidence to show that substances could have a role in controlling this disease, given that only some food supplements proved to be effective (and only rather weakly) in treating specific symptoms of this disease.

CONCLUSION

The results from these studies suggest that there is some difficulty in detecting COVID-19 super-spreaders, considering that many infected people are asymptomatic. Because of this great likelihood that the symptoms of COVID-19 will only be mild, the disease tends to be itself super-spreading. Another factor that also hinders detection of super-spreader individuals is that the term super-spreader is often incorrectly used. People who are in contact with larger numbers of other people are inevitably more likely to infect more individuals than are those who have contact with few or no people. However, this does not mean that someone who has infected more people has the biological characteristics that demonstrate greater potential to contaminate other people – which is what would identify this individual as a super-spreader.

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Performance of the Pandemic Medical Early Warning Score (PMEWS), Simple Triage Scoring System (STSS) and Confusion, Uremia, Respiratory rate, Blood pressure and age ≥ 65 (CURB-65) score among patients with COVID-19 pneumonia in an emergency department triage setting: a retrospective study

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STSS.
Triage scores.

ABSTRACT

BACKGROUND: Healthcare institutions are confronted with large numbers of patient admissions during large-scale or long-term public health emergencies like pandemics. Appropriate and effective triage is needed for effective resource use.

OBJECTIVES: To evaluate the effectiveness of the Pandemic Medical Early Warning Score (PMEWS), Simple Triage Scoring System (STSS) and Confusion, Uremia, Respiratory rate, Blood pressure and age ≥ 65 years (CURB-65) score in an emergency department (ED) triage setting.

DESIGN AND SETTING: Retrospective study in the ED of a tertiary-care university hospital in Düzce, Turkey.

METHODS: PMEWS, STSS and CURB-65 scores of patients diagnosed with COVID-19 pneumonia were calculated. Thirty-day mortality, intensive care unit (ICU) admission, mechanical ventilation (MV) need and outcomes were recorded. The predictive accuracy of the scores was assessed using receiver operating characteristic curve analysis.

RESULTS: One hundred patients with COVID-19 pneumonia were included. The 30-day mortality was 6%. PMEWS, STSS and CURB-65 showed high performance for predicting 30-day mortality (area under the curve: 0.968, 0.962 and 0.942, respectively). Age > 65 years, respiratory rate > 20/minute, oxygen saturation (SpO_2) < 90% and ED length of stay > 4 hours showed associations with 30-day mortality ($P < 0.05$).

CONCLUSIONS: CURB-65, STSS and PMEWS scores are useful for predicting mortality, ICU admission and MV need among patients diagnosed with COVID-19 pneumonia. Advanced age, increased respiratory rate, low SpO_2 and prolonged ED length of stay may increase mortality. Further studies are needed for developing the triage scoring systems, to ensure effective long-term use of healthcare service capacity during pandemics.

INTRODUCTION

Coronavirus disease 2019 (COVID-19), which is caused by severe acute respiratory syndrome coronavirus-2 (SARS-CoV-2), first appeared in several pneumonia cases of unknown etiology in Wuhan, China, in December 2019.[1,2] It was declared to be a pandemic by the World Health Organization (WHO) because it affected all countries within a short time. COVID-19 infection has been reported over a broad clinical spectrum, ranging from mild symptoms to severe acute respiratory distress syndrome, multiple organ dysfunction syndrome or even death.[3] Traditional public health measures have been found to be inadequate for preventing it[4] and no disease-specific treatment or vaccine has yet become available. According to the World Health Organization, more than 18 million cases and approximately 700,000 deaths have been reported.[5]

The increasing numbers of COVID-19 cases worldwide places a heavy burden on healthcare systems in many countries.[6] Healthcare institutions are suddenly confronted with large numbers of patient applications during large-scale or long-term public health emergencies such as pandemics. Moreover, such situations may cause difficulties with regard to medical resources and workforces.[7]

For this reason, it is essential to make the best use of opportunities in pandemics. During a pandemic, the most crucial issue consists of efficient use of capacity with good coordination in response to increasing demand.[8] The best way to use resources effectively during a pandemic is

to conduct appropriate triage.[9] Since it is impossible to know when the next pandemic will occur, the problems experienced during current pandemic periods need to be defined. In addition, the most appropriate triage method should be determined. There is a need for objective and reliable scoring systems that can predict disease progression at the time when patients arrive and guide physicians to decide whether to admit or discharge them.

The Confusion, Uremia, Respiratory rate, Blood pressure and age ≥ 65 years (CURB-65) score has been used as a safe predictor of 30-day mortality among patients with pneumonia for many years.[10] It also helps clinicians in making the decision to admit or discharge such patients.

The Pandemic Medical Early Warning Score (PMEWS), developed by Challen et al. for use in cases of influenza pneumonia, evaluates the patients' social and physiological parameters.[11] This pandemic score was developed by adding age, social isolation, chronic disease and performance status to the patient's vital parameters. In a comparison between the PMEWS and the CURB-65 score, the PMEWS performed better regarding assessment of the need for intensive care unit (ICU) admission and hospitalization, but lagged behind the CURB-65 score for predicting mortality.[11]

Talmor et al. developed the Simple Triage Scoring System (STSS) with the aims of enabling efficient resource use and identifying critically ill patients during a pandemic, but stated that it still needed modification and validation.[12] Adeniji et al. reported that the STSS could predict mortality and the use of critical care resources in situations of pandemic influenza.[13]

Like in the CURB-65 score, age, altered mental status and vital parameters are used in the STSS. Unlike in the CURB-65 score, no laboratory results are used either in the PMEWS or in the STSS. The different characteristics of these scoring systems enable evaluation of patients and fast decision-making in the triage setting, regarding admission.

OBJECTIVE

To our knowledge, there are not enough studies on triage scores relating to COVID-19. The aim of this study was to evaluate the performance of the Pandemic Medical Early Warning Score, Simple Triage Scoring System and Confusion, Uremia, Respiratory rate, Blood pressure and age ≥ 65 score for predicting intensive care unit admission, mechanical ventilation (MV) need and 30-day mortality among patients with COVID-19 pneumonia, and whether these are useful scoring systems.

METHODS

Study design

This was a retrospective and observational study. After obtaining approval from the local ethics committee (approval ID: 2020/85; June 1, 2020), patients diagnosed with COVID-19 pneumonia in our hospital's emergency department (ED) between March 11, 2020, and June 11, 2020, were included. Patient data were obtained from the hospital's electronic database and from the records of the hospital's ED.

This study was conducted in the ED of a tertiary-level university hospital, which receives approximately 75,000 patient admissions annually. The patients were followed up in six-bed pandemic tents or in two-bed isolation rooms within the 15-bed emergency department, and sampling was carried out there. On admission, swab samples were taken from the nasopharynx and oropharynx using the same stick.

Demographic information (age, gender and comorbidities), smoking status, complaints at the time of admission, vital values on admission (fever, pulse, respiratory rate, blood pressure, oxygen saturation and shock index), computed tomography results, emergency department and hospital length of stay (LOS), 30-day mortality, mechanical ventilation need and ICU admission were recorded on the study forms. The CURB-65, PMEWS and STSS scores were calculated.

Participants and measurements

Adult patients over 18 years old with real-time polymerase chain reaction (RT-PCR) positivity in samples taken to detect COVID-19 infection were included (n = 111). Patients whose data could not be accessed (n = 3), those referred by another center (n = 5) and those diagnosed with COVID-19 in another clinic (n = 3) were excluded. For patients with more than one RT-PCR test, the results from the tests done on admission were evaluated. Swab samples taken using plastic-coated sticks were sent to the laboratory in a viral transport medium. PCR testing was performed using a SARS-CoV-2 quantitative RT-PCR detection kit (Bioeksen R&D Technologies, Istanbul, Turkey) and Montania RT-PCR instruments (Anatolia Geneworks, Istanbul, Turkey).

Other studies in the literature[12,13] were used to determine the minimum sample size to be included in the present study. Accordingly, the minimum number of individuals, sampled at 80% statistical power with a 95% confidence interval and 5% type 1 error, was determined as 100.

In determining the CURB-65 score, each of the following parameters was calculated as one point: presence of confusion, blood urea nitrogen (BUN) > 19 mg/dl, respiratory rate ≥ 30 breaths/minute, systolic blood pressure < 90 mmHg or diastolic blood pressure ≤ 60 mmHg and age ≥ 65 years.[10] The CURB-65 score can range from 0 to 5 and was interpreted thus: patients with scores of 0 or 1 point can be discharged; 2 points should be admitted or kept under observation for a while; and ≥ 3 points must be admitted and the need for ICU admission must be considered.

For PMEWS, respiration rate, oxygen saturation, heart rate, systolic blood pressure, fever, consciousness level, age, social isolation, history of chronic disease and daily activity performance status were examined.[11] The patients' physiological values are scored between 0 and 3. However, for patients older than 65 years, one additional point is given, and there is one further point for social isolation status or chronic disease, or for performance status > 2.

The STSS score was calculated from the patients' vital parameters, shock index and age. The presence of respiratory rate > 30 breaths/minute, shock index (heart rate/systolic blood pressure) > 1, low oxygen saturation (SpO_2 < 90%), altered mental status (Glasgow Coma Scale, GCS < 15) and age > 65 years were each scored as one point.[12] The scores were interpreted thus: 0 or 1 point represented a mild risk of mortality; 2 points, medium risk; and ≥ 3 points, high risk.

Outcome

The primary outcomes of this study were the patients' performances relating to all three scores, for predicting all-cause 30-day mortality, ICU admission and mechanical ventilation need. The secondary outcomes were the effects from the patients' vitality on admission, demographic characteristics and hospital emergency department length of stay, in relation to mortality.

Data analysis

Descriptive statistics were presented as numbers and percentages. Numerical variables were summarized as the mean ± standard deviation or median (with interquartile range). The independent t test and Mann-Whitney U test were used to compare the groups according to distributions. The receiver operating characteristic (ROC) curve and the area under the ROC curve (AUC) with 95% confidence intervals were used to assess the accuracy of each score. Pearson's chi-square test and Fisher's exact test (when the expected number was less than five) were used for categorical variables. The statistical analyses were performed using the SPSS software for Windows, version 22 (IBM, Chicago, IL, United States). P < 0.05 was considered significant.

RESULTS

In total, 100 patients were included in the study. The patients' median age was 50.78 ± 16.75, and 54% of the patients were women. The RT-PCR results were positive for all the patients included in this study. The mortality rate among the patients included in this study was 6%, and all of the patients who died had been admitted to the intensive care unit. The mortality rates among patients with comorbid diseases and mechanical ventilator need were significantly higher (P < 0.05). Thoracic computed tomography imaging was performed on 90% of the patients. Mortality was not observed among the patients who did not undergo computed tomography imaging because their complaints were mild (n = 10), or among the patients whose imaging examinations did not show any pathological findings (n = 13). The distribution of the patients' clinical characteristics, symptoms, pathological computed tomography (CT) findings, mechanical ventilation need and hospitalization/discharge outcomes, in relation to 30-day mortality, is shown in **Table 1**.

In evaluating vital factors on admission, significant relationships with mortality were only found in relation to respiratory rate and oxygen saturation (P < 0.05). No significant relationship was found between mortality and other vital factors. There were significant relationships between advanced age and mortality and between prolonged emergency department length of stay and mortality (p < 0.05). Advanced age (> 65 years), increased respiratory rate (> 20/minutes), low SpO_2 (< 90%) and prolonged ED length of stay (> 4 hours) significantly increased mortality (P = 0.02, P = 0.02, P < 0.001 and P = 0.02, respectively). The relationships of patients' age, vital factors on admission, shock index and emergency department and hospital length of stay with mortality are shown in **Table 2**.

Significant relationships were found between all the PMEWS, CURB-65 and STSS scores and mortality, intensive care unit admission and mechanical ventilation need (P < 0.001). The mortality

Table 1. Distribution of patients' clinical characteristics, symptoms, pathological computed tomography findings, mechanical ventilation need and hospitalization/discharge outcomes, in relation to 30-day mortality

	n = 100	30-day mortality		P
		Yes	No	
Female	54	4	50	0.684
Comorbid disease	43	6	37	**0.005**
Smoking habit	19	1	18	1.0
Symptoms				
Fever	29	4	25	0.057
Cough	52	4	48	0.679
Dyspnea	15	2	13	0.220
Myalgia	15	1	14	1.0
Sore throat	7	0	7	1.0
Diarrhea	2	1	1	0.117
Loss of taste	3	0	3	1.0
Loss of smell	1	0	1	1.0
Headache	2	0	2	1.0
Asymptomatic	24	0	24	0.331
Pathological CT findings	77	6	71	0.385
Need for MV	15	6	9	**< 0.001**
Hospitalization/discharge outcomes				
Discharge	40	0	40	**< 0.001**
Ward admission	50	0	50	
ICU admission	10	6	4	

CT = computed tomography; MV = mechanical ventilation; ICU = intensive care unit.

P < 0.05 was considered statistically significant.

rates were found to be significantly higher when these scores were higher. These relationships are shown in **Table 3**.

Performance in predicting 30-day mortality was high, through using all three scores. The areas under the curve for PMEWS, CURB-65 and STSS were 0.968, 0.942 and 0.962, respectively. The sensitivity was 100% and the specificity was 81% for PMEWS ≥ 3. The sensitivity was 83% and the specificity was 93% for STSS ≥ 1.

Performance in predicting ICU admissions was high, through using all three scores. The areas under the curve for PMEWS, CURB-65 and STSS were 0.941, 0.898 and 0.878, respectively. The PMEWS had the highest result. The sensitivity was 80% and the specificity was 95% for PMEWS ≥ 5. The STSS score sensitivity was 90% and the specificity was 72% for predicting ICU admission.

Performance in predicting mechanical ventilation needs was high, through using all three scores. The areas under the curve for PMEWS, CURB-65 and STSS were 0.854, 0.867, and 0.820, respectively. The specificities for PMEWS ≥ 5 and CURB-65 ≥ 1 were 96% and 95%, respectively. The sensitivity for STSS ≥ 1 was 80%.

The performance of the scoring systems in predicting mortality, ICU admission and mechanical ventilation needs, in terms of their sensitivity, specificity, positive and negative predictive values and positive and negative likelihood ratios, are shown in **Table 4**. The receiver operating characteristic curves of the scores are shown in **Figure 1**.

DISCUSSION

It is essential to differentiate severe cases from mild cases at an early stage in situations of major global health problems such as pandemics. Effective triage on admission will prevent unnecessary hospitalizations and resource use.

We concluded that the PMEWS, CURB-65 and STSS scores successfully predicted patients' 30-day mortality, ICU admissions, and mechanical ventilation needs (P < 0.001). While the sensitivity for mortality shown by scores of PMEWS ≥ 3, STSS ≥ 1 and CURB-65 ≥ 1 were 100%, 83.3% and 83.3%, respectively, their specificities were 81.91%, 93.62% and 90.43% (P < 0.001). Accordingly, scores ≥ 3 from PMEWS were most sensitive for triage, whereas STSS ≥ 1 was most specific in predicting mortality among patients with COVID-19 pneumonia. The areas under the

Table 3. Comparison of the Pandemic Medical Early Warning Score (PMEWS), Confusion, Uremia, Respiratory rate, Blood pressure and age ≥ 65 (CURB-65) score and Simple Triage Scoring System (STSS) score, in relation to mortality, intensive care unit (ICU) admission and need for mechanical ventilation (MV)

	30-day mortality		P	ICU admission		P	Need for MV		P
	Yes	No		Yes	No		Yes	No	
PMEWS									
0-3	0	77		1	76		5	72	
4	1	6		1	6		1	6	
5	0	4		0	4		0	4	
6	0	3		1	2		1	2	
7	1	2	< **0.001***	2	1	< **0.001***	3	0	**< 0.001***
8	1	2		2	1		2	1	
12	1	0		1	0		1	0	
13	1	0		1	0		1	0	
14	1	0		1	0		1	0	
CURB-65									
0	0	62		1	61		2	60	
1	1	23		1	23		3	21	
2	2	7	< **0.001***	4	5	< **0.001***	6	3	**< 0.001***
3	1	2		2	1		2	1	
4	2	0		2	0		2	0	
STSS									
0	0	66		1	65		3	63	
1	1	22		3	20		5	18	
2	1	5	< **0.001***	2	4	< **0.001***	2	4	**< 0.001***
3	2	1		2	1		3	0	
4	2	0		2	0		2	0	

*P < 0.05 was considered statistically significant.

Table 2. Factors affecting mortality among COVID-19 pneumonia patients

	30-day mortality		P	All patients
	Yes	No		
Age[a] (year)	72.67 ± 15.73	49.38 ± 15.89	**0.001***	50.78 ± 16.75
SBP[b] (mmHg)	114.5 (89.5-141.5)	125 (117.75-140)	0.225**	125 (116.25-139.75)
DBP[a] (mmHg)	66.5 ± 13.47	75.83 ± 13.56	0.105*	75.27 ± 13.67
Heart rate[b] (beats/min)	90 (78.25-112.5)	88 (78.75-99.5)	0.566**	88 (79.0-100.5)
Respiratory rate[b] (breaths/min)	20 (14-27)	14 (14-16)	**0.028****	14 (14-16)
SpO_2[b] (%)	86.5 (57.5-93.25)	96 (94-98)	**0.002****	96 (94-98)
Fever[b] (°C)	36.15 (36.07-38.72)	36.8 (36.27-37.4)	0.541**	36.8 (36.2-37.4)
Shock index[b]	0.74 (0.65-1.1)	0.67 (0.59-0.77)	0.117**	0.67 (0.60-0.77)
LOS in ED[b] (hour)	5.5 (2.75-6.25)	3 (2-4)	**0.039****	3.0 (2-4)
LOS in hospital[b] (day)	6 (2.75-11)	4.5 (0-8)	0.186**	4.5 (0-8)

[a]mean ± standard deviation; [b]median (interquartile range); *independent t test; **Mann-Whitney U test.
SBP = systolic blood pressure; DBP = diastolic blood pressure; SpO_2 = oxygen saturation; LOS = length of stay; ED = emergency department; P < 0.05 was considered statistically significant.

curve for PMEWS ≥ 3, STSS ≥ 1 and CURB-65 ≥ 1 were determined as 0.968, 0.962 and 0.942, respectively. Therefore, we can say that all three scores can be used with high reliability for triage of COVID-19 pneumonia.

Whereas in our study PMEWS ≥ 3 showed high accuracy for predicting mortality, Ebrahimian et al. recommended that patients should be admitted to hospital when PMEWS ≥ 4.[14] Gray et al. reported that use of the PMEWS was beneficial in the prehospital period.[15] Although this score has not been evaluated among COVID-19 patients in any other studies, it has been stated that PMEWS could be used successfully among pandemic influenza patients.[11] Hence, we can say that it can be used in all triage settings.

In a study by Challen et al., it was concluded that the PMEWS was a better predictor than CURB-65 with regard to admission and critical care needs, but that it lagged behind CURB-65 for predicting mortality.[11] Although CURB-65 had high sensitivity and specificity in our study, it lagged behind PMEWS and STSS for predicting mortality. In evaluations regarding prediction of ICU admissions, the PMEWS had the most successful result, while the STSS had the lowest.

In forecasting the need for mechanical ventilation, the PMEWS and CURB-65 had high specificity but lower sensitivity. Rosenbaum reported that the numbers of mechanical ventilators and intensive care unit beds were insufficient in the COVID-19 pandemic.[16] Undoubtedly, accurate prediction of which patients may need mechanical ventilation and ICU admission will contribute towards effective use of resources.

However, the need for serum urea measurement to calculate the CURB-65 score prevents rapid assessment. This situation restricts the use of CURB-65 scores in triage settings. Comparison between

Table 4. Performance, sensitivity, specificity, likelihood ratios and predictive values of PMEWS, CURB-65 and STSS scores

	AUC	95% CI	Sensitivity (%)	Specificity (%)	+LR	–LR	PPV	NPV	P
Mortality									
PMEWS ≥ 3	0.968	0.912-0.993	100	81.91	5.53	0.0	26.08	100.0	**< 0.001***
CURB-65 ≥ 1	0.942	0.877-0.979	83.33	90.43	8.70	0.18	35.72	98.83	**< 0.001***
STSS ≥ 1	0.962	0.903-0.990	83.33	93.62	13.06	0.18	45.46	98.87	**< 0.001***
ICU admission									
PMEWS ≥ 5	0.941	0.875-0.978	80	95.56	18	0.21	66.68	97.72	**< 0.001***
CURB-65 ≥ 1	0.898	0.821-0.949	80	93.33	12	0.21	57.13	97.67	**< 0.001***
STSS ≥ 1	0.878	0.798-0.935	90	72.22	3.24	0.14	26.46	98.48	**< 0.001***
Need for MV									
PMEWS ≥ 5	0.854	0.769-0.917	60	96.47	17	0.41	74.99	93.18	**< 0.001***
CURB-65 ≥ 1	0.867	0.785-0.927	66.67	95.29	14.17	0.35	71.4	94.18	**< 0.001***
STSS ≥ 1	0.820	0.731-0.890	80	74.12	3.09	0.27	35.29	95.45	**< 0.001***

PMEWS = Pandemic Medical Early Warning Score; CURB-65 = Confusion, Uremia, Respiratory rate, Blood pressure and age ≥ 65; STSS = Simple Triage Scoring System; AUC = area under the curve; CI = confidence interval; +LR = positive likelihood ratio; –LR = negative likelihood ratio; PPV = positive predictive value; NPV = negative predictive value; ICU = intensive care unit; MV = mechanical ventilation.
*P < 0.05 was considered significant.

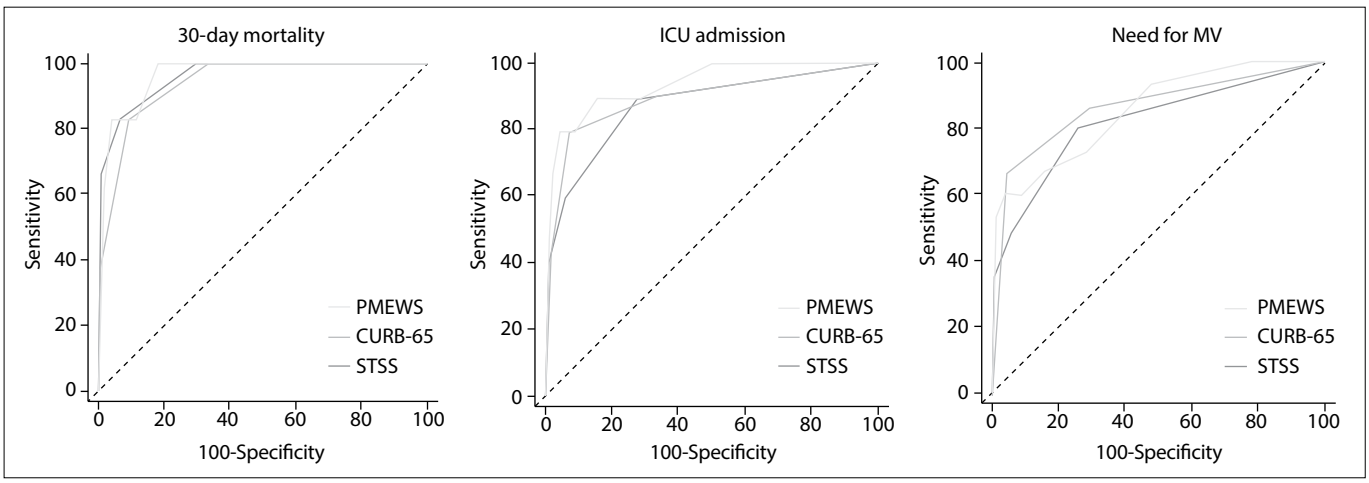

Figure 1. Receiver operating characteristic (ROC) curves for the Pandemic Medical Early Warning Score (PMEWS), Confusion, Uremia, Respiratory rate, Blood pressure and age ≥ 65 (CURB-65) score and Simple Triage Scoring System (STSS) score for 30-day mortality, intensive care unit (ICU) admission and need for mechanical ventilation (MV).

PMEWS and STSS shows that they have similar power for predicting mortality. Because STSS is calculated with fewer parameters, it is more practical and faster than PMEWS. We found that STSS could be calculated more easily and more quickly than PMEWS and CURB-65 in emergency room triage settings.

Talmor et al. developed the STSS for use in epidemics, and it was found to effectively predict ICU and mechanical ventilator need.[12] Those authors also noted that modification of this scale might be required, to incorporate data from a real pandemic situation.[12] In our study, STSS ≥ 1 predicted mortality, in addition to ICU admission and mechanical ventilator need. Morton et al. stated that STSS ≥ 2 was a perfect predictor for critical care among patients with influenza.[17]

A study by Su et al. among COVID-19 patients found that the cutoff of CURB-65 ≥ 2 had 60% sensitivity and 93.4% specificity for predicting ICU need.[18] In our study, we obtained similar specificity (93.3%) and higher sensitivity (80%) with a lower cutoff (CURB-65 score ≥ 1).

Evaluation of the relationship between age and mortality among patients diagnosed with COVID-19 pneumonia in our study showed that the ages of the patients who died were significantly higher (P = 0.001). The average age of the patients in our study was found to be 51 years. However, serious outcomes such as COVID-19-associated ICU admission or mortality showed highest prevalence at the ages of 70 and above, regardless of the underlying disease.[19] In another prospective cohort study, the average age at which death due to COVID-19 occurred was 70.2 years.[20]

In the Middle East respiratory syndrome (MERS) epidemic, advanced age was defined as an independent predictor of mortality.[21] This can be attributed to age-related defects in T-cell and B-cell functions, inability to control viral replication due to excessive production of type-2 cytokines and prolonged pro-inflammatory responses.[22] In our study, the average age of the patients who died was 72.6 years, and this age was similar to what had been reported in other studies in the literature. Therefore, advanced age should be considered to be an independent variable associated with poor outcomes for COVID-19 pneumonia patients in triage settings. In all three scoring systems that we used in our study, age was included as a criterion.

Dyspnea is a fundamental cause of emergency visits and admissions relating to COVID-19 pneumonia. In our study, 15% of the cases presented with shortness of breath and 52% with coughing. We found that the patients who died had higher respiratory rates and lower oxygen saturation levels on admission (P = 0.028 and P = 0.002, respectively). In a study by Zhou et al., it was observed that mortality was higher among patients with tachypnea.[23] In a study by Du et al., it was stated that the respiratory rate in the group that died was significantly higher than that of the survivors, and there was no difference in terms of other vital factors such as heart rate.[20] In a study by Zangrillo et al., similar to our study, mortality was higher among patients with advanced age and low SpO_2 values on admission.[24]

In line with data in the literature, we did not find any significant relationship between vital parameters (systolic and diastolic blood pressure, pulse rate and fever) and shock index, except for respiratory rate and SpO_2 (P > 0.05). Alveolar serous exudation, hyaline membrane formation, inflammatory infiltrations, necrosis of pneumocytes, vascular edema, microthrombus and pulmonary interstitial fibrosis have been detected in COVID-19 patients.[25] COVID-19 is a systemic disease that primarily injures the vascular endothelium, and if dyspnea is not managed, patients may have multiple organ failure even if they are not in an older age group.[26] Therefore, oxygen therapy is life-saving for patients with COVID-19 pneumonia who have severe respiratory distress or hypoxia.

In our study, the emergency department length of stay of the patients who died was significantly higher (P = 0.039). Patients with advanced age, comorbid disease and worse clinical conditions on admission are further investigated in the emergency department and are referred for consultations at other clinics.

Additional treatments are given to these patients to stabilize their clinical condition. This situation prolongs patients' emergency department length of stay. In a study by Sabaz et al., prolongation of emergency department length of stay among critically ill patients was associated with worse consequences and increased mortality.[27] Moreover, emergency department length of stay significantly prolonged the inpatient length of stay in a study by Liew et al.[28]

In the literature, there is no study comparing the relationship between emergency department length of stay among patients with COVID-19 pneumonia and occurrences of mortality. Therefore, our study provides the first data in the literature showing that emergency department length of stay affects mortality. Further studies are needed with regard to emergency department length of stay and the causes and outcomes of delays among patients with COVID-19 pneumonia.

In our study, no significant relationship was found between the length of stay in hospital and mortality (P = 0.186). In a study by Shao et al., in which 136 in-hospital cardiac arrest patients were evaluated, the length of stay in the hospital was reported to be seven days.[29] In our study, while the length of stay in hospital in the group that died was six days (interquartile range, IQR: 2.7-11 days), it was 4.5 days (IQR: 0-8) in the group of survivors. Liu et al. reported that patients with severe COVID-19 pneumonia and lymphopenia stayed longer in the hospital.[30] In another study, it was concluded that there was no significant difference in mortality, with regard to length of stay in the ICU.[23]

The Turkish Ministry of Health has recommended that treatments for patients who are hospitalized due to COVID-19 pneumonia should be completed in the same hospital. In this way, the patients' isolation is provided safely, and their compliance with

the treatment is controlled. This recommendation may cause similar lengths of stay in hospital among patients.

The primary limitation of this study is that it was conducted in a single center, with a study group consisting of patients admitted to the emergency department of a tertiary-level university hospital. The low number of cases in the city where the study was conducted caused the number of patients included in this study to be limited. Extensive multicenter studies are needed for the validation of these scoring systems.

The secondary limitation of this study is that it was based on medical records. It was a cross-sectional analysis with a small number of participants. We included all COVID-19 pneumonia patients who were admitted to the emergency department during the study period, and only a few (n = 11) were then excluded. Patients with positive real-time polymerase chain reaction results were included in the study. The patient group may have been affected by the false positivity and negativity of the reference test. Also, there may have been false-negative results, depending on the sampling technique and the region sampled.

CONCLUSION

The Pandemic Medical Early Warning Score, Simple Triage Scoring System and Confusion, Uremia, Respiratory rate, Blood pressure and age > 65 score can be used safely in triage settings, to determine the prognosis for patients diagnosed with COVID-19 pneumonia. Furthermore, these scores can be used for predicting mortality, ICU admission and mechanical ventilation need. These scores can help in managing resources effectively during a pandemic period. Advanced age, high respiratory rate and low SpO_2 values significantly increased the mortality among COVID-19 pneumonia patients. Prolonged emergency department length of stay increases mortality. Especially in pandemics, there is a need to apply objective and reliable triage scoring systems that have been verified through comprehensive studies.

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Estimating Brazilian states' demands for intensive care unit and clinical hospital beds during the COVID-19 pandemic: development of a predictive model

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Compartmental model.

ABSTRACT

BACKGROUND: The fragility of healthcare systems worldwide had not been exposed by any pandemic until now. The lack of integrated methods for bed capacity planning compromises the effectiveness of public and private hospitals' services.

OBJECTIVES: To estimate the impact of the COVID-19 pandemic on the provision of intensive care unit and clinical beds for Brazilian states, using an integrated model.

DESIGN AND SETTING: Experimental study applying healthcare informatics to data on COVID-19 cases from the official electronic platform of the Brazilian Ministry of Health.

METHODS: A predictive model based on the historical records of Brazilian states was developed to estimate the need for hospital beds during the COVID-19 pandemic.

RESULTS: The proposed model projected in advance that there was a lack of 22,771 hospital beds for Brazilian states, of which 38.95% were ICU beds, and 61.05% were clinical beds.

CONCLUSIONS: The proposed approach provides valuable information to help hospital managers anticipate actions for improving healthcare system capacity.

INTRODUCTION

The novel severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) disease[1-3] was first reported in Wuhan, China, in December 2019. Since then, political leaders and healthcare managers have endeavored to estimate the demand for intensive care unit (ICU) and clinical beds to guard against the possibility of collapse of the healthcare system. Moreover, political leaders have adopted proactive non-pharmaceutical interventions (NPIs) to reduce fatalities arising from bed shortages. Although the quarantine and travel restrictions in Wuhan delayed progression of the epidemic on an international scale, thereby reducing case importations by nearly 80% until mid-February,[4-6] the virus has since then spread rapidly both domestically and internationally.[5,7,8] In Brazil, confirmed cases started to be seen in state capital municipalities and then moved towards non-metropolitan cities, and the numbers of cases continue to grow in every state.[9,10]

Brazil identified its first COVID-19 case on February 25, 2020, and its first death on March 17, 2020. A lack of consensus on public healthcare policy[11-12] compromised use of integrated and coordinated NPIs to reduce COVID-19 mortality and healthcare demand. Moreover, the lack of integrated methods for bed capacity planning compromised the effectiveness of public and private hospitals' services.

Mathematical models are used to evaluate the efficacy of specific interventions that were implemented in the past, in order to identify future strategies and effectively inform public health policy.[13,14] The challenge in this work consists of forecasting the numbers of individuals requiring hospitalization and predicting the availability of hospital beds for such patients, taking into account the technical limitations of the data,[15-17] infection rates and under-reporting of cases[18] because of low numbers of tests. Therefore, we limited our analysis to the official data.[19,20]

Tertiary-care hospital beds are not equally available for all citizens. In Brazil, there are 2.4 beds/1,000 inhabitants and 34,318 ICU beds. 54% of the ICU beds are public, assigned to 78% of the population, while the remaining 22% of the population that has access to private care receive this medical care on 46% of the ICU beds.

In the following sections, we briefly describe the model and the estimates for the required numbers of ICU and clinical beds for each Brazilian state that would be needed to avoid healthcare system collapse.

OBJECTIVES

The purpose of this paper was to present a combined approach to estimation of Brazilian states' demands for ICU and clinical beds during a pandemic.

METHOD

ICU and clinical bed dynamics

Consider a compartmental model[21,22] in which the population is divided into susceptible (S), exposed (E), infectious (I) and recovered (R) individuals (SEIR model). A rate of β of *S* individuals in contact with *I* (S-I contact) becomes E and progresses over the course of the incubation period at a rate σ, to state I. While a rate γ of I recovers from the disease, a rate μ_I of I evolves to death. A fraction ξ of R (recovered individuals) may become (or not, if $\xi = 0$) re-susceptible (S) and, therefore, a SEIRS model.

The effect of testing a segment of the population is modeled by introducing the rate of transmission for individuals with detected infection (β_D), detected exposed state (D_E) and detected infectious state (D_I). Let ψ_E and ψ_I be the probabilities of positive tests for exposed and infected individuals, and Q, the rate of individuals with detected infection interacting with the population. Then D_E and D_I result from the rates $\theta_E\psi_E$ and $\theta_I\psi_I$ of testing exposed E and infected I individuals, respectively. The model describes the full spectrum of disease. Let N be the estimate of an affected population. Thus, $N = S + E + I + D_E + D_I + R$.

To represent the ICU and clinical bed dynamics, consider that a fraction of infected individuals is asymptomatic (I_A). The rate α for symptomatic cases ($I_S = I - I_A$) requiring hospitalization (H) is αI_S. Let *T* be the number of planning days during the pandemic with *t* corresponding to each admission day at the hospital. For clinical bed dynamics, consider L_S and L_f as the average lengths of stay (LoS) of surviving patients and patients who died, respectively. For surviving patients in ICU beds, the average length of stay is $L_b + L_d + L_a$, where L_b represents the surviving patients in clinical beds who are re-directed to ICU beds, L_d is the average LoS of surviving patients in ICU beds, and L_a, the average LoS in clinical beds among surviving patients after being re-directed from ICU beds. For deceased victims of ICU bed dynamics, the average LoS is $L_c + L_i$, representing the average periods for which a deceased patient will stay in clinical and ICU beds, respectively.

Given the average length of stay metrics for ICU and clinical dynamics, we calculate admission and leave days for each patient profile. For a surviving clinical patient, whose admission day is t, the expected day on which this patient leaves the clinical bed is $T_o = t + L_S - 1$. A clinical patient who progressed to death is expected to be removed from the hospital in $T_f = t + L_f - 1$. A surviving ICU patient is admitted in $T_i = t + L_b$. In $T_r = T_i + L_d$, the patient returns to the clinical bed, and in $T_c = T_r + L_a - 1$, the patient leaves the clinical bed. For a deceased ICU patient, the admission day is $T_d = t + L_c$, and $T_u = T_d + L_i - 1$ is the expected day on which the patient is removed from the hospital.

Let H_t be the daily admission of patients to hospitals, and τ the fraction of hospitalized cases that require critical care in the ICU. Also, consider ζ and η to be the rates of critical patients who evolve to death in ICU beds and clinical beds, respectively.

The integrated model is presented in **Figure 1**. The model equations and data are available in a **Data Repository** that is available from https://github.com/joaoflavioufmg/webcovid19.

Data sources and measurements

The model data included the social distancing index, which ranges from 30%, as observed at earlier times in the COVID-19 pandemic, to 100% in a possible lockdown situation.[23] The latter would be expected to reduce the transmission rate of the model by 74%.[24] Furthermore, the basic reproduction number, which is the average number of secondary cases generated per case, was set to 2.9 in the case of the Brazilian outbreak.[15] After the first month, we set customized transmission rate values for each Brazilian state and also took the time-varying reproduction number into consideration.[16] We used data from official reports on symptomatic infections.[19,20] The asymptomatic fraction has been estimated variously in different reports,[25] as follows: 18% on the Diamond Princess ship;[26] 31% in repatriation flight screening;[27] and 50%-75% in the Italian village of Vo'Euganeo.[28] The average infection lethality ratio and the percentage of symptomatic cases requiring hospitalization were obtained from recent studies[25,29] and were adjusted for each Brazilian state according to its demographic pyramid.[30]

The percentage of symptomatic cases requiring hospitalization was estimated from the confirmed cases of SARS-CoV-2 infection in each state,[31-56] taking its demographic pyramid and the estimated incidence for each age group into account.[25] Thus, we estimated that 6.6% to 7.7% (95% confidence interval, CI) of the cases of symptomatic infection in Brazil would require hospitalization.

The average proportion of the patients requiring critical care in an ICU was estimated to be 26.11% of the hospitalized cases, considering recent experience.[25] We used the numbers of ICU and clinical beds for the month of April 2020 obtained from official Brazilian data sources.[57] According to general bed utilization reports from before the pandemic,[58] 34% of clinical beds and 21% of ICU beds were available for patients infected with COVID-19. The input data is presented in **Table 1**.

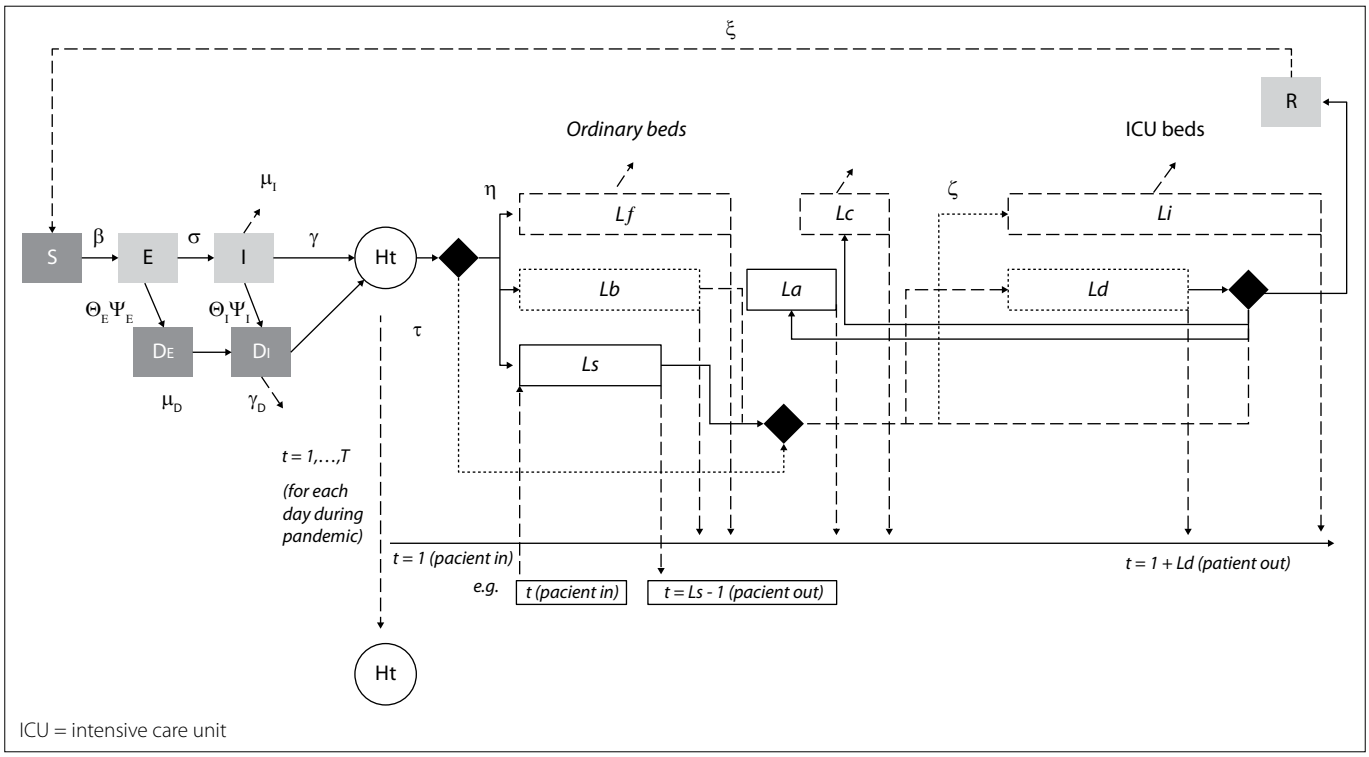


Figure 1. Model for susceptible (S), exposed (E), infectious (I), recovered (R) and re-susceptible (S) individuals (SEIRS) in Brazilian states: Pandemic model integrated with dynamic intensive care unit and clinical hospital beds.

Table 1. Model parameters for each Brazilian state

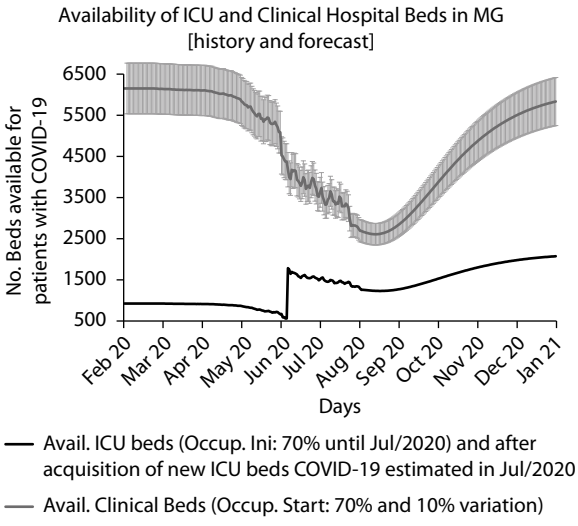
States	Population	Social distancing index (%)	Basic reproduction number	Hospital ratio of symptomatic cases	ICU beds	Clinical beds
Acre (AC)	894,47	47.36	2.20	0.0559	48	765
Alagoas (AL)	3,351,092	43.29	2.06	0.0802	299	3,382
Amazonas (AM)	4,207,714	43.94	2.81	0.0729	271	3,299
Amapá (AP)	861,773	50.78	3.27	0.0606	46	609
Bahia (BA)	14,930,424	41.80	2.20	0.0681	1,478	17,737
Ceará (CE)	9,187,886	47.83	2.85	0.0920	802	11,144
Distrito Federal (DF)	3,052,546	36.40	2.30	0.0633	917	4,388
Espírito Santo (ES)	4,064,052	39.20	2.44	0.0705	716	5,338
Goiás (GO)	7,116,143	36.40	1.96	0.0695	1,053	10,497
Maranhão (MA)	7,114,598	41.60	2.75	0.0804	572	8,23
Minas Gerais (MG)	21,292,666	38.00	1.82	0.0774	3,096	27,87
Mato Grosso do Sul (MS)	2,809,394	37.20	1.88	0.0556	352	3,499
Mato Grosso (MT)	3,526,220	37.50	2.01	0.0581	592	4,773
Pará (PA)	8,690,745	43.10	2.99	0.0842	609	8,448
Paraíba (PB)	4,039,277	48.68	2.61	0.0715	2,006	17,163
Pernambuco (PE)	9,617,072	52.62	2.43	0.1117	454	4,937
Piauí (PI)	3,280,697	44.59	2.02	0.0704	1,408	13,191
Paraná (PR)	11,516,840	43.07	1.83	0.0761	227	4,432
Rio de Janeiro (RJ)	17,366,189	46.56	1.99	0.0970	3,978	20,594
Rio Grande do Norte (RN)	3,534,165	43.95	1.92	0.0715	431	4,497
Rondônia (RO)	1,796,460	45.97	2.35	0.0604	231	2,869
Roraima (RR)	631,181	44.28	2.80	0.0503	25	854
Rio Grande do Sul (RS)	11,422,973	46.37	1.83	0.0740	1,63	19,971
Santa Catarina (SC)	7,252,502	42.74	1.95	0.0653	843	10,541
Sergipe (SE)	2,319,032	40.61	2.31	0.0554	241	2,149
São Paulo (SP)	46,289,333	45.86	1.94	0.0882	8,324	54,698
Tocantins (TO)	1,590,248	41.04	2.05	0.0545	125	2,123

ICU = intensive care unit.

RESULTS

The model considers two different periods of the pandemic: May and August 2020. It uses the historical records of COVID-19 cases[59] to estimate future infections for each state and project the ICU and clinical bed use for a period of 365 days. **Figure 2** shows an illustrative example of a forecast for August 2020, for the state of Minas Gerais. The model periodically adjusts to the real number of cases, thus providing a fair estimate of future cases of infection. Historical records of infection and future estimates feed the dynamic bed model, which forecasts a reduction in ICU and clinical bed capacity of the state healthcare system. In May 2020, the ICU bed capacity for Minas Gerais was different from the capacity in August 2020. Thus, we adopted a simplified assumption considering a single capacity increase in July 2020. The monitoring of bed procurement did not form part of the scope of the present study.

Accordingly, the model forecasts the possibility of healthcare collapse, i.e. 100% utilization of ICU and clinical beds. Thus, the demand for ICU and clinical beds is established at the peak of



ICU = intensive care unit.

Figure 2. Intensive care unit and clinical bed model for the state of Minas Gerais (MG).

Table 2. Model projection of peak bed utilization and demand for new hospital beds

States	Peak ICU bed utilization	Peak clinical bed utilization	ICU bed demand	Clinical bed demand	SUS provision
Acre (AC)	100% (June)	85% (June)	63	142	50 (24%)
Alagoas (AL)	100% (June)	100% (July)	162	286	232 (52%)
Amazonas (AM)	100% (May)	100% (June)	166	293	199 (43%)
Amapá (AP)	100% (May)	100% (June)	38	91	32 (25%)
Bahia (BA)	100% (July)	100% (July)	715	463	1000 (85%)
Ceará (CE)	100% (May)	81%	767	1053	749 (41%)
Distrito Federal (DF)	74%	92%	0	0	337
Espírito Santo (ES)	100% (June)	100% (June)	137	156	636 (217%)
Goiás (GO)	71%	93%	0	0	546
Maranhão (MA)	100% (May)	100% (June)	337	24	390 (108%)
Minas Gerais (MG)	100% (August)	100% (August)	954	1133	1461 (70%)
Mato Grosso do Sul (MS)	71%	85%	0	0	306
Mato Grosso (MT)	72%	88%	0	0	426
Pará (PA)	100% (May)	100% (June)	467	852	376 (29%)
Paraíba (PB)	100% (June)	100% (June)	452	1851	277 (12%)
Pernambuco (PE)	100% (May)	85%	329	0	925 (281%)
Piauí (PI)	100% (July)	100% (July)	282	506	356 (45%)
Paraná (PR)	71%	84%	0	0	818
Rio de Janeiro (RJ)	100% (June)	100% (July)	516	2914	941 (27%)
Rio Grande do Norte (RN)	100% (August)	84%	78	0	272 (349%)
Rondônia (RO)	100% (June)	81%	85	0	152 (179%)
Roraima (RR)	100% (May)	78%	24	0	35 (146%)
Rio Grande do Sul (RS)	100% (July)	100% (July)	841	686	1006 (66%)
Santa Catarina (SC)	100% (July)	91%	151	0	988 (654%)
Sergipe (SE)	100% (May)	100% (June)	95	221	166 (53%)
São Paulo (SP)	100% (June)	100% (July)	2014	2572	3807 (83%)
Tocantins (TO)	100% (May)	100% (June)	196	659	99 (12%)

ICU = intensive care unit; SUS = Sistema Único de Saúde (Brazilian National Health System).

infections, since the proportion of symptomatic cases requiring hospitalization produces the peak of capacity utilization of ICU and clinical beds. Although the maximum utilization of bed capacity occurred in May, June and July 2020, the estimate of SARS-CoV-2 infection levels continues to grow in the projection, which produces shortages of ICU and clinical beds for the states. Overall, the results suggest that 0.81% of the population had become infected by May 2020 and that this percentage was 2.87% by August 2020, excluding deaths and individuals who had recovered. Therefore, the majority of the population remains potentially vulnerable. **Table 2** presents the results from the model projection of peak bed utilization and the demand for new hospital beds.

The outcomes show that the Brazilian states require 22,771 additional beds, of which 8,869 (38.95%) are ICU beds, and 13,902 (61.05%) are clinical beds. Populous states, like São Paulo, Rio de Janeiro and Minas Gerais account for nearly 40% of the projected demand.

DISCUSSION

Our method projected in advance the lack of ICU and clinical beds from May to July 2020. From March to April 2020, technical notes and print and digital media[60] warned about the estimated maximum utilization rate of public and private hospitals' bed capacity. These warnings were borne out by reality in most states, as also shown through the model's projections.

These findings provide evidence that SARS-CoV-2 transmission in Brazil is not under control, and the number of active cases remains stable or is even growing in some states, despite the physical distancing policies adopted so far. This suggests that further action is required to prevent higher rates of mortality. Overall, these findings have filled an important gap in estimating the deficit of ICU and clinical beds within the Brazilian healthcare system, across the country. Furthermore, our study also provides a flexible tool that allows healthcare decision-makers to forecast the impact of the pandemic impact and to implement policies for reducing COVID-19 mortality.

The model was implemented in the Python software (Python Language Reference, version 3.8.2, available from http://www.python.org; Python Software Foundation, Amsterdam, 1995). The programming routine automatically captures historical and updated data on COVID-19 cases from a web-based repository that aggregates official data from all states and municipalities that present confirmed cases. The initial model[61] evolved from a simplified estimate on a spreadsheet to a sophisticated approach embedded in a web-based system that captures data, runs models and displays the results.[59]

The web-based system can be accessed online at https://labdec.nescon.medicina.ufmg.br/webcovid19/. It provides valuable up-to-date information for healthcare managers in advance, which is very useful because acquiring a large number of ICU and clinical beds in a short period is difficult.

The government has implemented a hospital bed census and has obtained additional ICU and clinical beds. Up to November 2020, the Brazilian Ministry of Health had ordered 16,582 beds from suppliers. The cost of these additional beds will be US$ 437 million or R$ 2.34 billion.[62] Although the Ministry of Health has provided 73% of the overall projected demand, this provision of 16,582 hospital beds differs from (and is lower than) the projected demand for beds at the state level, as presented in **Table 2**. Meanwhile, during pandemics, we suggest that temporary hospitals should be provided, with the supplementary numbers of ICU and clinical beds for each state. This should incorporate use of NPIs, including physical distancing and personal protection policies[63] such as use of masks, in order to avoid overloading the healthcare system.

In Brazil, physical distancing policies have reduced the intensity of transmission, thereby contributing towards saving many lives. However, in many states, the number of COVID-19 cases remains stable or is even rising, which indicates that distancing control policies should be intensified rather than loosened. Experiences have provided evidence that physical distancing policies have reduced SARS-CoV-2 infection rates,[24] and have also provided evidence that person-to-person activities have increased the SARS-CoV-2 infection rate.[64] These findings have demonstrated that economic, cultural, educational or social events involving proximity are dangerous during the COVID-19 pandemic. We identified certain limitations in our study that provide opportunities for future research. Our model is deterministic and assumes discrete values and a uniformly spread population; therefore, a geographical analysis on the spread of the virus is urgently needed in order to determine location-based transmission rates. Additionally, we used an average physical distancing index because physical distancing policies in several states were activated and deactivated at various times. One promising approach for future investigations may comprise formulation of a stochastic model with a multiperiod physical distancing index.

CONCLUSION

We proposed an integrated approach towards evaluation of the impact of the COVID-19 pandemic on the healthcare system capacity of Brazilian states, through estimating the demand for ICU and clinical beds for each state. The integrated model was applied to two periods of the pandemic for each state and it showed that healthcare would collapse at different times if bed demand, estimated as 22,771 beds, were not satisfied. The government has provided 16,582 hospital beds for the Brazilian states; however, the numbers of beds diverges from the estimated demand projections at the state level.

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A case of COVID-19 with papulovesicular rash that progressed to retiform purpura, accompanied by cherry angiomas

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Cherry angiomas.
Eruptive.

ABSTRACT

CONTEXT: Various skin manifestations have been reported in coronavirus disease. It may be difficult to determine the etiology of these lesions in view of the increased frequency of handwashing during the pandemic, along with occurrences of irritant contact dermatitis and allergic contact dermatitis due to disinfectant use; usage of herbal medicine and supplements to strengthen the immune system; and urticarial or maculopapular drug eruptions due to COVID-19 treatment. The variety of associated skin manifestations seen with COVID-19 makes it challenging to identify virus-specific skin manifestations. Petechiae, purpura, acrocyanosis and necrotic and non-necrotic purpura, which can be considered as manifestations of vascular involvement on the skin, have been reported.

CASE REPORT: Here, we report a case of eruptive cherry angiomas, which was thought to have developed due to COVID-19, with a papulovesicular rash on distal extremities that progressed over time to reticular purpura.

CONCLUSION: The case presented had a papulovesicular rash at the onset, which evolved to retiform purpura, and eruptive cherry angiomas were observed. It should be kept in mind that dermatological signs may vary in patients with COVID-19.

INTRODUCTION

Coronavirus disease-2019 (COVID-19) has seriously affected global health since December 2019.[1] It was declared a pandemic by the World Health Organization (WHO) on April 11, 2020.[2]

The most serious manifestation of the disease is severe acute respiratory failure; however, skin manifestations have been reported with increasing frequency in the literature. Although the pathophysiology of COVID-19 is not yet known, some theories have been suggested. One possibility for its pathogenesis is microvascular injury, for which vascular occlusive manifestations have been detected in biopsies and autopsies.[3-5] Manifestations of cutaneous vascular involvement such as petechiae, purpura, acrocyanosis and necrotic and non-necrotic purpura have been reported in association with COVID-19.[5-7]

Because of the increased frequency of handwashing, along with occurrences of irritant contact dermatitis and allergic contact dermatitis due to disinfectant use, consumption of herbal medicine and supplements to strengthen the immune system prior to infection and the possibility of urticaria or maculopapular drug eruptions post-infection, it may be challenging to determine the etiology of skin lesions. It is difficult to clarify whether these are caused by viruses or are induced by the immune system, and also whether they are virus-specific or nonspecific.[6,7] Clinical manifestations can be better understood if there are reports of specific skin lesions that develop through COVID-19.

Here, a case of eruptive cherry angioma accompanied by papulovesicular rash on the distal extremities that evolved to reticular purpura, which was thought to have developed secondary to COVID-19, is presented.

OBJECTIVE

Petechiae and purpuras are generally thought to be a symptom of serious systemic disease and these lesions have been reported in relation to coronavirus infection. Information about COVID-19-related skin symptoms is expanding day by day. Petechiae relating to COVID-19, which are generally observed in severe cases, can also be seen in uncomplicated cases, as in our patient. We believe that the unique clinical course of our patient will provide guidance if a similar situation were to develop.

CASE REPORT

A 52-year-old male patient came to our clinic for a consultation regarding rashes on his fingers, arms and legs. It was learned from the patient's story that he had been screened for the novel coronavirus (2019-nCoV) because his wife had tested positive two days previously. A reverse transcription polymerase chain reaction (RT-PCR) test for severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) was found to be positive. The samples were obtained using a nasopharyngeal swab.

He had complaints of mild weakness and myalgia and he had been using tablets of diltiazem (120 mg/day), doxazosin (4 mg/day), atorvastatin (10 mg/day) and acetylsalicylic acid (100 mg/day) for five years due to essential hypertension and coronary artery disease. The patient did not complain of coughing or dyspnea, and no lung involvement was detected on computed tomography (CT). In laboratory tests, acute-phase reactants were found to be within the normal range: procalcitonin 0.005 ng/ml, sedimentation 12 mm/h and C-reactive protein (CRP) 8 mg/l. The patient was accepted as a COVID-19 case and treatments with hydroxychloroquine (600 mg BID for one day and then 400 mg BID for the following five days) and azithromycin (500 mg daily for five days) were started. Two days after the onset of constitutional symptoms, vesicular skin lesions started to develop on the finger's side as can be seen in **Figure 1**.

Informed consent was obtained from the patient for publication of clinical pictures, and permission to report on this case was granted by the local ethics committee.

The patient's first dermatological signs consisted of vesicles on the sides of his fingers (**Figure 1**) and millimetric erythematous papulovesicular eruptions, which were concentrated on the extensor aspect of the lower legs and flexor aspect of the arms (**Figure 2**). Initially, the patient was evaluated as having irritant contact dermatitis, and administration of mometasone furoate ointment and cetirizine tablet (20 mg/day) was started. After three days, it was noticed that the patient's existing lesions began to acquire a petechial-purpuric appearance (**Figure 3**) and cherry angioma-like lesions appeared on his upper arms, extending from the inner side to the armpit, and on the upper lateral aspects of the trunk (**Figure 4**).

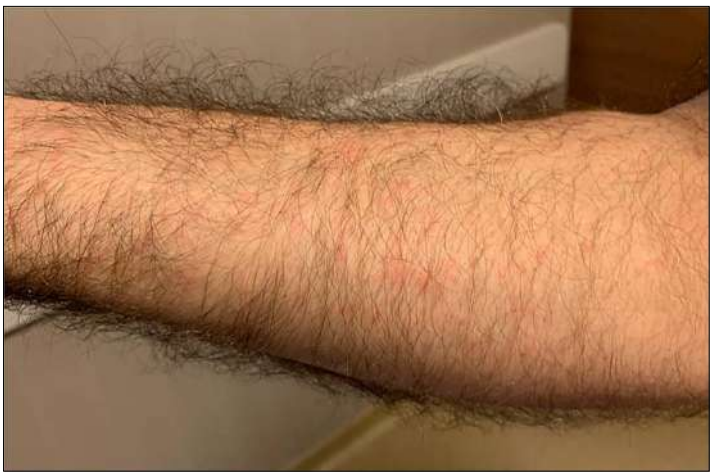

Figure 2. Millimetric erythematous papulovesicles, particularly on the flexor side of the arms.

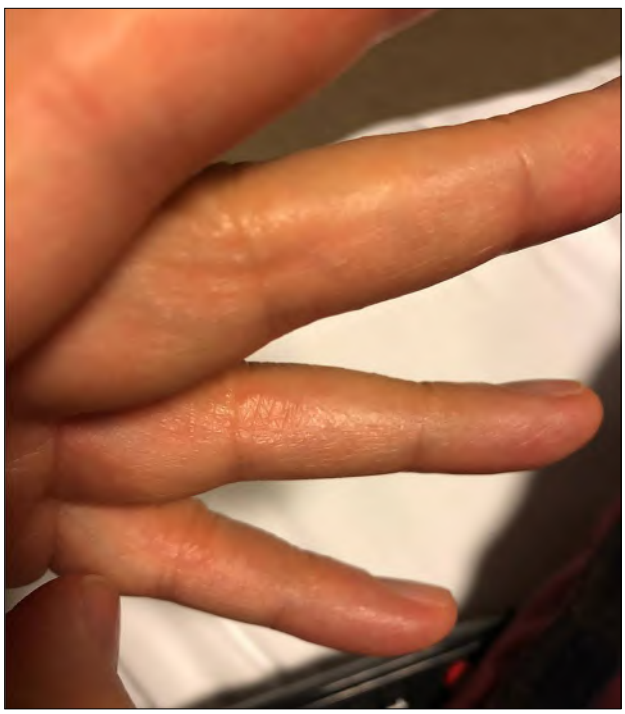

Figure 1. Vesicles on the sides of the fingers.

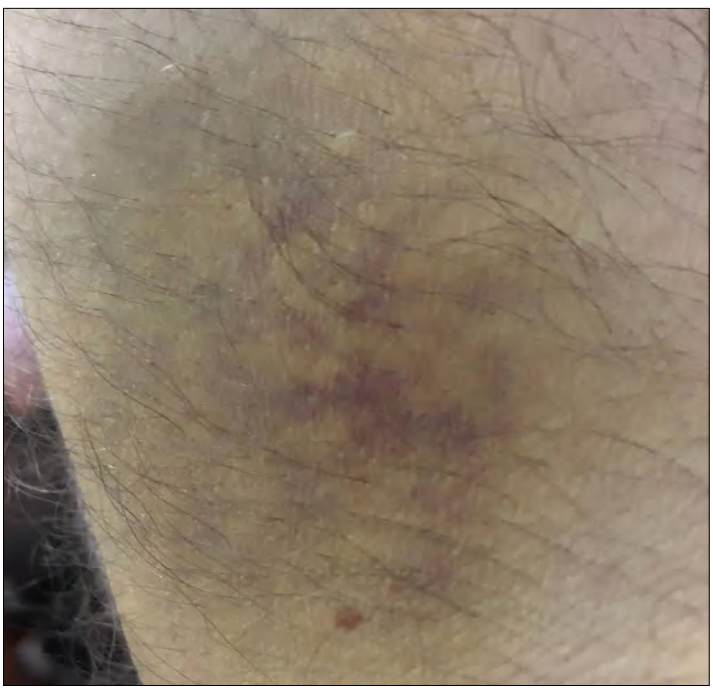

Figure 3. Retiform petechial-purpuric appearance beginning to occur on the patient's arm.

In laboratory tests, antinuclear antibody levels, antithrombin-3 levels, complete blood count, liver function tests and coagulation parameters were found to be within the normal range and conditions that cause vasculitis were ruled out. No histopathological examination of the skin lesions was performed because the patient did not agree to undergo a biopsy.

The patient developed severe weakness and severe muscle pain in his legs, which could be interpreted as restless leg syndrome. The skin manifestations gradually regressed leaving a reticular purpuric appearance. Some of the cherry angioma-like lesions disappeared after a brown crust had formed, while others persisted.

DISCUSSION

The variety of skin manifestations associated with COVID-19 makes it difficult to identify virus-specific skin manifestations. In the literature, several classifications have been made using skin manifestations associated with COVID-19.[5] The cutaneous manifestations of the disease have been grouped into five clinical patterns: 1) pseudo-chilblain; 2) vesicular; 3) urticarial; 4) maculopapular; and 5) livedo/necrosis. These patterns are now being confirmed by other authors.[5-8]

Attempts to understand the clinical-anatomopathological patterns of COVID-19 are being made. In a study examining skin and lung tissue from five patients, the thrombotic microvascular injury was detected through biopsies. It was claimed that the presence of livedo or necrosis correlated with greater severity of COVID-19.[5] In addition, vascular lesions have been reported in younger and milder cases.[6]

In the literature, histopathological examination of a biopsy taken from a case with retiform purpura showed thrombi in small cutaneous vessels. There was also C3 and C9 deposition, thereby demonstrating complement activation.[5] In the present case, no biopsy was taken because the patient refused to undergo this procedure. However, other systemic causes of purpura, such as thrombocytopenia and bleeding diathesis, were investigated and ruled out. Severe pain was present in the patient's leg muscles, which may suggest that formation of vasculopathy is not limited only to cutaneous vessels but also affects larger vessels. In the present case, no thrombus or pneumonia was detected in the lungs, which confirmed the previously reported observation that purpura might also be seen in mild cases.[7]

Cherry angiomas are generally seen on the trunk in middle-aged adults. Their pathogenesis is not well understood. It has been suggested that immune dysregulation of the skin could be a predisposing factor for the development of eruptive cherry angiomas.[9] Cherry angiomas in COVID-19 cases have only been rarely reported in the literature. Eruptive cherry angioma of the back has been reported.[7] Cherry angiomas were noticed in the case of our patient when the lesions gained reticular purpuric characteristics. The simultaneous occurrence of two types of lesions may indicate a common etiopathogenesis. In a previous study, it was determined histopathologically that angiotensin-converting enzyme 2 (ACE2) receptors were secreted from endothelial cells and that the virus caused endotheliitis through this receptor.[10] Retiform purpura and eruptive cherry angioma formation in the patient could be caused by endotheliitis. The occurrences of lesions on the patient's extremities made it easier to recognize and monitor them.

Endothelial cell involvement in COVID-19 patients was recently observed. It was demonstrated histologically that these cells express ACE2 receptors, through which SARS-CoV-2 manages to infect the host, accompanied by viral elements and inflammatory cells. These findings suggest that SARS-CoV-2 infection may produce endotheliitis in different organs, including the skin, as a direct effect from the presence of the virus and host's inflammatory response.[10] Maculopapular rash, one of the skin manifestations associated with coronavirus, is the most frequently reported skin manifestation, although cases of retiform purpura and, rarely, cherry angioma have also been reported (**Table 1**).

CONCLUSION

Our case presented with a papulovesicular lesion at the onset, which progressed to retiform purpura, accompanied by eruptive cherry angiomas that became partly crusted and regressed, according to the patient. We did not find any cases with a similar course in the literature available. It should be kept in mind

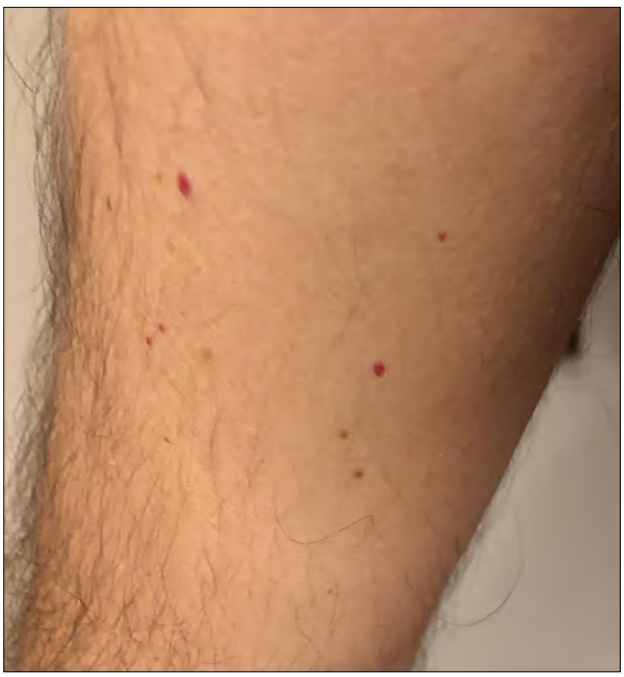

Figure 4. Cherry angioma-like lesions on the medial aspect of the upper arm, extending to the armpit.

Table 1. A systematic review of the literature.

Database	Search strategy	Results
MEDLINE/ PubMed	(Skin manifestations) AND Purpura (retiform) AND (COVID-19)	4 reviews 4 original articles 3 case reports
	Cherry angiomas	1 original article
EMBASE	Skin manifestations) AND Purpura (retiform) AND (COVID-19)	4 reviews 4 original articles 3 case reports
	Cherry angiomas	1 original article
LILACS	Skin manifestations) AND Purpura (retiform) AND (COVID-19)	4 reviews 4 original articles 3 case reports
	Cherry angiomas	1 original article

The search in these databases was conducted in October 2020.

that dermatological signs may vary in patients with COVID-19. Clinicians should therefore be careful about this.

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Venous sinus thrombosis during COVID-19 infection in pregnancy: a case report

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Pregnancy.
Headache.
Female.

AUTHORS' KEY WORDS:
Venous sinus thrombosis.
Hypercoagulability.
Infectious disease.

ABSTRACT

BACKGROUND: Although it is known that the new coronavirus disease (COVID-19), which was first seen in Wuhan, China, in December 2019 and has affected the whole world, mainly targets the respiratory tract, cases of this disease with a wide clinical spectrum are emerging as information is shared.

CASE REPORT: We present the case of a pregnant woman who was diagnosed with venous sinus thrombosis after she developed headache and hemiparesis. Polymerase chain reaction (PCR) positivity lasted for two weeks after COVID-19 had been diagnosed.

CONCLUSIONS: In patients with suspected COVID-19, especially in the presence of causes of hypercoagulability and presence of atypical features, venous sinus thrombosis needs to be kept in mind in making the differential diagnosis.

INTRODUCTION

The effects of COVID-19 are not limited to the lungs alone. After the virus enters the body, it causes various symptoms through viremia.[1] COVID-19 has been implicated in occurrences of cardiovascular and thromboembolic complications due to systemic inflammation and coagulopathy, in the light of the increasing amount of data that has become available over time.[2-8] On the other hand, some published papers have argued that the signs and symptoms of severe COVID-19 infection are more similar to the pathophysiology and phenotype of complement-mediated thrombotic microangiopathy (TMA), rather than to sepsis-induced coagulopathy or diffuse intravascular coagulation (DIC).[8] It has been suggested that COVID-19 predisposes patients to thrombotic pathological conditions in both the venous and the arterial circulation due to inflammation, platelet activation, endothelial dysfunction and stasis.[4] Nevertheless, cases of neurological and cardiac involvement in COVID-positive patients with TMA have also been reported.[9]

While the mechanism for the susceptibility to thrombosis that has been seen among COVID-19 patients continues to be debated, we wanted through this report to share information regarding the common venous thrombus of the central nervous system that emerged during the subclinical course of COVID-19 in a pregnant patient, which caused rapid parenchymal infarction.

CASE REPORT

A 22-year-old patient who was 35 weeks pregnant was evaluated in the emergency department with a complaint of right-sided weakness. The COVID-19 polymerase chain reaction test was performed and was found to be positive. However, she did not have fever or respiratory distress and then was followed up at home without medication.

The patient started to have throbbing headaches that did not respond to analgesic treatment (paracetamol 1000 mg/day) for four days. The intensity of her headaches gradually increased, such that she was being awakened from sleep, and this condition was accompanied by nausea and vomiting.

After this four-day period, she again felt weakness on her right side when she woke up in the morning. Twelve hours later, she went back to the emergency department because her weakness was increasing. At the emergency department, the patient was found to be normotensive, conscious, cooperative and oriented in a neurological examination. No fundus examination was performed, given that she was COVID-positive. Examinations on the patient's visual field and vision showed normal results. Other cranial nerve examinations were normal. Her muscle strength ratio was 3/5 in the upper right extremity, 2/5 in the lower right extremity and 5/5 in the upper

and lower left extremities. The foot sole skin reflex of the right lower extremity consisted of an extensor response. She presented decreased speech fluency and had difficulty in word finding, which were diagnosed as mild motor aphasia. Laboratory tests revealed high levels of fibrinogen (899 g/l; normal is 180-400) and D-dimer (6.38 mg/l; normal is 0-2). It was noted that the patient had also had high levels of fibrinogen (665 g/l) and D-dimer (2.2 mg/l) in examinations performed 10 days previously.

Diffusion magnetic resonance imaging (MRI) showed cortical diffusion restriction in the left parietal region (**Figure 1a**) and a hypointense response in the apparent diffusion coefficient (ADC) (**Figure 1b**). The result from the diffusion MRI was suggestive of venous sinus thrombosis. Widespread loss of flow in the superior sagittal sinus and right transverse sinus, suggesting partial venous thrombosis in the left transverse sinus, was observed in brain magnetic resonance imaging (**Figure 2a**) and

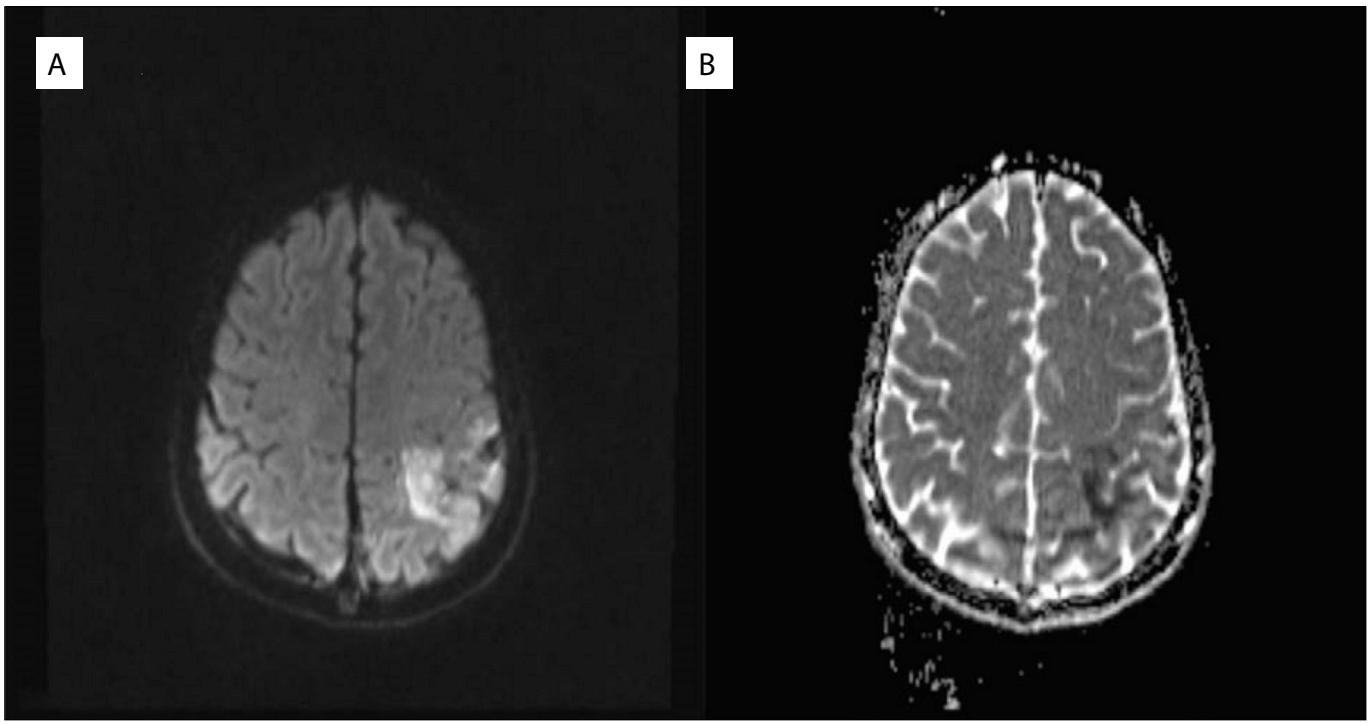

Figure 1. a) Diffusion magnetic resonance imaging; b) Apparent diffusion coefficient.

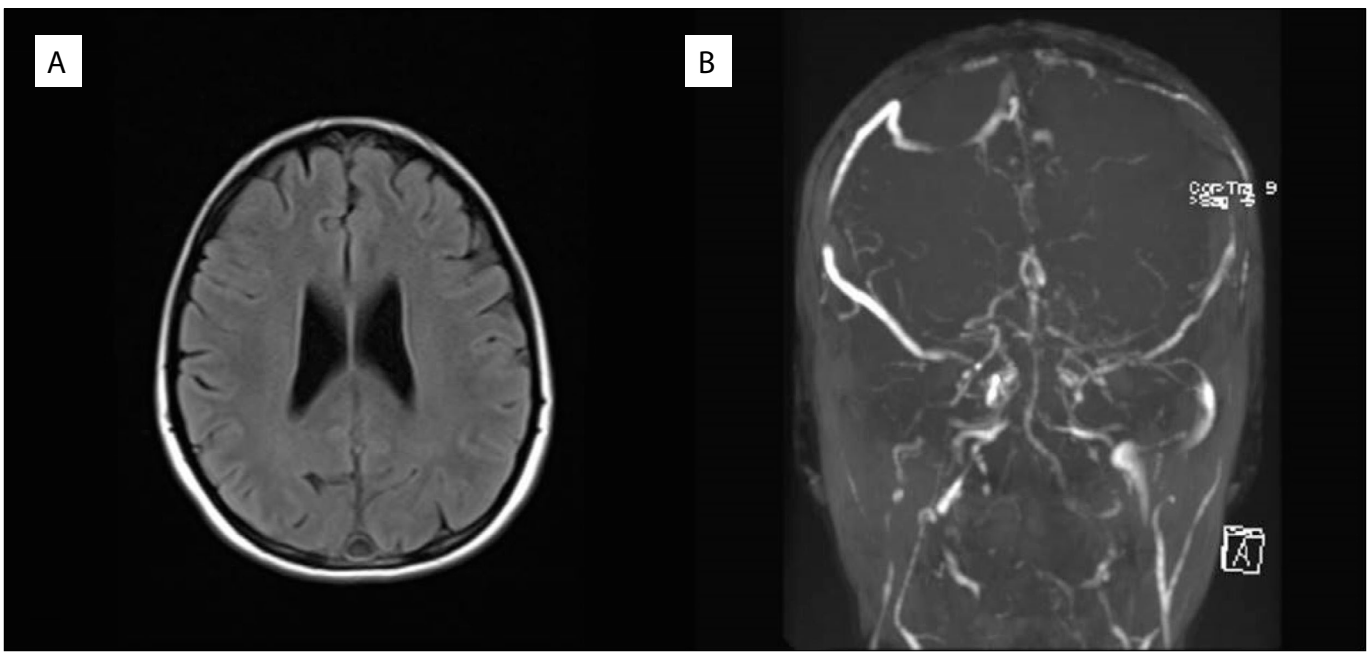

Figure 2. a) Cranial magnetic resonance imaging; b) Magnetic resonance imaging venography.

magnetic resonance venous angiography (**Figure 2b**). The brain MRI and magnetic resonance venography confirmed the diagnosis of venous sinus thrombosis. Thrombosis was not investigated in other parts of the body.

The polymerase chain reaction was repeated and the result was again positive. The patient was then hospitalized with the diagnoses of COVID-19 infection and venous sinus thrombosis. Other genetic, hematological and rheumatological examinations were planned, in order to investigate the etiology of her condition. Anticoagulant treatment (low molecular weight heparin) was started after the patient had been found to present a low platelet count (107,000/mm^3), through evaluation of a peripheral blood smear.

Diffuse contractions were observed in a non-stress test (NST), and tocolysis was started, consisting of nifedipine and betamethasone treatment. However, the patient's labor could not be stopped after 18 hours of hospitalization. She was then admitted for an emergency cesarean section because the intracranial pressure was increasing. A healthy baby was delivered.

Subsequently, the patient's postpartum headache complaints decreased and her speech became fluent without any change in muscle strength deficit. Her thrombocyte counts decreased to 67,000/mm^3. Anticoagulant therapy was continued, with peripheral smear follow-ups. Thoracic computed tomography was performed on the patient, who did not present respiratory distress, and the findings were compatible with COVID-19 pneumonia after birth (**Figure 3**). There was an increase in infection parameters, and the patient was started on hydroxychloroquine and ceftriaxone treatment.

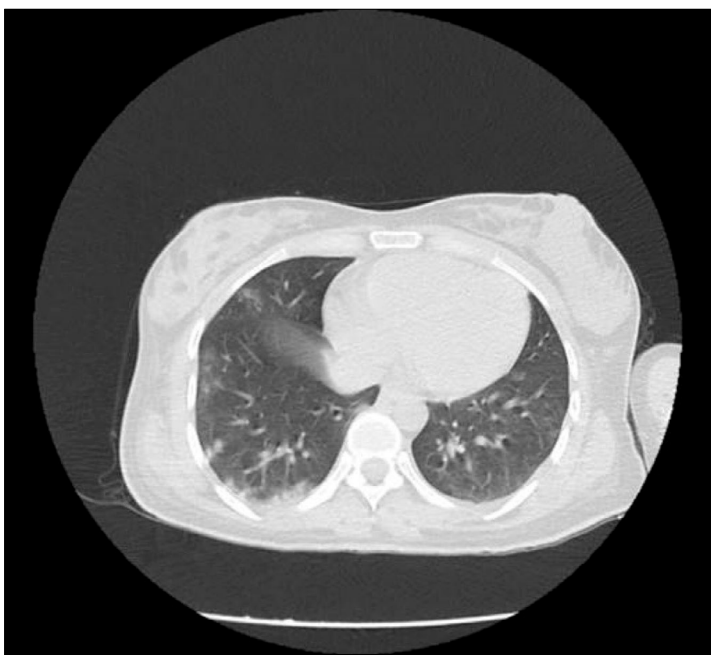

Figure 3. Thoracic computed tomography.

In the examinations performed to ascertain risk factors, the patient was found to be positive for antinuclear antibodies (ANA) and showed prothrombin heterozygous mutation. The patient was negative for anti-cardiolipin antibodies and anti-double stranded DNA (dsDNA), and tests on lupus anticoagulant, homocysteine, protein C, protein S and antithrombin 3 showed results within normal limits.

On the third day following the birth, the patient's headache complaint became completely resolved, her thrombocyte counts stopped decreasing and her thrombocytopenia improved over the subsequent days. The infection parameters regressed. Partial regression of the lesions was observed on control thoracic computed tomography. The patient's general condition stabilized and she was discharged on the 10th day of hospitalization, with muscle strength 4-5/5 on the right side, which was mobilized without support. Continuation of low molecular weight heparin (LMWH) treatment was planned, along with neurological and hematological control tests at a polyclinic.

DISCUSSION

It is known that the new coronavirus disease (COVID-19), which was first seen in Wuhan, China, in December 2019 and has affected the whole world, mainly targets the respiratory tract. Cases of this disease with a wide clinical spectrum are emerging as information is shared.

Although the mechanism for thrombotic events in the course of COVID-19 remains unclear, it is known that there is a tendency for such events to occur within the course of this disease. Pulmonary embolism was shown to be the cause of death in an autopsy series.[6] The etiology of embolic events is generally multifactorial: it is accepted that these events are triggered by environmental factors on the basis of genetic predisposition. Nonetheless, no reports on underlying genetic or other acquired causes in cases of COVID-19-positive pulmonary embolism have yet been published in the literature.

An increasing number of case reports and series on COVID-19-positive patients are describing a wide variety of neurological symptoms. Encephalopathy has been reported in a total of 93 patients, including 16 (7%) out of 214 hospitalized patients with COVID-19 in Wuhan, China, and 40 (69%) out of 58 patients in intensive care with COVID-19 in France. To date, encephalitis has been described in eight patients and Guillain-Barré syndrome in 19 patients. SARS-CoV-2 has been detected in the cerebrospinal fluid (CSF) of some patients. Anosmia and agnosia are common and may occur in the absence of other clinical features. Unexpectedly, acute cerebrovascular disease has also emerged as an important complication: stroke was reported in 2-6% of patients hospitalized with COVID-19 in a cohort study.[10]

Li et al. stated that in a retrospective study in which 219 COVID-19 positive patients were screened, 10 of these patients (4.6%) were

ischemic and one of them presented hemorrhagic cerebrovascular disease (0.5%), after an average of 10 days after the onset of COVID-19. They pointed out that the mean age of these patients was greater and their cardiovascular and cerebrovascular risk factors were more severe.[11]

COVID-19 is thought to predispose patients to thrombotic pathological conditions in both venous and arterial circulation due to inflammation, platelet activation, endothelial dysfunction and stasis.[4] The initial signs of coagulopathy due to COVID-19 have been found to be marked increases in fibrin/fibrinogen-degradation products and D-dimer levels. It was observed that our patient had high levels of fibrinogen and D-dimer from the time when she was diagnosed with COVID-19 to the time when she was diagnosed with venous sinus thrombosis.

In the early stages of the disease, abnormalities in prothrombin time, partial thromboplastin time and platelet count are uncommon.[5] Detection of deep vein thrombosis (58%) as the autopsy finding among more than half of the 12 patients who died of COVID-19, and pulmonary embolism as the cause of death among one third of the patients, has emphasized the importance of not ignoring the tendency towards occurrences of thrombosis in the course of this disease. Hence, anticoagulants should be included during treatment planning.[6] Analysis on the data on 184 patients with COVID-19 infection who were monitored in an intensive care unit showed that 31% of them had thrombotic complications. Thus, prophylaxis for thrombosis was strongly recommended for patients hospitalized with this diagnosis.[7]

On the other hand, some published papers have argued that the signs and symptoms of severe COVID-19 infection are more similar to the pathophysiology and phenotype of complement-mediated thrombotic microangiopathy (TMA), rather than to sepsis-induced coagulopathy or diffuse intravascular coagulation (DIC).[8] Thrombotic microangiopathy is characterized by organ damage such as microangiopathic hemolytic anemia, thrombocytopenia, and neurological, renal and cardiac dysfunction. Thrombocytopenia and neurological deficits were also observed in our patient. In another study, anemia, increased lactate dehydrogenase (LDH), thrombocytopenia and organ damage (neurological in all patients and cardiac in one) were explained by thrombotic microangiopathy in three patients with a diagnosis of COVID-19.[9]

Cerebral venous thrombus differs significantly from arterial infarctions in terms of risk factors. Hypercoagulability is an important risk factor and an important cause of stroke in young people. Women are affected three times more often than men. The most common symptoms are headache, seizures and focal neurological deficits. The diagnosis can be confirmed by magnetic resonance imaging, computed tomography-venography or catheter angiography.

The primary treatment for venous sinus thrombosis is anticoagulation, based on the limited evidence from randomized trials. Although a small series of cases has indicated that endovascular therapy may be promising, these data require confirmation through a randomized trial. Decompressive surgery can be lifesaving for patients at risk of herniation. The prognosis is generally better than that for arterial stroke.[12] Although venous sinus thrombosis was previously considered to be a life-threatening condition, it is known that the mortality rate in these cases declines over time. Moreover, increased clinical awareness, development of neuroimaging techniques and improvement in therapeutic management have provided better prognoses through enabling earlier diagnosis and identification of less severe cases.[13]

Pregnancy and the puerperium are common causes of transient prothrombotic conditions. About 2% of pregnancy-related strokes can be attributed to venous sinus thrombosis. In the puerperium, the rate of venous sinus thrombosis is 12 cases per 100,000 births. This venous rate in the puerperal period is only slightly lower than that of arterial stroke. Women are at risk of venous thromboembolic events during pregnancy and for up to six to eight weeks after delivery. Most cases of pregnancy-related venous sinus thrombosis are seen in the third trimester or, more often, in the puerperium, when the body prepares for delivery through hypercoagulation. In a paper published in Canada, it was reported that frequency of venous sinus thrombosis in the postpartum period is much higher than during pregnancy. In the puerperium period, the presence of infection and use of instrumental delivery or cesarean section increase the risk of venous sinus thrombosis. During pregnancy, it is known that the risk of venous sinus thrombosis increases in the presence of hypertension, infections and excessive vomiting, and as the maternal age increases.[14] The European Academy of Neurology has recommended that treatment for acute venous sinus thrombosis should start with oral anticoagulant therapy (vitamin K antagonists) for 3-12 months, according to risk factors.[15]

Another risk factor with a relationship to venous sinus thrombosis that is clearly known is inflammation. Venous sinus thrombosis is associated with systemic inflammatory conditions such as Behçet's disease and inflammatory bowel disease, in addition to infections such as otitis, mastoiditis, sinusitis, dental infections and skin abscesses in neighboring tissues and meningitis.[13] In the anamnesis and examination of our patient, no finding suggesting adjacent tissue infection or Behçet's or inflammatory bowel disease was found.

Antinuclear antibody positivity can be seen in autoimmune diseases, especially systemic lupus erythematosus, but it is not a laboratory test specific to autoimmune diseases. Since antinuclear antibody positivity can be observed in acute or chronic infectious processes,[16] it was planned that our patient would undergo this

examination after discharge. The anamnesis of our patient was negative for rheumatological diseases.

The etiology of venous sinus thrombosis can be explained in terms of the classical Virchow triad, i.e. blood flow stasis, vessel wall changes and changes in blood content. We believe that the combination of pregnancy and systemic inflammation due to COVID-19 caused thrombosis in our patient, on the basis of genetic prothrombin heterozygous mutation.

One of the clinical manifestations of COVID-19 is nonspecific headache, as is also frequently observed during other viral infections. However, this symptom can often be mild enough to lag behind other clinical findings. If there is no visual impairment, focal neurological deficit or seizure, venous sinus thrombosis can be neglected in the differential diagnosis. Our patient was diagnosed not after occurrences of headache and nausea-vomiting, but after admission to the hospital because of the accompanying symptoms of right hemiparesis. In our case, like what has been described in the literature,[11] the central nervous system event started on the ninth day after COVID-19 infection began, and a stroke occurred on the 13th day. Thus, within four days, the rapid clinical progression resulted in parenchymal ischemia. The neurological clinical findings rapidly improved in parallel with the end of pregnancy, start of administration of low molecular weight heparin and decrease in infection parameters.

Reports correlating COVID-19, headache and pregnancy are very rare (**Table 1**).

CONCLUSION

Headache is one of the common symptoms of COVID-19. In the presence of other risk factors accompanying COVID-19, the risk of thromboembolic events increases significantly. Among patients with suspected COVID-19, considering venous sinus thrombosis in the differential diagnosis may be life-saving, through enabling early diagnosis and treatment. This is especially so in the presence of causes of hypercoagulability such as pregnancy, malignancy and presence of atypical features like analgesic unresponsiveness, awakening from sleep, visual impairment, neurological deficits or seizures.

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Table 1. Search of the literature in medical databases for case reports on COVID-19, pregnancy and headache on November 6, 2020

Database	Search strategies	Papers found	Papers related (to pregnancy, headache and COVID-19)	Etiology	Main neurological symptom
MEDLINE (via PubMed)	COVID-19 [MESH] Pregnancy [MESH] Headache [MESH] Case Report [ptyp]	2	2	Spinal anesthesia 1 Pituitary apoplexy 1	Headache
Cochrane	COVID-19 [MESH] Pregnancy [MESH] Headache [MESH] Case Report [ptyp]	0	0	0	0
Embase	COVID-19 [MESH] Pregnancy [MESH] Headache [MESH] Case Report [ptyp]	0	0	0	0

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Subclinical thyroid disorders should not be considered to be a non-classical risk factor for cardiovascular diseases

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Dear Editor,

I read with interest the editorial about subclinical thyroid disorders as a non-classical risk factor for cardiovascular disease.[1] Although the editorial discusses some particularly important issues regarding the epidemiology of cardiovascular diseases and points out that there is a high burden of underdiagnosed subclinical thyroid diseases, especially among women and individuals with low socioeconomic status, some remarks about this need to be made.

There is no doubt about the importance of studying the association of subclinical thyroid disorders and cardiovascular risk. However, this association is weak and there is no evidence that treatment of these disorders is associated with reduced cardiovascular outcomes. Epidemiology, like science itself, is not value-free and it may be used as a tool to support predetermined ideas, as has been pointed out by many commentators.[2] In the case of subclinical thyroid disorders, although many studies have shown that they have an association with surrogate markers for cardiovascular disease, their associations with clinical outcomes are less clear. The magnitude of the association is low and, hence, presence of such an association might only be a representation of residual confounding. Moreover, no randomized trial on treatment effect has been conducted.[3]

Sir Richard Doll has suggested that for an epidemiological study to be reasonably convincing, the lower limit of the 95% confidence level of increased risk should fall above a threefold increase (> 200% increase).[2,4] Other authors have even suggested that a fourfold increase in risk should be the lower limit.[2,4] On the other hand, subtler risks, such as the 30 to 50% increase in risk that has been observed in some studies on subclinical thyroid disorders, are not compelling. However, use of subclinical thyroid disorders as a novel cardiovascular risk factor would affect a large segment of the population (high prevalence of subclinical thyroid disorders) and have a potentially huge negative impact on public health, through transforming healthy people into sick people, without the expected benefits from treating a true risk factor.

We are increasingly embedded in a culture of overuse of medical services and medicalization of society. Our never-ending search for risk factors has been very favorable to and has been stimulated by the biomedical industry. Over the last few decades, we have gradually seen a change in preventive strategies such that high-risk strategies have become prioritized through reducing the cutoff points of traditional risk factors and creating new ones.

In fact, this sort of high-risk strategy has departed from the original strategy conceptualized by Geoffrey Rose almost three decades ago.[5] This misinterpretation of Rose's concept tries to encompass some of the characteristics of the original population strategy, to produce an intermediate type of prevention strategy that only exhibits the downsides of both the high-risk and the population strategy. It may also produce more fear and morbidity than what it is supposed to prevent, through transforming healthy people into sick individuals.

Therefore, I fear that attributing the status of a new cardiovascular risk to subclinical thyroid disorders is a misunderstanding that may reinforce the overmedicalization of an already medicalized society that perfectly suits a neoliberal approach to healthcare.[6] This leads to labeling (i.e. heightened awareness of pseudo-risk factors), a range of psychological and physical side-effects, rising healthcare costs and overutilization of healthcare services without delivering better outcomes.

Healthcare needs to be directed towards sick and suffering people, such that prevention is left to interventions that are mostly outside the healthcare system. Indeed, the distinction between clinical care and prevention of future disease is essential for any robust healthcare system to thrive.

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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]

Short communications

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

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

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

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

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

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

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

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

FORMAT: FOR ALL TYPES OF ARTICLES

Title page

The title page must contain the following items:

1. Type of paper (original article, review or updating article, short communication or letter to the editor);
2. Title of the paper in English, which should be brief but informative, and should mention the study design.[14] Clinical trial, cohort, cross-sectional or case-control study, and systematic review are the most common study designs. Note: the study design declared in the title should be the same in the methods and in the abstract;
3. Full name of each author. The editorial policy of the *São Paulo Medical Journal* is that abbreviations of authors' names must not be used; therefore, we ask that names be stated in full, without using abbreviations;
4. Place or institution where the work was developed, city and country;
5. Each author should indicate the way his/her name should be used in indexing. For example: for "João Costa Andrade", the indexed name could be "Costa-Andrade J." or "Andrade JC", as preferred;
6. The author's professional background (Physician, Pharmacist, Nurse, Dietitian or another professional description, or Undergraduate Student); and his/her position currently held (for example, Master's or Doctoral Student, Assistant Professor, Associate Professor or Professor), in the department and institution where he/she works, and the city and country (affiliations);
7. Each author should present his/her ORCID identification number (as obtained from HYPERLINK "http://www.orcid.org/" www.orcid.org);
8. Each author must inform his contribution, preferably following the CRediT system (see above in Authorship);
9. Date and venue of the event at which the paper was presented, if applicable, such as congresses, seminars or dissertation or thesis presentations.
10. Sources of financial support for the study, bursaries or funding for purchasing or donation of equipment or drugs. The protocol number for the funding must be presented with the name of the issuing institution. For Brazilian authors, all grants that can be considered to be related to production of the study must be

declared, such as fellowships for undergraduate, master's and doctoral students; along with possible support for postgraduate programs (such as CAPES) and for the authors individually, such as awards for established investigators (productivity; CNPq), accompanied by the respective grant numbers.

11. Description of any conflicts of interest held by the authors (see above).
12. Complete postal address, e-mail address and telephone number of the author to be contacted about the publication process in the Journal (the "corresponding author"). This author should also indicate a postal address, e-mail address and telephone number that can be published together with the article. *São Paulo Medical Journal* recommends that an office address (rather than a residential address) should be informed for publication.

Second page: abstract and keywords

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

The following headings must be used in the structured abstract:

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

References

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

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

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

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

At the end of each reference, please insert the "PMID" number (for papers indexed in PubMed) and the "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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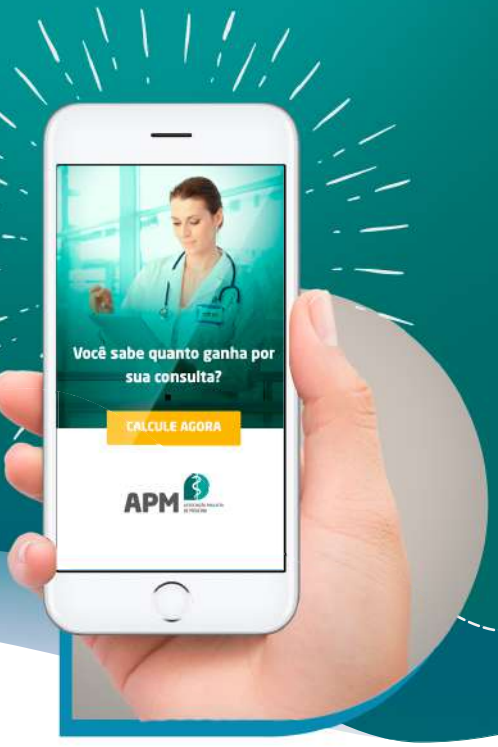

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