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Evidence-based medicine

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Evidence-based medicine (EBM) originated from the new science that resulted from combining the methods of epidemiology and clinical research. At a time when clinicians and epidemiologists were beset by rivalry, Archibald Cochrane integrated knowledge from these two fields and created what came to be known as clinical epidemiology. With help from his collaborators, including Professor Kerr L. White, he set out his clamor for efficacy, effectiveness and efficiency in clinical teaching, practice and research.

EBM crowns the fundamental concepts of medicine and healthcare through requiring evidence of effectiveness, efficiency and safety to guide decision-making such that there will be greater likelihood of making correct decisions. The concept of EBM was introduced at the beginning of the 1990s and was followed by establishment of the Cochrane Collaboration in 1992,by Professor Iain Chalmers in Oxford.[1]

Cochrane Brazil was founded in 1996 (under the name "Centro Cochrane do Brasil", i.e. Cochrane Center of Brazil), one year after I was first elected as Scientific Director of the São Paulo Medical Association (Associação Paulista de Medicina, APM). In the same year, the postgraduate course that today is named the Postgraduate Program on Evidence-Based Healthcare was founded at the São Paulo Medical School (Escola Paulista de Medicina), Federal University of São Paulo (Universidade Federal de São Paulo, UNIFESP).

Supporting medical practices on the basis of the best evidence, coming from rigorous methodologies that give this evidence comparative validity, is a civilizing process. This process was started by René Descartes at the beginning of the 18th century and was followed by publication of the first controlled clinical trial by James Lind.[2] Lind's work brought in the cure for scurvy and changed the course of human history. Moreover, it changed Brazilian history through avoidance of thousands of deaths among professionals of strategic importance for this country's development, who were brought to Brazil by Dom João VI in 1808.[3] In 1834, Alexander Louis went against the prevailing practice of treating all diseases through bloodletting, by conducting comparative studies (with or without bloodletting). He found that there was no benefit from this cruel practice, which was based on fanciful beliefs and on the authority of certain individuals who called themselves doctors.[4,5]

In 1948, Bradford Hill and Archibald Cochrane conducted the first blinded randomized controlled clinical trial, to test use of streptomycin for treating tuberculosis.[6] The study design in itself represented a revolution within medicine, since it created randomization and started "blinded" reading of radiographs by three observers. Furthermore, this study provided the first description of the cure for tuberculosis. In this manner, blinded randomized clinical trials became the research design model for comparing any proposed new treatment with placebo initially, if ethical, and subsequently with the traditional treatment when necessary.

The entire new methodology that was proposed had the objective of rationalizing how studies were conducted, with the aim of supplanting the bias caused through fantasies, emotions, beliefs and interests. In particular, it aimed to combat financial interests: not only among individuals but also among major corporations that seek to make profits. Few attitudes can lead to so much efficiency and avoid so much suffering and waste of money and lives as the use of evidence for making decisions, not only in relation to human health and the right to healthcare but also in relation to education, agriculture, veterinary science, social science and so on.

Deviation from this civilizing path is unthinkable. To recommend treatments without any scientific basis would be equivalent to regressing to the year 1650. It would throw back medical

care by centuries, waste money, opportunities and lives and represent choosing irresponsible management of all these values.

In the postgraduate program at UNIFESP, more than 300 master's and doctoral students have now graduated, to become involved in teaching and research. The Cochrane Library has now published more than 8,000 systematic reviews that map out important subjects relating to prevention, diagnosis and treatment of greater efficiency and safety for human health. Moreover, it has published the references of almost one million randomized clinical trials, which it has made available to everyone.

With support from the APM and from the Coordination Office for Improvement of Higher-Education Personnel (Coordenação de Aperfeiçoamento de Pessoal de Nível Superior, CAPES),Cochrane Brazil has been placing all this information at the disposal of all Brazilians since 2001. This information is available simply by accessing the website of Cochrane Brazil (www.cochranebrazil.org.br).

We will be returning to this topic with further details.

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Arteriosclerosis in Brazil. Findings from the Brazilian Longitudinal Study of Adult Health (ELSA-Brasil)

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Do not panic if you confuse "atherosclerosis" and "arteriosclerosis". Few people, including teachers and researchers in the medical world, can describe in few words the difference between these pathological conditions, which have distinct impacts on clinical practice and epidemiological studies (Lotufo PA, SPMJ, 2016).[1]

Briefly, arteriosclerosis relates to increased stiffness of the walls of major arteries and is correlated with greater age and higher blood pressure. On the other hand, atherosclerosis is a pathological process involving the endothelium of the tunica media and intima and relates to oxidation of cholesterol followed by a complex inflammatory chain. The degree of arteriosclerosis can be measured by some of the devices addressing different physiological characteristics of the blood circulation throughout the arterial tree.[2]

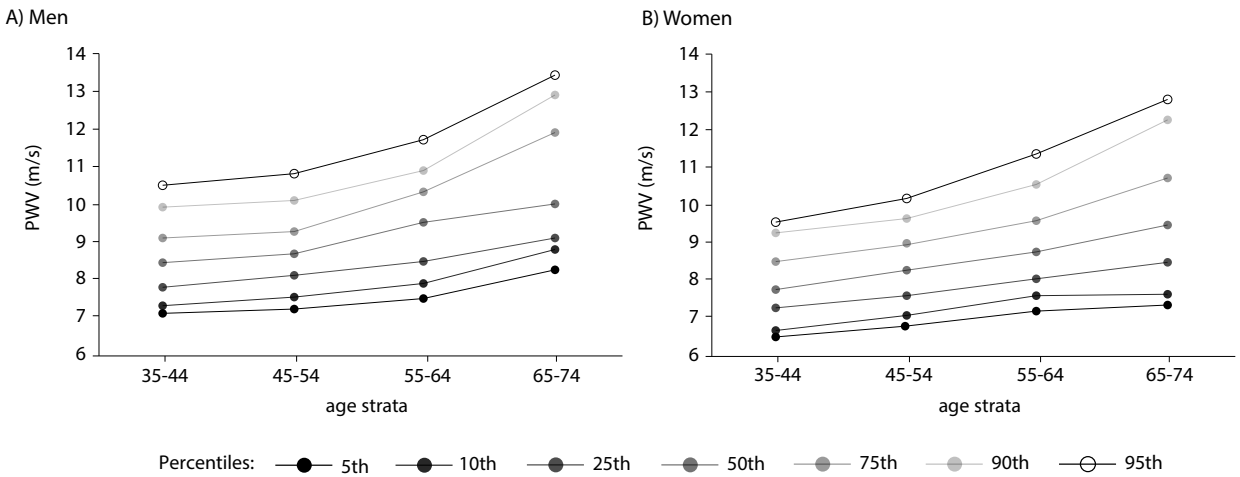
The most popular measurement is pulse-wave velocity, most commonly between the carotid and femoral arteries. This measurement is relatively easy and safe to make, but its clinical use is not yet recommended. However, clinical and epidemiological studies are changing the meanings of vascular diseases and hypertension. The physiological index most commonly determined has been the carotid-femoral pulse-wave velocity (cf-PWV). The higher the cf-PWV is, the more rigid and less distensible the major arteries will be. Stiffness of the aorta is associated with adverse health outcomes relating to hemodynamics, such as left-ventricular hypertrophy and diastolic heart failure. Moreover, high cf-PWV increases pulsatility in the capillary tree in organs that have high flow and low resistance, such as the brain (leading to white-matter lesions) and the kidney (leading to low glomerular filtration rate and albuminuria).[3] An increase of one standard deviation in aortic PWV has been found to be associated with nonfatal cardiovascular events (47%), cardiovascular mortality (47%) and all causes of death (42%).[4]

The Brazilian Longitudinal Study of Adult Health (ELSA-Brasil) is a cohort of 15,105 women and men aged 35-74 years who have been followed up since a baseline visit in 2008-2010 that is evaluating both atherosclerosis and arteriosclerosis. A summary of the findings of atherosclerosis in ELSA-Brasil has been published elsewhere.[1] Here, we aim to describe the findings relating to arteriosclerosis or, more precisely aortic stiffness as measured through the pulse-wave velocity.[5,6]

Figure 1 shows the cf-PWV according to age among 2158 apparently healthy men and women and indicates that it has a monotonic association with age. Among those subjects, men had higher values than women. There were no differences in the slope of cf-PWV versus age according to ethnicity/skin color after adjustment, thus confirming that age and mean arterial pressure have a substantial effect on pulse-wave velocity.[5]

Other classical risk factors have been seen to slightly influence the slope of the "pulse-wave velocity versus age" curve, such as diabetes, obesity and smoking, but the most influential risk factor is blood pressure. Nonetheless, the impact of these risk factors is marginal compared with the influence of aging, with a mean elevation of 0.05 m/s for each year of age, compared with 0.1 m/s per year for the whole ELSA-Brasil cohort including people with cardiovascular risk factors.[6]

In conclusion, arterial stiffness is strongly associated with aging. However, diminishing the burden of traditional risk factors can moderate the evolution of arteriosclerosis.



Adapted from reference #6.

Figure 1. Percentiles of carotid-femoral artery pulse wave velocity according to age strata among apparently healthy participants at the ELSA-Brasil baseline (2008-2010).

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Strategies to optimize MEDLINE and EMBASE search strategies for anesthesiology systematic reviews. An experimental study

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KEY WORDS:
Evidence-based medicine.
MEDLINE.
Databases, bibliographic.
Medical subject headings.
Anesthesiology.

ABSTRACT

BACKGROUND: A high-quality electronic search is essential for ensuring accuracy and comprehensiveness among the records retrieved when conducting systematic reviews. Therefore, we aimed to identify the most efficient method for searching in both MEDLINE (through PubMed) and EMBASE, covering search terms with variant spellings, direct and indirect orders, and associations with MeSH and EMTREE terms (or lack thereof).

DESIGN AND SETTING: Experimental study. UNESP, Brazil.

METHODS: We selected and analyzed 37 search strategies that had specifically been developed for the field of anesthesiology. These search strategies were adapted in order to cover all potentially relevant search terms, with regard to variant spellings and direct and indirect orders, in the most efficient manner.

RESULTS: When the strategies included variant spellings and direct and indirect orders, these adapted versions of the search strategies selected retrieved the same number of search results in MEDLINE (mean of 61.3%) and a higher number in EMBASE (mean of 63.9%) in the sample analyzed. The numbers of results retrieved through the searches analyzed here were not identical with and without associated use of MeSH and EMTREE terms. However, association of these terms from both controlled vocabularies retrieved a larger number of records than did the use of either one of them.

CONCLUSIONS: In view of these results, we recommend that the search terms used should include both preferred and non-preferred terms (i.e. variant spellings and direct/indirect order of the same term) and associated MeSH and EMTREE terms, in order to develop highly-sensitive search strategies for systematic reviews.

INTRODUCTION

A high-quality electronic search is essential for ensuring accuracy and comprehensiveness among the records retrieved when conducting systematic reviews.[1] The quality of the records retrieved depends on the way in which sensitive search strategies are formulated and on the use of appropriate electronic and non-electronic databases.[2] To achieve such quality, the researchers need to be familiar with the controlled retrieval languages and the tools available in each database.[3]

With the introduction and dissemination of evidence-based medicine within anesthesiology, there has been a growing focus on evaluation of the coverage, scope and limitations of databases[4-6] and search strategies[2,7-9] for anesthesiology-related systematic reviews.

For the purposes of indexing and searching, sets of equivalent terms are generally treated as having the same meaning, and as such, are represented by a single preferred term.[10] Non-preferred terms include variant spellings (e.g. closed-circuit anesthesia versus closed circuit anesthesia), direct and indirect ordering (e.g. anesthesia, rebreathing, versus rebreathing anesthesia) and synonyms (e.g. neoplasm and cancer). It is important to take into account both preferred and non-preferred terms in developing sensitive search strategies.

Furthermore, it is important to select all search terms that may represent the subject under investigation, for inclusion in the search strategy. Inclusion of both database subject headings and text words retrieves papers that would not have been found if only the subject headings had

been searched for.[11] Terms can be selected based on terms used by the authors of the article, or on keywords, or by consulting a controlled vocabulary or thesaurus (i.e. MeSH and EMTREE terms for the MEDLINE and EMBASE databases, respectively).

To assist researchers in identifying appropriate terms for a sensitive search strategy, librarians and educators recommend consulting and including preferred and non-preferred terms from a controlled database vocabulary.[11] However, by using all available terms in the thesaurus (i.e. subject headings), strategy development may be lengthy and very laborious. One additional factor influencing the choice of terms within anesthesiology is the users' own practical clinical experience.

OBJECTIVE

In this paper, we explored the use of preferred and non-preferred search terms and MeSH/EMTREE terms in the MEDLINE and EMBASE search strategies for systematic reviews with anesthesiology. The purposes of this study were to ascertain:

1. whether variant spellings and inclusion of direct and indirect ordering of the same terms retrieved the same number of records; and
2. whether inclusion of appropriate MeSH and EMTREE terms retrieved a larger number of records than would use of either MeSH alone or EMTREE alone.

METHODS

In our experimental study, we selected 37 terms in the field of anesthesiology from the MeSH and EMTREE databases, and then we analyzed 37 search strategies that were derived from those terms. These search strategies were adapted to include search terms with variant spellings, direct and indirect ordering, and related MeSH and EMTREE terms. The adapted searches were re-run in the MEDLINE (via PubMed) and EMBASE databases (**Table 1**). We did not impose any year restrictions. The databases were searched starting from their inception: Elsevier MEDLINE via PubMed from 1946 to January 2017; and Elsevier EMBASE from 1947 to January 2017. The cutoff date was January 15, 2017.

We chose simple terms in the field of anesthesiology through discussion with our co-authors with expertise in anesthesiology. These terms were searched for in the MeSH database, from which 237 potential subject headings were retrieved. From these, we selected 37 MeSH terms that met the inclusion criteria, after removal of duplicates. Therefore, if a MeSH term presented only one of the main two criteria described above, we excluded it.

In adapting the search strategies, the so-called preferred and non-preferred terms were identified based on the following search term eligibility criteria:

1. variant spellings,
   1.1. with or without a hyphen (e.g. closed-circuit anesthesia versus closed circuit anesthesia);
   1.2. with or without a space (e.g. anti-inflammatory agents, non-steroidal versus antiinflammatory agents, nonsteroidal);
   1.3. American or British English (e.g. inhalation anesthesia versus inhalation anaesthesia); and
2. direct or indirect order (e.g. anesthesia, rebreathing, versus rebreathing anesthesia). For simplicity, the use of variant spellings for a given term is hereafter referred to as "with variations", and the use of only one spelling for a given term is referred to as "without variations". EMTREE terms were selected based on the corresponding preferred term for a MeSH term.

The original and adapted search strategies were run on the same day to avoid differences in the number of indexed records in the databases searched. The searches in MEDLINE and EMBASE were conducted using a consistent approach, with preservation of default configurations for both indexes, and without any application of language, period, type of study or other filters.

Sample size

To estimate the sample size, we assumed that, across all the search strategies analyzed, 95% of the adapted search strategies with different models would show the same number of retrieved references. An error rate of 7% within a 95% confidence interval

Table 1. Comparison of results retrieved through the 37 search strategies, either with or without use of variations in the MEDLINE (via PubMed) and EMBASE databases

Comparison between with and without variations		Equal numbers of results retrieved (%)	Greater number of results retrieved with variations (%)	Smaller number of results retrieved with variations (%)	P-value
MEDLINE via PubMed	MeSH	27 (73.0)[a]	10 (27.0)[b]	0 (0.0)[c]	P < 0.0001
	MeSH + EMTREE	20 (54.0)[a]	16 (43.3)[a]	1 (2.7)[b]	P < 0.0001
	EMTREE	21 (56.8)[a]	14 (37.8)[a]	2 (5.4)[b]	P < 0.0001
EMBASE	MeSH	12 (32.4)[a]	25 (67.6)[b]	0 (0.0)[c]	P < 0.0001
	MeSH + EMTREE	10 (27.0)[a]	26 (70.3)[b]	1 (2.7)[c]	P < 0.0001
	EMTREE	16 (43.3)[a]	20 (54.0)[a]	1 (2.7)[b]	P < 0.0001

a, b, c = values followed by the same letter did not differ significantly.

was assumed. Based on these assumptions, it was necessary to analyze approximately 37 search strategies, according to the following equation:

$$E = Z\sqrt{pq/n}$$

Where E is the sample error (0.07); Z is a constant relative to a 95% confidence interval (1.96); p corresponds to the expected proportion of records retrieved; and q is the complement of p regarding the total number of systematic reviews (1 – P).

Statistical analysis

We used Kruskal-Wallis ranked analysis of variance and the SAS software (SAS 9.3 Help and Documentation, SAS Institute Inc., Cary, NC, USA) for the statistical analysis. We expressed the number of searches as absolute numbers and percentages. We considered P-values of less than 0.05 to be statistically significant.

RESULTS

The numbers of results retrieved across all 37 sets of search strategies are shown in **Tables 1 to 5**.

Table 2. Comparison of results retrieved through the 37 search strategies, considering use of MeSH and EMTREE terms separately or in association, with variations, in the MEDLINE database (via PubMed)

Use of MeSH and EMTREE terms separately or in association, with variations		Equal numbers of results retrieved (%)	Greater number of results retrieved with the first variable† (%)	Smaller number of results retrieved with the first variable† (%)	P-value
MEDLINE via PubMed	MeSH† versus MeSH + EMTREE	3 (8.1)[a]	0 (0.0)[b]	34 (91.9)[b]	P < 0.0001
	EMTREE† versus MeSH + EMTREE	15 (40.6)[a]	2 (5.4)[b]	20 (54.0)[a]	P < 0.0001
	MeSH† versus EMTREE	0 (0.0)[a]	12 (32.4)[b]	25 (67.6)[c]	P < 0.0001

†First variable is the one that is quoted first in the comparison of interest. a, b, c = values followed by the same letter did not differ significantly.

Table 3. Comparison of results retrieved through the 37 search strategies, considering use of MeSH and EMTREE terms separately or in association, without variations, in the MEDLINE database (via PubMed)

Use of MeSH and EMTREE terms separately or in association, without variations		Equal numbers of results retrieved (%)	Greater number of results retrieved with the first variable† (%)	Smaller number of results retrieved with the first variable† (%)	P-value
MEDLINE via PubMed	MeSH† versus MeSH + EMTREE	6 (16.2)[a]	0 (0)[b]	31 (83.8)[c]	P < 0.0001
	EMTREE† versus MeSH + EMTREE	12 (32.4)[a]	4 (10.8)[b]	21 (56.8)[a]	P = 0.0010
	MeSH† versus EMTREE	1 (2.7)[a]	12 (32.4)[b]	24 (64.9)[c]	P < 0.0001

†First variable is the one that is quoted first in the comparison of interest. a, b, c = values followed by the same letter did not differ significantly.

Table 4. Comparison of results retrieved through the 37 search strategies, considering use of MeSH and EMTREE terms separately or in association, with variations, in the EMBASE database

Use of MeSH and EMTREE terms separately or in association, with variations		Equal numbers of results retrieved (%)	Greater number of results retrieved with the first variable† (%)	Smaller number of results retrieved with the first variable† (%)	P-value
EMBASE	MeSH† versus MeSH + EMTREE	7 (18.9)[a]	1 (2.7)[b]	29 (78.4)[c]	P < 0.0001
	EMTREE† versus MeSH + EMTREE	13 (35.1)[a]	0 (0)[b]	24 (64.9)[c]	P < 0.0001
	MeSH† versus EMTREE	2 (5.40)[a]	13 (35.1)[b]	22 (59.5)[c]	P < 0.0001

†First variable is the one that is quoted first in the comparison of interest. a, b, c = values followed by the same letter did not differ significantly.

Table 5. Comparison of results retrieved through the 37 search strategies, considering use of MeSH and EMTREE terms separately or in association, without variations, in the EMBASE database

Use of MeSH and EMTREE terms separately or in association, without variations		Equal numbers of results retrieved (%)	Greater number of results retrieved with the first variable† (%)	Smaller number of results retrieved with the first variable† (%)	P-value
EMBASE	MeSH† versus MeSH + EMTREE	9 (24.3)[a]	1 (2.7)[b]	27 (73.0)[c]	P < 0.0001
	EMTREE† versus MeSH + EMTREE	15 (40.6)[a]	4 (10.8)[b]	18 (48.6)[a]	P = 0.0045
	MeSH† versus EMTREE	4 (10.8)[a]	12 (32.4)[b]	21 (56.8)[c]	P < 0.0001

†First variable is the one that is quoted first in the comparison of interest. a, b, c = values followed by the same letter did not differ significantly.

In the MEDLINE via PubMed database, in comparing search strategies with variant spellings, the majority of the search strategies retrieved the same number of records through the three different approaches: 73.0% in the strategies only using MeSH terms; 54.0% using MeSH and associated EMTREE terms; and 56.8% only using EMTREE terms (P < 0.0001) (**Table 1**). With regard to EMBASE, the searches with variations recovered more records than the ones without variations: only using MeSH terms, 67.7%; using the association of MeSH with EMTREE terms, 70.3%; and only using EMTREE terms, 54.0% (P < 0.0001) (**Table 1**).

Among the search strategies conducted in MEDLINE through PubMed with variations, the majority retrieved a smaller number of results through only using MeSH, compared with using MeSH and EMTREE together (91.9%); only using EMTREE, compared with using MeSH and EMTREE together (54.0%); and only using MeSH compared with only using EMTREE (67.6%) (P < 0.0001) (**Table 2**). Similar results were found using search strategies without variations, through comparing only using MeSH (83.8%) and only using EMTREE (56.8%) with using MeSH and EMTREE together; and through comparing only using MeSH with only using EMTREE terms (64.9%) (P < 0.0001 for all comparisons) (**Table 3**).

In EMBASE, search strategies involving associated MeSH and EMTREE terms identified more records than those only using MeSH terms or only using EMTREE terms, regardless of term variation (P < 0.0001) (**Tables 4 and 5**).

DISCUSSION

There are already many articles that explain the rules for searches in the literature. However, these are related to the use of filters rather than the construction of the search strategy itself. Furthermore, there are very few studies testing models for search strategies applicable to systematic reviews. The search strategy model that we used in this study is found in clinical practice among scientific investigators who wish to perform systematic reviews. However, this model had never been scrutinized through the rigor of scientific methodology.

Therefore, in this study, we compared the numbers of records with inclusion of variant spellings and inclusion of direct and indirect ordering, by means of three different formulations (i.e. MeSH, MeSH + EMTREE, and EMTREE) using identical search strategies. In other words, the same keywords and Boolean operators were used to test variant spellings, direct and indirect orders and associations of MeSH and EMTREE terms (or lack thereof) in MEDLINE via PubMed and in EMBASE, to identify the best approaches towards formulating search strategies for systematic reviews within anesthesiology. In this study, we did not aim to analyze the relevance of the papers retrieved (i.e. specificity).

Among the 37 search strategies run in MEDLINE via PubMed, 10 formulated only using MeSH terms retrieved fewer articles when the search was done without variations. In EMBASE, 20 search strategies formulated only using EMTREE terms retrieved more records when they were run with variations than without variations. While it may be ideal from a feasibility and efficiency perspective to conduct searches without variations, accounting for these variations appears integral to the formulation of a sensitive search strategy.

No variables were identified as being clearly predictive of search strategies in which inclusion of variations might be more beneficial in terms of the numbers of records identified. We initially hypothesized that searches using preferred terms that presented a higher number of non-preferred terms might be associated with differences in numbers of records identified when searched for with or without variations. However, both the searches formulated using the term "headache", which presented the greatest number of non-preferred terms (57 terms), and the searches using the term "delayed emergence from anesthesia" (55 non-preferred terms) retrieved the same number of records in searches conducted with and without variations, in MEDLINE with the use of MeSH terms alone.

We also considered whether the type of variation could have interfered with the results. However, no such association was found between the type of variation and the number of records identified.

The number of search strategies formulated only using MeSH terms in MEDLINE that retrieved the same number of results with or without variations was greater than the number of strategies formulated only using EMTREE terms in EMBASE that did the same. This may indicate that the controlled vocabulary of MeSH might be more structured, while EMTREE terms are more comprehensive.

In many published systematic reviews, we noticed that MeSH terms alone were often used in the search strategies. However, after we ran the searches only using MeSH, using MeSH plus EMTREE and only using EMTREE, we found that the numbers of results retrieved through the searches analyzed were greater using MeSH plus EMTREE in MEDLINE than using the same association in EMBASE. Considering that the EMBASE index system has greater depth than MEDLINE,[12] especially in relation to the field of pharmacology, in which most of our terms were classified (45%), use of an association of both MeSH and EMTREE terms in EMBASE has a lower impact than does use of the same association in the MEDLINE database. Therefore, if researchers want to find the maximum number of results through a search strategy for a particular topic, they should use both MeSH and EMTREE.

Our study has several limitations that should be considered. Firstly, while 37 studies provided us with an adequate sample size based on sample size calculations, a larger systematic analysis on search strategies might provide findings of greater robustness.

Secondly, while the number of hits identified is one means of measuring the comprehensiveness of search strategies, no effort was made to examine the records identified regarding their relevance to the given research question. It is possible that certain search strategies identified more records but were less focused on the research question, or missed eligible studies that were identified through other search strategies. Thirdly, our analysis was limited to the MEDLINE and EMBASE electronic databases. To achieve a more comprehensive analysis, other electronic databases and other indexed sources commonly used in systematic review searches should be evaluated, to better inform effective search strategy formulation when using these sources.

There are very few studies evaluating different models for building searching strategies. A study[9] with the aim of identifying the best method for searching in MEDLINE through PubMed, which considered whether parentheses, double quotation marks and truncation should be used or whether a simple search or search history should be used, found that there was no need to use phrase-searching parentheses to retrieve studies. However, the authors of that study recommended the use of double quotation marks when an investigator was attempting to retrieve articles in which a term appeared to be exactly the same as what was proposed in the search form.

Given that systematic reviews use rigorous methods to identify, critically appraise and synthesize relevant research studies, we also need to be aware of the best tools for implementing comprehensive search strategies, depending on the clinical question, in order to ensure that the results will be as current as possible and not be biased. Identifying optimal strategies for developing comprehensive and sensitive search strategies is fundamental to conducting rigorous systematic reviews.[13]

Our study found that the number of records retrieved in the MEDLINE (via PubMed) and EMBASE databases when search strategies were formulated using MeSH and/or EMTREE terms with variations (including variant spellings and direct and indirect ordering) differed from the number retrieved through the same strategies without these variations. Furthermore, using associated MeSH and EMTREE terms when conducting searches in both the MEDLINE (via PubMed) and EMBASE databases identified a greater number of records than did using only the EMTREE terms or only the MeSH terms.

CONCLUSIONS

In view of these results, we recommend inclusion of all preferred and non-preferred terms (variant spellings and direct/indirect orders of terms), and associated MeSH and EMTREE terms, when searching the MEDLINE (via PubMed) and EMBASE databases, in formulating sensitive search strategies for systematic reviews.

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It should read:
"Volpato ESN, Betini M, Puga ME, Agarwal A, Cataneo AJM, Oliveira LD, Bazan R, Braz LG, Pereira JEG, El Dib R"

Hepatitis C: evaluation of outcomes and georeferencing of cases in Santa Cruz do Sul, Brazil, between 2002 and 2015. A cross-sectional study

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KEY WORDS:
Hepatitis C.
Genotype.
Prevalence.
Death.

ABSTRACT

BACKGROUND: Hepatitis C virus infection is one of the main causes of chronic liver disease, with high death rates. The aim here was to analyze case outcomes, sociodemographic and clinical characteristics and spatial distribution among patients diagnosed with hepatitis C in the city of Santa Cruz do Sul (RS), Brazil.

DESIGN AND SETTING: Cross-sectional study on 200 cases of hepatitis C in Santa Cruz do Sul that were notified between 2002 and 2015.

METHODS: Secondary data including sociodemographic and clinical variables and type of outcome (death, follow-up, abandonment or clinical cure) were gathered. The spatial distribution analysis on hepatitis C virus cases according to outcome was based on information regarding residential address.

RESULTS: 58.5% of the patients were 41 years of age and over, 67% were males and 92.5% had the chronic form of the disease. The most frequent transmission route was illicit drug injection (29%); 15.1% of the patients presented coinfection with the human immunodeficiency virus (HIV). Regarding outcomes, 31% achieved clinical cure, 10% died and 20% abandoned follow-up. The cases studied were mainly located in regions of the city characterized by lower socioeconomic status, with high frequency of places used for drug trafficking.

CONCLUSION: The population consisted of adults aged 41 years and over, mostly with chronic hepatitis C. The most common transmission routes were illicit drug injection and blood transfusions. There were high rates of HIV coinfection and abandonment of disease monitoring and predominance of cases in neighborhoods with low socioeconomic status.

INTRODUCTION

The hepatitis C virus (HCV) is one of the leading causes of chronic liver disease worldwide and is characterized as a silent disease that is difficult to identify in most patients.[1,2] Approximately 15%-45% of infected individuals spontaneously clear the virus within six months of infection without any treatment, and the remaining 55%-85% of them may progress to persistent chronic infection. It has been estimated that the risk of developing cirrhosis within 20 years is 15%-30% in those with chronic HCV infection, and the risk of developing hepatocellular carcinoma is 1%-4% per year.[3,4] At a global level, around 71 million people have HCV, with approximately 399,000 deaths annually.[5]

In Brazil, the data show that the numbers of deaths due to HCV have been increasing over time in all regions. Between 2000 and 2015, 46,314 deaths related to HCV were identified.[1] The southern region presented a coefficient of mortality due to HCV as the underlying cause of death for 1.5/100,000 inhabitants. In the state of Rio Grande do Sul (RS), this coefficient was 2.8/100,000 inhabitants, which was almost three times larger than the national mean for the same period.[1] The data on the extent and spatial distribution of HCV outcomes in the city of Santa Cruz do Sul (RS) is limited, which thus highlights the usefulness of the present study.

The main route for HCV transmission is the parenteral route, through direct or percutaneous contact with contaminated blood. Additionally, it is also transmitted through sexual activity and the vertical route.[1-3] The groups at greatest risk of contracting HCV are illicit drug users, individuals with piercings and tattoos that were made using contaminated tools, HIV-positive

patients, individuals who received blood before 1992, healthcare professionals and patients undergoing hemodialysis.[1-3] Other less common forms of contamination are the parenteral route, which may occur through medical, dental, manicure and acupuncture procedures; and sharing of objects within the household.[6,7]

HCV prevention and control depends on a complex assessment of HCV infection, which involves correlation of risk factors and estimation of factors that accelerate disease progression.[8,9] Because there is no vaccine for HCV, or any type of post-exposure prophylaxis, proper epidemiological evaluation is essential for planning primary HCV prevention in any population. Follow-up of HCV-positive individuals by the healthcare team is of utmost importance, rather than sporadic medical evaluation. Such follow-up is required in order to establish what the treatment should be and to ensure adherence to treatment. HCV treatment is available free of charge through the Brazilian National Health System (SUS).[10]

In the light of this situation, the objective of the present study was to analyze case outcomes, sociodemographic and clinical characteristics and spatial distribution among HCV cases that were notified between 2002 and 2015 in the city of Santa Cruz do Sul (RS), Brazil.

METHODS

A cross-sectional study was carried out, in which all HCV cases diagnosed and notified in the urban area of the municipality of Santa Cruz do Sul (RS), Brazil, between 2002 and 2015, were included. HCV infection was defined as the presence of HCV ribonucleic acid (HCV-RNA) and anti-HCV antibodies in serum or plasma.[1] A positive HCV antibody test was taken to indicate exposure to HCV, which could represent current or past infection. A positive HCV-RNA test indicated current HCV infection.[11] Santa Cruz do Sul is located in the central region of the state of Rio Grande do Sul, at a distance of 155 km from the state capital, Porto Alegre. The estimated population of Santa Cruz do Sul is 127,516 inhabitants and its human development index is 0.773.[12]

Secondary data collection was carried out from March 2016 to August 2017, at the viral hepatitis reference unit of Santa Cruz do Sul (RS). The data were collected from the Notifiable Diseases Information System (SINAN), Mortality Information System (SIM) and Laboratory Environment System (GAL) of the Ministry of Health and from electronic records (Fly Saúde) of the Municipal Health Department of Santa Cruz do Sul.

The data collection tool included the following sociodemographic variables: gender, age, ethnicity, schooling level and occupation; and clinical variables: associated diseases, clinical form of the disease, probable source of infection and HCV genotype. These data were collected from SINAN. Data relating to case outcome (death, follow-up, abandonment or clinical cure) were collected from SIM, electronic records and GAL. Situations in which patients had not come to their medical appointments for the last six months were considered to constitute abandonment of treatment. Situations in which patients had undetectable levels of HCV-RNA four weeks after treatment were considered to constitute clinical cure. Patients whose cases had been notified to SINAN but for whom there were no data in electronic records, SIM or GAL were considered to be unlocatable.

The spatial distribution of HCV cases was determined based on information regarding the residential address found in SINAN. The distribution analysis on the cases was performed using the representation technique, by counting points according to the case outcome. The graphical representation of the mapping was produced using the Quantum GIS 2.14.3-Essen (QGIS) software. To create thematic maps, the Google Earth Pro software, which is available free of charge at https://www.google.com.br/earth/download/gep/agree.html and the Quantum GIS 2.14.3-Essen (QGIS) software, which is also available free of charge at https://www.qgis.org/en/site/forusers/download.html, were used. The geoprocessing sector of the municipality of Santa Cruz do Sul, at http://www.santacruz.rs.gov.br/geo/, provided free vector base maps of the urban area of the municipality, along with vector maps of the streets and avenues, districts and urban perimeter. These data were entered into the QGIS software, which was used to produce all thematic and spatial distribution editions of the maps. The outcomes from the HCV cases were georeferenced using Google Earth Pro software and were then exported in kml (Keyhole Markup Language) format. These points were inserted as an overlay in the QGIS, so that they could be located. The final layouts of the maps were also produced using the QGIS software.

The data were input and analyzed using the SPSS software, version 23.0. A descriptive analysis was carried out, which included investigation of the frequency distribution of sociodemographic, clinical and outcome variables. The data were presented as absolute numbers, frequencies and/or means.

This project was approved by the Research Ethics Committee of Universidade de Santa Cruz do Sul (UNISC), under number 1,361,022.

RESULTS

A total of 200 cases were analyzed. Sociodemographic, clinical and outcome data are shown in **Table 1**. Regarding age, 58.5% of the patients were aged 41 years or older, with a range from 13 to 75 years. There were 134 male cases (67%).

Thirty patients (15.1%) were coinfected with HCV and HIV and, among these patients, eight (26.7%) had abandoned their treatments. The chronic form of HCV was identified in 185 patients (92.5%). Regarding the sources of infection, the most frequent of these, reported by individuals evaluated here, were illicit drug use (29%) and blood transfusions (12.5%) (**Table 1**).

Twelve patients (6%) were institutionalized in a prison when their cases were notified, and five of these (41.7%) subsequently abandoned their treatments.

Death was reported in a total of 20 cases (10%). HCV was the underlying cause of death in nine cases (45%), HIV in three (15%) and other causes in eight (40%). A total of 73 patients (36.5%) were classified as either having abandoned their treatments or being unlocatable. Among these, 16 (21.9%) were coinfected with HCV and HIV.

It was possible to describe the spatial distribution of HCV cases in relation to 172 patients (86%). The numbers of HCV cases were higher in regions of the municipality with lower socioeconomic status and high frequency of places used for drug trafficking, and in the regional prison (**Figure 1**).

DISCUSSION

This study population predominantly comprised adult individuals aged 41 years and over. The reported transmission routes were, most frequently, illicit drugs and blood transfusions. Among all the cases, 92.5% had chronic hepatitis, 52% had genotype 1, 10% died, 31% achieved clinical cure and 15.1% were coinfected with HIV.

In a study carried out among HCV-positive individuals who were attended at a public service in Porto Alegre, Brazil, it was found that the mean age of the individuals assessed was 40.1 years.[13] Other studies have also shown higher numbers of cases among individuals older than 40 years of age.[13,14] Similar results were observed in our study. The diagnosis of hepatitis C is more frequent in adulthood and among the elderly, given that it is a silent and chronic disease, and because these individuals may have undergone some type of surgery with inadequately sterilized instruments and unsafe blood transfusions before the year 1993, when there was no screening for hepatitis C in blood banks yet.[14,15]

Regarding sex, the hepatitis C cases were predominant among male individuals (67%), thus corroborating other studies.[13,16] In Brazil, 106,637 HCV cases occurred among males between 1999 and 2015, representing 58.5% of all cases.[1] The higher prevalence of hepatitis C virus infection among males can be explained by their exposure to risk factors, or by the fact that the diagnosis of HCV is made when men are blood donation volunteers.[15] HCV infection affects both men and women, but there are no comprehensive studies confirming that men are more vulnerable to this infection.[15]

The main routes of HCV transmission have been found to be illicit drugs, blood transfusions (mainly before 1992), sharing of materials for drug use, lack of personal hygiene and presence of tattoos and piercings.[17,18] The risk of sexual transmission is low, but recent data have shown that promiscuous male homosexual activity is associated with HCV infection.[18] In the present study, 29% of the patients reported drug use and 12.5% had had blood transfusions, but the year of the blood transfusion was not mentioned.

Table 1. Sociodemographic, clinical and outcome characterization of the population with hepatitis C virus in the municipality of Santa Cruz do Sul (RS), 2002-2015

Variable	n = 200	%
Sex		
Male	134	67
Female	66	33
Age (years)		
13-20	3	1.5
21-30	26	13
31-40	54	27
41-50	60	30
> 50	57	28.5
Ethnicity		
Caucasian	164	82
Non-Caucasian	36	18
Level of schooling		
Illiterate	2	1
Elementary school (incomplete/complete)	164	67
High school (incomplete/complete)	134	32
Occupation		
Retired	49	24.5
Driver	17	8.5
Factory worker*	38	19
Teacher	11	5.5
Mason	24	12
Farmer	5	2.5
Soccer player	3	1.5
Prison inmate	12	6
Beauty professional†	14	7
Unknown	27	13.5
In prison		
Yes	12	6
No	188	94
Associated diseases		
HIV/AIDS	30	15.1
HBV	2	1
HAV	1	0.5
Clinical form		
Acute hepatitis	15	7.5
Chronic hepatitis	185	92.5
Probable source of infection		
Sexual	9	4.5
Transfusion	25	12.5
Illicit drug use	58	29.0
At home	1	0.5
Surgical treatment	6	3.0
Unknown	101	50.5
HCV genotype		
Genotype 1	104	52.0
Genotype 2	10	5.0
Genotype 3	58	28.5
Unknown	28	14.5
Outcome		
Clinical cure	62	31.0
Undergoing follow-up	45	22.5
Unlocatable	33	16.5
Abandonment of treatment	40	20.0
Death	20	10.0

HCV = hepatitis C virus; HIV/AIDS = human immunodeficiency virus/acquired immunodeficiency syndrome; HBV = hepatitis B virus; HAV = hepatitis A virus; *tobacco industry worker; †manicurist, hairdresser, beautician.

These results agree with data from the Brazilian Ministry of Health, in which it was reported that use of drugs was the main route for HCV transmission among the cases notified (29.2%).[1] In another study, conducted in Palhoça, state of Santa Catarina (SC), which was based on HCV notifications in the years 2008 to 2010, the risk factors most often involved in disease transmission were use of illicit injection drugs (34.5%), use of inhalable drugs and crack (33.5%) and blood transfusions (28.6%).[14]

Coinfection with HIV is common among hepatitis C carriers, since these viruses have similar transmission routes, mainly through

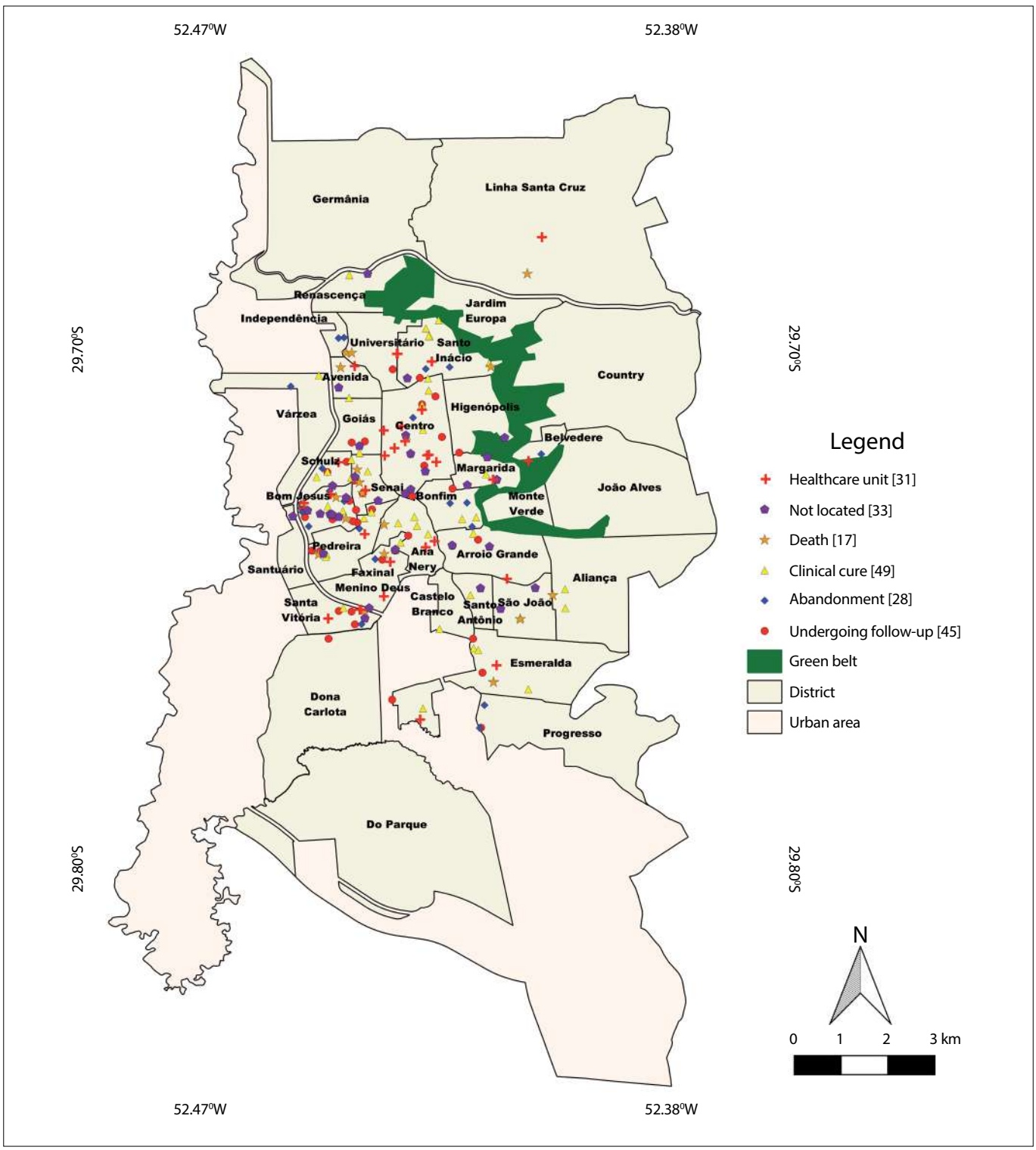

Figure 1. Map of the municipality of Santa Cruz do Sul (RS) showing the spatial distribution of hepatitis C virus cases, classified according to the genotype.

the parenteral route.[19] In the present study, 15.1% of the individuals had HCV/HIV coinfection. About 2.3 million people living with HIV around the world are coinfected with HCV.[20] The HCV/HIV coinfection rate for Brazil between 2007 and 2016 was 9.8% and it varied according to the region.[1] The southern region had the highest coinfection rate in Brazil (13.3%), and this was similar to what was observed in the present study. In cases in which coinfection occurs, the host's immune response is impaired and the prognosis for both infections is worsened: liver impairment is accelerated, with progression to cirrhosis, liver failure and liver carcinoma, which can lead to the death of the infected individual.[19,21] Antiretroviral therapy, which improves the survival of HIV-infected patients, may contribute towards liver injury and lead to hepatotoxicity in cases of coinfection, thereby accentuating the liver injury caused by the hepatitis virus. The risks of hepatotoxicity in coinfected patients are three to four times higher than in non-infected patients, due to liver disorders.[21]

Regarding the form of the disease, 92.5% of the individuals in the present study had the chronic form and 10% of them died. A systematic review of the literature suggested that approximately 130-150 million people are living with chronic hepatitis C.[22] In Brazil, between 1999 and 2016, more than 155,000 cases of chronic HCV cases were confirmed.[1] Between 1990 and 2013, the number of deaths worldwide due to viral hepatitis increased from 0.89 million to 1.45 million.[23]

In the absence of treatment, 20-30% of hepatitis B virus (HBV) and HCV-infected individuals will develop hepatocellular carcinoma or cirrhosis. It has been estimated that this will lead to 19 million deaths between 2015 and 2030 (11.8 million due to HBV and 7.2 million due to HCV) around the world.[23] In the present study, 22 cases (11%) developed cirrhosis or hepatocellular cancer.

Treatment for hepatitis is available free of charge through the Brazilian public health system (SUS) and has the purpose of reducing the risk of developing cirrhosis and liver carcinoma. The most widely used pharmacological treatment for HCV was for many years based on a combination of interferon and ribavirin.[24] Treatment regimens based on interferon may be problematic because of the high frequency of adverse effects and the inconvenience of weekly injections. Thus, their effectiveness may be limited especially among patients whose clinical condition is more severe.[24,25]

Recently, the introduction of therapeutic regimens including new drugs such as sofosbuvir and daclatasvir has shown positive results regarding HCV treatment.[26] Among the patients analyzed here, it was seen that 31% presented clinical cure, regardless of the therapeutic regimen used. Recently identified symptomatic or non-symptomatic acute infection is an important HCV control measurement. Late treatment onset is associated with a worse sustained virological response (SVR). A situation of SVR consists of non-detection of HCV-RNA 12 or 24 weeks after treatment. If the infection has been recently treated, SVR rates may reach values greater than 80%.[27]

One limitation of this study was indeed the impossibility of evaluating the therapeutic regimens used individually. A total of 33% of the patients were considered to be unlocatable in any of the public information systems investigated. Some of these patients may have sought treatment within the private sector.

Among the patients of the present study, 45 (22.5%) are still being followed up, and 40 (20%) abandoned their treatment. HCV is a disease that requires discipline among patients and understanding from healthcare professionals, and situations that can significantly interfere with the success of follow-up and treatment adherence need to be identified rapidly.[27] Thus, it is crucial that healthcare professionals should establish a solid relationship with their patients.[10,21] To establish proper treatment for patients with chronic HCV, it is extremely important that their medical records, anamnesis and physical examination should be rigorously completed and that they are included within the routine of screening and referral services. The same is true regarding filling out forms that are used in disease notification and requests for examinations. Adherence to healthcare services among patients with chronic hepatitis C is essential, for the healthcare strategy to be successful.[27]

During the pretreatment period, it is also necessary to make a careful evaluation of patients' comorbidities and coinfections caused by HBV and HIV, along with their clinical, psychiatric and social conditions.[21,28] Because of the pathophysiological characteristics of chronic HCV infection, at least four consultations per year are required. This routine should be individualized among patients for whom therapy was recently started or in situations in which the risk of adverse events requires priority care.[21]

Genotype 1 (52%) was most prevalent in the present study, which confirms that in RS and Brazil, genotype 1 is the one most frequently identified. This is also the genotype that is the most resistant and the most difficult to treat.[14] HCV genotype 1 is most prevalent worldwide (49.1%), followed by genotypes 3 (17.9%), 4 (16.8%) and 2 (11.0%).[29] Silva et al. evaluated genotype distribution in a population of more than 1,500 patients living in the states of RS and SC. These data confirmed that genotypes 1 (53.9%) and 3 (40.7%) were most prevalent in southern Brazil, with frequencies that were similar to those found in the present study.[30]

According to the assessment of the geographical distribution of HCV cases, there was higher prevalence of cases in the districts where the populations showed the highest levels of social vulnerability and in a prison where 12 cases (6%) were identified. These districts have low socioeconomic levels and include many places that are used for drug trafficking. Oliveira et al. carried out a geoprocessing analysis on HCV cases in São Paulo and found that HCV infection was associated with low socioeconomic level.[23] One hypothesis that corroborates the greater presence of HCV cases in regions with low socioeconomic status could be that such individuals lack knowledge about HCV infection routes, such as the sharing of razors, use of

pliers, tattooing with non-sterile material, unprotected sexual intercourse and use of needles shared among drug users.[2-6]

HCV infection and other forms of viral hepatitis are diseases that have an impact on public health worldwide. Although many data suggest that HCV infection could be eliminated over the next 15-20 years, good understanding of HCV infections is still required in order to develop strategies for preventing new infections.[31] In this regard, support for health promotion and establishment of surveillance, prevention and control measures for these diseases is crucial for improving patients' quality of life and decreasing disease transmission.

CONCLUSION

This population of HCV cases that were diagnosed and notified between 2002 and 2015 in the municipality of Santa Cruz do Sul, was characterized by adult individuals aged 41 years and over, who mostly had chronic hepatitis C and were undergoing treatment. The main transmission routes were illicit drugs and blood transfusions. There were high rates of HIV coinfection and abandonment of disease monitoring, and the cases were predominantly in neighborhoods with low socioeconomic status. In this regard, the present study helps to alert the health authorities about the importance of this disease and the need to implement coping strategies, while also encouraging other studies, with the aim of improving the understanding of the HCV infection situation in other locations.

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Survival outcome among patients with Ewing's sarcoma of bones and joints: a population-based cohort study

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Survival analysis.
Retrospective studies.

ABSTRACT

BACKGROUND: The aim here was to elucidate the current survival condition of patients diagnosed with Ewing's sarcoma of the bones and joints and determine independent risk factors associated with the prognosis.

DESIGN AND SETTING: Retrospective cohort study based on the Surveillance, Epidemiology and End Results (SEER) database in the United States.

METHODS: We identified 397 patients who were diagnosed with Ewing's sarcoma of the bones and joints between January 2004 and December 2013. The multivariate Cox proportional hazards model was used to determine factors associated with the risk of death by adjusting for various factors.

RESULTS: The one, two and five-year disease-specific survival rates were 89.08%, 78.08% and 62.47%, respectively. The factors related to death were age (≥ 18 years versus < 18 years; hazard ratio, HR = 1.77; 95% confidence interval, CI: 1.38-2.31); tumor site (extremity versus spine and pelvis; HR = 2.03; 95% CI: 1.31-2.62); tumor size (> 10 cm versus ≤ 10 cm; HR = 1.78; 95% CI: 1.34-2.56); and type of treatment (surgery alone versus radiotherapy with surgery; HR = 0.51; 95% CI: 0.38-0.89; or radiotherapy alone versus radiotherapy with surgery; HR = 1.61; 95% CI: 1.10-2.39; or no treatment versus radiotherapy with surgery; HR = 1.86; 95% CI: 1.23, 2.58).

CONCLUSIONS: Patients with Ewing's sarcoma showed poor survival in situations of age ≥ 18 years, tumor size > 10 cm, receiving radiotherapy alone and receiving no treatment. Patients undergoing surgery alone had better survival.

INTRODUCTION

Ewing's sarcoma is a rare cancer that accounts for less than 10% of all malignancies existing in the human body. It stems from primitive neuroepithelial cells, which are able to differentiate into various mesenchymal cells, and has a propensity to metastasize to distant sites at an early stage . This cancer typically occurs in adolescents and young adults, accompanied by a very poor prognosis. It is considered to be a high-grade malignancy, ranking second in the list of malignant bone tumors.[1-7] It is commonly considered to be an extremely aggressive osteolytic cancer that usually occurs in the bones of the limbs and pelvis and it can metastasize to distant locations such as bone marrow, the lungs and other soft tissues at an early stage.[1,3,7]

In the United States, the overall incidence rate of Ewing's sarcoma is approximately 0.1 case per 100,000 individuals per year, and this rate had not undergone any obvious change over past 30 years. An estimated 90% of these patients are under 20 years old, and the death rate is approximately 0.05 cases per 100,000 individuals per year. Additionally, most cases of Ewing's sarcoma of the bones and joints are found in the limbs, pelvis or spine.[4,8]

Nonetheless, there is a lack of survival studies on Ewing's sarcoma arising in the bones and joints and associated prognostic factors, based on up-to-date data on nationwide populations.

OBJECTIVE

The purpose of this study was to demonstrate the survival conditions of patients with Ewing's sarcoma of the bones and joints and determine independent risk factors associated with their prognosis.

METHODS

The Surveillance, Epidemiology and End Results (SEER) database named "Incidence-SEER 18 Regs Research Data + Hurricane Katrina Impacted Louisiana Cases, Nov 2015 Sub (1973-2013 varying)"

was selected to perform a population-based search for patients suffering from Ewing's sarcoma of the bones and joints between January 2004 and December 2013.

The SEER Program[9] is supported by the National Cancer Institute of the United States and has provided statistical information on tumor cases since 1973. It collects data on cases diagnosed with cancer throughout the United States, with an estimated 28% of the United States population covered. The SEER registry is a validated database that is frequently applied for cancer survival studies. The National Cancer Institute does not require institutional review board approval for SEER studies because it is an unidentified public-use database.

Histological International Classification of Diseases (ICD) codes (ICD-0-3) were used to identify Ewing's sarcoma (9260/3), (9364/3). Site-specific codes (C40.0-C40.3, C40.8, C40.9, C41.2, C41.4 and C41.8) were used to screen for tumors originating in the extremities, pelvis and spine, while the codes for bones of the skull and face, mandible, rib, sternum, clavicle and associated joints were not included.

The following primary data were drawn from the database for analysis: age at diagnosis, sex, race, tumor site, tumor size, tumor grade, type of treatment, cause of death and survival in months. Patients diagnosed through either autopsy or the death certificate were excluded. Those who presented secondary malignancies at the time of diagnosis or whose diagnoses were not confirmed by means of histopathological evaluation were also excluded. Cases without complete information were excluded. The inclusion and exclusion procedure is showed in the flow chart of **Figure 1**.

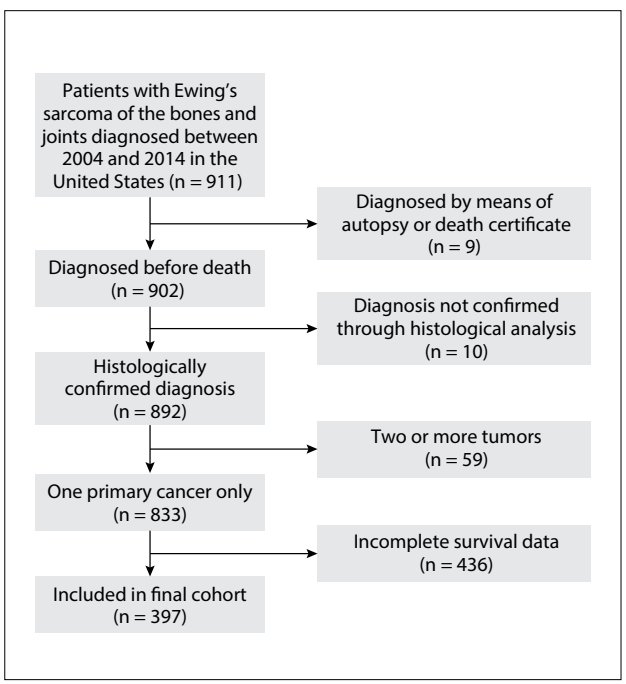

Figure 1. Flow chart for selection of the study cohort.

Well-differentiated and moderately differentiated histological features were classified as low grade while poorly-differentiated and undifferentiated histological types were classified as high grade. The pathological tumor-node-metastasis (pTNM) classification was used in cases of patients who underwent tumor resection, because their tumor gradings could be confirmed through analysis under a microscope. Because the sixth edition of the staging system of the American Joint Commission on Cancer was used in the SEER database starting in 2004 and the most recent update for this database was in 2013 (which was when the present study began), we chose to use this period (2004 to 2013) for the present study.

The main result from this study was the disease-specific survival (DSS). Descriptive statistics were calculated for all factors. The DSS was calculated by means of the Kaplan-Meier method, and the log-rank test was applied to appraise the deviations. We calculated hazard ratios (HRs) and the 95% confidence interval (CI) in the Cox proportional hazards model after adjusting for various variables. The SEER*Stat application version 8.3.2 (IMS Inc., USA) was used to extract primary data. All statistical analyses was finished in the SPSS software, version 23 (IBM Corp., USA). Differences between groups were taken to be statistically significant when the P value was less than 0.05.

RESULTS

During the 10-year period, 397 patients diagnosed with Ewing's sarcoma of the bones and joints were included (249 males and 148 females). **Table 1** shows the distribution of the patients' characteristics in the study. The mean age (with SD) at diagnosis was 18.5 (12.4) years. 65.1% of the patients were aged < 18 years. Tumors arising from the extremities accounted for 55.1%. 378 tumors (95.2%) were histologically confirmed to be poorly-differentiated or undifferentiated tumors. The mean tumor size at the time of diagnosis was 10.3 cm (5.3). 86 patients (21.6%) received surgery with radiotherapy, 139 (35.1%) underwent surgical resection alone, 102 (25.7%) underwent radiotherapy alone and 70 (17.6%) received no treatment.

The overall one, two and five-year survival rates after diagnosis were 89.08%, 78.08% and 62.47%, respectively (**Figure 2**). The five-year relative survival rates were 78.4%, 66.9%, 47.8% and 44.8% for patients receiving surgery, surgery with radiotherapy, radiotherapy alone and no therapy, respectively (**Figure 3**). Overall, patients with tumor size ≤ 10 cm had a higher five-year survival rate than did those with tumor size > 10 cm (70.8% versus 52.4%; P < 0.001) (**Figure 4**). The five-year survival rate were 68.7% and 50.2% for those < 18 and ≥ 18 years (**Figure 5**).

Table 2 shows the results from univariate and multivariate Cox proportional hazards analyses. Age ≥ 18 years (HR = 1.77; 95% CI = 1.33-2.01), tumor originating in the spine and pelvis (HR = 2.03; 95% CI = 1.31-2.62), tumor size > 10 cm (HR = 1.78;

95% CI = 1.24-2.35), radiotherapy alone (HR = 1.61; 95% CI = 1.10-2.39) and no treatment (HR = 1.86; 95% CI = 1.23-2.58) were associated with increased risk of mortality, while receiving surgery alone (HR = 0.51; 95% CI = 0.38-0.89) was an independent predictor for longer survival.

DISCUSSION

In our study, we found that the one, two and five-year DSS rates were 89.08%, 78.08% and 62.47%, respectively. These proportions were reported to be higher in a previous investigation.[10] This difference may reflect that the prognosis of Ewing's sarcoma originating bones and joints is much worse than that of Ewing's sarcoma of other parts of human body. Early screening and diagnosis seem to be more important among people at high risk of having Ewing's sarcoma of bones and joints.

The development of diagnostic methods based on molecular techniques has had a great effect, because typical chromosomal translocations are commonly detected in Ewing's sarcoma tissue. The reverse transcription-polymerase chain reaction (RT-PCR) and fluorescent in-situ hybridization (FISH) are the most frequent measures applied in fusion gene analysis.

It has been reported that the t(11;22) (q24;q12) translocation is found in 85% of cases of Ewing's sarcoma.[11,12] Yang et al.[13] further ascertained that FISH and RT-PCR could be applied as reliable molecular diagnostic approaches in cases of Ewing's sarcoma,

Table 1. Characteristics of patients with Ewing's sarcoma of the bones and joints

Characteristic	Total	
	N	%
Patients	397	100
Sex		
Female	148	37.2
Male	249	62.8
Age, years		
< 18	251	63.2
≥ 18	146	36.8
Mean (with standard deviation)	18.5 (12.4)	-
Median	17.8	-
Race		
White	351	88.4
Black	15	3.8
Other	31	7.8
Tumor site		
Extremity	219	55.1
Spine and pelvis	178	44.9
Tumor grade		
Low	19	4.8
High	378	95.2
Tumor size		
≤ 10	173	43.6
> 10	224	56.4
Mean (with standard deviation)	10.3 (5.3)	-
Median	9.6	-
Treatment		
Surgery with radiotherapy	86	21.6
Surgery alone	139	35.1
Radiotherapy alone	102	25.7
None	70	17.6

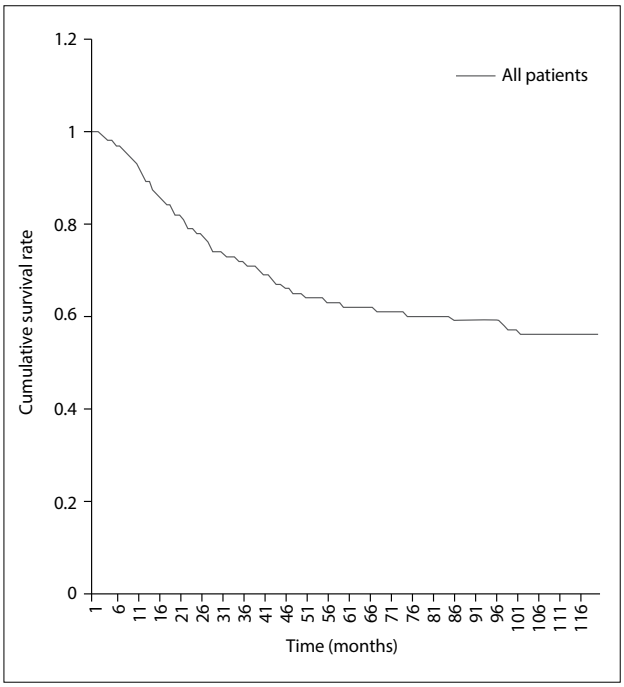

Figure 2. Kaplan-Meier survival curve for all patients.

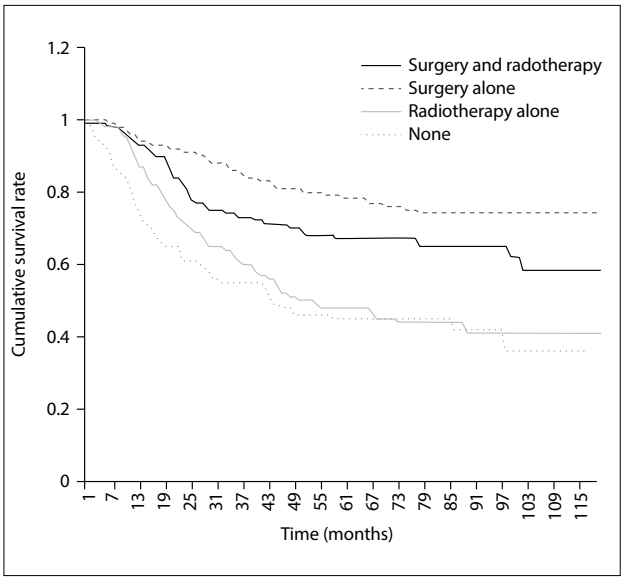

Figure 3. Kaplan-Meier survival curves for all patients, stratified according to type of treatment.

and that FISH displayed features of greater sensitivity and stability. Furthermore, in a meta-analysis on 1,412 cases, Li et al.[14] declared that high levels of serum lactate dehydrogenase (LDH) presaged lower DSS among patients with Ewing's sarcoma. However, information on these specific molecular indicators is not documented in the SEER database.

The influence of age on survival has always been a matter of debate, with contrary outcomes reported from different studies.

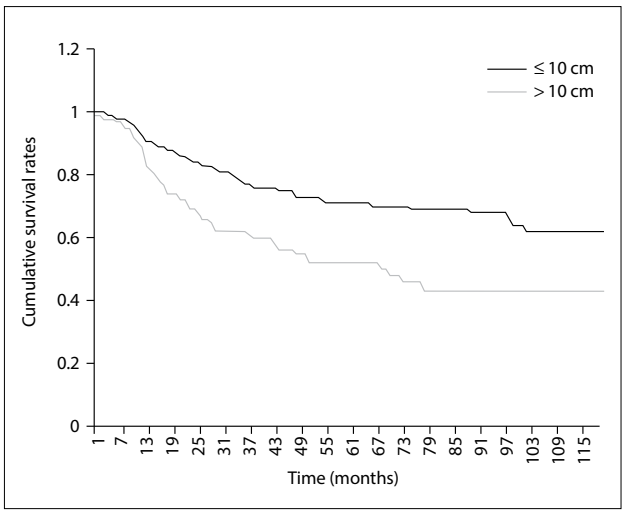

Figure 4. Kaplan-Meier survival curves for all patients, stratified according to tumor size.

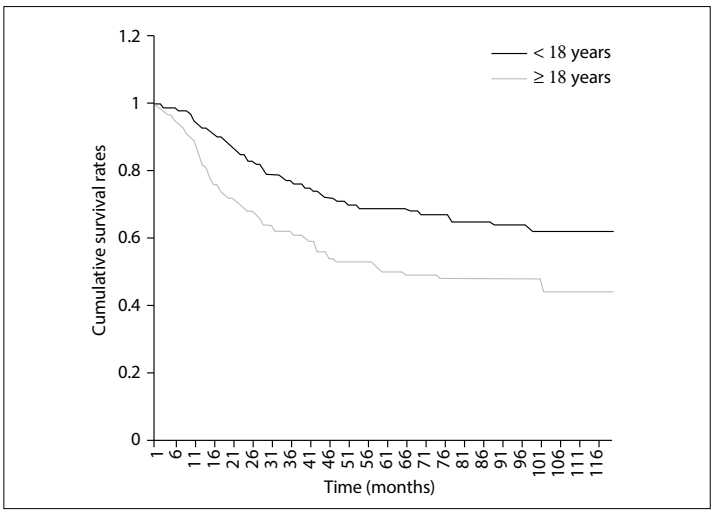

Figure 5. Kaplan-Meier survival curves for all patients, stratified according to age.

Table 2. Cox model with hazard ratios and 95% confidence intervals for mortality associated with covariates, among patients with Ewing's sarcoma of bones and joints

Variable	Crude			Adjusted*		
	HR	(95% CI)	P-value	HR	(95% CI)	P-value
Sex						
Female	1	(reference)		1	(reference)	
Male	1,47	(1.12-1.93)	**< 0.05**	1.19	(0.98-1.71)	0.074
Age						
< 18 years	1	(reference)		1	(reference)	
≥ 18 years	1,89	(1.47-2.44)	**< 0.05**	1.77	(1.38-2.31)	**< 0.05**
Race						
White	1	(reference)		1	(reference)	
Black	1.68	(1.27-2.07)	**< 0.05**	1.52	(1.37-1.86)	0.075
Other	0.63	(0.49-1.53)	0.38	0.91	(0.68-1.74)	0.84
Tumor site						
Extremity	1	(reference)		1	(reference)	
Spine and pelvis	2.57	(1.74-2.79)	**< 0.05**	2.03	(1.31-2.62)	**< 0.05**
Tumor grade						
Low	1	(reference)		1	(reference)	
High	2.37	(0.77-4.29)	0.81	-	-	-
Tumor size						
≤ 10 cm	1	(reference)		1	(reference)	
> 10 cm	2.01	(1.46-2.77)	**< 0.05**	1.78	(1.34-2.56)	**< 0.05**
Treatment						
Radiotherapy with surgery	1	(reference)		1	(reference)	
Surgery alone	0.61	(0.42-0.92)	**< 0.05**	0.51	(0.38-0.89)	**< 0.05**
Radiotherapy alone	1.66	(1.24-2.51)	**< 0.05**	1.61	(1.10-2.39)	**< 0.05**
None	2.27	(1.53-3.38)	**< 0.05**	1.86	(1.23-2.58)	**< 0.05**

HR = hazard ratio; CI = confidence interval. *Adjusted for sex, age, race, tumor site, tumor size and treatment.

In our study, most of the patients included were young, i.e. under 18 years of age, and the median age of our cohort was 17.8 years at the time of diagnosis. This was almost identical to the results reported previously in the worldwide literature, i.e. that most cases of Ewing's sarcoma not surprisingly emerged before the second decade of life, and that younger patients were likely to have a better prognosis.[15-17] Regarding the reasons for this phenomenon, Lee et al.[18] and Grevener et al.[16] found that fewer cases among adult patients were treated with chemotherapy. Moreover, elderly patients were more likely to have several comorbidities, including diabetes mellitus hypertension or secondary cancers, which made the situation much more complex.

Tumor size was considered to be a prognostic indicator in our study. We found that the mean size was 10.3 cm, which was almost consistent with the results declared in previous studies. We noticed that sizes larger than 10 cm were associated with a negative impact on DSS. However, there is no consensus regarding any critical cut-off size that might indicate a completely different prognosis for this disease.[19-23] In a study on 182 patients, Fizazi et al.[24] found that tumor size greater than 10 cm was an independent prognostic factor for survival. Canter[25] also recommended that patients with tumors larger than 10 cm should accept neoadjuvant chemotherapy and investigational therapies, because they were at a high risk of relapse and disease-specific death.

Even so, several studies have asserted that 8 cm might be a more appropriate boundary value. In a retrospective analysis on 220 patients at St. Jude Children's Research Hospital, Rodriguez-Galindo et al.[23] found that neoplasm size larger than 8 cm affected survival adversely.

In our analysis, tumors arising from the spine and pelvis were an independent factor for poorer survival. The proportion of the patients who accepted surgery was 56.0%, while 47.5% received radiotherapy. We found that surgery alone, radiotherapy alone, and no treatment were independent risk factors.

There are several explanations for this phenomenon. Oberlin et al.[26] asserted that it was recommendable that smaller and more peripheral tumors should be dealt with through surgical resection, while larger and more central unresectable entities should be managed with radiotherapy. On the other hand, Granowetter et al.[27] pointed out that radiotherapy was not appropriate for patients in whom there was no proof of microscopic remainders of malignant tissue after they underwent operations.

Normally, it is accepted that surgery will provide a decisive partial cure. Only when the neoplasm is unresectable or after palliative surgery should radiation therapy be considered. Such patients' prognoses have been found to be relatively much worse than those of patients who underwent surgery alone.[10,28]

In a retrospective study on 512 cases, Bacci et al.[29] concluded that surgical resection is more ideal than radiation therapy for patients with Ewing's sarcoma of the extremities for whom adequate surgical margins can be achieved. In cases of insufficient surgical margins, high-dose radiotherapy is recommended, while reduced-dose radiotherapy is ineffective.

Furthermore, the main population affected by Ewing's sarcoma of the bones and joints consists of young people, mostly in their teenage years. For these individuals, excessive exposure to radiation may result in retardation of the development of bones and other organs. This may have side effects of greater severity than those of surgery, which may produce less morbidity. Although surgery is the practice most often used for local control, there are very few randomized controlled trials directly comparing the effects of surgery with those of radiotherapy, and the relative positions of these techniques remain contentious.[28]

In addition, race, sex and tumor grade were not independent factors after adjusting for different variables in our Cox multivariate regression model. On the other hand, these valuables were reported to be independent risk factors in relation to other bone cancers in some previous studies.[19,20,22,30,31] Further study regarding whether these factors should be considered as independent risk indicators for the prognosis of patients with Ewing's sarcoma of the bones and joints is needed.

Our analysis was based on the data documented in the SEER database, which means that we need to acknowledge that there were some limitations relating to our study. Firstly, some variables including data on comorbidities, surgical margins, extent of surgical resection, tumor recrudescence and use of targeted therapy in managing this cancer were missing or not recorded in the database. Secondly, because of the principle of anonymity in the SEER Program, it was impossible for us to contact the patients in order to gain additional information. Thirdly, it also should not be ignored that because of the existence of confounders, the consequences deduced from a retrospective analysis would normally be of lower methodological grade than those from randomized controlled trials. Finally, we were unable to evaluate some specific molecular indicators, such as Ewing's Sarcoma-Friend leukemia integration 1 transcription factor (EWS-FLI1) and serum LDH, which help in making an early diagnosis and in judging the prognosis.

In spite of these limitations, use of the SEER Program database has significant advantages, in that it provides possibilities for conducting studies of this nature based on large populations suffering from rare types of cancer.

CONCLUSION

In conclusion, the contemporary five-year DSS rate of Ewing's sarcoma of the bones and joints was 62.47%. Age ≥ 18 years, tumors originating in the spine and pelvis, tumor size > 10 cm, receiving radiotherapy alone and no treatment were independent risk factors for poor DSS, while surgery alone was an

independent protective factor for better survival. Further investigations combining multiple fields of the gene modulation and molecular mechanism- are expected to elucidate better treatment strategies for cases of Ewing's sarcoma of the bones and joints.

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Foot health and quality of life among university students: cross-sectional study

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ABSTRACT

BACKGROUND: Foot problems are believed to reduce quality of life and are increasingly present. Even among young adults of university age, untreated foot problems can lead to postural and mobility problems. Accordingly, our aim here was to determine the relationship between foot health and quality of life and general health among male and female university students.

DESIGN AND SETTING: Observational cross-sectional quantitative study conducted at the Podiatric Medicine and Surgery Clinic of the University of Coruña, Ferrol, Spain.

METHODS: A sample of 112 participants of median age 22 years came to a health center, where self-reported data were registered, including professional activity, and scores obtained through the Foot Health Status Questionnaire (FHSQ) were compared.

RESULTS: In Section One of the FHSQ, the university students recorded lower scores of 66.66 in the footwear domain and 60 in the general foot health domain and higher scores of 84.37 in the foot pain domain and 93.75 in the foot function domain. In Section Two, they obtained lower scores of 60 in the overall health domain and 62.50 in the vigor domain and higher scores of 100 in the physical activity and 87.50 in the social capacity domain. Differences between males and females were evaluated using the Wilcoxon rank-sum test, which showing statistical significance ($P < 0.05$) regarding the dimensions of footwear and general foot health.

CONCLUSIONS: These university students' quality of life relating to foot health was poor. This appears to be associated with the university period, regardless of gender.

INTRODUCTION

One of the most critical periods in human development is between the ages of 18 and 33 years, which is the bridge between childhood and adulthood.[1] During this period of physical, psychological, social and sexual development, young people gradually assume responsibility for their own health.[2] In addition, this age group has specific foot health issues that differ from those of other age groups, such as ankle sprains, tinea pedis, onychomycosis, plantar warts and ingrown toenails.[3-6] They are also subjected to different kinds of general changes, such as greater autonomy, control over their lifestyle, control over physical activity and development of attitudes and beliefs about health and financial problems.[7,8]

Even at this age, untreated foot problems can lead to scoliosis, postural problems, slower walking speeds, uneven plantar pressure distribution, difficulty in carrying out daily activities, increased risk of falling and appearance of neurological diseases,[9,10] all of which can affect these individuals' academic achievement, quality of life, personal autonomy and wellbeing.[11] Poor foot health is now recognized by the governments in general as an important public health issue because of its negative impact on individuals and on society. This includes difficulty in putting on shoes, pain, gait disorders, reduced walking speed, variation in plantar pressures and risk of falling.[12-14]

Despite the extent of this problem, the relationship between foot health and quality of life during this developmental period has not been studied. In the general population, the prevalence of foot health problems is between 71% and 87%. The problems relate to claw toes, hallux valgus, hammer toes, overlapping toes, hallux extensus, pes planus, Morton's neuroma, tailor's bunions, plantar fasciitis and pes cavus.[15,16] Although these problems are multifactorial, they may predict loss of independence, vulnerability,[17] defenselessness[18] and reduced quality of life and wellbeing.

Based on these issues, it is important to consider illnesses and deformities of the foot, postural alterations and other underlying diseases as factors to be taken into account when planning treatment and preventive care activities. Moreover, there is a need for care and follow-up regarding foot health for university students that so far remains unattended. Such issues need to be addressed in seeking to ensure better quality of life and wellbeing for university students.

Thus, we sought to determine the state of foot health among male and female university students and its relationship to their overall quality of life and general health. At present little is known about the factors that affect the development of foot health. Foot problems are predisposing factors for the appearance of injuries in later life that could be prevented through implementing programs to improve the general condition of university students' feet.

METHODS

This study was approved by the Research Ethics Committee of the University of Coruña, in Coruña, Spain. All participants gave written informed consent. Ethical standards for research on human beings based on the Declaration of Helsinki (World Medical Association) and the Convention of the Council of Europe on human rights and biomedicine, as well as those based on UNESCO's Universal Declaration on the Human Genome and Human Rights and those of other appropriate national or institutional organizations were adhered to.

Respondents

Students between the ages of 18 and 33 years of similar socioeconomic level participated in this cross-sectional study between September 2014 and May 2015. Participants were recruited from the Clinic of Podiatric Medicine and Surgery (CPMS), which provides treatment for foot diseases and disorders at the University of Coruña, in Ferrol, Spain. Advertisements were placed on the CPMS website and in University newsletters. Information leaflets were provided to students clinicians, students from another health science college of the University like nursing, medicine or physiotherapy. Additionally, notices were placed on local bulletin boards.

These students came to the Podiatric Medicine and Surgery Clinic. They were eligible for inclusion in the study through a non-probability consecutive sampling technique. The inclusion criteria were that they needed to be healthy volunteers without any relevant medical records or family history and that they gave consent for enrollment into the study. The exclusion criteria included immunodepression, histories of trauma and foot surgery, neurological alterations and lack of or only partial autonomy in performing daily activities.[19]

Data collection

All measurements were made by a single researcher. Height, weight and body mass index (BMI) were determined during the visit to the clinic. The students then completed the Foot Health Status Questionnaire (FHSQ). This self-administered questionnaire on health-related quality of life is intended specifically for the foot and has been recognized as a validated test.[20,21] Foot-specific and general health-related quality of life was assessed using version 1.03 of the FHSQ,[22] which contains three sections. The first section consists of 13 questions reflecting four domains relating to foot health (**Appendix 1**): foot pain, foot function, footwear and general foot health. The first section has demonstrated high degrees of content, criterion and construct validity (Cronbach α = 0.89-0.95) and high retest reliability (intraclass correlation coefficient = 0.74-0.92).[23] It has been shown to be the most appropriate measurement of foot health-related quality of life for pathological skin and nail conditions and for neurological, orthopedic and musculoskeletal disorders, among others.[24,25]

Each domain has a specific number of questions (**Appendix 2**): four on pain, four on function, three on footwear and two on general foot health. The assessment of pain and function is based on physical phenomena; the evaluation of footwear uses practical aspects of availability and shoe comfort; and the perception of general foot health is based on the patients' self-assessment of the state of their feet. Each question allows several answers, and these are placed on a Likert-type ordinal scale (words or phrases corresponding to a numerical scale). The descriptors for these scales vary for each domain, and the person completing the questionnaire should choose only one response, i.e. whichever response is thought to be the most appropriate. The questionnaire does not provide an overall score but, rather, it generates an index for each domain. To obtain these indices, the responses are analyzed through computer software (FHSQ, version 1.03). After processing the data, the software produces a score ranging from 0 to 100. A score of zero represents the worst state of health for the foot, while 100 is the best possible condition.

The second section of the FHSQ includes questions that reflect four general health-related domains (**Appendix 2**): general health, physical activity, social capacity and vigor. The domains and questions in this section are largely adapted from the Medical Outcomes Study 36-Item Short-Form Health Survey,[24] which has been validated for use in the Australian population.[25] Specific questions of the FHSQ that assess section 2 domains are shown in **Appendix 2**.

Lastly, the third section contains questions asking for sociodemographic data such as the participants' age and sex and about their medical records.

Sample size

The smallest clinically important difference in FHSQ scores is 21 points.[21,22] Assuming a standard deviation of around 29 for a bilateral hypothesis and an alpha of 5%, at least 94 students would be

needed to detect a 21-point difference with 80% power. Students were enrolled consecutively until the sample size was achieved.

Statistical methods

Continuous variables were expressed as the median and interquartile range. Differences between men and women were compared using independent t tests if the data were normally distributed or the Wilcoxon rank-sum test if not. The data were analyzed using the SPSS statistics package. Alpha was set at 0.05, and all tests were two-tailed. The Foot Health Status Questionnaire version 1.03 was used to obtain quality-of-life scores relating to foot health.

RESULTS

A total of 112 university students of less than 33 years of age were enrolled. The sample analyzed included 85 women (75.9%) and 27 men (24.1%) between 18 and 33 years of age. Most students were normal weight (BMI of 22.27 kg/m^2). These results are shown in **Table 1**.

Table 1 also shows the clinical domains of the FHSQ questionnaire and the sociodemographic characteristics of the informants. As can be seen, most of the informants were normal weight (BMI = 22.27 kg/m^2). All variables showed non-normal distribution ($P < 0.05$), and therefore the Wilcoxon rank-sum test was used.

Table 2 shows a comparison of the scores obtained through the FHSQ. Section One of the FHSQ evaluated four specific foot domains, namely pain, function, health and footwear. The median scores were higher in relation to assessment of pain and function, and lower in relation to foot health and footwear. Section Two gave an assessment of four domains of general wellbeing: overall health, physical function, social capacity and vigor. In this section, the median foot pain scores for men and women were 87.50 and 81.25 respectively and the function scores for men and women were both 93.75, The foot health scores were 85 and 60 for men and women respectively, and the footwear scores were 75 and 58.33 for men and women respectively (**Table 2**). The median scores for physical function and social capacity were significantly lower than those for overall health and vigor, for both men and women. The differences between males and females were statistically significant ($P < 0.05$) for the dimensions of the FHSQ questionnaire that assessed footwear and general foot health. These results appear in **Table 2**.

DISCUSSION

The purpose of this study was to determine the relationship between quality of life and foot health among male and female university students, given that the high prevalence of foot problems has been recognized by the governments as a threat to public health.

Foot health is essential to university students, in that it enables them to have greater autonomy, have control over their lifestyles and do physical activity.[26] In a study on the population in Spain aged 40 years or older, the following prevalences of podiatric medical abnormalities were found: claw toe (69.7%), hallux valgus (38.0%) and hallux extensus (15.8%).[15] The prevalences increased with age and were higher among females.[27]

The results from the few studies on this topic indicate that the impact of foot health on quality of life is not as obvious as it appears

Table 1. Sociodemographic and clinical characteristics of the sample population

	Total group Median (IQ range) n = 112	Male Median (IQ range) n = 27	Female Median (IQ range) n = 85	P-value Male versus female
Age, years	22 (3)	23 (5)	22 (3)	0.562
Weight (kg)	63 (19.5)	80 (18)	58 (11)	0.000
Height (cm)	168 (12.5)	180 (7)	165 (10)	0.000
Body mass index (kg/m^2)	22.27 (4.25)	24.03 (4.79)	21.80 (4.07)	0.009

IQ = interquartile.

Table 2. Comparisons of Foot Health Status Questionnaire survey scores for total group and gender groups

	Total group Median (IQ range) n = 112	Male Median (IQ range) n = 27	Female Median (IQ range) n = 85	P-value Male versus female
Foot pain	84.37 (18.12)	87.50 (15)	81.25 (24.37)	0.122
Foot function	93.75 (18.75)	93.75 (12.50)	93.75 (18.75)	0.127
Footwear	66.66 (41.66)	75 (18.333)	58.33 (41.66)	0.005
General foot health	60 (27.5)	85 (25)	60 (30)	0.037
Overall health	60 (20)	60 (20)	60 (20)	0.730
Physical activity	100 (5.56)	100 (5.56)	100 (5.56)	0.170
Social capacity	87.50 (25)	87.50 (25)	87.50 (25)	0.176
Vigor	62.50 (25)	68.75 (25)	62.50 (25)	0.103

IQ = interquartile.

to be.[15,28] On the other hand, our results confirm that female university students have lower median footwear and general health scores than those of men, thus indicating that they have poorer quality of life in relation to these two domains. We did not find any differences in any other domain. This finding is consistent with studies from other authors.[29-32]

Furthermore, our students had lower median scores for general health and vigor. This situation is associated with greater limitations in carrying out a wide range of physical activities, a lack of energy for participating in activities and an increased risk of becoming socially isolated.[8,22]

Given these results, it seems necessary to point out the importance of medical and podiatric care and follow-up, with the aim of preventing the appearance of illnesses and deformities of the foot. This is fundamental for enabling improvement of university students' health, quality of life and autonomy.

We were unable to compare our results with those of other studies, given the differences in criteria and methodological variations, because we did not find any similar studies on quality of life relating to foot health.

This shows that there is a need for further research on this topic, in order to find out about the different therapeutic interventions used by professionals within podiatry and medicine that might improve foot health and quality of life, not only among university students but also in the general population.

Our study includes several important limitations that need to be acknowledged. Firstly, this study was performed in a clinic of podiatric medicine and surgery with a small number of participants. Secondly, expanding data collection to other countries may help to identify whether there is any culture in which this association does not exist and identify the mechanisms involved in foot health and health in general. Lastly, the recruitment methodology showed several drawbacks relating to the relatively small sample size. A more diverse sample, including individuals from several countries, would be beneficial for improving the strength of such studies.

This highlights the need for further research on the importance of medical and podiatric care and follow-up for the feet and for health in general, in order to prevent the appearance of illnesses and deformities of the feet and maintain the overall health of the body. This is fundamental for enabling improvement of university students' health, quality of life, wellbeing and autonomy.

CONCLUSIONS

Over this study period, these university students had poor quality of life relating to foot health. This appears to be associated with the university period, regardless of gender. Therefore, there is a need to develop foot health behavior that enables proper care and follow-up for the feet. This is extremely important for preventing the appearance or development of lesions, pain, infections or deformities, in order to enhance the quality of life of university students. Future studies seeking to identify significant factors influencing the quality of life relating to foot health among university students need to be pursued.

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Appendix 1. Basic domains for foot and overall health, assessed using the Foot Health Status Questionnaire

Domain	Theoretical construct	Meaning of lowest score (0)	Meaning of highest score (100)
Foot pain	Type, severity and duration. Evaluation of foot pain in terms of type of pain, severity and duration	Extreme pain in the feet and significant if acute in nature	Free from pain, no discomfort
Foot function	Evaluation of the feet in terms of impact on physical functions	Severely limited for the performance of numerous physical activities due to their feet, such as walking, working and moving about	Patients are able to carry out all physical activities desired, such as walking, working and climbing stairs
General foot health	Self-perception of the feet (assessment of body image with respect to feet)	Perception of poor condition and status of the feet	Perception of excellent condition and status of the feet
Footwear	Lifestyle relating to footwear and feet	Great limitations to finding suitable footwear	No problem obtaining suitable footwear. No limitations with respect to footwear
General health	Evaluation of subject´s self-reported health status	Poor perception of health status	Very good general health status
Physical activity	Evaluation of ability in terms of impact on physical function	Severely limited in performing a broad range of physical activities	Can perform all desired physical activities with no impairment or disability
Social Capacity	Self-perceptions of ability to socially interact	Limited ability to interact without problems, socially isolated	Good ability to interact socially and experiences no isolation
Vigor	Lifestyle issues related to perceived energy and activity participation	Lacks energy to do things	No problems with energy levels

Appendix 2. Questions of the Foot Health Status Questionnaire in sections 1 and 2

Section 1: foot health

1. What level of foot pain have you had during the past week?
2. How often have you had foot pain?
3. How often have you had foot pain?
4. How often did you get sharp pains in your feet?
5. Have your feet caused you to have difficulties in your work or activities?
6. Were you limited in the kind of work you could do because of your feet?
7. How much does your foot health limit you walking?
8. How much does your foot health limit you climbing stairs?
9. How would you rate your overall foot health?
10. It is hard to find shoes that do not hurt my feet.
11. I have difficulty in finding shoes that fit my feet.
12. I am limited in the number of shoes I can wear.
13. In general, what condition would you say your feet are in?

Section 2 domains: overall health

14. In general, how would you rate your health:
15. The following questions ask about activities you might do during a typical day. Does your health now limit you in these activities?
a. Vigorous activities, such as running, lifting heavy objects, or (if you wanted to) your ability to participate in strenuous sports.
b. Moderate activities, such as cleaning the house, lifting a chair, playing golf or swimming.
c. Lifting or carrying bags of shopping.
d. Climbing a steep hill.
e. Climbing one flight of stairs.
f. Getting up from a sitting position.
g. Walking more than a kilometer.
h. Walking one hundred meters.
i. Showering or dressing yourself.
16. This question asks to what extent your physical health or emotional problems have interfered with your normal social activities with family, friends, neighbors or social groups.
17. These questions are about how you feel and how things have been with you during the past month. For each question, please give the one answer that comes closest. How much of the time during the past 4 weeks:
a. Did you feel tired?
b. Did you have a lot of energy?
c. Did you feel worn out?
d. Did you feel full of life?
18. During the past 4 weeks, how much of the time have your emotional problems or physical health interfered with your social activities (like visiting with friends, relatives, etc.)?
19. How true or false is each of the following statements for you?
a. I seem to get sick a little easier than other people.
b. I am as healthy as anybody I know.
c. I expect my health to get worse.
d. My health is excellent

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HIV-1 genetic diversity and resistance to antiretroviral drugs among pregnant women in Ribeirão Preto (SP), Brazil. Cross-sectional study

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KEY WORDS:
HIV-1.
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ABSTRACT

BACKGROUND: Increasing genetic diversity of HIV-1 and emergence of drug-resistant mutations may reduce the efficacy of antiretroviral therapy and prophylaxis that are used to prevent mother-to-child transmission. The aim of this study was to assess the genetic diversity and prevalence of drug-resistant mutations among HIV-infected pregnant women.

DESIGN AND SETTING: Cross-sectional study at an outpatient clinic for infectious diseases within gynecology and obstetrics.

METHODS: This study evaluated the dynamics of HIV-1 subtypes and the prevalence of transmitted and acquired drug-resistant mutations among 38 HIV-infected pregnant women (20 previously exposed to antiretroviral therapy and 18 naive), in Ribeirão Preto (SP), Brazil, between 2010 and 2011. Genotyping was performed by means of molecular sequencing of the protease and reverse transcriptase regions of the HIV-1 pol gene.

RESULTS: Subtype B was identified in 84.2% of the samples, recombinant forms between B and F in 7.9%, subtype F1 in 5.3% and the recombinant form K/F in 2.6%. No mutation associated with transmitted drug resistance was detected in the samples from the naive pregnant women, whereas mutations associated with acquired drug resistance were found in 35.0% of the pregnant women previously exposed to antiretroviral therapy.

CONCLUSION: The results showed that subtype B predominated, while there was low prevalence of sequences with transmitted drug resistance.

INTRODUCTION

The estimates show that 781,000 people in Brazil are infected with the human immunodeficiency virus (HIV-1), of whom 35.0% are women.[1] In 2015 there were 7,901 HIV-infected pregnant women, with an estimated detection rate of 2.7 per 1,000 live births.[2] In the state of São Paulo alone, in 2014, it was estimated that there were 2,616 HIV-infected pregnant women.[3]

Preventive interventions such as combined antiretroviral therapy (cARVT), delivery by means of caesarean section, chemoprophylaxis using zidovudine (for both parturient and newborn) and avoidance of breastfeeding have decreased HIV-1 mother-to-child transmission throughout the world, to levels below 2.0% in some regions.[4] The Brazilian government has provided free access to cARVT to all HIV-1-infected individuals through the National Health System (Sistema Único de Saúde, SUS)[5] since 1996 (zidovudine distribution started in 1991).[6] These actions have resulted in stabilization of disease prevalence over the last few years,[1] decreases in HIV/AIDS-related mortality and morbidity,[7] and reduction in mother-to-child transmission to 3.4 per 100,000 inhabitants under 5 years of age in 2012.[8] However, selection of HIV-1 resistant variants during treatment or transmission significantly impacts the effectiveness of cARVT, thus compromising the sustainability of national treatment, care and prevention programs.

Antiretroviral resistance arises from mutations in the viral genes that encode the molecular targets of therapy.[9] Although the prevalence of transmitted drug resistance is still low in Brazil, it has increased significantly, especially in the Southeast, the most populous region of the country.[10,11] This reinforces the need for epidemiological studies on groups that are vulnerable to infection in Brazil, in particular in regions of the country that are neither state capitals (or the national

capital) nor coastal regions.[1] The aim of this study was to assess the genetic diversity and prevalence of drug-resistant mutations among HIV-infected pregnant women.

METHODS

Ethical considerations and study population

The project and informed consent statement were approved both by the Research Committee of the Department of Gynecology and Obstetrics and by the Ethics Committee of the University Hospital of Ribeirão Preto School of Medicine, University of São Paulo (procedural no. 13411/2009). All participants were informed about the aim of the study and signed the consent statement before participation.

This study included 38 HIV-1-infected pregnant women who were living in Ribeirão Preto, São Paulo, Brazil. They were enrolled during prenatal care at the outpatient clinic for infectious diseases within gynecology and obstetrics of the University Hospital, Ribeirão Preto School of Medicine, University of São Paulo, between March 2010 and September 2011. Blood samples were collected before the patients started to receive cARVT or before any treatment switch, and plasma was stored in a freezer at -70 °C. Data on the diagnoses and the clinical and epidemiological characteristics of the pregnant women, their use of cARVT during prenatal care and their antiretroviral regimens were obtained from the women's medical records.

Gene sequencing

Viral RNA was extracted by using the QIAamp Viral RNA mini-kit (QIAGEN, Germany), with reverse transcription into cDNA (RT-PCR) and polymerase chain reaction (PCR) amplification using both "in-house" methodology and the Trugene commercial system (Trugene HIV-1 genotyping assay, Siemens Diagnostics, USA). The entire protease (PR) and 75% of the reverse transcriptase (RT) were sequenced in an automatic sequencer. All DNA sequences were analyzed using the OpenGene DNA sequencing system (Trugene, Siemens) and, for the 'in-house' sequencing, the Applied Biosystems ABI3130xl system (Applied Biosystems, USA). Chromatograms were verified using the SeqMan v7 software (LaserGene; DNAStar, USA) and were then compared with HIV-1 reference sequences. The sequences obtained here were submitted to GenBank under the accession numbers MF554758 to MF554780 and MF669076 to MF669087.

Resistance and phylogenetic analysis

To define the HIV-1 genetic subtype, interpretations of DNA sequences were made using both the Brazilian algorithm and the REGA HIV-1 tool, version 3.0. The transmitted drug resistance profile was evaluated using the Stanford HIV resistance database, and presence of transmitted drug resistance was evaluated using the Stanford Calibration of Resistant Population (CRP) tool [Stanford HIV-1 Drug Resistance Mutation (SHDRM) database]. Recombinant samples were evaluated by means of the simplot and bootscanning software, which compares sequences with reference sequences in the Los Alamos HIV database. Phylogenetic trees were constructed by aligning the sequences with the most representative reference sequences of the various pure and recombinant subtypes of the HIV-1 M group, which were obtained from the Los Alamos HIV-1 database. Maximum-likelihood (ML) trees were estimated using the MEGA 6 software. Bootstraps of 1,000 replicates were used and values greater than 70% were presented in the trees.

A significance level of 5% was used for all statistical tests. These tests were performed in the SAS software, version 9 (Statistical Analysis System, SAS Institute Inc, USA).

RESULTS

Characteristics of the study population

Eighteen pregnant women (47.4%) were naive, while 20 (52.6%) had already used antiretroviral therapy before the current pregnancy or were using it during the pregnancy (cARVT-exposed). Most of the women enrolled (81.6%) had been diagnosed with HIV infection during prenatal care for the current or a previous pregnancy.

Table 1 presents the characteristics of the pregnant women included. The mean age of the naive pregnant women was 26.4 years (standard deviation, SD = 6.0), while the mean age of the cARVT-exposed pregnant women was 29.2 years (SD = 4.0). The mean numbers of pregnancies and deliveries were higher among the cARVT-exposed women: on average, these women began prenatal care at an earlier gestational stage than did the naive pregnant women (35.0% vs. 21.0% in the first trimester). Most participants (86.8%) were asymptomatic. Viral load distribution was similar between the cARVT-exposed and naive pregnant women ($P = 0.65$), although with greater variation in the cARVT-exposed women. The median CD4+ T lymphocyte count was greater among the cARVT-exposed pregnant women, and the median CD8+ T lymphocyte count was greater among the naive pregnant women, but there was no statistical difference for either of these parameters between the two groups ($P = 0.76$ and $P = 0.59$, respectively).

At the first outpatient visit, it was observed that, among the 20 cARVT-exposed pregnant women, six were undergoing a therapy regimen. In this subgroup, 27.8% had used or were using monotherapy, whereas 15.0% had used a three-drug regimen. The most commonly used drug combination was zidovudine + lamivudine + nelfinavir (50.0%), followed by zidovudine + lamivudine + lopinavir/ritonavir (44.4%), zidovudine + lamivudine + efavirenz (22.2%) and zidovudine + lamivudine + other drugs (11.1%). Because the drug combinations used varied over time, the percentages do not total 100%.

In addition to HIV infection, 38.9% of the naive and 50.0% of the cARVT-exposed pregnant women presented other sexually transmitted infections (STIs), like syphilis, trichomoniasis, *Ureaplasma*, genital warts or grade I cervical intraepithelial neoplasia. STIs plus genital infection (vaginal candidiasis and bacterial vaginosis) were also observed in 22.2% of the naive pregnant women and in 10.0% of the cARVT-exposed pregnant women. There were no statistically significant differences in viral load or in CD4+ and CD8+ T lymphocyte counts among women with STIs (P = 0.93, P = 0.41 and P = 0.26, respectively) or among those with STIs plus genital infections (P = 0.23, P = 0.14 and P = 0.18, respectively), in comparison with the women who did not have any of these conditions.

Diversity of HIV subtypes

Subtype B was identified in 84.2% of the samples, F1 in 5.3%, recombinant forms B/F and F/B in 7.9% and the unique recombinant form (URF) K/F in 2.6%. Most circulating recombinant forms (CRFs) were composed of subtypes B and F1, and phylogenetic analysis showed that these had a close relationship to CRF29_BF, which was described in the city of São Paulo (SP), Brazil (http://www.hiv.lanl.gov/content/sequence/HIV/CRFs/CRFs.html).

Table 1. Characteristics of HIV-1 infected pregnant women stratified according to combined antiretroviral therapy (cARVT) use. Ribeirão Preto (SP), Brazil, 2010-2011

Variables	Naive (n = 18)	cARVT-exposed (n =20)
Age, years, mean (SD)	26.4 (6.0)	29.2 (4.0)
Race, n (%)		
Black	2 (11.1)	2 (10.0)
Mixed race	5 (27.8)	5 (25.0)
White	11 (61.1)	14 (70.0)
Education, n (%)		
≤ 8 years	14 (77.8)	16 (80.0)
9-11 years	4 (22.2)	4 (20.0)
Marital status, n (%)		
Cohabitating	7 (38.9)	9 (45.0)
Divorced/separated	2 (11.1)	2 (10.0)
Married	5 (27.8)	4 (20.0)
Single	4 (22.2)	5 (25.0)
Illicit drug use, n (%)	8 (44.4)	6 (30.0)
Start of prenatal care, mean (SD)	22 w + 6 d (10 w + 6 d)	17 w + 6 d (7 w)
Number of pregnancies, mean (SD)	3.7 (2.4)	4.7 (2.5)
Number of deliveries, mean (SD)	2.2 (2.4)	3.2 (2.0)
Viral load, copies/ml, median (IQ)	9,521 (3,847–27,985)	10,995 (4,977–43,110)
CD4+ T lymphocytes, cells/mm³, median (IQ)	299 (193–554)	333 (270–392)
CD8+ T lymphocytes, cells/mm³, median (IQ)	812 (624–947)	694 (535–950)

SD = standard deviation; w = weeks; d = days; IQ = interquartile range.

Among the naive pregnant women, 83.4% presented subtype B and 5.6% had subtype F1, while the recombinant forms B/F and K/F were also present in one pregnant woman each. Among the cARVT-exposed pregnant women, subtype B was also the most prevalent, with an incidence of 85.0%, followed by the recombinant form B/F (10.0%) and subtype F1 (5.0%).

Subtype F1 sequences comprised a separate cluster, and were identical to sequences from the southeastern region of Brazil. A cluster among subtype B sequences was observed, suggesting that there was an epidemiological relationship between the different viral isolates and, consequently, that viruses were introduced into the region in a monophyletic fashion with subsequent spreading of these subtypes in the region. Identification of highly divergent recombinant samples (115) and other recombinants (68 and 110) suggested that these viruses have only recently been introduced among pregnant women in Ribeirão Preto (**Figure 1**).

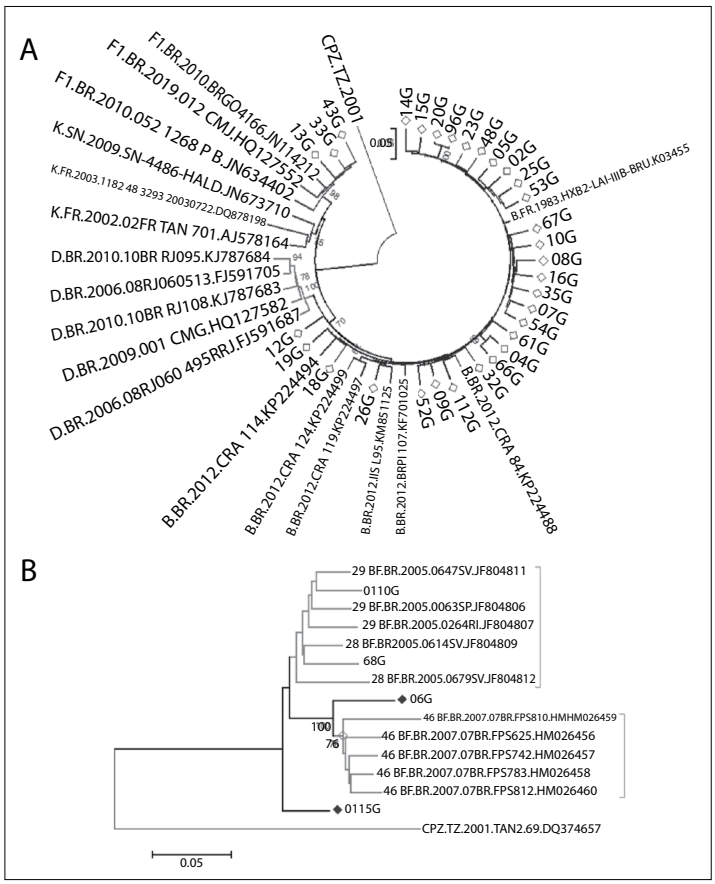

Figure 1. Subtype classification of sequences. A) Maximum likelihood tree of PR/RT region. HIV-1 reference sequences of pure subtypes (B, D, F1 and K) were included. The branch support values (aLRT > 0.90) are indicated at key nodes. Each HIV-1 clade found in the Brazilian samples is indicated in the figure. Horizontal branch lengths are drawn to scale with the bar at the bottom indicating nucleotide substitutions per site. B) ML tree of PR/RT region of the inter-subtype recombinant samples. HIV-1 reference sequences of CRFs.

Prevalence and drug resistance patterns of HIV

No major mutation responsible for drug resistance was present in the sequences obtained from the naive pregnant women. However, three samples (16.7%) had accessory mutations to non-analogous nucleoside reverse transcriptase inhibitors (NNRTIs): mutations V108I, E138A and V179D, associated with efavirenz and rilpivirine (**Table 2**). Accessory mutations related to protease inhibitors (PIs), such as the L10I and K20R polymorphisms, were also detected in one sample (5.6%). No case of mutation associated with analogous nucleoside/nucleotide reverse transcriptase inhibitors (NRTI) was observed.

Among the sequences from the cARVT-exposed pregnant women, 35.0% displayed resistance to antiretroviral drugs. Four sequences (20.0%) presented drug-resistant mutations to NRTI, 15.0% to PIs and 5.0% to NNRTIs. The M184V mutation was the most prevalent (15.0%), followed by mutations associated with RT

Table 2. HIV-1 subtypes and resistance mutations associated with analogous nucleoside/nucleotide reverse transcriptase inhibitors (NRTI), non-analogous nucleoside reverse transcriptase inhibitors (NNRTI) and protease inhibitors (PI)

	PW*	Subtype	Drug-resistant mutations			Other mutations		
			NRTI	NNRTI	PI	NRTI	NNRTI	PI
Naive	04G	B	–	–	–	–	–	–
	06G	B/F	–	–	–	–	–	–
	09G	B	–	–	–	–	V108I	–
	13G	K/F	–	–	–	–	–	–
	14G	B	–	–	–	–	–	–
	18G	B	–	–	–	–	–	–
	19G	B	–	–	–	–	–	–
	23G	B	–	–	–	–	–	–
	25G	B	–	–	–	–	V179D	–
	26G	B	–	–	–	–	–	–
	33G	F	–	–	–	–	–	–
	48G	B	–	–	–	–	–	–
	52G	B	–	–	–	–	E138A	–
	54G	B	–	–	–	–	–	–
	68G	B	–	–	–	–	–	L10I, K20R
	84G	B	–	–	–	–	–	–
	95G	B	–	–	–	–	–	–
	112G	B	–	–	–	–	–	–
Exposed to cARVT	2G	B	M184V	–	–	–	–	–
	05G	B	–	–	–	–	–	–
	07G	B	D67N, T69D, K219R	–	–	–	–	–
	08G	B	–	–	–	–	–	–
	10G	B	M184V	–	–	–	P225H	–
	12G	B	–	–	–	–	–	–
	15G	B	–	–	–	–	–	–
	16G	F/B	–	–	–	–	–	L10V, K20R
	20G	B	–	–	M46IL	–	–	–
	32G	B	–	–	–	–	–	–
	35G	B	–	–	–	–	–	–
	43G	F	–	–	–	–	–	–
	53G	B	–	–	–	–	–	–
	61G	B	–	–	–	–	E138A	–
	66G	B	–	–	–	–	–	–
	67G	B	–	–	–	–	–	–
	96G	B	–	–	M46L	–	–	–
	98G	B	D67N, T69N, K70R, M184V, T215F, K219EQ	–	I50L	–	–	–
	110G	F/B	–	K103N	–	V75M	–	–
	115G	B	–	–	–	–	–	L10V, K20R

cARVT = combined antiretroviral therapy; PW = pregnant women; NRTI = nucleoside/nucleotide reverse transcriptase inhibitors; NNRTI = non-analogous nucleoside reverse transcriptase inhibitors.

thymidine inhibitors (TAM) (10.0%). The V75M mutation associated with resistance to didanosine and stavudine was detected in one sample (5.0%). Three samples displayed K103N, E138A and P225H mutations, one per sample. Two samples showed concomitant mutations associated with NRTI and PI (sample 98), and NRTI and NNRTI (sample 110). Two samples had the M46L mutation (10.0%) and one had the I50L mutation (5.0%) associated with atazanavir. Also, the most prevalent accessory mutations were L10I/V and K20M/R (10%), which were detected in two sequences (samples 16 and 115). None of the samples from the cARVT-exposed pregnant women showed resistance to three classes of drugs. The number of antiretroviral regimens previously used was associated with the presence of drug-resistant viruses (P = 0.041).

The cARVT-exposed pregnant women had 2.10-fold higher prevalence of antiretroviral resistance (95% CI = 0.64-6.93), compared with the naive pregnant women, and 2.03-fold greater drug resistance and intermediate drug resistance (95% CI = 0.75-5.45). The prevalence of antiretroviral drug resistance was 11.2% in the samples from the naive pregnant women with intermediate resistance to etravirine, whereas only 5.0% of the samples from the cARVT-exposed pregnant women showed possible resistance to the same antiretroviral drug. Possible resistance to didanosine was the most prevalent form of resistance among the cARVT-exposed pregnant women (20.0%), followed by resistance to lamivudine (15.0%). Resistance to efavirenz was observed in 10.0% of the cARVT-exposed pregnant women. Resistance to fosamprenavir and to indinavir was also observed in 10.0% of the cARVT-exposed pregnant women.

Polymorphisms in protease genes were observed in all the samples from the naive pregnant women, with the exception of one sample, and in three samples from the cARVT-exposed pregnant women. The polymorphism M36I/M36L was the most frequent, present in 12 samples from the naive pregnant women (66.7%) infected with HIV-1 subtypes B, F, B/F and K/F, and in 10 samples (50.0%) from the cARVT-exposed pregnant women infected with HIV-1 subtypes B, F and B/F. Next came L63P/L63Q/L63S, present in 33.3% of the naive pregnant women and in 20.0% of the cARVT-exposed pregnant women; and L10I/L10V in 22.2% of the naive pregnant women and in 25.0% of the cARVT-exposed pregnant women. The M36I mutation was not associated with any virus subtype (P = 0.77).

No case of mother-to-child transmission of HIV was diagnosed among the pregnant women included in this study.

DISCUSSION

In this study, subtype B was the most common form of HIV-1 (84.2%) found among the pregnant women in Ribeirão Preto. This was consistent with other data from Brazil[12-20] with the exception of the southern states, where subtype C has been found to prevail.[21] To a lesser extent, presence of recombinant forms between subtypes B and F, K and between F and subtype F1 was also found. Subtype C was not observed in the samples, but the prevalence of this subtype is increasing in Brazil,[22] apparently with disease progression characteristics differing from those of subtype B.[23] Subtype F is the second most common form in the cities of Santos[24,25] and Rio de Janeiro[18] and in the states of Minas Gerais[19] and Pará.[20] Despite the small sample size, the number of samples presenting recombinant subtype B/F and two highly divergent recombinant samples because of genetic diversity and the complexity of HIV epidemic dynamics was striking. Subtype F showed a monophyletic introduction, given that the three samples are grouped into a single arm.

This study did not identify any major mutations of transmitted drug resistance in the samples from naive pregnant women. In a study carried out in Goiânia[26] and in another in Rio de Janeiro,[18] transmitted drug resistance among naive pregnant women was identified in 9.3% and 17.2% of them, respectively. Studies on HIV-1 infected individuals without antiretroviral exposure have reported prevalences of transmitted drug resistance ranging from 4.2% to 18.2%.[12,13,16,17,25,27] Ferreira et al.[22] found that the prevalence of transmitted drug resistance in São Paulo and Campinas was 7.6% and that 76.0% of these cases carried mutations for resistance to NNRTIs.

Among the cARVT-exposed pregnant women, major resistance mutations were present in 35.0%. However, this may have been an overestimation, due to the small sample size in this study. The most frequent mutation was M184V, which caused resistance to lamivudine and intermediate resistance to abacavir and didanosine, along with increased susceptibility to zidovudine, stavudine and tenofovir. Three pregnant women whose HIV-1 strains presented this mutation had already used cARVT containing lamivudine. Other studies on patients who had already been treated with several antiretroviral regimens also observed higher frequency of the M184V mutation, in up to 88.0% of the individuals evaluated.[14,17,24]

It was expected to find drug-resistant mutations among women who had had a diagnosis of HIV infection for a longer time, had had a previous event of opportunistic infection and presented a worse clinical and immunological stage of the disease. However, cARVT-exposed pregnant women who had had a diagnosis of HIV infection for up to five years did not have any mutations in the reverse transcriptase segment and only had accessory mutations present in protease segment. On the other hand, among the five pregnant women who had had a diagnosis of HIV infection for 10 years or more, only one did not have any major drug-resistant mutations (data not shown).

Although this study was conducted using samples collected in 2010 and 2011, this is the first to address the diversity and drug resistance of mutations in HIV-infected pregnant women in Ribeirão Preto.

CONCLUSION

HIV-1 subtype B predominated among the pregnant women in Ribeirão Preto, state of São Paulo. This epidemiological pattern resembled what has been described in other regions of Brazil, except for the southern region. The results obtained in this study showed that no major mutations conferring drug resistance were found in the naive pregnant women, but that major mutations were found in 35.0% of the cARVT-exposed pregnant women.

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Athlete's heart in a Brazilian paralympic judo team. Case series study

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Exercise.
Exercise test.
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ABSTRACT

BACKGROUND: Athlete's heart is a term describing the cardiovascular effects of long-term conditioning among highly trained athletes. It is a variation of normal standards.

DESIGN AND SETTING: Case series study at the cardiology division of a public university hospital.

METHODS: We studied 14 visually handicapped paralympic athletes (8 men) in the national judo team. They were 26.3 ± 6.4 years old, with body mass index 25 ± 14, and had been practicing judo for 9.2 ± 7.9 years. Clinical evaluations, electrocardiograms, exercise testing and echocardiograms were performed by independent observers.

RESULTS: Signs of athlete's heart were found in all athletes, comprising left ventricular hypertrophy (5 cases), sinus bradycardia (5), T-wave juvenile pattern (3), T wave juvenile pattern (3), left atrial hypertrophy (2) and increased left ventricular volume (9 cases; 62.22 ± 6.46 ml/m^2). There were very strong correlations between left ventricular mass/body surface and endurance time (r: 0.91) and estimated peak oxygen uptake (r: 0.8). The correlations between left ventricular internal diastolic dimension and endurance time (r: 0.91) and estimated peak oxygen uptake (r: 0.8) were strong. Despite increased left ventricular dimensions (4 cases), atrial dimensions (1) and relative wall thickness (4), all athletes had normal left ventricular mass/body surface (89.98 ± 21.93 g/m^2). The exercise testing was normal: exercise duration 706 ± 45 seconds and estimated peak oxygen uptake 62.70 ± 9.99 mlO_2/min.

CONCLUSIONS: Signs of athlete's heart were seen frequently in the paralympic judo team. These demonstrated the presence of mild cardiac adaptations to training.

INTRODUCTION

Athlete's heart is a term used to describe the cardiovascular effects of long-term conditioning that are observed among highly trained athletes.[1] The first report was made by Henschen among Swedish skiers in 1899.[2] This condition includes clinical, electrocardiographic and echocardiographic signs and the prognostic implications are good.[3,4] It gives rise to increased left ventricular dimensions, as a cardiovascular adaptation to long-term athletic training. It also frequently enlarges the wall thickness and the mass of the heart.[5,6]

Athlete's heart is a variation of normal standards. Occurrences of cardiac adaptations to training among disabled athletes have been already observed. Among Brazilian elite disabled athletes, signs of athlete's heart have been found to occur in 33% of clinical evaluations, 55% of electrocardiograms, 15% of vectorcardiograms and 5% of echocardiograms.[7]

At least one of these signs has been found to be presented by 51% of disabled athletes.[7] These individuals were found to have reasonably high prevalence of coronary risk factors (51%), despite a low likelihood of coronary events.[8]

The aim of the present case series study was to assess occurrences of athlete's heart among the Brazilian paralympic judo team.

METHODS

We studied the entire national paralympic judo team, comprising 14 athletes, who were all visually handicapped. Eight of them were men. The paralympic athletes were 26.3 ± 6.4 years old, with body mass index (BMI) = 25 ± 14 kg/m^2, and had been practicing judo for 9.2 ± 7.9 years. Clinical evaluations, electrocardiograms (ECG), exercise testing and echocardiograms were

performed by independent observers. Examinations were performed during periods of peak training. ECG evaluations followed the third guidelines of the Brazilian Society of Cardiology regarding analysis and issuing of electrocardiographic reports and the criteria of Corrado et al. for diagnosing athlete's heart.[9]

All the subjects underwent symptom-limited evaluations on a treadmill (TM48 Trackmaster, JAS System, Pensacola, Florida, USA), in accordance with the Bruce protocol (TEB, Apex 2000 System, São Paulo, Brazil). Echocardiograms were recorded on the ATL Ultramark 8 and 9 devices (Bothell, WA, USA), using a 3.0-MHz phased-array transducer.

We evaluated left ventricular volume (LVV), left ventricular mass/body surface (LVM/BS), relative wall thickness (RWT), diastolic interventricular septum thickness (IVSTd), diastolic posterior left ventricular wall thickness (PLVWTd), left ventricular internal diastolic dimension (LVIDd), left ventricular ejection fraction (LVEF), percentage of fractional shortening (PFS), left atrial dimension (LAD) and right ventricular end diastolic inner diameter (RV-EDD).[10]

Prior to the evaluation, informed consent was obtained from each patient. The study protocol conformed with the ethical guidelines of the 1975 Declaration of Helsinki, as reflected through a priori approval from our institution's human research committee (CAAE: 62709816.2.0000.5505).

Pearson correlation coefficients (r) were used to estimate relationships between the exercise test results and echocardiographic variables. The significance level was taken to be $P < 0.05$. All data were expressed as mean ± standard deviation (SD).

RESULTS

The results are described in **Tables 1** and **2**. The clinical evaluation showed that most of the paralympic athletes (n = 12) were asymptomatic and apparently healthy (n = 10). One subject showed obesity, asthma and mild arterial hypertension; another presented obesity and two others had asthma. Systolic mild cardiac murmurs were detected in two paralympic athletes.

The left ventricular volume was increased in nine athletes (62.22 ± 6.46 ml/m^2), ranging from 52 ml/m^2 to 95 ml/m^2. Despite the increased left ventricular dimensions (n = 4), atrial dimensions (n = 1) and relative wall thickness (n = 4), all the athletes had normal left ventricular mass/body surface (89.98 ± 21.93 g/m^2). The right ventricular dimensions were also within normal values. The ejection fraction (66.23 ± 2.94) and the percentage of fractional shortening ($36.29 \pm 2.18\%$) were also normal. The Doppler echocardiography did not detect any significant valvular regurgitant flow.

The results from exercise testing were normal for all subjects. There were no cases of ischemic ST depressions on ECG, or any cases of arrhythmias or hypotension. In the exercise testing, the exercise duration was 706 ± 45 seconds and the estimated peak

Table 1. Clinical, electrocardiographic and echocardiographic findings among athletes in the Brazilian paralympic judo team

Data	n
Age (years)	26.3 ± 6.4
Men	8 (57%)
Women	6 (43%)
Clinical findings	
Visually handicapped	14 (100%)
Systolic murmurs	2
Electrocardiogram	
Sinus rhythm	15
Nonspecific interventricular conduction defect	7
Left ventricular hypertrophy	5
Sinus bradycardia	3
T wave juvenile pattern	3
Left atrial hypertrophy	2
Atrioventricular block, first degree	1
Echocardiogram	
Increased left ventricular volume	9
Increased left ventricular internal diastolic dimension	4
Increased relative wall thickness	4
Increased interventricular septum thickness	1
Increased interventricular septum thickness	1
Variables	**Mean ± standard deviation**
Exercise testing	
Rest heart rate (bpm)	66 ± 4
Exercise time (sec)	706.35 ± 44.54
Estimated peak oxygen uptake (mlO_2/minute)	62.70 ± 9.99
Echocardiogram	
Left ventricular volume (g/m^2)	62.22 ± 6.46
Left ventricular mass/body surface (g/m^2)	87.98 ± 21.93
Relative wall thickness (g/m^2)	0.39 ± 0.04
Interventricular septum thickness (mm)	8.92 ± 1.53
Posterior left ventricular wall thickness (mm)	9.57 ± 1.22
Left ventricular internal diastolic dimension (mm)	49.46 ± 1.41
Left ventricular ejection fraction	0.66 ± 0.29
Percentage of fractional shortening (%)	36.29 ± 2.12
Left atrial dimension (mm)	38.07 ± 1.41
Right ventricular end diastolic inner diameter (mm)	20.71 ± 1.41

Table 2. Correlations between endurance time and echocardiographic variables among 14 paralympic judo players

Variable	Pearson's coefficient
Left ventricular mass/body surface	0.91
Left ventricular internal diastolic dimension	0.91
Interventricular septum thickness	0.48
Posterior left ventricular wall thickness	0.42
Right ventricular end diastolic inner diameter	0.21
Left atrial dimension	0.03

oxygen uptake reached 62.70 ± 9.99 mlO_2/minute. According to the criteria of the American Heart Association, the physical fitness was excellent (in 7% of the cases), good (36%), regular (21%) and weak (7%). This was not assessed in 29% of the cases because these individuals were under 20 years of age.[11] Signs of athlete's heart were found in 100% of the disabled athletes.

The correlations between the variables are presented in **Table 2**. There were very strong correlations between left ventricular mass/body surface (LVM/BS) and endurance time (r = 0.91) and estimated peak oxygen uptake (r = 0.8). The correlations between left ventricular internal diastolic dimension (LVIDd) and endurance time (r = 0.91) and estimated peak oxygen uptake (r = 0.8) were also strong.

DISCUSSION

We studied the Brazilian paralympic judo team to assess occurrences of althlete's heart. All the subjects were apparently health subjects and performed athletic activities national level. One subject presented obesity (BMI = 36.8 kg/m^2), slight asthma and mild recent hypertension; one had obesity (BMI = 38.5 kg/m^2); and another two had mild asthma. All the other subjects had BMI ranging from 20.4 to 28.4 kg/m^2. These data probably did not interfere with the myocardial findings.

During judo training and competitions, a high static component is required, comprising more than 50% of the estimated percentage of maximal voluntary contraction; and a low dynamic component comprising less than 40% of the estimated percentage of maximal oxygen uptake.[12] Strength training results in marked elevations in systolic and diastolic blood pressure. It induces large sudden pressure overloads and concentric left ventricular hypertrophy. Sometimes, it increases the left ventricular diameter.[13]

The maximal oxygen uptake in elite judo players has ranged from 45 ± 10 mlO_2/kg/minute (Germany, 1971) to 59.62 mlO_2/mg/min[14,15] Our athletes reached an excellent estimated oxygen uptake level (62.70 ± 9.99 mlO_2/kg/min). For 60% of our athletes, their fitness level was considered to be good/excellent.

Aerobic power and capacity levels have been found to be similar between Brazilian elite and non-elite judo players. VO_2max did not differ (P > 0.05) between the groups: elite (VO_2max = 58.13 ± 10.83 mlO_2/kg/min) versus non-elite (VO_2max = 63.28 ± 10.55 mlO_2/kg/min).[16] Despite occurrences of lower aerobic capacity among other paralympic athletes, the exercise duration according to the Bruce protocol among our athletes was 706.35 ± 44.54 seconds and the estimated peak oxygen uptake was 62.70 ± 9.99 mlO_2/kg/minute.

We found ECG abnormalities in nine athletes and increased echocardiographic measurements in six athletes. Nine subjects presented increased left ventricular volume, although there were no increases in right ventricular end diastolic inner diameter. This measurement may differentiate between normal hearts and exercise-related right ventricular adaptations and is the only parameter recommended for measurement within athletes' routine training.[14]

We registered very strong correlations between left ventricular mass/body surface and endurance time, thus showing the relationship between training and left ventricular hypertrophy, considering that judo is a martial art involving a high static component. There were also strong correlations between the left ventricular internal diastolic dimension of estimated peak oxygen uptake, considering that judo is also a sport involving a high dynamic component.[17]

Although intense endurance exercise may cause acute dysfunction of the right ventricle, chronic structural changes and reduced levels of right ventricle function in some athletes[18], we did not find any correlations between right ventricle dimensions and functional variables. The long-term clinical significance of these data warrants further study.[18]

Athlete's heart is a term used to describe the cardiovascular effects of long-term conditioning that is observed in highly trained athletes.[1] In our study, nine athletes showed ECG signs of athlete's heart and six athletes presented left ventricular hypertrophy on echocardiograms. Among all the subjects, eleven individuals (79%) were assessed as presenting athlete's heart. These data must be considered in clinical evaluations and management.

CONCLUSION

Signs of athlete's heart were highly prevalent manifestations among these paralympic judo players. This demonstrated that these disabled athletes presented mild cardiac adaptations to training.

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Association between multidrug resistance-1 C3435T gene polymorphism and right ventricular dysfunction in patients with chronic obstructive pulmonary disease: cross-sectional study

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Ventricular dysfunction, right.
Circulation, Pulmonary.

ABSTRACT

BACKGROUND: Right ventricular (RV) dysfunction may develop over the course of chronic obstructive pulmonary disease (COPD) and is an important predictor of morbidity and mortality. Polymorphism of the multidrug resistance-1 (MDR-1) gene has been correlated with worse clinical findings among patients with COPD. Our aim here was to investigate the relationship between MDR-1 C3435T gene polymorphism and RV dysfunction in COPD patients.

DESIGN AND SETTING: This was a cross-sectional study investigating the relationship between RV dysfunction and genetic defects in COPD patients.

METHODS: Forty-one consecutive patients diagnosed with COPD and hospitalized due to acute exacerbation were enrolled. Polymorphism was analyzed using the strip assay technique. RV parameters were evaluated, and RV dysfunction was identified via transthoracic echocardiography. Patients were categorized into three groups according to gene polymorphism: MDR-1 CC (wild type, n = 9), MDR-1 CT (heterozygote mutant, n = 21) or MDR-1 TT (homozygote mutant, n = 11).

RESULTS: The study included 14 males and 27 females (mean age 65 ± 11 years). The mean systolic pulmonary artery pressure was 31.4 ± 8 mmHg in the wild-type group, 42.2 ± 12 mmHg in the heterozygote mutant group and 46.5±14 mmHg in the homozygote mutant group (P = 0.027). Presence of RV dilatation was significantly different among the three groups (33%, 71%, and 100%, respectively; P = 0.005). In multiple logistic regression analysis, MDR-1 C3435T gene polymorphism (OR = 9.000, P = 0.019) was an independent predictor of RV dysfunction after adjustment for potential confounders.

CONCLUSION: MDR-1 C3435T gene polymorphism was associated with RV dysfunction in patients with COPD.

INTRODUCTION

Chronic obstructive pulmonary disease (COPD) gives rise to important morbidity and mortality over its progressive course. Pulmonary hypertension (PHT), right ventricular (RV) failure and cor pulmonale may develop over this course, and these are important predictors of morbidity and mortality in COPD. There is a growing volume of data on the roles of pulmonary and systemic inflammation and genetic factors in the onset and progression of COPD.[1-4]

The multidrug resistance-1 (MDR-1) gene, which is responsible for drug resistance, has a role in transportation of ions and peptides and in elimination of toxic substances.[5] It has been suggested that the multidrug resistance associated protein-1 (MRP-1), which is a product of this gene, has a role in antioxidative metabolism in the lungs. MRP-1 is expressed to a lesser extent in the bronchial epithelium of COPD patients than in that of healthy subjects.[6] MRP-1 levels have ben correlated with the severity of COPD.[7] Furthermore, single nucleotide C3435T gene polymorphism of the MDR-1 gene is associated with reduced MRP-1 levels.[8]

The aim of the present study was to investigate the impact of this gene polymorphism on RV dysfunction in patients with COPD.

METHODS

This study was performed in accordance with the Declaration of Helsinki for Human Research, and was approved by Cumhuriyet University Institutional Review Board (protocol number 2010/70, June 2010).

Forty-one consecutive patients who had previously been diagnosed with COPD and had been hospitalized due to acute exacerbation were enrolled into the study. Patients with other cardiopulmonary diseases were excluded. After informed consent had been obtained, a 5-ml peripheral blood sample was taken from each participant for genetic analysis. The patients were categorized into three groups according to this genetic analysis: MDR-1 CC (wild type), MDR-1 CT (heterozygote mutant) or MDR-1 TT (homozygote mutant).

Total genomic DNA was extracted from 100-ml blood samples using the Invitek kit (Invisorb spin blood, Invitek, Germany). The MDR-1 gene was amplified in a biotin-labeled single multiplex amplification reaction and was evaluated for the 3435 C > T polymorphism. The polymerase chain reaction (PCR) was performed in a Perkin-Elmer Geneamp 9600 thermal cycler. The protocol consisted of an initial melting step of 2 minutes at 94 °C, followed by 35 cycles of 15 seconds at 94 °C, 30 seconds at 58 °C and 30 seconds at 72 °C, and a final elongation step of 3 minutes at 72 °C. Polymorphism analysis was performed using the strip assay technique (ViennaLab, PGX-HIV Strip Assay GmbH, Austria), which is based on reverse hybridization.

Echocardiographic examinations were performed via the Vivid 7 system (GE Healthcare, Wauwatosa, WI, USA) with 2.5 to 5-MHz probes. The ejection fraction was calculated by means of the modified Simpson method. Chamber sizes were defined in accordance with recent guidelines.[9] In order to evaluate right ventricular (RV) dysfunction, the presence of RV dilatation, increased tricuspid regurgitation jet flow rate and increased systolic pulmonary artery pressure (sPAP) were evaluated on echocardiography. RV dimensions were evaluated in accordance with the most recent guideline,[9] and RV dimension > 3.4 cm in the basal plane or > 3.8 cm at midplane was used to designate RV dilatation as per the guidelines. Right atrium size was measured across the minor-axis dimension, extending from the lateral border of the right atrium to the interatrial septum.[9] Valvular regurgitations were graded into categories (trivial, mild, moderate or severe) via combinations of Doppler jet color flow signal intensity and vena contracta width, in accordance with the guideline recommendations.[10] Systolic pulmonary artery pressure was calculated as shown previously.[11] Echocardiography was performed twice by two experienced cardiologists who were blind to the patients' genotype.

Hypertension was deemed to be present in situations of blood pressure > 140/90 mmHg on more than two occasions during office measurements or being on antihypertensive treatment. Diabetes mellitus was deemed to be present in situations of fasting blood glucose ≥ 126 mg/dl or being on antidiabetic treatment. Individuals who continued smoking during index admission were considered to be current smokers. Heart rate and laboratory findings such as C-reactive protein levels, sedimentation rate and arterial blood gas levels were evaluated. The study was performed in accordance with the Declaration of Helsinki for Human Research, and was approved by our institutional review board.

Parametric data were expressed as mean ± standard deviation, and categorical data as percentages. The Statistical Package for the Social Sciences 15.0 (SPSS, Inc., Chicago, Illinois, USA) was used to perform statistical procedures. Comparisons between groups were performed by using one-way analysis of variance (ANOVA) with post-hoc analysis by means of Tukey's honest significant difference (HSD) test or an independent-sample t test. The Kruskal-Wallis test or the Mann-Whitney U test was used for normally or abnormally distributed data, respectively. Categorical data were evaluated by means of the chi-square test, as appropriate. Multivariable logistic regression analysis was used to evaluate independent clinical parameters that predicted RV dysfunction. A P-value of 0.05 was considered significant.

RESULTS

The study included 14 males and 27 females, with a mean age of 65 ± 11 years. The baseline characteristics of the patients with COPD, classified into three categories according to their MDR-1 C3435T gene polymorphism, are presented in **Table 1**. The baseline characteristics, laboratory findings and echocardiography parameters (except for sPAP and RV dilatation) did not differ among the three groups (P > 0.05).

The mean sPAP was 31.4 ± 8 mmHg in the wild-type (CC) group, 42.2 ± 12 mmHg in the heterozygote mutant (CT) group and 46.5 ± 14 mmHg in the homozygote mutant (TT) group (P = 0.027; **Figure 1**). The presence of RV dilatation was significantly different among the three groups (33%, 71%, and 100%, respectively, P = 0.005, **Table 1**). In the multivariate logistic regression analysis, MDR-1 C3435T gene polymorphism (odds ratio = 9.000; 95% confidence interval = 1.446-56.022; P = 0.019) was found to be associated with RV dysfunction after adjustment for potential confounders (age, gender, oxygen saturation, presence of hypertension, diabetes mellitus, smoking and atrial fibrillation).

DISCUSSION

The findings from this study demonstrated that C3435T polymorphism of MDR-1 gene was associated with RV dysfunction in patients with COPD.

Right ventricular dysfunction is associated with shorter survival and frequent episodes of exacerbation in cases of COPD.[12,13] Hypoxic vasoconstriction, mechanical stress on hyperinflated lungs, loss of capillaries, inflammation and toxic effects from cigarette smoke are the pathophysiological mechanisms for pulmonary hypertension (PHT) and also for RV dysfunction in COPD.[11]

In COPD, PHT is more prevalent at advanced stages, but it is generally moderate, with mean sPAP < 50 mmHg. The patients in the present study were at stage 2 or 3 and their mean sPAP was

41.0 ± 13 mmHg. The rate of cigarette smoking was 27% among all the patients and it did not differ between the groups. The underlying pathophysiological mechanisms for elevation of sPAP can be considered to have been similar between all the groups. The differences in RV dysfunction among the three groups can be explained in terms of the confounding effects of C3435T polymorphism in this process, caused especially by excessive inflammation.

We previously reported that there was a high frequency of C3435T polymorphism of the MDR-1 gene in patients with COPD, compared with healthy controls.[14] The association between the MDR-1 gene and the presence and severity of COPD has also been clearly described.[4,15] This association was attributed to the roles of the MDR-1 gene and MRP-1 in the antioxidant system and inflammation process. MRP-1 plays an important role in normal lung physiology through protecting against toxic xenobiotics and endogenous metabolites.[5] Cigarette smoke extracts inhibit MRP-1 activity in bronchial epithelial cells in vitro.[16] MRP-1 plays a role in combating the toxic effects of smoking and in the removal of oxidative stress metabolites.[17,18] The MDR-1 gene also plays a role in cell regeneration.[19] Pro-inflammatory cytokines decrease the amount of products (MRP-1) secreted from cells.[20] A decrease in MRP-1 expression and activity has been observed during inflammation.[21] Lower levels of MRP-1 due to MDR-1 C3435T polymorphism, as previously noted, could be the cause of excessive inflammation and thus a higher proportion of RV dysfunction.

CONCLUSION

It is not known which patients with COPD will develop RV dysfunction, even though the factors contributing to the development of RV dysfunction are known. This study showed that patients with COPD who carry the mutant allele for the MDR-1

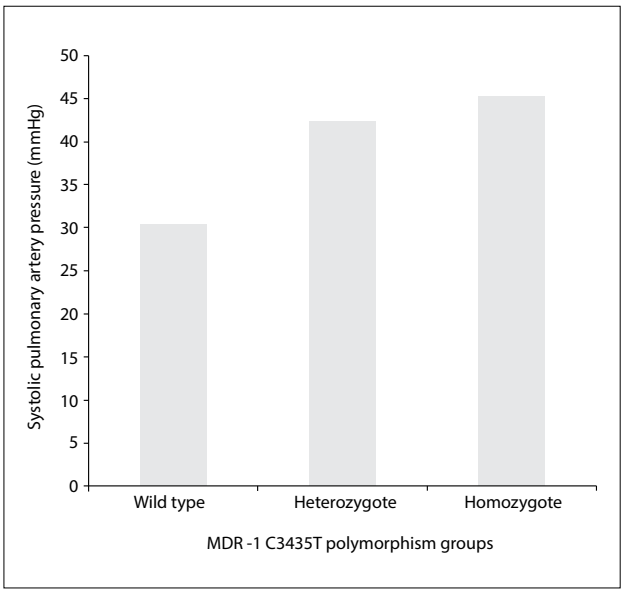

Figure 1. Comparison of systolic pulmonary artery pressure (sPAP) levels between the groups.

Table 1. Baseline characteristics of study patients

	Wild type (n = 9)	Heterozygote mutants (n = 21)	Homozygote mutants (n = 11)	P
Baseline characteristics				
Age (years)	66 ± 11	64 ± 13	67 ± 10	0.760
Gender (male/female)	5/4	6/15	3/8	0.308
Hypertension	6 (67%)	15 (71%)	8 (73%)	0.952
Diabetes mellitus	1 (11%)	5 (24%)	5 (46%)	0.205
Smoking	4 (44%)	5 (24%)	2 (18%)	0.379
Atrial fibrillation	2 (22%)	10 (48%)	6 (55%)	0.310
Echocardiography parameters				
Ejection fraction (%)	60 ± 3	59 ± 5	59 ± 4	0.751
Left ventricular diastolic dysfunction	7 (78%)	17 (81%)	11 (100%)	0.269
Mitral regurgitation (trivial/mild/moderate/severe)	2/7/0/0	7/11/3/0	2/9/0/0	0.312
Aortic regurgitation (trivial/mild/moderate/severe)	7/2/0/0	14/5/2/0	8/3/0/0	0.721
Left atrium size (cm)	4.2 ± 1.3	4.1 ± 0.6	4.4 ± 0.5	0.632
Tricuspid regurgitation (trivial/mild/moderate/severe)	1/5/3/0	0/11/7/3	0/6/4/1	0.555
Systolic pulmonary artery pressure (mmHg)	31.4 ± 8.4	42.2 ± 12.3	46.5 ± 14.3	0.027
Right ventricular dilatation	3 (33%)	15 (71%)	11 (100%)	0.005
Laboratory parameters				
C-reactive protein (mg/l)	14 ± 11	29 ± 30	20 ± 28	0.463
Sedimentation (mm/s)	12 ± 12	15 ± 18	16 ± 20	0.862
Arterial pH	7.42 ± 0.05	7.41 ± 0.04	7.44 ± 0.05	0.301
pO_2 (torr)	57 ± 10	55 ± 19	59 ± 15	0.811
pCO_2 (torr)	43 ± 9	42 ± 8	44 ± 8	0.814
Oxygen saturation (%)	88 ± 11	86 ± 9	88 ± 8	0.881

gene are at high risk of development of RV dysfunction. Future studies with larger groups may reveal whether these genetic alterations have any significant impact on RV dysfunction or not.

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Translation and cultural adaptation of the stroke impact scale 2.0 (SIS): a quality-of-life scale for stroke

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Quality of life.
Translations.
Stroke.

ABSTRACT

BACKGROUND: No specific quality-of-life scale for stroke patients has previously been translated and evaluated for reproducibility, for use in the Portuguese language. Internationally, the instrument for this purpose is the Stroke Impact Scale 2.0 (SIS). Use of of SIS enables comprehensive analysis on the impact of mild and moderate stroke on patients' lives. The aims here were to translate SIS into Portuguese, adapt it culturally, evaluate its reproducibility and correlate it with SF-36 among stroke patients.

DESIGN AND SETTING: Translation and validation study.

METHODS: The process of initial and retrograde translation was performed, in addition to cultural adaptation to the Brazilian language and culture. SIS was applied to 40 patients, who answered the questions three times. On the first day, the scale was applied twice by two independent researchers (to evaluate interobserver reproducibility). Fifteen days later, the scale was applied for a third time by another researcher (intraobserver reproducibility). The intraclass correlation coefficient (ICC) was used to measure the reproducibility of the SIS scale.

RESULTS: The reproducibility of the whole scale was very good (ICC: 0.73 to 0.99). Intraobserver reproducibility in all domains was also very good (ICC: 0.85 to 0.95). Comparison of SIS with SF-36 showed that the domains of strength, mobility and activities of daily living (ADLs) correlated moderately with the functional capacity domain, as did the ADL domain with general health status. The other correlations were weak. The depression domain showed a moderate negative correlation with the memory and communication domains.

CONCLUSION: The translation of the SIS 2.0 scale was easy to understand and it had good reproducibility among stroke patients.

INTRODUCTION

Among chronic non-communicable diseases, those of the circulatory system are the main cause of mortality worldwide, including Brazil, which has one of the highest rates in South America. Among cardiovascular diseases (CVDs), cerebrovascular disease has specific characteristics within Brazilian realities and is one of the most neglected diseases in the country.[1]

The incidence of stroke is increasing due to increased life expectancy and changes in lifestyle. It has been estimated that in South America it will become more evident over the next decades for the same reasons. Stroke mortality in Brazil has been reported to be the highest in South America for both sexes.[2]

Stroke has major impacts on individuals' sensory motor function and gives rise to disorders of language comprehension and orientation. When death does not occur, stroke has multiple negative consequences on individuals' lives, such as institutionalization, great dependence on other people and cognitive and communicative impairment.[3] It gives rise to a great need for care, since it affects human functions, and it disrupts not only the patient's life but also the lives of the entire family because of its sequelae. Most stroke survivors are left with permanent sequelae for which constant care is required. However, the implications of these consequences on the quality of life of these patients have not yet been assessed in depth, and neither have the prospects for these patients. Evaluations on stroke have usually been limited to neurological impairment and disability. Measuring the quality of life (QOL) after stroke could provide a spectrum of related answers for the many issues surrounding stroke.[4]

According to the World Health Organization (WHO), the concept of health is not merely the absence of disease, but the individual's perception of complete physical, mental and social wellbeing.[5]

Health-related QOL is investigated through self-evaluation by patients across multiple dimensions that are not limited to physical, social and emotional concepts. Measuring QOL is potentially more relevant to patients than are measurements of impairment or disability. QOL is also an important prognostic indicator for stroke, and it enables a broader description of the disease.[6]

Evaluating health and the effects of treatments involves assessing changes to the frequency and severity of diseases and estimating wellbeing. One way to assess patients' wellbeing is through quality-of-life questionnaires. Instruments for measuring quality of life are a useful way to transform subjective measurements into objective data that can be quantified and analyzed, and are important for checking the impact of interventions on patients' health and quality of life.[7]

There are few specific quality-of-life questionnaires for patients with stroke. The scales that have most commonly been used to measure these results are the Rankin scale, Barthel index and National Institutes of Health stroke scale (NIHSS).[8-10] However, these are not sensitive enough to assess mild stroke and do not assess quality of life dimensions such as mood, communication and function. Moreover, no quality-of-life questionnaire specific for stroke patients has been translated and validated for use in the Portuguese language. Internationally, the instrument for this purpose is the Stroke Impact Scale 2.0 (SIS).[11]

The aim of this study was to translate the SIS questionnaire into Brazilian Portuguese, to perform cultural adaptation on it and to evaluate its reproducibility.

METHODS

Patients

The study included 40 clinically stable patients who had been diagnosed with stroke at Escola Paulista de Medicina (EPM) - Universidade Federal de São Paulo (Unifesp), according to their consecutive arrival at the outpatient clinic.

The patients selected were over 18 years of age and had a minimum score in the Mini-Mental State Examination (MMSE) ≥ 24 for literate individuals and ≥ 13 for illiterate individuals. Patients who were admitted to the hospital, experienced changes in medication and/or did not participate in all evaluations were excluded.

The patients signed a free and informed consent statement and the protocol was approved by the Ethics Committee for Medical Research of Hospital São Paulo - Unifesp (no. 582/08).

Questionnaire structure

The SIS consists of 64 questions divided into eight areas and an independent measurement of the patient's overall perception of his or her percentage recovery after stroke, graded from zero (no recovery) to 100 (full recovery), in a format similar to a visual analogue scale. The domains are: strength, hand function, mobility, activities of daily living, instrumental activities of daily living, memory, communication, mood and social participation. The number of questions in each domain ranges from 4 to 11 and their scores range from 5 to 1, according to the degree of difficulty, amount of time and strength expended, depending on the dimension. The higher the score is, the better the quality of life is. Four of these dimensions (hand function, mobility, activities of daily living and instrumental activities of daily living) can be evaluated together to form a single domain called the physical domain. The SIS uses the scoring algorithm from the Medical Outcomes Study 36-item Short-Form Survey (SF-36) and is scored as follows for each dimension:

$$\text{Scoring: } \frac{[(\text{real score} - \text{lowest possible score})] \text{ X } 100}{\text{possible score amplitude}}$$

This scale is aimed towards evaluating other important issues, i.e. other than physical issues, that can substantially interfere in the quality of life of stroke patients from the patients' own point of view or that of their caregivers.

Translation into Portuguese and cultural adaptation

In the first stage of this study, two local translators who are native speakers of the Portuguese language and bilingual in English were recruited. Two versions of the questionnaire in Portuguese were produced by them.

In the second stage, a third person, who was also a native Portuguese speaker and bilingual in English, carried out an evaluation on the two translations and reconciled them into a single version.

In the third stage, a fourth translator, who did not have access to the original version of the questionnaire, translated the reconciled version back to the original language (English). So far, the translation process was similar to that used for the translation of the Saint George Questionnaire for Respiratory Diseases,[12] Airways Questionnaire (AQ 20)[13] and functional assessment of cancer therapy-brain (FACT-BR).[14]

In the fourth stage, the group responsible for the research compared the version translated into English with the original version in order to detect any friction relating to culture, thus generating a Portuguese version that would be applied to a sample of patients.

This questionnaire and an interview were applied to 10 consecutive patients who were being followed up at the neurovascular clinic of EPM-Unifesp, and these patients participated in the stage of translation and cultural adaptation of the questionnaire.

The aim of the interview was to evaluate the difficulties that patients might have in understanding the questionnaire and verify patients' interpretations in all areas. In the event of any problems, the interviewer would need to find an alternative means for

testing or conversions, or ask the individual to suggest an alternative. After the questionnaire had been applied to these patients and final corrections had been made, the questionnaire was deemed to have reached its final version.

Reproducibility assessment on SIS 2.0

To assess reproducibility, the SIS 2.0 questionnaire (final release) was applied to 40 patients from the previous stage. The questionnaire was administered three times to each patient. Only two researchers participated in administering the questionnaires. At the first appointment, SIS 2.0 was applied twice on the same day, at different times by two different researchers (researchers 1 and 2) who did not have access to the responses from each other's applications. This procedure was used to analyze interobserver reproducibility by means of the agreement analysis, presented by the intraclass coefficient correlation (ICC). Cronbach's alpha was also calculated. After a period of 15 days, SIS 2.0 was applied once again by researcher 1, to study intraobserver reproducibility.

Statistical analysis

The data were analyzed regarding normality of distribution, using the Shapiro-Wilk test. The data showed parametric distribution and were expressed as means and 95% confidence intervals (95% CI). Descriptive statistical analysis was used for demographic and clinical characterization of the patients evaluated. To compare pairs of independent samples, we used the Student t test.

To measure reliability, we used the intraclass correlation coefficient (ICC) and presented the 95% confidence interval (95% CI). The ICC was characterized as follows: good reliability 0.80-1.0; fair reliability 0.60-0.79; and poor reliability < 0.60.[15] The statistical significance level was set at $P < 0.05$. Statistical analyses were performed with the aid of the SPSS 17.0 software.

RESULTS

A total of 52 stroke patients participated in this study: 52 were initially recruited, 2 were excluded (one was excluded because he did not return for the second visit, and one because he did not answer the questionnaire), thus resulting in a sample of 50 patients who completed the study. The sample only included two illiterate individuals, but the questionnaire had to be read out for all of the individuals assessed because their educational level was low and they had difficulty in reading. Out of the 50 patients who completed the study, 10 participated in the stage of translation and cultural adaptation of the questionnaire and 40 participated in the questionnaire reproducibility study. All of the patients remained clinically stable and the treatment was not changed during the interval of fifteen days between the questionnaire applications.

In the group that participated in the translation and cultural adaptation, five patients (50%) were female. The average age was 45.2 ± 11.4 years. For the reproducibility study, 23 patients (57.5%) were female. The patients' characteristics are shown in **Table 1**.

The patients' cognition was assessed by means of the MMSE questionnaire. The minimum score given was 20 and the maximum was 35. The average length of time taken to answer the MMSE questionnaire was 6.27 ± 2.26 minutes, with a range from 3 to 11 minutes.

The intraclass correlation coefficient for analysis of intraobserver variability (total scores assessed 15 days apart) showed the value of 0.95 (95% CI: 0.75-0.99). The analysis of interobserver variability assessed on the same day also showed ICC of 0.95 (95% CI: 0.73-0.99), and these two reproducibility values were considered to be very good (**Table 2**).

The ICC from the analysis of reproducibility of the various domains assessed over a 15-day interval was very good and ranged from 0.75 to 0.99 (**Table 2**). The ICC from the analysis of interobserver reproducibility of the fields was also considered to be very good (0.73 to 0.99) (**Table 3**).

Also regarding the assessment of reproducibility, the averages for the eight domains were compared between the two times that the questionnaire was administered by the same researcher (**Table 4**) and on the same day by two different researchers (**Table 5**).

The eight domains showed excellent internal consistency, with Cronbach's alpha ranging from 0.75 to 0.99 (**Table 6**).

Table 1. Demographic characteristics of the 40 patients evaluated for the assessment on reproducibility

Variables	Data
Age (years), mean ± SD	61.10 ± 11.5
Gender, n (%)	
Female	23 (57.5)
Male	17 (42.5)
MMSE score, mean ± SD	26.22 ± 3.33
Type of stroke, n (%)	
Ischemic	39 (97.5)
Hemorrhagic	1 (2.5)

SD = standard deviation; m = mean; n = absolute number; MMSE = mini-mental state examination.

Table 2. Intraobserver reproducibility of each domain

	ICC	Confidence interval	P
Strength	0.86	(0.73-0.92)	< 0.0001
Hand function	0.99	(0.98-0.99)	< 0.0001
Mobility	0.92	(0.85-0.96)	< 0.0001
Activities of daily living	0.93	(0.86-0.96)	< 0.0001
Memory	0.89	(0.78-0.94)	< 0.0001
Communication	0.87	(0.75-0.93)	< 0.0001
Mood	0.75	(0.53-0.86)	< 0.0001
Social participation	0.93	(0.87-0.96)	< 0.0001

ICC = intraclass correlation coefficient; P = significance level.

Table 3. Interobserver reproducibility of each domain

	ICC	Confidence interval	P
Strength	0.92	(0.85-0.96)	< 0.0001
Hand function	0.99	(0.98-0.99)	< 0.0001
Mobility	0.88	(0.77-0.94)	< 0.0001
Activities of daily living	0.96	(0.93-0.98)	< 0.0001
Memory	0.85	(0.71-0.92)	< 0.0001
Communication	0.84	(0.69-0.92)	< 0.0001
Mood	0.73	(0.50-0.86)	< 0.0001
Social participation	0.94	(0.89-0.97)	< 0.0001

ICC = intraclass correlation coefficient; P = significance level.

Table 4. Mean, standard deviation and difference between the two visits (V1 and V2)

	V1 mean ± SD	V2 mean ± SD	Δ	P
Strength	44.4 ± 3.8	45 ± 3.6	-0.625	0.81
Hand function	69.2 ± 5.2	69.4 ± 5.2	-0.144	0.89
Mobility	77.0 ± 3.3	81.0 ± 3.4	-4.063	0.03
Activities of daily living	81.4 ± 2.8	81.1 ± 3.2	-0.186	0.90
Memory	75.7 ± 2.9	80.3 ± 3.0	-4.523	0.02
Communication	81.6 ± 3.4	85.9 ± 2.7	-4.334	0.04
Mood	52.8 ± 2.3	58.7 ± 1.7	-5.833	0.01
Social participation	57.9 ± 3.0	54.7 ± 3.1	3.260	0.04

Δ = difference between the two evaluations; SD = standard deviation.

Table 5. Values found for the interobserver evaluation

	Evaluator 1 mean ± SD	Evaluator 2 mean ± SD	Δ	P
Strength	44.4 ± 3.8	44.8 ± 3.7	-0.460	0.82
Hand function	69.2 ± 5.2	68.6 ± 5.3	0.631	0.58
Mobility	77.0 ± 3.3	77.1 ± 4.0	-0.083	0.97
Activities of daily living	81.4 ± 2.8	82.1 ± 2.8	-0.651	0.55
Memory	75.7 ± 2.9	78.1 ± 2.9	-2.385	0.26
Communication	81.6 ± 3.4	85.0 ± 2.6	-3.398	0.14
Mood	52.8 ± 2.3	54.3 ± 1.7	-1.464	0.44
Social participation	57.9 ± 3.0	57.0 ± 2.9	0.972	0.49

Δ = difference between the two evaluations; SD = standard deviation.

Table 6. Internal consistency of the eight domains

Domains	Cronbach's alpha
Strength	0.86
Hand function	0.99
Mobility	0.92
Activities of daily living	0.93
Memory	0.89
Communication	0.88
Mood	0.75
Social participation	0.93

DISCUSSION

The absence of instruments for assessing quality of life that have been translated and validated for use in Brazilian Portuguese among stroke patients has limited research in this field in this country. We decided to translate and culturally adapt SIS 2.0 and assess its reproducibility because this is an instrument that specifically assesses the impact of stroke on these patients' quality of life. The protocol followed enabled proper translation of the original questionnaire, thus making it possible to use it for evaluating Brazilian patients with a diagnosis of stroke.

For an instrument analyzing the conditions of a patient to be considered appropriate for use within the scientific community, it needs to be reproducible.[15] Reproducibility means that the same results are obtained when the questionnaire is applied at different times, to patients who present the same conditions. The SIS 2.0 questionnaire was reviewed regarding its intraobserver and interobserver agreement and calculation of intraclass correlations showed good agreement, both for application by the same investigator and for application by two different researchers.

For the intraclass correlation coefficient to demonstrate that an instrument is reproducible, the minimum acceptable value for this coefficient needs to be greater than or equal to 0.70 if the questionnaire is new, or greater than 0.80 if the questionnaire is old.[16] In our study, the coefficients found were greater than or equal to 0.73, thus demonstrate the excellent reproducibility of the translated version of SIS.

Although there was no statistically significant intraobserver difference between the averages for some areas of the questionnaire in assessing the reproducibility, the important point is that the ICC was considered strong in all areas (0.75-0.99). Some of the responses to the questionnaire showed changes 15 days after the first application. This was probably because the questions that generated these responses related to feelings that could change over a 15-day period, for example, "I feel that I am a burden to others". Another important point to be taken into consideration is that the possible answers often do not differ much between each other, for example "very" and "extremely". Something may have been qualified as "very" in the first interview and, 15 days later, it may become "extremely." Clinically, this change does not have any significant importance, but if taken in isolation, these two responses might be counted as if a change had occurred.

After the questionnaire had been applied during the interviews with the 10 patients in the adjustment phase, the lead researcher analyzed the main difficulties. This wide-ranging translation and adaptation process involving several steps made it possible to achieve linguistic equivalence between the words in the source language and target language. It was fully expected that certain problems would have to be addressed, such as the word *stroke*. From a semantic point of view, the word *stroke* (which literally

means a "hit") is a good example of how a difference between the source and target languages can distort meaning from a transcultural perspective. The word *stroke* was translated in the first version as "acidente vascular", but all the patients suggested that this should be changed to the word "derrame".

Regarding the assessment of reproducibility, the two researchers involved in the questionnaire had had specific training, thus making application of the questionnaires a homogeneous process. For it to be possible for questionnaires to be self-administered, they need to be simple and straightforward and must not lead to doubt among the patients.[17] If the questionnaire fulfills these requirements, the need for training for the people who will apply it will be low, but this may lead to some possibility of creating a confounding factor.[17]

Regarding demographic characteristics relating to sex, age and schooling, the patients evaluated in our study were similar to those assessed in the original study that led to the SIS 2.0 questionnaire.[11]

Although patients who did not achieve the minimum score in the MMSE were excluded, this questionnaire enables the possibility that the interviewer can read it aloud, which is critical for its application to Brazilian populations, in which 40% are functional illiterates.[18]

The translation and cultural adaptation of SIS 2.0 contributes a further instrument that can be used in future studies on stroke patients, with the particular aim of assessing their quality of life. In general, this is a parameter that has been little reported in neurovascular assessments. Until now, most studies have used the SF-36 scale (Medical Outcomes Study 36-Item Short-Form Health Survey)[19] to assess general wellbeing and the Barthel index[9] to evaluate functional capacity, but these scales do not have the capacity to assess the quality of life of stroke patients.

CONCLUSION

The resultant translation and adaptation of the SIS questionnaire (version 2.0) for use in the Portuguese language under Brazilian culture conditions was found to be easy for the patients to understand and had good reproducibility. This opens the possibility for its use among Brazilian stroke patients and allows evaluation of specific treatments.

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Validation of single measurement of 12-hour urine excretion for estimation of sodium and potassium intake. A longitudinal study

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Diet.
Urine specimen collection.
Validation studies.

ABSTRACT

BACKGROUND: Evaluation of sodium and potassium intake can be carried out using different methods. Biological markers are able to capture intra and inter-individual variability and are used as separate measurements of consumption. The aim of this study was to test the validity of a single measurement of urinary sodium and potassium excretion as representative of habitual intake.

DESIGN AND SETTING: Longitudinal study, federal university.

METHODS: Food consumption data from a sample of adult university students and public servants (25 to 74 years old) were collected through 24-hour records and 12-hour urinary sodium and potassium excretion at five different times over a one-year period. The dietary data were entered into a nutritional research data software system and the sodium and potassium intakes were estimated. The variables were tested for normal distribution using the Kolmogorov-Smirnov test. One-way analysis of variance or the Kruskal-Wallis test was used to evaluate means. Correlations between measurements using Pearson or Spearman coefficients were calculated. The degree of agreement between the five measurements was given by the intraclass correlation coefficient.

RESULTS: Satisfactory agreement was found between the five measurements of urinary sodium and potassium excretion over a year, with little variability in consumption.

CONCLUSION: A single measurement of urinary sodium and potassium accurately estimated the usual average consumption of these electrolytes. This can be used in population-based studies.

INTRODUCTION

One of the great challenges of nutritional epidemiology is to accurately determine the sodium and potassium intake in individuals' diets.[1] The dietary methods used to evaluate these nutrients may present different biases arising both from the information provided by individuals (through memory) and from the portion sizes and analytical instruments used in translating this nutrient information.[2]

Specifically, evaluation of sodium intake is complex due to the great variability within and between individuals.[3] However, this situation is not identified in dietary methods for evaluating intake, since the amounts of ingredients in recipes, including salt, are standardized.[4] The highest amounts of dietary sodium come from manufactured foods,[5] which have known compositions that are the same for all consumers of that product, with little variation between different brands. Nonetheless, if a significant portion of the sodium intake comes from salt that is added during food preparation or through use of manufactured seasonings, it becomes more difficult to use dietary methods to accurately identify the amounts of this nutrient and its variability among individuals.

For this reason, 24-hour urinary excretion has been used as a marker of daily sodium intake, since under normal conditions 95% of what is ingested is eliminated through urine.[6] Although not subject to the errors mentioned in relation to dietary methods, 24-hour urinary collection requires greater adherence by the individuals involved and presents higher costs. Considering the difficulties of collecting urine for 24 hours, 12-hour urine collection overnight has now been validated and has been used to estimate the daily sodium and potassium intake.[7] However, given the great variability of sodium intake between different days, a single measurement may represent a limiting factor for the use of this method.

Although questionnaires, records or reminders are easier to use, they make it impossible to identify the variability among individuals in relation to addition of salt and seasonings in food preparation. This is minimized through measurement of urinary excretion.

The objective of the present study was to test the validity of a single measurement of urinary sodium and potassium excretion as representative of habitual intake. Thus, we evaluated the variability of the measurements throughout the year, while the participants' usual diet did not change.

METHODS

A longitudinal study was conducted on a sample of university students and public servants approached in a university, comprising adults (25 to 74 years old) of both sexes. Sociodemographic, anthropometric and hemodynamic data were collected, as well as data on dietary intake and urinary sodium and potassium excretion, at five different time points during a one-year period. All the procedures were carried out in the Cardiovascular Research Clinic of the Health Sciences Center of the Federal University of Espírito Santo (Universidade Federal do Espírito Santo, UFES). Before data collection was started, a pilot study on 10 people was carried out in order to calibrate the interviewers and researchers.

To calculate the sample size, we made assumptions of a correlation coefficient of approximately 0.6, statistical power of 80% and significance level of 5%. Thus, the sample size was established as 100 individuals. Nonetheless, we took into account the possibility that participants might be lost because of the requirement that 12-hour urine collections would need to be performed five times over a 12-month period. Therefore, 164 individuals were invited to participate.

Individuals with renal disease who were undergoing dialysis, pregnant women and individuals with cognitive limitations were excluded. Participants whose volumes of 12-hour urine collection were lower than 250 ml were excluded from the analysis.

Data collection

Eligible participants at the university were approached and informed about the study and invited to participate. Soon after they had signed an informed consent statement, instructions were given and the material for the first urine collection was delivered. At that time, the participants were also informed of the timetable for the urine collection and food registration over the year. They also received a photographic album containing full-size photos of utensils to enable estimation of the sizes of the portions consumed, for the 24-hour food registration.

Urine collection and anthropometric evaluation

Urine collection was performed on five occasions, with three-month intervals between them. On the first and last occasions, urine was collected over a 24-hour period, divided into two periods of 12 hours: daytime (from 7 am to 7 pm) and nighttime (from 7 pm to 7 am the following morning). On the other occasions, only a 12-hour urine collection was made, at night.

The urine was collected at home by the participants in sterile, previously labeled bottles after verbal and written instructions had been given regarding the collection times and storage conditions (in the refrigerator) to be observed for the urine bottles. For the analyses, we only used 12-hour night urine.

On the day when the participants handed over the first urine sample and food registry forms at the cardiovascular clinic, they underwent anthropometric and hemodynamic evaluations, in accordance with standardized techniques. A structured questionnaire was applied in order to investigate their use of medications and dietary supplements, along with their lifestyle habits. Weight was measured at the baseline and at the end of the study.

After the urine samples had been handed over, the volumes were measured in a graduated cylinder (10 ml) and all the aliquots were sent to the university laboratory to determine the sodium and potassium concentrations by means of the selective electrode method. The total amount of electrolyte excretion over the 12-hour periods was determined by multiplying the concentration by the volume of urine collected.

24-hour food registration

The nutrient intake was obtained by means of a 24-hour food register on all five occasions on which urine was collected. The participants were encouraged to record in detail all food and beverages consumed over the 24-hour period, with the aid of an album containing full-size photos of utensils, in order to estimate the sizes of the portions/volumes consumed. Data on the food register were checked by the researchers at the time when the forms were delivered.

The nutritional composition of the food items reported in the food register was estimated through identifying these items in the database of the Nutrition Data System for Research (NDSR) of the University of Minnesota.[8] In addition, the Brazilian Table of Food Composition (TACO),[9] of the State University of Campinas (Universidade Estadual de Campinas, UNICAMP), was used to identify the following foods: "*farinha de mandioca*" (cassava flour), *"farofa"*, *"pirão"*, *"dobradinha"*, *"cajá"* and *"açaí com guaraná"* (açaí pulp with guaraná syrup).

The nutritional composition of local preparations was calculated based on the individual components of each preparation, according to information in technical publications from teaching and research institutions. For each 100 grams of edible parts of the foods and preparations, the values of total energy (kcal), sodium (mg) and potassium (mg) were calculated. Energy adjustments were performed using the residual method, to correct the estimates for sodium and potassium intake.[10]

Variables studied

The following data were collected and analyzed: sex, age (years), self-reported race/color (black, brown, white, indigenous and yellow), schooling, socioeconomic class (evaluated according to the Brazilian economic classification criteria, proposed by the Brazilian Association of Market Research Companies[11]), weight (kg), height (cm), energy (kcal), sodium and potassium from the dietary record (g) and urinary excretion of sodium and potassium (g).

Height was measured using a wall-mounted stadiometer (Seca, model 2161814009) with an accuracy of 1 mm. Individuals needed to be in a standing position, barefoot, looking straight ahead. Height measurements were made during the inspiratory period of the respiratory cycle. Body weight was measured with the subject still barefoot, on an electronic scale (Toledo, model 2096PP), with a capacity of 200 kg and a precision of 50 g. The body mass index (BMI) was calculated from body weight (in kg) divided by height in meters squared (m^2).

Statistical analysis

The normality of distribution of the continuous variables was determined by the by means of the Kolmogorov-Smirnov test. Pairs of means were compared using Student's t test and comparisons between more than two means were made using one-way analysis of variance (ANOVA). Continuous variables were correlated by means of the Pearson and Spearman coefficients in cases of symmetrical and asymmetrical distribution, respectively. The strength of the association was considered null for $r < 0.25$, weak for $0.25 \leq r < 0.5$, moderate for $0.5 \leq r < 0.75$ or strong for $r \geq 0.75$.[2]

The degree of agreement between the five measurements over the course of the year was given by means of the intraclass correlation coefficient, also called the reproducibility coefficient (RC). The intraclass correlation coefficient estimates the fraction of the total variability of measurements that is due to variations between individuals. For the intraclass correlation coefficient assessment, the following classification was used: weak, intraclass correlation coefficient < 0.4; satisfactory, 0.4 ≤ intraclass correlation coefficient < 0.75; and excellent, intraclass correlation coefficient ≥ 0.75.

The data were tabulated and expressed as means and standard deviations, percentages or ratios. The significance level for all tests was set at 5%. Statistical analyses were performed using the Statistical Package for the Social Sciences (SPSS) for Windows, version 18.0.1.

Ethical considerations

This project was approved by the Research Ethics Committee of the Health Sciences Center, UFES (no. 057586/2012), and all participants signed an informed consent statement.

RESULTS

Out of the 164 individuals who were invited to participate, 103 completed the urine collections on all five occasions, as presented in **Figure 1**. Data from these 103 participants of mean age of 48.3 ± 12 years were analyzed. Individuals with renal disease who were undergoing dialysis, pregnant women and individuals with cognitive limitations were excluded. A total of 154 people fulfilled the first 12-hour urine collection, 124 the second, 110 the third, 108 the fourth and 107 the fifth. Volumes of 12-hour urine collection < 250 ml were excluded from the analysis. After all the exclusions, the final sample for analysis purposes comprised 103 people.

Table 1 shows the characteristics of the sample. The majority were female (64.1%), of socioeconomic class B (53.4%), with higher levels of schooling (80.6%) and white race/color (50.5%). At the first interview, one third of the participants reported adding

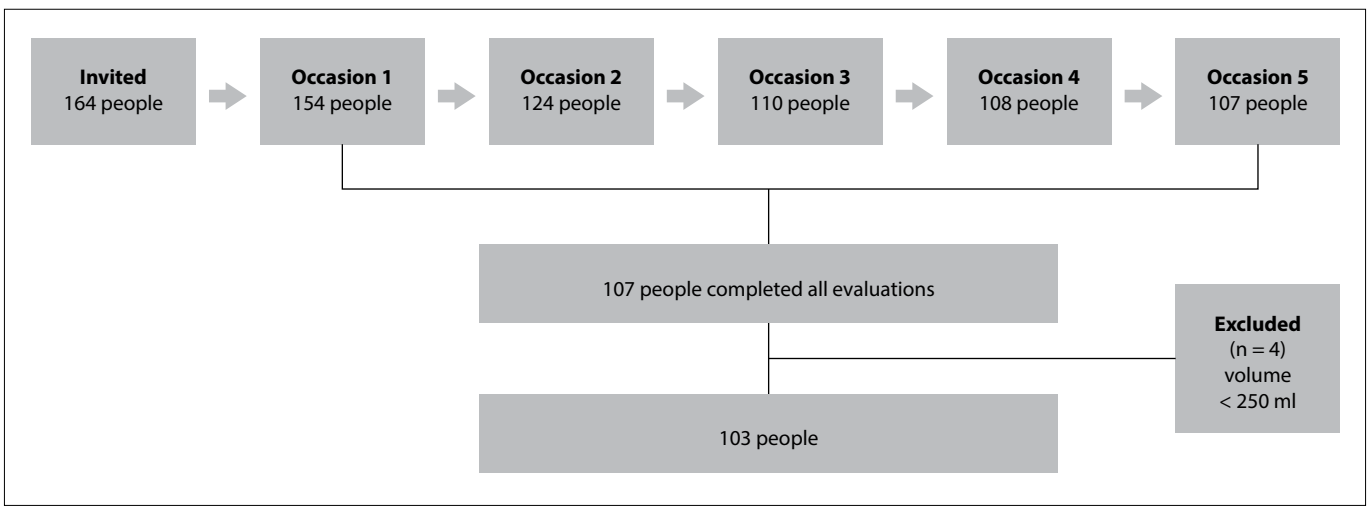

Figure 1. Sample description.

salt to table preparations (34%), 20.4% reported having a diagnosis of hypertension, 8.7% had diabetes and 55.4% were overweight (overweight or obese).

Table 2 presents the participants' averages and standard deviations for sodium intake terciles on the five occasions over the one-year period. The participants in the first tercile presented a mean salt intake that was within the current recommendation (up to 5 g/day), in four out of the five evaluations. In the last tercile, the mean value reached more than three times the recommendation, in four out of the five evaluations.

Table 3 shows the nighttime 12-hour urinary excretion data regarding sodium and potassium and the estimated salt consumption and energy consumption, and the intake of these same nutrients estimated from the 24-hour food register. Significant differences were observed between the means for urinary excretion of sodium (P = 0.009) and potassium (P < 0.001), but no differences in the values of sodium and energy consumption were observed between the five occasions. The estimates of salt intake in g/day remained constant in both methods, but the mean values found through the 24-hour food register were always lower than the values for salt intake estimated from urinary sodium excretion. A small but significant fluctuation (P = 0.042) in the estimates of potassium intake from the 24-hour food register was found. The only significant difference in relation to the urinary sodium measurement was from the fourth to the fifth occasion. **Table 3** also shows that there was satisfactory agreement between the measurements of urinary excretion over the one-year period for both sodium (intraclass correlation coefficient = 0.65; P < 0.001) and potassium (intraclass correlation coefficient = 0.58; P < 0.001), and for estimated salt consumption (intraclass correlation coefficient = 0.64; P < 0.001).

Table 1. Characterization of the sample studied. VALSA Study – Vitória (ES), 2015

Variable	n	%
Sex		
Female	66	64.1
Male	37	35.9
Schooling		
Elementary and high school	20	19.4
Undergraduate and postgraduate university	83	80.6
Race/color		
White	52	50.5
Mixed	51	49.5
Socioeconomic class		
A	30	29.1
B	55	53.4
C	18	17.5
Nutritional status		
Normal	46	44.6
Overweight*	57	55.4
Hypertension diagnosis	21	20.4
Diabetes mellitus diagnosis	9	8.7
Use of salt shaker	35	34

*Overweight = body mass index ≥ 25 kg/m^2.

Table 2. Mean and standard deviations (SD) (95% confidence interval) of 12-hour urinary sodium measurements, according to consumption terciles on five occasions over a one-year period. VALSA Study, Vitória (ES), 2015

Occasion	1st tercile	2nd tercile	3rd tercile
	Mean ± SD (95% CI)	Mean ± SD (95% CI)	Mean ± SD (95% CI)
1	5.2 ± 1.4 (2.4-6.8)	8.6 ± 1.1 (6.8-10.3)	12.6 ± 2.1 (10.6-20.3)
2	4.7 ± 1.4 (1.6-6.3)	8.2 ± 0.9 (7.0-10.0)	15.0 ± 5.4 (10.1-31.0)
3	4.6 ± 1.1 (2.1-6.4)	7.9 ± 0.9 (6.4-9.6)	15.4 ± 5.4 (9.9-33.2)
4	3.9 ± 1.3 (0.7-5.5)	7.7 ± 1.0 (5.6-9.5)	15.1 ± 5.4 (9.8-31.2)
5	4.6 ± 1.3 (1.9-6.6)	9.0 ± 1.4 (6.7-11.2)	14.2 ± 2.9 (11.4-27.7)

CI = confidence interval.

Table 3. Mean and standard deviations (SD) of 12-hour nocturnal urinary excretion of sodium and potassium, and estimated salt consumption, on the five occasions evaluated. VALSA Study, Vitória (ES), 2015

Occasion	12-hour urinary excretion		
	Sodium (g/day)	Potassium (g/day)	Estimated salt consumption (g/day)
	Mean ± SD	Mean ± SD	Mean ± SD
1	3.7 ± 1.5	0.9 ± 0.6#	9.2 ± 3.6
2	4.3 ± 2.2	1.1 ± 0.60#	10.6 ± 5.5
3	3.9 ± 2.0	1.1 ± 0.52	9.9 ± 5.0
4	3.5 ± 1.7#	1.0 ± 0.5	8.8 ± 4.3
5	4.3 ± 2.2#	1.1 ± 0.6#	10.9 ± 5.5
P-value	0.009*	0.001**	0.553**
ICC (P-value)	**0.65 (< 0.001)**	**0.54 (< 0.001)**	**0.65 (< 0.001)**
	24-hour food registry		
	Energy (kcal)	Sodium (g/day)	Potassium (g/day)	Estimated salt consumption (g/day)
	Mean ± SD	Mean ± SD	Mean ± SD	Mean ± SD
1	2228 ± 750	3.4 ± 1.3	3.4 ± 1.8#	7.4 ± 2.8
2	2127 ± 818	3.1 ± 1.5	3.2 ± 1.4	6.8 ± 3.2
3	2001 ± 709	3.1 ± 1.5	2.9 ± 1.5#	6.7 ± 3.3
4	2197 ± 695	3.4 ± 1.5	3.2 ± 1.6	7.4 ± 3.3
5	2121 ± 723	3.3 ± 1.8	2.9 ± 1.4#	7.2 ± 3.9
P-value	0.219*	0.175**	0.042**	0.245**
ICC (P-value)	0,64 **(< 0.001)**	0.49 **(< 0.001)**	0.65 **(< 0.001)**	**0.64 (< 0.001)**

*Analysis of variance; **Kruskal-Wallis; #difference between means.
ICC = intraclass correlation coefficient; SD = standard deviation.

Table 4 shows the correlations between urinary sodium and potassium values and estimated salt consumption obtained on each of the occasions, and shows the averages for the five evaluations. It can be seen that all the correlations were positive and that most of them presented statistical significance. It is important to note that the correlations of the sodium measurements between the first, second and fifth occasions and the averages for the five occasions were moderate (from 0.51 to 0.75), while the correlation between the third occasion and the overall mean was strong (r = 0.76). In relation to potassium, all the correlations were positive, but some were not as significant as those of the fourth occasion in relation to the other measurements. However, a positive and significant correlation was found between the fourth measurement and the mean for the five observations. The measurements of sodium and potassium from the urine collection on the fourth occasion were the ones that differed from the others. A similar result was found in relation to the estimated salt consumption.

In addition, analyses were performed to evaluate the correlation between the 24-hour urinary excretion measurements and the 12-hour nocturnal measurements (data not shown in the table). A strong correlation was found between the 24-hour and 12-hour measurements for both sodium and potassium on the first occasion. On the fifth occasion, the strong correlation remained for sodium, while for potassium the correlation was moderate (r = 0.66; P < 0.001).

Table 4. Correlation (r) between measurements of urinary sodium and potassium excretion and estimated salt consumption over a one-year period (five occasions and mean). VALSA Study, Vitória (ES), 2015

Occasion	Occasion				
	1	2	3	4	5
	Sodium				
1	1.000	0.215*	0.349**	0.190	0.290**
2	0.215*	1.000	0.396**	0.126	0.216*
3	0.349**	0.396**	1.000	0.242*	0.464**
4	0.190	0.126	0.242*	1.000	0.168
5	0.290**	0.216*	0.464**	0.168	1.000
Estimated mean	**0.510****	**0.617****	**0.763****	**0.471****	**0.712****
	Potassium				
1	1.000	0.148	0.265**	0.172	0.205*
2	0.148	1.000	0.384**	0.002	0.206*
3	0.265**	0.384**	1.000	0.062	0.306**
4	0.172	0.002	0.062	1.000	0.088
5	0.205*	0.206*	0.306**	0.088	1.000
Estimated mean	**0.583****	**0.586****	**0.646****	**0.343****	**0.566****
	Estimated salt				
1	1.000	0.215*	0.349**	0.190	0.290**
2	0.215*	1.000	0.396**	0.126	0.216*
3	0.349**	0.396**	1.000	0.242*	0.464**
4	0.190	0.126	0.242**	1.000	0.168
5	0.290**	0.216*	0.464**	0.168	1.000
Estimated mean	**0.510****	**0.617****	**0.763****	**0.471****	**0.712****

* P < 0.05; ** P < 0.01.
Estimated mean = mean of five occasions.

DISCUSSION

Satisfactory agreement was found between the five measurements of urinary excretion obtained from a 12-hour period at night, over a one-year period, showing little variability in consumption. Therefore, our data suggest that a single measurement of urinary sodium and potassium provided estimates of reasonable accuracy for the usual mean consumption and may be used in population studies on adults.

Given that the intraclass correlation coefficient is an estimate of the fraction of the total variability of measurements that is due to variations between individuals, it can be inferred that there was relative variability over the one-year period. Nonetheless, it can also be inferred that this did not compromise the use of a single measurement for estimating the usual sodium and potassium intake of the group, because of the level of agreement that was found when using the intraclass correlation coefficient.

The sodium values found on the five occasions over the one-year period, both from urinary excretion and from the registry, were higher than the recommended values but lower than those that were found in a similar study conducted in the city of Vitória, Espírito Santo, Brazil[12] and in studies on employees at the same institution as in that study.[13,14] This may have been related to the low use of manufactured seasonings, in comparison with natural condiments, which was much cited by the group in the present study.

According to Nakasato,[15] the main source of sodium in food comes from cooking salt, although this micronutrient is present in almost all foods that have undergone some form of industrial process, such as breads, biscuits and sausages, among others. Significant levels of sodium are also found in meats, butter and cheeses. Although the sodium values from the food records of the present study were below those found in urinary excretion, they were probably still elevated, and it has been shown that food records underestimate sodium intake[18]

The sodium values from the urinary excretion and from the registry were transformed into amounts of salt (g). At all times and from both methods, the estimated salt values were above the current recommendation of up to 5 g/day. The estimated intake of salt ascertained through the food register was, on average, 22% lower than the values estimated from urinary excretion. It is likely that this difference arose because the 24-hour food register did not detect addition of salt, or the salt contained in the manufactured seasonings that are used in food preparation.[16] In food composition tables, the amount of salt in the preparations is defined a priori, and no computation is made regarding further addition of salt or of products that participants in such studies may add during the preparation of foods, such as ready-made seasonings and soy sauce, among others that are rich in sodium.

Sodium intake seemed to be underestimated through the dietary method, and this occurred independently, i.e. without any correlation with the values estimated from urinary excretion. This could

be expected, because the food register was filled out on the day of urine collection, but not all sodium is eliminated immediately after consumption because urinary excretion depends on a large number of factors, including water balance and osmosis, blood pressure and production of hormones, among others.[17] Thus, a set of food records compiled over a one-year period can contribute towards clarifying the sources of nutrients and thereby identifying whether excess sodium in the diet is related to higher addition of salt and manufactured seasonings, or whether it comes from processed foods, which cannot be observed by using the biomarker.

Also, as expected, there was a significant correlation between the energy values and the estimates of sodium and potassium intake from the 24-hour food register. Considering that 24-hour food registers are less subject to information bias than are other instruments for estimating food consumption, and that the data were checked by the researchers at the time when the forms were delivered, problems relating to the method used and to the quality of information were minimized in this study.

In a recent study, the sodium values from urinary excretion and from a food frequency questionnaire were similar,[15] probably due to overestimation of consumption through the dietary method used. In the present study, the mean values for sodium and potassium were lower because the food record evaluated the instantaneous consumption, i.e. what was consumed on the day recorded. Since there were five 24-hour records over the course of the year, the mean from these may have represented the habitual consumption of these nutrients, without the more frequent overestimation observed in food frequency questionnaires.[18]

It is important to emphasize that the sample consisted mostly of women, with a mean age of 48 years, in higher socioeconomic classes and with high schooling levels. These characteristics may determine healthier eating habits.[19] In addition, the fact that most of them were women meant that their consumption of food was generally lower, which therefore decreased the average consumption of the group. Another issue relates to higher education levels, which may lead to healthier food choices because of greater access to information about nutrition.

The differences found in relation to potassium through the two methods probably related to seasonal consumption of fruits and vegetables, which are important sources of this nutrient.[20] It is also possible that the lower consumption was already an expected effect from some actions taken by manufacturers with the aim of reducing the sodium levels in processed foods. However, it is more likely that the individuals added less salt to the food during the preparation and used less industrialized seasonings.

CONCLUSION

Measurement of 12 hours of nocturnal urinary excretion of sodium and potassium can be used to evaluate habitual consumption of these nutrients in population studies, since good agreement among the five measurements evaluated over a one-year period was observed. However, it is important to take into account other information, especially factors relating to dietary habits and behavior and the types of food consumed, in relation to these nutrients.

The biological marker, in this case, is the one that best reproduced the consumption of these nutrients, but it is not able to identify the amounts of sodium/salt added to the food. Thus, the single 12-hour urinary excretion measurement can be used to evaluate changes to the population's behavior regarding sodium and potassium intake, and it may contribute towards monitoring of governmental actions aimed at reducing sodium intake and, consequently, improving health conditions and the cardiovascular morbidity and mortality profile.

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Translation and validation of the Brown attention-deficit disorder scale for use in Brazil: identifying cases of attention-deficit/hyperactivity disorder among samples of substance users and non-users. Cross-cultural validation study

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KEY WORDS:
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ABSTRACT

BACKGROUND: The Brown Attention-Deficit Disorder Scale (BADDS) was developed as a self-report assessment that was designed to screen for presence of symptoms of attention deficit hyperactivity disorder (ADHD). The objective here was to translate and validate the adult self-report BADDS for use in Brazil.

DESIGN AND SETTING: Cross-cultural validation study conducted in an addiction unit at a public university hospital.

METHODS: This study included a control group (n = 100) and a drug-user group (n = 100). Both groups included subjects aged 18 to 60 years old. The control group had no prior diagnosis of drug addiction and the drug-user group included participants with a diagnosis of addiction. Each participant answered Brazilian Portuguese translations of both the BADDS and the Adult Attention Deficit Hyperactivity Disorder Self-Report Scale (ASRS) questionnaires, in paper-and-pencil format.

RESULTS: The drug-user group scored higher than the control group on both scales. The mean scores on ASRS were 27.26 (standard deviation, SD: 11.99) and 25.85 (SD: 8.65) respectively ($P > 0.05$). The mean scores on BADDS were 79.56 (SD: 29.61) and 79.31 (SD: 18.09), respectively ($P > 0.05$). Cronbach's alpha for BADDS was 0.95. BADDS presented fair sensitivity (72% accuracy) and fair specificity (88% accuracy).

CONCLUSION: This study provides discriminative validity evidence for use of BADDS among Brazilian adults with substance-use disorders.

INTRODUCTION

Until recently, it was believed that attention deficit hyperactivity disorder (ADHD) was exclusively a pediatric condition.[1] However, current research indicates that 60% to 70% of children diagnosed with ADHD continue to manifest symptoms into adulthood.[2] Persistence of symptoms of ADHD can have a pressing impact on the safety and personal relationships of patients, as well as having secondary effects in adulthood such as lost days of productivity and continual negative feedback or social and educational disadvantages.[3] A recent study that used the Diagnostic and Statistical Manual of Mental Disorders-IV (DSM-IV) criteria for ADHD, which was conducted in both developed and underdeveloped countries, estimated that the worldwide prevalence of ADHD was 3.4% and showed that it was higher among underdeveloped countries.[4]

Currently, there are no biomarkers available for diagnosing ADHD. All diagnoses require careful assessments by clinicians through interviews and appropriate classification criteria.[5] Two diagnostic tools are used today to classify this disorder: DSM-5 and the International Statistical Classification of Diseases and Related Health Problems (ICD-10).

These two diagnostic tools define ADHD as a hyperkinetic disorder, a disorder characterized by inattention, hyperactivity and impulsivity with onset in childhood or adolescence. It is believed that the current diagnostic criteria (both DSM-5 and the ICD-10) are inadequate for evaluation of adults because they focus on early childhood problems and they do not fully account for developmental and maturation changes.[6] The symptoms and functional impairments identified among adults for making a diagnosis of ADHD tend to be different from those observed among children.

In cases of diagnosing children, parents and teachers play a key role in recognizing, identifying and rating the child, based on standardized evaluation scales.[7] On the other hand, for adults, there is usually no one who has observed symptoms or problems with their behavior. Therefore, the diagnosis of the disorder is based upon a self-report of behaviors. Research has indicated that adolescents and adults with ADHD often underestimate their symptoms,[8] thus making diagnosis much more difficult.

Many people who suffer from ADHD may also be at risk of having co-occurring psychiatric disorders or chronic illnesses. It has been estimated that more than 87% of adults with ADHD have some form of comorbidity.[9] A study conducted in the United States in 2008 demonstrated that adults with ADHD had comorbidities involving anxiety (47%), mood disorders (38%), impulse control (20%) and substance-use disorders (SUD) (15%).[10] The prevalence of having a comorbidity involving substance use is significantly higher among individuals with ADHD than among those without ADHD.[11] It has been shown that adults with substance-use disorders are at higher risk of presenting ADHD and earlier onset of ADHD, with greater severity of SUD and chronic SUD.[12] Furthermore, ADHD has been linked to lower remission rates for cigarette smoking and SUD.[12] Since the impact of comorbidity between ADHD and SUD in adulthood is significant, earlier diagnosis, treatment and healthcare delivery are relevant for patient prognosis.[12] This highlights the importance of studying this specific population of substance users with ADHD as a comorbidity.

In order to enhance and assist the diagnostic process for some psychiatric conditions, standardized instruments are becoming increasingly necessary. Standardized assessment instruments are widely disseminated within research and have increasingly been used as a resource for evaluating different aspects of mental health. In clinical practice, standardized instruments are critical for screening and diagnosing patients. Currently, researchers use self-report questionnaires as a critical part of screening and diagnosing patients with ADHD. Limitations exist because the screening and diagnosis tool is unavailable in other countries.

To improve the reach of the Brown Attention-Deficit Disorder Scale (BADDS) in Brazil, the aim of this study was to translate and validate it for use in Portuguese among a Brazilian sample of drug users and among a sample of people with no history of drug use.

METHOD

Study design, setting and ethics

This was a translation and cross-cultural validation study, conducted at the Federal University of São Paulo (Universidade Federal de São Paulo, UNIFESP). The ethics committee of UNIFESP approved the study (June 7, 2013; no. 17280313.2.1001.5505) All participants signed an informed consent statement.

Questionnaire translation

BADDS is a self-report questionnaire that is used for screening adults with a possible case of ADHD.[13] Differently from other scales like ASRS, BADDS does not contain any DSM-5 criteria. The questions in BADDS are not driven in terms of inattention-hyperactivity-impulsivity symptoms, but instead assess functional impairment in five areas, through 40 questions. These five areas are as follows:

1. organizing and prioritizing work and activation for work;
2. focusing on tasks, sustaining this focus and shifting attention to tasks;
3. regulating alertness and sustaining effort, and the ensuing processing speed;
4. managing frustration and modulating emotions; and
5. using working memory and accessing recall.

Each question has a possible score from 1 to 4. The higher the cluster score and overall score are, the higher the risk is that the individual has ADHD.

All individuals who complete the BADDS questionnaire are classified into three groups: i) possible, but unlikely to have ADHD, if the score is less than 40; ii) possible, but unconfirmed ADHD, if the score is between 40 and 54; and iii) highly likely but unconfirmed ADHD, if the score is above 55.

A 2008 study demonstrated that BADDS was more reliable than were other instruments that were based on the DSM-IV criteria.[14] The information provided by the patient via this self-report questionnaire and through information from someone close to the patient is more accurate for assessing ADHD symptoms than is use of the DMS-5 criteria.

The paper-and-pencil format of BADDS was translated into Portuguese. The translation was conducted using a two-step procedure, known as the back-translation method, as recommended by Brislin (1973) and by Smit (2006).[15,16] According to these authors, two bilingual translators are required in order to come to a consensus regarding any translational difficulties or discrepancies.[15,16] In our case, a bilingual psychiatrist first translated the items from English to Portuguese, followed by back-translation into English conducted by a linguist. The discrepancies between the two versions were resolved by reaching a consensus between the two bilingual professionals.

ASRS is currently the most accepted and most widely used self-report questionnaire for screening for ADHD symptoms.[17] The questionnaire asks directly about the existence of inattention-hyperactivity-impulsivity symptoms, in the way in which these are presented in the DSM-5 criteria. It consists of 18 questions, with scores for each question ranging from 0 to 4. Zero means that no symptoms were present within the last six months, while 4 indicates that all symptoms were present within the last six months. The composite scores of this questionnaire, similarly to BADDS, classifies patients

into categories depending on the risk of ADHD. Patients with scores between 0 and 16 are considered to be individuals with an unlikely risk of having ADHD; patients with scores between 17 and 23 are considered to be individuals with a likely chance of having ADHD; and finally, individuals with scores of 24 and over are considered to present a high likelihood of having ADHD.

ASRS was chosen as the gold standard for this study. The main reason for this choice was that the Addiction Unit did not have enough trained psychiatrists to perform a complete ADHD diagnosis on these 100 subjects. It is important to state that this unit is not specifically designed for research purposes and that this evaluation would imply a significant increase in the psychiatrists' workload.

Participants

The validation study sample consisted of two groups. One group (control group) consisted of a convenience sample of 100 students from UNIFESP, in accordance with the following inclusion criteria: i) between the ages of 18 and 60 years; ii) either female or male; iii) literate, independent of education level, socioeconomic level or ethnicity; and iv) no prior diagnosis of psychiatric conditions or drug addiction (according to self-report).

The second group (drug users) comprised 100 adults who were currently attending an outpatient facility, the Addiction Unit of UNIFESP (through the Guidance and Attendance Program for Substance Dependents; Programa de Orientação e Atendimento a Dependentes, PROAD). At this facility, patients participate in weekly group therapy sessions and are individually evaluated by a psychiatrist at least once a month. This trained psychiatrist is responsible for making the diagnosis of drug dependence, using the DSM-5 criteria. Individual sessions with a psychologist may form part of the treatment, depending on the needs of each patient. For our second group, the same inclusion criteria were used, with the addition that all patients had a diagnosis of substance dependence, which had been assessed and diagnosed by a psychiatrist in accordance with the DSM-5 criteria. All substances except tobacco were included in the assessment.

All participants in both groups answered two self-report questionnaires: BADDS and the Adult ADHD Self-Report Scale (ASRS). Aside from age, gender and psychiatric diagnosis, no other sociodemographic or clinical information was collected.

Statistical analysis

The total scores on both scales were tested in order to check for normal distribution, which was confirmed. Chi-square tests were used to analyze categorical data, while t tests were used to analyze parametric continuous variables. The internal consistency of BADDS was measured by means of the Cronbach's alpha method. Alpha was computed by correlating the score for each scale item with the total score for each individual observation, and then making comparisons with the variance for all individual item scores.[18]

The participants' scores were compared using the means that were obtained through the two questionnaires, to determine criteria for concurrent and discriminant validation measurements for BADDS. Given the scores from each questionnaire, several cutoff points were verified for sensitivity and specificity, in increments of 10 (instead of the usual one-by-one increments of scores that are used for most of the instruments available).

To analyze cutoff points, the receiver operating characteristic (ROC) curve was used. The statistical significance level was taken to be 0.05. The statistical analysis software Statistical Package for the Social Sciences (SPSS 22.0) for Windows was used.

RESULTS

Within the drug-user group, men comprised 87% of the sample, whereas in the control group, men represented 47% of the total sample. The drug-user group scored higher than the control group in both ADHD instruments. The mean score from the ASRS questionnaire in the drug-user group was 27.26 (SD: 11.99), compared with 25.85 (SD: 8.65) in the control group ($P > 0.05$). The mean scores from the BADDS questionnaire were 79.56 (SD: 29.61) and 79.31 (SD: 18.09), respectively ($P > 0.05$). Cronbach's alpha from BADDS was 0.95.

Table 1 summarizes the results from the ROC analysis (**Figure 1**). The optimum cutoff score was 50, as shown in **Table 1**. Scores below 50 indicate a negative diagnosis for ADHD, whereas scores of 51 and over indicate a positive diagnosis. Using this threshold, the substance abuse scale detected true positives (sensitivity) with 72% accuracy and true negatives (specificity) with 88% accuracy. For both groups, the area under the curve was 0.891.

DISCUSSION

This study demonstrated that BADDS, a tool for diagnosing ADHD among adults, has high internal consistency and differentiates possible cases of ADHD among people with concurrent substance use and people without a psychiatric diagnosis. The scale has fair sensitivity and specificity.

These results encourage use of BADDS for identifying possible ADHD cases, both in clinical practice and in research. Screening for ADHD using this scale enables greater agility in reaching diagnostic confirmation of ADHD. Moreover, this tool results in the following:

1. higher quality for the service, given that a standard is created for diagnostic investigation;
2. improvement of adherence to treatment, since patients can track their progress through reductions in the scores; and
3. greater focus of the available resources on individuals who are accurately screened positive, so that they can be evaluated by a psychiatrist or a psychologist.

Table 1. Cutoff points compared between control group, addiction unit group (treated at PROAD) and both groups together (total)

Cutoff[a]	Total[b]		PROAD[c]		Control group[d]	
	Sensitivity	Specificity	Sensitivity	Specificity	Sensitivity	Specificity
10	1	0	1	0	1	0
20	0.985	0.225	0.985	0.322	0.985	0.129
30	0.971	0.451	0.971	0.516	0.971	0.387
40	0.869	0.693	0.956	0.709	0.782	0.677
50	0.724	0.887	0.869	0.935	0.579	0.838
60	0.492	0.951	0.652	0.967	0.333	0.935
70	0.318	1	0.478	1	0.159	1
80	0.246	1	0.391	1	0.101	1
90	0.137	1	0.217	1	0.057	1
100	0.050	1	0.101	1	0	1
110	0.028	1	0.057	1	0	1
120	0.014	1	0.028	1	0	1
> 120	0	1	0	1	0	1

[a]Cutoff points as presented in the method section; [b]Total = scores of the PROAD and control groups together; [c]PROAD = scores of the addiction unit group; [d]Control group = scores of the control group.

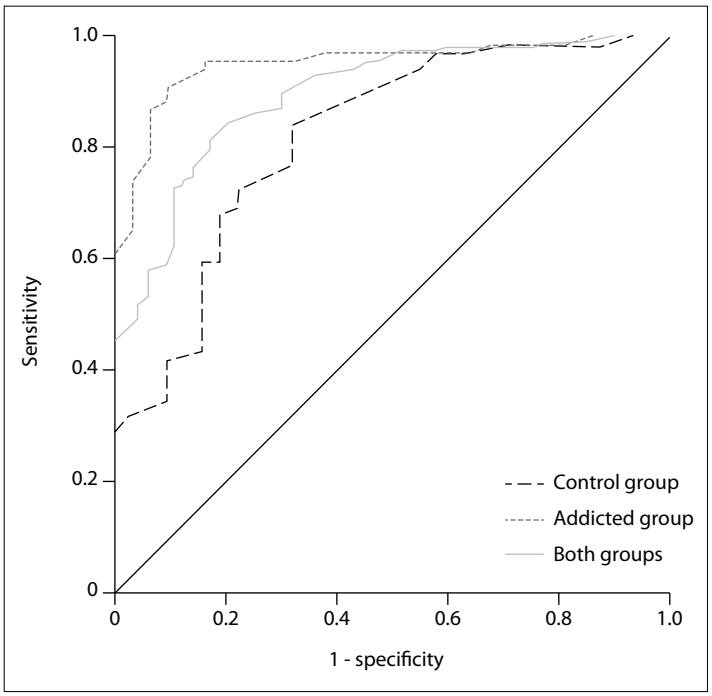

Figure 1. Receiver operating characteristic curve of the control group (n = 100), addicted group (n = 100) and both groups together (n = 200).

In this context, it is essential to develop and validate these important tools, not only to improve the diagnostic process, but also to allocate resources where needed.

Once validated, the BADDS scale can become a screening tool that could improve psychiatric care and provide resources for those who truly are ADHD-positive. The self-report format, the non-medical language and the fact that the questions do not examine only the presence of symptoms make the Brown Attention-Deficit Disorder Scale a valuable instrument for use by any healthcare professional who wants to optimize ADHD healthcare services (**Annex 1**).

Diagnosing psychiatric disorders is complex, and this is even more so when they are associated with other psychiatric comorbidities, as is the case with ADHD. The lack of biomarkers to identify psychiatric conditions makes validation tools necessary, to minimize diagnostic difficulties.

Screening instruments are useful and increase the quality of healthcare services. Validated screening tools provide cost-effectiveness strategies, reinforce diagnostic accuracy and allow exploration of different aspects of mental health. In addition, they adds to the body of knowledge of overall mental health examination and care.

Since the demand for mental health facilities is greater than the number of care services available in Brazil, validation of the BADDS questionnaire provides the possibility of extrapolating the sphere of psychiatric consultation offices and could be a way to reduce the gap in mental health facilities. It could reduce the burden on mental health facilities, while simultaneously correctly identifying cases of adults living with ADHD.

Limitations

Some limitations of the present study need to be noted. Because a self-report questionnaire was used, rather than psychiatric interviews, the questions were subject to interpretation by the participants and to possible information bias. Moreover, a psychiatric interview should be the gold standard, but this was not possible because of limitations to the capacity of our facility. In addition, this was a cross-sectional survey and therefore associations do not imply causation. Lastly, although sensitivity and specificity are characteristics of each test, positive and negative predictive values depend on the prevalence of the condition studied within a given sample. Therefore, in populations with low prevalence of ADHD, the positive predictive value tends to be low and the negative predictive values tend to be high. This means that, although the findings through

an instrument might rule out a diagnosis of ADHD, there is a high chance that any positive results will in fact be false positives.

CONCLUSION

In summary, this study conducted on a Brazilian sample demonstrated that BADDS has discriminative validity for making diagnoses of ADHD. The ROC curve analyses showed the usefulness of BADDS for detecting adults who need ADHD treatment, particularly among those with substance-use disorders.

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Annex 1. Brown Attention-Deficit Disorder Scale (BADDS) and Adult Self-Report Scale (ASRS) for ADHD

BADDS
1. Ouve e tenta prestar atenção em reuniões, aulas ou conversas, mas a mente frequentemente se dispersa; perde informações de importância?
a. Nunca b. Uma vez por semana ou menos c. Duas vezes por semana d. Quase diariamente
2. Sente muita dificuldade para iniciar tarefas (exemplo: atividades burocráticas ou realizar contatos com outras pessoas)?
a. Nunca b. Uma vez por semana ou menos c. Duas vezes por semana d. Quase diariamente
3. Sente-se demasiadamente estressado ou sobrecarregado com tarefas que deveriam ser manejáveis (exemplo: "de jeito nenhum consigo fazer tudo isso agora, isto está fora do meu alcance" – apesar da situação não ser tão ruim assim)?
a. Nunca b. Uma vez por semana ou menos c. Duas vezes por semana d. Quase diariamente
4. "Sai do ar" involuntária e frequentemente durante leituras necessárias; pensa em coisas que não têm nada a ver com o que está sendo lido?
a. Nunca b. Uma vez por semana ou menos c. Duas vezes por semana d. Quase diariamente
5. Perde o foco com facilidade; inicia uma tarefa e em seguida muda para algo menos importante?
a. Nunca b. Uma vez por semana ou menos c. Duas vezes por semana d. Quase diariamente
6. Perde o fio da meada do que acabou de ser lido e precisa retomar a leitura; compreende as palavras, mas simplesmente não guarda o que foi lido?
a. Nunca b. Uma vez por semana ou menos c. Duas vezes por semana d. Quase diariamente
7. É muito esquecido com relação ao que foi dito, feito ou ouvido nas últimas 24 horas?
a. Nunca b. Uma vez por semana ou menos c. Duas vezes por semana d. Quase diariamente
8. Lembra-se de alguns detalhes das leituras, mas não consegue assimilar a ideia central?
a. Nunca b. Uma vez por semana ou menos c. Duas vezes por semana d. Quase diariamente
9. Frustra-se com facilidade e é muito impaciente?
a. Nunca b. Uma vez por semana ou menos c. Duas vezes por semana d. Quase diariamente
10. Fica confuso quando recebe muita coisa para fazer, tem dificuldade para estabelecer prioridades, organizar-se e começar?
a. Nunca b. Uma vez por semana ou menos c. Duas vezes por semana d. Quase diariamente
11. Adia os afazeres, frequentemente deixa-os de lado (exemplo: "farei depois" ou "farei amanhã")?
a. Nunca b. Uma vez por semana ou menos c. Duas vezes por semana d. Quase diariamente
12. Sente-se sonolento ou cansado durante o dia, mesmo após uma noite satisfatória de sono?
a. Nunca b. Uma vez por semana ou menos c. Duas vezes por semana d. Quase diariamente
13. É desorganizado; tem muita dificuldade para monitorar planos, dinheiro ou tempo?
a. Nunca b. Uma vez por semana ou menos c. Duas vezes por semana d. Quase diariamente
14. Não consegue completar tarefas no tempo planejado; precisa de um tempo extra para concluir satisfatoriamente?
a. Nunca b. Uma vez por semana ou menos c. Duas vezes por semana d. Quase diariamente
15. Planeja fazer coisas, mas esquece (exemplo: desligar aparelhos, comprar coisas na loja, retornar ligações telefônicas, ir a compromissos, pagar contas, cumprir deveres)?
a. Nunca b. Uma vez por semana ou menos c. Duas vezes por semana d. Quase diariamente
16. Critica-se ou os outros o criticam por ser preguiçoso?
a. Nunca b. Uma vez por semana ou menos c. Duas vezes por semana d. Quase diariamente
17. A qualidade de seus trabalhos é inconsistente; o seu desempenho é completamente flutuante; esquiva-se das tarefas a menos que esteja sob pressão?
a. Nunca b. Uma vez por semana ou menos c. Duas vezes por semana d. Quase diariamente
18. É sensível a críticas; ressente-se profundamente ou por um tempo prolongado; torna-se excessivamente defensivo?
a. Nunca b. Uma vez por semana ou menos c. Duas vezes por semana d. Quase diariamente
19. Demora para reagir ou ter iniciativa; é lento ou faz tudo devagar; não se atira de imediato para as atividades; demora para responder a perguntas ou se aprontar para algo?
a. Nunca b. Uma vez por semana ou menos c. Duas vezes por semana d. Quase diariamente
20. Irrita-se com facilidade; é "pavio curto" e tem ataques repentinos de raiva?
a. Nunca b. Uma vez por semana ou menos c. Duas vezes por semana d. Quase diariamente
21. É muito rígido ou perfeccionista (tem que fazer as coisas sempre do mesmo jeito, é "cricri")?
a. Nunca b. Uma vez por semana ou menos c. Duas vezes por semana d. Quase diariamente
22. É criticado por não alcançar todo o seu potencial (ex., "poderia fazer muito melhor se ao menos... me esforçasse mais ou trabalhasse mais consistentemente")?
a. Nunca b. Uma vez por semana ou menos c. Duas vezes por semana d. Quase diariamente
23. Pega-se "sonhando acordado" ou preocupado com os próprios pensamentos?
a. Nunca b. Uma vez por semana ou menos c. Duas vezes por semana d. Quase diariamente
24. Tem dificuldade para expressar raiva de maneira adequada; não consegue se impor?
a. Nunca b. Uma vez por semana ou menos c. Duas vezes por semana d. Quase diariamente
25. Perde o fio da meada e não vai até o final; seu esforço se dissipa rapidamente?
a. Nunca b. Uma vez por semana ou menos c. Duas vezes por semana d. Quase diariamente

Continue...

Annex. Continuation

BADDS				
26. Dispersa-se com facilidade por barulhos ou atividades do ambiente; precisa verificar qualquer outra coisa que esteja acontecendo?				
a. Nunca	b. Uma vez por semana ou menos	c. Duas vezes por semana	d. Quase diariamente	
27. Tem muita dificuldade para acordar de manhã; acha extremamente difícil levantar-se da cama e começar a fazer as coisas?				
a. Nunca	b. Uma vez por semana ou menos	c. Duas vezes por semana	d. Quase diariamente	
28. Na escrita, necessita repetidamente apagar, rasurar ou recomeçar devido a erros pequenos?				
a. Nunca	b. Uma vez por semana ou menos	c. Duas vezes por semana	d. Quase diariamente	
29. Com frequência se sente desencorajado, triste ou para baixo?				
a. Nunca	b. Uma vez por semana ou menos	c. Duas vezes por semana	d. Quase diariamente	
30. Tende a se isolar de seus pares, é reservado e tímido; não se associa muito com amigos da mesma idade?				
a. Nunca	b. Uma vez por semana ou menos	c. Duas vezes por semana	d. Quase diariamente	
31. Parece apático ou desmotivado (os outros pensam que não se importa absolutamente com o seu trabalho)?				
a. Nunca	b. Uma vez por semana ou menos	c. Duas vezes por semana	d. Quase diariamente	
32. Fica com olhar fixo e distante; parece estar no "mundo da lua"?				
a. Nunca	b. Uma vez por semana ou menos	c. Duas vezes por semana	d. Quase diariamente	
33. Na escrita, frequentemente deixa de fora palavras ou letras?				
a. Nunca	b. Uma vez por semana ou menos	c. Duas vezes por semana	d. Quase diariamente	
34. Apresenta caligrafia desleixada e difícil de ler?				
a. Nunca	b. Uma vez por semana ou menos	c. Duas vezes por semana	d. Quase diariamente	
35. Esquece-se de levar – ou não lembra onde deixou – itens importantes como chaves, lápis, contas e documentos ("Sei que está aqui em algum lugar; apenas não consigo encontrar agora..."')?				
a. Nunca	b. Uma vez por semana ou menos	c. Duas vezes por semana	d. Quase diariamente	
36. Parece não estar ouvindo ou recebe reclamações dos outros a respeito?				
a. Nunca	b. Uma vez por semana ou menos	c. Duas vezes por semana	d. Quase diariamente	
37. Os outros precisam lembrá-lo de começar ou de manter-se engajado em tarefas que precisam feitas?				
a. Nunca	b. Uma vez por semana ou menos	c. Duas vezes por semana	d. Quase diariamente	
38. Apresenta dificuldade de memorização (ex., nomes, data, informações do trabalho)?				
a. Nunca	b. Uma vez por semana ou menos	c. Duas vezes por semana	d. Quase diariamente	
39. Entende mal as orientações para preencher formulários, realizar tarefas etc.?				
a. Nunca	b. Uma vez por semana ou menos	c. Duas vezes por semana	d. Quase diariamente	
40. Inicia atividades (exemplo: papelada, afazeres), mas não finaliza?				
a. Nunca	b. Uma vez por semana ou menos	c. Duas vezes por semana	d. Quase diariamente	

ASRS				
1. Com que frequência você comete erros por falta de atenção quando tem de trabalhar num projeto chato ou difícil?				
a. Nunca	b. Raramente	c. Algumas vezes	d. Frequentemente	e. Muito frequentemente
2. Com que frequência você tem dificuldade para manter a atenção quando está fazendo um trabalho chato ou repetitivo?				
a. Nunca	b. Raramente	c. Algumas vezes	d. Frequentemente	e. Muito frequentemente
3. Com que frequência você tem dificuldade para se concentrar no que as pessoas dizem, mesmo quando elas estão falando diretamente com você?				
a. Nunca	b. Raramente	c. Algumas vezes	d. Frequentemente	e. Muito frequentemente
4. Com que frequência você deixa um projeto pela metade depois de já ter feito as partes mais difíceis?				
a. Nunca	b. Raramente	c. Algumas vezes	d. Frequentemente	e. Muito frequentemente
5. Com que frequência você tem dificuldade para fazer um trabalho que exige organização?				
a. Nunca	b. Raramente	c. Algumas vezes	d. Frequentemente	e. Muito frequentemente
6. Quando você precisa fazer algo que exige muita concentração, com que frequência você evita ou adia o início?				
a. Nunca	b. Raramente	c. Algumas vezes	d. Frequentemente	e. Muito frequentemente
7. Com que frequência você coloca as coisas fora do lugar ou tem de dificuldade de encontrar as coisas em casa ou no trabalho?				
a. Nunca	b. Raramente	c. Algumas vezes	d. Frequentemente	e. Muito frequentemente
8. Com que frequência você se distrai com atividades ou barulho a sua volta?				
a. Nunca	b. Raramente	c. Algumas vezes	d. Frequentemente	e. Muito frequentemente
9. Com que frequência você tem dificuldade para lembrar de compromissos ou obrigações?				
a. Nunca	b. Raramente	c. Algumas vezes	d. Frequentemente	e. Muito frequentemente
10. Com que frequência você fica se mexendo na cadeira ou balançando as mãos ou os pés quando precisa ficar sentado (a) por muito tempo?				
a. Nunca	b. Raramente	c. Algumas vezes	d. Frequentemente	e. Muito frequentemente
11. Com que frequência você se levanta da cadeira em reuniões ou em outras situações onde deveria ficar sentado (a)?				
a. Nunca	b. Raramente	c. Algumas vezes	d. Frequentemente	e. Muito frequentemente

Continue...

Annex. Continuation

ASRS				
12. Com que frequência você se sente inquieto (a) ou agitado (a)?				
a. Nunca	b. Raramente	c. Algumas vezes	d. Frequentemente	e. Muito frequentemente
13. Com que frequência você tem dificuldade para sossegar e relaxar quando tem tempo livre para você?				
a. Nunca	b. Raramente	c. Algumas vezes	d. Frequentemente	e. Muito frequentemente
14. Com que frequência você se sente ativo (a) demais e necessitando fazer coisas, como se estivesse "com um motor ligado"?				
a. Nunca	b. Raramente	c. Algumas vezes	d. Frequentemente	e. Muito frequentemente
15. Com que frequência você se pega falando demais em situações sociais?				
a. Nunca	b. Raramente	c. Algumas vezes	d. Frequentemente	e. Muito frequentemente
16. Quando você está conversando, com que frequência você se pega terminando as frases das pessoas antes delas?				
a. Nunca	b. Raramente	c. Algumas vezes	d. Frequentemente	e. Muito frequentemente
17. Com que frequência você tem dificuldade para esperar nas situações onde cada um tem a sua vez?				
a. Nunca	b. Raramente	c. Algumas vezes	d. Frequentemente	e. Muito frequentemente
18. Com que frequência você interrompe os outros quando eles estão ocupados?				
a. Nunca	b. Raramente	c. Algumas vezes	d. Frequentemente	e. Muito frequentemente

Oral squamous cell carcinoma: a clinicopathological study on 194 cases in northeastern Brazil. A cross-sectional retrospective study

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KEY WORDS:
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Carcinoma, squamous cell.

ABSTRACT

BACKGROUND: Only a few studies have evaluated the clinicopathological features of oral squamous cell carcinoma (SCC) in Brazil, and most were conducted in the most industrialized region of the country, i.e. the southeastern region. The aim of this study was to evaluate the clinicopathological features of this malignant neoplasm in northeastern Brazil.

DESIGN AND SETTING: Retrospective study performed in an oral pathology laboratory in Recife, Brazil.

METHODS: All cases of oral SCC that occurred between 2000 and 2015 were studied. Clinical data were recorded and histological slides were reviewed. Statistical analysis was performed using the chi-square test ($P \leq 0.05$).

RESULTS: A total of 194 cases were evaluated. The male-to-female ratio was 1.5:1. The mean age was 65.4 years, and only 6.6% of the cases occurred in patients younger than 41 years. Most tumors consisted of well-differentiated SCC (54.6%).

CONCLUSIONS: The findings of this study highlight the higher prevalence of oral SCC among women and the increasing number of cases among young patients. Thus there is no specific risk group for oral SCC, as in the past. This fact needs to be taken into consideration in clinical routine care, so that apparently innocuous malignant lesions do not go unnoticed in these individuals.

INTRODUCTION

Squamous cell carcinoma (SCC) is a well-recognized malignant neoplasm that is responsible for more than 90% of oral malignancies.[1-4] Worldwide, 405,000 new cases of oral cancer are expected every year.[3] It is the seventh most common type of cancer among Brazilians.[5]

The etiology of these tumors is multifactorial. Tobacco and alcohol consumption are the most determinant etiological factors, especially when acting synergistically.[3,5] Other associated factors include excessive exposure to ultraviolet light (for lip carcinomas), diets lacking fruits and vegetables, poor oral hygiene and betel nut chewing (especially in Asian populations). Although the true prevalence remains a matter of debate, high-risk HPV infection has also been described as an etiological factor.[5,6]

Although the epidemiological profile has changed over time, with considerable regional variations,[6] there is still higher prevalence of oral cancer among males, which is consequential to greater exposure to risk factors among men. Oral SCC usually affects older individuals, after the fifth decade of life,[4] with a reported mean age of 62 years.[2,5] The usual clinical presentation is a painless ulcer on the border of the tongue or floor of the mouth.[2,5]

Only a few studies have evaluated the clinicopathological features of oral SCC in Brazil, and most of these were conducted in the most industrialized region of the country, i.e. the southeastern region.[7-9] Thus, the objective of this study was to evaluate the clinicopathological features of oral SCC diagnosed in a less economically developed geographic area using the records from an oral pathology laboratory in the northeastern region of Brazil.

METHODS

This study was approved by the local research ethics committee, under protocol no. 44536715.8.0000.5208. This was a cross-sectional, retrospective study.

All cases of squamous cell carcinoma that were diagnosed in the Oral Pathology Laboratory of the Federal University of Pernambuco, Recife, Brazil, between 2000 and 2015, were included in the study. All clinical records were reassessed, and the main clinical and epidemiological parameters were collected, including gender, age, place of origin of the patient, patient's occupation, symptoms reported by the patient at the initial consultation, duration of complaints, tumor location, clinical presentation of the lesion, tumor size, first diagnostic hypothesis and presence of deleterious habits (smoking, alcohol consumption, or both).

In the same way as done in previous studies,[1,10] the variable of age was subdivided into six groups: patients aged less than 41 years, between 41 and 50, between 51 and 60, between 61 and 70, between 71 and 80 and over 80. The locations of the tumors included the following regions: border of oral tongue, alveolar mucosa and gingiva (including the retromolar area and buccal mucous fold), floor of mouth and ventral tongue, hard/soft palate, lower lip (including mucosa and vermilion) and buccal mucosa.

The clinical aspects of the lesions were classified into four groups: ulcerated, leukoplakia, leukoerythroplakia and lesions that presented an ulcerated component with areas of leukoerythroplakia. The symptoms were divided into two groups: the first group comprised patients who presented any painful symptoms relating to the lesion (including spontaneous or induced pain); and the second group comprised patients who were asymptomatic at the initial consultation.

All cases were reviewed under a microscope. The histopathological analysis and grading were performed in accordance with the classification proposed by the World Health Organization (WHO) in 2017,[11] based on the degree of cell differentiation. The tumors were classified as follows: well-differentiated, when they showed tissue architecture similar to the normal pattern of the squamous epithelium; moderately differentiated, when they presented some degree of nuclear pleomorphism and mitotic activity, and little keratinization; and poorly differentiated, when they presented predominance of immature cells, numerous typical and atypical mitoses, and minimal keratinization. All microscopic SCC variants were also considered in the study.

The data collected were analyzed using the Statistical Package for the Social Sciences (SPSS), version 20.0. Descriptive statistical analysis was performed for all variables described above. Cases for which data were not available in the clinical records, or were incomplete, were not included in the analysis. The variables were analyzed by means of the chi-square test, taking the significance level to be 5% ($P < 0.05$). For the statistical analysis, the numerical variables were grouped, as follows: age (≤ 45 years and > 45 years); duration of complaints (< 3 months, 3-6 months and > 6 months); and tumor size (2.0 cm, 2.1-4.0 cm and > 4.0 cm).

RESULTS

Out of the 4,727 oral lesions diagnosed over a 15-year period, 250 were malignant (5.28%). From these, 194 cases (77.6%) were squamous cell carcinomas. The majority of the cases evaluated (97.4%) came from the public health service, and the remaining from private services (2.6%).

Most cases occurred in men, with 118 cases (60.8%), representing a male-to-female ratio 1.5:1. The age group most affected was the seventh and eighth decades of life (51.9%). The mean age among the cases was 65.4 years and the age range was from 26 to 94 years. Twelve cases (6.6%) were in patients under 41 years of age.

The border of the tongue was the most common site (51 cases; 26.7%), followed by the floor of the mouth/ventral tongue (36 cases; 18.8%) and the alveolar mucosa/gingiva/retromolar area (32 cases; 16.8%). The hard/soft palate and the lower lip were affected in 25 (13.1%) and 21 cases (11%), respectively.

Most patients (112; 68.7%) reported a duration of complaints of up to 6 months. Complaints for periods over 12 months had the lowest prevalence, with 22 cases (13.5%). Clinically, ulcerated lesions (76 cases; 46.3%) were most commonly observed, followed by leukoplakia (30 cases; 18.3%) and leukoerythroplakia (20 cases; 12.2%). Most lesions (76 cases; 76.0%) were of sizes smaller than 4 cm; among these, 38 (38%) were lesions smaller than 2.0 cm and the remaining 38 (38%) were lesions between 2.1 and 4.0 cm. Lesions over 4.0 cm were present in 24 cases (24.0%) (Table 1).

The diagnostic hypothesis most frequently reported by the practitioners was squamous cell carcinoma, in 145 cases (78.0%). Leukoplakia (5 cases; 2.7%) was the second most cited hypothesis, followed by actinic cheilitis (3 cases; 1.6%). Other hypotheses that were raised included erythroplakia, papilloma, traumatic ulcer, fibrous hyperplasia, lichen planus and frictional keratosis, which together represented 16.1% of the sample studied.

Regarding the patient's occupation, most patients were retired (28.5%), followed by farmers (23.1%) and housewives (11.5%) (**Table 1**). Only in 58 clinical records was it reported that the patients were either exposed or non-exposed to the main risk factors (tobacco and alcohol). Among these, there were 28 cases of smokers, one of a chronic alcoholic patient, and 29 of exposure to both factors. Most (70.1%) of the clinical records, corresponding to 136 cases, did not include this information.

Patients who reported either spontaneous or induced pain accounted for 75 cases (38.7%). Thirty-five patients (12.9%) were asymptomatic. In the largest proportion of the cases (94; 48.5%), this information was not available.

Analysis on the histological grade showed that most cases consisted of well-differentiated SCC, representing 106 cases (54.6%).

Moderately and poorly differentiated SCC represented, respectively, 72 cases (37.1%) and 10 cases (5.2%). Among the microscopic variants of SCC, two cases were diagnosed as verrucous carcinomas, two cases consisted of microinvasive carcinoma, one case consisted of basaloid SCC and one case was diagnosed as acantholytic SCC.

Table 1. Clinical features, occupation and risk factors among patients with oral squamous cell carcinomas in the sample studied

Variables	Number of cases	%
Gender (n = 194)		
Male	118	60.8
Female	76	39.2
Age (n = 181)		
< 41 years	12	6.6
41 to 50 years	20	11.0
51 to 60 years	40	22.1
61 to 70 years	47	25.9
71 to 80 years	47	25.9
> 80 years	15	8.3
Tumor site (n = 191)		
Border of oral tongue	51	26.7
Floor of mouth/ventral tongue	36	18.8
Alveolar mucosa/gingiva/retromolar area	32	16.8
Hard/soft palate	25	13.1
Lower lip	21	11
Buccal mucosa	14	7.3
Others	12	6.3
Duration of complaints (n = 163)		
< 3 months	65	39.9
4-6 months	47	28.8
7 to 12 months	29	17.8
> 12 months	22	13.5
Clinical appearance (n = 164)		
Ulcer	76	46.3
Leukoplakia	30	18.3
Leukoerythroplakia	20	12.2
Ulcer with leukoerythroplakia areas	17	10.4
Other	22	12.9
Tumor size (n = 100)		
< 2.1 cm	38	38.0
2.1 to 4.0 cm	38	38.0
4.1 to 6.0 cm	17	17.0
> 6.0 cm	7	7.0
Occupation (n = 130)		
Retired	37	28.5
Farmer	30	23.1
Housewife	15	11.5
Mason	10	7.7
Housekeeper	7	5.4
Others	31	23.8
Patients exposed to risk factors (n = 58)*		
Tobacco	28	48.3
Alcohol	1	1.7
Tobacco and alcohol	29	50.0

*Only in 58 clinical records was the patient's exposure to the main risk factors (tobacco and alcohol) reported.

Correlations between the variables revealed that moderately differentiated SCC occurred more frequently on the border of the tongue and floor of the mouth ($P < 0.05$). Most cases that appeared in the form of leukoplakia were diagnosed in patients with durations of complaints of up to 6 months ($P = 0.001$). The number of smokers was significantly lower among the patients under 45 years of age ($P = 0.02$). The associations between age and occupation ($P = 0.06$), symptoms ($P = 0.9$), duration of complaints ($P = 0.3$), clinical features ($P = 0.8$), size of the tumor ($P = 0.85$) and histopathological grading ($P = 0.45$) were not significant. The associations between tumor size and gender ($P = 0.58$), occupation ($P = 0.41$), clinical features of the lesion ($P = 0.06$), duration of complaints ($P = 0.34$) and histopathological grading ($P = 0.47$) were not statistically significant. In addition, no association between duration of complaints and clinical features ($P = 0.1$) was observed, or between clinical features and histopathological grading ($P = 0.3$).

DISCUSSION

In this study, the male-to-female ratio was 1.5:1, similar to what has been observed in other reports.[1,10] Although higher prevalence among males is still commonly seen, it has been reported that this gender ratio is decreasing. This has been attributed to changes in the social context of women's lives, such that they may be exposing themselves more significantly to the usual risk factors for oral SCC.[1,8,12,13]

SCC is usually a disease of elderly people, with peak incidence in the sixth and seventh decades of life.[1,7,12] However, approximately 0.4 to 3.6% of oral cancers occur in young patients, i.e. those less than 40 years old.[14] The incidence rises to close to 6% among patients up to 45 years old.[5,7,13] Ribeiro et al.[7] showed that the rate was 12% among patients in this age group. In the present study, the youngest patient was 26 years old, and 8.8% of the patients were under 45 years of age. Recent research has shown that the incidence of oral cancer in this younger population has been increasing significantly. The evidence suggests that the traditional risk factors would be less active in these patients, which thus draws attention to the influence of nutritional and biological factors such as HPV infection (especially HPV16). However, the mechanisms of viral action in these cases have not yet been well established.[7,8,13]

The increased risk of oral cancer among alcohol and tobacco users is well known.[9,12] Consumption of both alcohol and tobacco together has a multiplicative effect and this has been implicated in about 75% of all head and neck SCC cases.[12] In the present study, 50% of all the patients who were asked whether they used alcohol or tobacco said that they used both of these substances. Among the patients who were asked this question, 48.3% were smokers. However, this information was not reported by the majority (70.1%) of the practitioners who

sent the specimens for histopathological diagnosis, thus showing the professionals' negligence regarding obtaining this information. These data emphasize that there is a need to guide practitioners regarding the importance of constantly providing educational guidance on oral cancer to patients. Such guidance is currently the main way of preventing the disease. Nevertheless, despite the missing information, the confirmed data indicated that the percentage of smokers and drinkers was lower than in previous studies,[15,16] in which the proportion of smokers and drinkers among the patients was up to 90%. Recent trends have shown results similar to those of the present investigation.[17]

The most frequent clinical characteristic in the initial consultation was the presence of an ulcer (46.3%), and this was similar to the findings of Pires et al.[8] However, SCC may appears as white or red lesions, which are characterized as leukoplakia, erythroplakia or leukoerythroplakia.[13] Although many cases of SCC do not show previous evidence of a potentially malignant disorder,[13] it is essential that practitioners, especially dentists, should be aware of this group of lesions. In the present study, 18.3% of the cases consisted of leukoplakia and the majority of the patients had complained about the lesion for a maximum time of 6 months. Pain may account for 30 to 40% of complaints among patients with oral SCC, which usually is related to lesions at an advanced clinical stage.[2]

The clinical presentation of oral SCC can vary considerably and the initial tumors can often be subtle and asymptomatic, which may represent a diagnostic challenge in this early clinical stage.[13] Nevertheless, more recent studies have shown that patients with oral cancer have been diagnosed at an earlier stage of disease.[8,12] Those findings were similar to what was observed in the present study, in which 76% of the cases presented tumor sizes smaller than 4 cm at the initial consultation. Considering that those studies were also conducted at specialized diagnostic and treatment services, it needs to be considered that this scenario of findings was influenced by the health surveillance provided by these centers to these populations. On the other hand, it should also be considered that the information filled out by the professional, in some cases, might not represent the real size of the lesion. In the present series, in 60% of the cases, the duration of complaints reported by the patients was more than six months, thus probably indicating larger tumors.

It has been reported that patients delay their complaints about issues of this nature for approximately six months, although this length of time is variable.[18] It has been estimated that such delays, for more than three months, lead to significant worsening of the prognosis.[19] Affective factors such as fear and denial, and cultural issues, may be associated with delay in seeking a healthcare professional.[20] Moreover, it was found in another study that most patients believed that the lesion would not be serious and that it would be resolved without any treatment.[21] In addition to the patient's delay, there may be a professional delay of between 1 and 5 months. Although there was no information on professional delays in the present study, it has been shown that limitation of the oral examination to teeth and gums and lack of knowledge of oral mucosal lesions may constitute factors that are associated with delays in diagnosing oral SCC.[18]

Oral SCCs are usually histologically graded as well or moderately differentiated,[1,8,10] as observed in the present series. The histopathological grading usually shows weak influence on the prognosis for the lesions, mainly because of the subjective nature of the evaluation and the small size of biopsies in tumors that have great heterogeneity.[22] In the present study, moderately differentiated cases were significantly more frequently diagnosed on the border of the tongue and the floor of the mouth, and such cases are known to have more dubious prognoses.[23] There was no correlation between histopathological grading and the age of the patients affected.

Although this series presented interesting and relevant data, it is important to highlight some limitations of the study. Its retrospective design and consequent scope for missing information in relation to risk factors like smoking and alcohol, in addition to absence of data on neck status, treatment and outcome, prevented a more complete analysis. Despite this, the study revealed important clinicopathological and demographic features of an oral SCC series in a Brazilian region that had been poorly studied. This data may be valuable for practitioners in planning preventive measures and diagnosing the disease.

CONCLUSION

The findings of this study highlight the higher prevalence of oral SCC among women and the increasing numbers of cases among young patients. Thus, the current trends indicate that there is no specific risk group for oral SCC, as in the past. This fact needs to be taken into consideration in clinical routine care, so that apparently innocuous malignant lesions do not go unnoticed in these individuals. Moreover, these findings are similar to observed in other Brazilian regions.

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What do Cochrane systematic reviews say about cardiac arrest management?

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ABSTRACT

CONTEXT AND OBJECTIVE: Cardiac arrest is associated with high morbidity and mortality and imposes a significant burden on the healthcare system. Management of cardiac arrest patients is complex and involves approaches with multiple interventions. Here, we aimed to summarize the available evidence regarding the interventions used in cardiac arrest cases.

DESIGN AND SETTING: Review of systematic reviews (SRs), conducted in the Discipline of Evidence-Based Medicine, Escola Paulista de Medicina, Universidade Federal de São Paulo.

METHODS: A systematic search was conducted to identify all Cochrane SRs that fulfilled the inclusion criteria. Titles and abstracts were screened by two authors.

RESULTS: We included nine Cochrane SRs assessing compression techniques or devices (three SRs), defibrillation (two SRs) and other interventions (two SRs on hypothermia interventions, one on airway management and one on pharmacological intervention). The reviews included found qualities of evidence ranging from unknown to high, regarding the benefits of these interventions.

CONCLUSION: This review included nine Cochrane systematic reviews that provided a diverse range of qualities of evidence (unknown to high) regarding interventions that are used in management of cardiac arrest. High-quality evidence was found by two systematic reviews as follows: (a) increased survival until hospital discharge with continuous compression, compared with interrupted chest compression, both administered by an untrained person and (b) no difference regarding the return of spontaneous circulation, comparing aminophylline and placebo, for bradyasystolic patients under cardiac arrest. Further studies are needed in order to reach solid conclusions.

INTRODUCTION

Sudden cardiac arrest is an important cause of death and is responsible for 15% of total mortality in the United States.[1] Its occurrence is associated with a poor prognosis, despite the numerous interventions that are available for treating this condition.[2]

Occurrences of sudden cardiac arrest are usually associated with an underlying structural heart disease, and coronary heart disease is the most frequent form (two thirds of the cases). Other heart diseases such as myocarditis and hypertrophic cardiomyopathies are also common causes. When there is no structural disease, most cases occur due to arrhythmia, for which there are very many etiologies.[1,3,4]

Several criteria have been used to define cardiac arrest in the medical literature. In 2006, the American College of Cardiology/American Heart Association/Heart Rhythm Society (ACC/AHA/HRS) established the standard definition for cardiac arrest as "sudden cessation of cardiac activity so that the victim becomes unresponsive, with no normal breathing and no signs of circulation. If corrective measures are not taken rapidly, this condition progresses to sudden death". In current clinical practice, cardiac arrest is reversed mainly by cardiopulmonary resuscitation and/or cardioversion or defibrillation, or cardiac pacing.[5]

Despite the importance of cardiac arrest, there is uncertainty regarding the use of most interventions that have been recommended for its management. Several guidelines for its treatment are available, but an analysis of the best evidence is always useful, to guide further studies and to update the recommendations with the best unbiased evidence. Hence, synthesis studies such as the present review are imperative for enabling critical analysis and for summarizing the results from primary research on cardiac arrest patients.

The aim of the present review was to identify and summarize the evidence from Cochrane systematic reviews (SRs) relating to interventions for managing cardiac arrest in any setting.

METHODS

Design and setting

This was a review of Cochrane systematic reviews (SRs), conducted within the Discipline of Evidence-Based Medicine of Escola Paulista de Medicina, Universidade Federal de São Paulo (EPM-Unifesp). This article was specifically developed for the section Cochrane Highlights, which is an initiative for disseminating Cochrane reviews. This initiative results from a formal partnership between the São Paulo Medical Journal and Cochrane, and it is supported by Cochrane Brazil.

Inclusion criteria

Types of study

We included SRs published in the Cochrane Database of Systematic Reviews (CDSR). Protocols for SRs and withdrawn or previous versions of single SRs were not included. No limit for publication date was applied.

Types of participants

The participants comprised patients who had been diagnosed as presenting cardiac arrest, regardless of the setting (pre-hospital or in-hospital) or their age or sex.

Types of intervention

We considered SRs assessing any intervention (either pharmacological or non-pharmacological), whether applied separately or combined with others.

Types of outcomes

We considered any clinical or laboratory outcome, as evaluated by the authors of the SRs included.

Search for reviews

We conducted a sensitive search in the Cochrane Database of Systematic Reviews (CDSR) (via Wiley) on February 24, 2018, using the MeSH term "Heart Arrest" and all related variants, in titles, abstracts and keywords. The detailed search strategy is presented in **Table 1**.

Selection of reviews

The titles and abstracts were screened by two authors (RLP and RR) independently. Any disagreements were resolved by reaching a consensus. The SRs that met the inclusion criteria were selected and summarized by five authors (RLP, JT, CAS, BS, GA).

Presentation of results

The results from the search and the SRs included were presented through a narrative approach (qualitative synthesis).

RESULTS

Search results

Our search strategy retrieved 543 references and, after screening the titles and abstracts, nine systematic reviews (SRs) were found to fulfill our inclusion criteria and were considered for qualitative synthesis.[6-14]

Reviews included

We present a short individual summary of each SR included. Details about the characteristics of interventions, comparisons, outcomes and quality of evidence are presented in **Table 2**.

Compression techniques or devices

Active chest compression-decompression with a hand-held suction device

This review[6] had the aim of evaluating the use of active compression-decompression (ACD) for cardiopulmonary resuscitation (CPR), consisting of application of a hand-held suction device to the sternum. Ten randomized clinical trials (RCTs) were included, assessing either out-of-hospital settings (eight RCTs; 4,162 participants) or in-hospital settings (two RCTs; 826 participants).

Regarding out-of-hospital settings, no differences were found between active compression-decompression for cardiopulmonary resuscitation with a hand-held suction device and standard manual cardiopulmonary resuscitation (STR) regarding mortality either immediately (relative risk [RR] 0.98; 95% confidence interval [95% CI] 0.94 to 1.03; ten RCTs; 4,162 participants) or

Table 1. Search strategy

#1 MeSH descriptor: [Heart Arrest] explode all trees (in titles, abstracts and keywords)
#2 (Arrest, Heart) OR (Cardiac Arrest) OR (Arrest, Cardiac) OR (Cardiopulmonary Arrest) OR (Arrest, Cardiopulmonary) OR (Heart Arrest, Induced) OR (Induced Heart Arrest) OR (Cardiac Arrest, Induced) OR (Induced Cardiac Arrest) OR (Out-of-Hospital Cardiac Arrest) OR (Cardiac Arrest, Out-of-Hospital) OR (Cardiac Arrests, Out-of-Hospital) OR (Out of Hospital Cardiac Arrest) OR (Out-of-Hospital Cardiac Arrests) OR (Out-of-Hospital Heart Arrest) OR (Heart Arrest, Out-of-Hospital) OR (Heart Arrests, Out-of-Hospital;) OR (Out of Hospital Heart Arrest) OR (Out-of-Hospital Heart Arrests) OR (Heart Massages) OR (Massage, Heart) OR (Massages, Heart) OR (Sinus Arrest, Cardiac) OR (Cardiac Sinus Arrests) OR (Sinus Arrests, Cardiac) OR (Cardiac Sinus Arrest)
#3 #1 OR #2
#4 #3 Filter: in Cochrane Reviews

until hospital discharge (RR 0.99; 95% CI 0.98 to 1.01; nine RCTs; 3,412 participants). Despite the lack of long-term evaluation, there was no significant difference between the groups regarding severe neurological impairment (RR 3.11; CI 95% 0.98 to 9.83; four RCTs; 107 participants) or moderate neurological impairment (RR 0.98; CI 95% 0.34 to 2.79; four RCTs; 107 participants). Combined analysis (any neurological impairment) also found no difference (RR 1.71; CI 95% 0.90 to 3.25; five RCTs; 144 participants). There was no difference in the frequencies of complications (such as fractures and pneumothorax or hemothorax) between the groups (RR 1.09; 95% CI 0.86 to 1.38; seven RCTs; 3,032 participants).

Table 2. Characteristics of interventions, comparisons, outcomes and quality of evidence

Compression techniques or devices				
Intervention	**Comparators**	**Population**	**Main findings**	**GRADE[17]**
Active chest compression-decompression (ACDR)[6]	Standard cardiopulmonary resuscitation (SCR)	Out-of-hospital or in-hospital cardiac arrest patients	Similar results were found for out-of-hospital and in-hospital cardiac arrest: there were no differences between the groups regarding mortality up to hospital discharge, neurological impairment or complications (such as fractures and pneumothorax and hemothorax).	Not assessed
Mechanical chest compression[10]	Manual (standard) chest compression	Cardiac arrest patients	One RCT found improved neurological function and survival until hospital discharge, favoring mechanical chest compression. This result was inconsistent with others included in the RCT but no quantitative synthesis was performed because of heterogeneity of the data.	Very low to moderate
Continuous chest compression[12]	Interrupted chest compression	Non-asphyxial out-of-hospital cardiac arrest	When performed by an untrained person, continuous chest compression achieved higher rates of survival until hospital discharge but no difference in neurological outcomes. When performed by a trained person, there was no difference between the groups regarding survival or neurological outcomes.	Moderate to high
Defibrillation				
Intervention	**Comparators**	**Population**	**Main findings**	**GRADE[17]**
Biphasic transthoracic defibrillation[8]	Monophasic transthoracic defibrillation	Out-of-hospital cardiac arrest	No difference between the groups regarding survival until hospital discharge. No difference regarding failure to defibrillate and return of spontaneous circulation.	Not assessed
Delayed defibrillation[13]	Immediate defibrillation	Out-of-hospital cardiac arrest	No difference between the groups was found regarding survival until hospital discharge, good neurological outcome and return of spontaneous circulation.	Low
Other interventions				
Intervention	**Comparators**	**Population**	**Main findings**	**GRADE[17]**
Aminophylline[9]	No intervention	Bradyasystolic cardiac arrest	No difference between the groups regarding survival until hospital discharge and return of spontaneous circulation.	Low to high
Pre-hospital cooling[7]	In-hospital cooling	Cardiac arrest patients	There was a lack of data for quantitative synthesis, but the individual RCTs included did not find differences between the groups.	Very low
Hypothermia[11]	No intervention	Cardiac arrest patients	Conventional cooling was more likely to achieve a positive neurological outcome, increased survival and higher rates of adverse events (pneumonia and hypokalemia).	Low to moderate
Emergency intubation[14]	Other airway management techniques (bag-valve-mask ventilation, esophageal gastric tube or combi-tube)	Acutely ill and injured patients	For the comparison ETI versus bag-valve-mask ventilation and subsequently ETI, there was no difference between the groups regarding survival and good neurological outcome at hospital discharge. For the comparisons ETI versus esophageal gastric tube and ETI versus combi-tube, there was no difference in survival between the groups at hospital discharge.	Not assessed

RCTs = randomized clinical trials; ETI = endotracheal intubation.

*GRADE (Grading of Recommendations Assessment, Development and Evaluation) has the aim of assessing the quality of the evidence. From this, the results are classified as having high quality of evidence (high confidence that the estimated effect is close to the true effect); moderate quality of evidence (likely that the estimated effect is close to the real effect but there is a possibility that it is not); low quality of evidence (limited confidence in the effect estimate) or very low quality of evidence (the true effect is likely to be substantially different from the estimate effect).

The in-hospital analysis found similar results, although these results were only supported by two RCTs. No difference in immediate mortality (RR 0.98; 95% CI 0.88 to 1.08; two RCTs; 826 participants) or at-discharge mortality (RR 1.00; 95% CI 0.95 to 1.05; two RCTs; 826 participants) was found. The neurological impairment analysis found that there was no difference between the groups regarding moderate impairment (RR 0.5; 95% CI 0.10 to 2.59; two RCTs; 93 participants), severe impairment (RR 1.95; 95% CI 0.59 to 6.50; two RCTs; 93 participants) or impairment of any severity (RR 1.19; 95% CI 0.50 to 2.86; two RCTS; 93 participants). Nor was there any difference in the complications found (RR 0.97; 95% CI 0.49 to 1.93; one RCT; 773 participants).

The authors concluded that the use of ACD with a hand-held suction device for CPR was not associated with any benefit in relation to cardiopulmonary resuscitation.

For further details, refer to the original abstract, available at: http://onlinelibrary.wiley.com/doi/10.1002/14651858.CD002751.pub3/full.

Mechanical versus manual chest compression for cardiac arrest

This review[10] assessed the efficacy and safety of mechanical chest compression in comparison with manual chest compression in cardiopulmonary resuscitation. Six RCTs were included (n = 1,166), although only one study reported the main clinical outcome of survival until hospital discharge with "good neurological function" (defined as cerebral performance category scores[15] of 1 or 2). The group that underwent mechanical chest compression had shorter survival than the group with manual chest compression (RR 0.41; 95% CI 0.21 to 0.79; one RCT; 767 participants).

Three RCTs assessed survival until hospital discharge. Because of the clinical and methodological diversity between them, no pooled analysis was performed and the data were reported only narratively. One RCT reported a higher frequency of survival favoring the mechanical compression group (OR 2.81; 95% CI 1.26 to 6.24; one RCT; 152 participants) while the other two found that there was no difference between the groups: (OR 0.76; 95% CI 0.44 to 1.41; one RCT; 767 participants) and (OR 0.81; 95% CI 0.26 to 2.53; one RCT; 147 participants).

The authors concluded that there was insufficient evidence to reach any solid conclusion between the interventions evaluated. Further studies of good methodological quality with well-reported results would be needed to reduce the uncertainties.

For further details, refer to the original abstract, available at: http://onlinelibrary.wiley.com/doi/10.1002/14651858.CD007260.pub3/full.

Continuous versus interrupted chest compression for cardiopulmonary resuscitation of non-asphyxial out-of-hospital cardiac arrest

This review[12] compared continuous versus interrupted chest compression for cardiopulmonary resuscitation among patients with non-asphyxial out-of-hospital cardiac arrest. Four RCTs were included (n = 26,742). The authors decided to divide the analysis into two groups: CPR performed by an untrained person or by a trained professional.

The analysis on CPR performed by an untrained person showed the following:

- Increased survival until the outcome of hospital discharge favoring the continuous chest compression group (RR 1.21; 95% CI 1.01 to 1.46; three RCTs; 3,031 participants).
- No difference between groups regarding neurological outcomes at hospital discharge (RR 1.25; 95% CI 0.94 to 1.66; one RCT; 1,286 participants).

The analysis on CPR performed by a trained professional was reported in one cluster RCT and showed the following:

- No statistical difference in the risk of survival between the group that received continuous chest compression (9.0%) and the group that received interrupted chest compression group (9.7%) (adjusted risk difference, ARD -0.7%; 95% CI -1.5% to 0.1%; one RCT; 23,711 participants).

The authors concluded that there was moderate to high quality of evidence supporting the use of continuous compression when CPR was performed by an untrained person. One large RCT showed that there was no statistically significant difference between the interventions when the CPR was performed by a trained professional.

For further details, refer to the original abstract, available at: http://onlinelibrary.wiley.com/doi/10.1002/14651858.CD010134.pub2/full.

Defibrillation

Biphasic versus monophasic waveforms for transthoracic defibrillation in out-of-hospital cardiac arrest

This review[8] aimed to compare the use of biphasic and monophasic defibrillators in situations of out-of-hospital cardiac arrest. It included 4 RCTs (n = 552). The main outcome was failure to achieve return of spontaneous circulation (ROSC), and no difference was found between the groups (RR 0.86; 95% CI 0.62 to 1.20; four RCTs; 552 participants). Failure to defibrillate was also assessed and there was no difference in relation to the first shock (RR 0.84; 95% CI 0.70 to 1.01; three RCTs; 450 participants), in relation to up to three shocks (RR 0.81; 95% CI 0.61 to 1.09; two RCTs; 317 participants) or in relation to failure to achieve ROSC after the first shock (RR 0.92; 95% CI 0.81 to 1.04; two RCTs; 285 participants). There was no difference in survival until hospital admission (RR 1.05; 95% CI 0.90 to 1.23; three RCTs; 383 participants) or in survival until hospital discharge (RR 1.05; 95% CI 0.78 to 1.42; four RCTs; 550 participants).

The authors concluded from the results from this review that there was a lack of precision in evaluations on biphasic and monophasic waveforms. The data showed that there was no benefit from using a biphasic defibrillator, although further studies would be warranted to increase the confidence in these results. For further details, refer to the original abstract, available at: http://onlinelibrary.wiley.com/doi/10.1002/14651858.CD006762.pub2/full.

Cardiopulmonary resuscitation (CPR) plus delayed defibrillation versus immediate defibrillation for out-of-hospital cardiac arrest

This review[13] compared CPR plus delayed defibrillation versus immediate defibrillation among patients who suffered out-of-hospital cardiac arrest. Four RCTs were included (n = 3,090). There was no difference between the groups regarding survival until hospital discharge (RR 1.09; 95% CI 0.54 to 2.2; three RCTs; 658 participants), good neurological recovery at hospital discharge (RR 1.12; 95% CI 0.65 to 1.93; three RCTs; 2834 participants), return to spontaneous circulation (RR 0.94; 95% CI 0.77 to 1.15; three RCTs; 658 participants) or survival at one year afterwards (RR 0.77; 95% CI 0.24 to 2.49; two RCTs; 456 participants).

The authors' conclusion was that the overall quality of evidence was low (mainly due to the risk of bias among the studies included and the imprecision of the results). There was no difference between the two interventions, and further studies would be needed to reduce the uncertainties of this analysis.

For further details, refer to the original abstract, available at: http://onlinelibrary.wiley.com/doi/10.1002/14651858.CD009803.pub2/full.

Other interventions

Aminophylline for bradyasystolic cardiac arrest among adults

This review[9] aimed to determine the effects (harm and benefits) of aminophylline administered to patients who suffered bradyasystolic cardiac arrest. Five RCTs (n = 1,186) were included. All of them were performed in pre-hospital settings.

There was no difference between aminophylline and placebo administration regarding the following outcomes:

- Survival until hospital discharge (odds ratio, OR 0.58; 95% CI 0.12 to 2.74; five RCTs; 1,254 participants).
- Return of spontaneous circulation (OR 1.15; 95% CI 0.89 to 1.49; five RCTs; 1,254 participants).
- Survival until admission (OR 0.92; 95% CI 0.61 to 1.37; five RCTs; 1,254 participants).

There were insufficient data to evaluate neurological outcomes and adverse events. The authors concluded that prehospital administration of aminophylline was not associated with any improvement in clinical outcomes. For further details, read the original abstract, available at: http://onlinelibrary.wiley.com/doi/10.1002/14651858.CD006781.pub3/full.

Pre-hospital versus in-hospital initiation of cooling for survival and neuroprotection after out-of-hospital cardiac arrest

This review[7] evaluated the initiation setting (pre-hospital versus in-hospital) of cooling applied to cardiac arrest patients. Seven RCTs were included (n = 2,369). The authors' aim was to assess the major clinical outcome of survival (short and long-term), along with neurological outcomes and safety outcomes (serious adverse events). Despite the considerable number of RCTs and participants, the authors did not perform any pooled analysis (quantitative synthesis) because of the existence of methodological heterogeneity. They stated that none of the RCTs found any statistical differences between the two intervention groups, but this may have been influenced by lack of statistical power and low event rates in single studies.

Further studies with good methodological quality and preplanned outcomes need to be conducted to reduce the uncertainty regarding where to initiate cooling among patients who have suffered cardiac arrest. Another key point is that this review performed a head-to-head analysis. The use of hypothermia compared with inactive control was studied in another Cochrane systematic review, discussed below.[11]

For further details, and to access the full report on all the RCTs included, refer to the original abstract, available at: http://onlinelibrary.wiley.com/doi/10.1002/14651858.CD010570.pub2/full.

Hypothermia for neuroprotection among adults after cardiopulmonary resuscitation

The purpose of this review[11] was to investigate the effects (efficacy and safety) of therapeutic hypothermia after cardiac arrest. Six RCTs (n = 1,412) were included. The main results were the following:

- Conventional cooling was more likely to achieve a positive neurological outcome (RR 1.94; 95% CI 1.18 to 3.21; four RCTS; 437 participants) than was no cooling.
- Conventional cooling also increased the survival (RR 1.32; 95% CI 1.10 to 1.65; three RCTs; 383 participants).
- The incidence of the adverse effect of pneumonia was higher in the intervention group (RR 1.15; 95% CI 1.02 to 1.30; two RCTs; 1,205 participants). There was also higher incidence of hypokalemia (RR 1.15; 95% CI 1.03 to 1.84; two RCTs; 975 participants).

The overall quality of the evidence was considered low to moderate. The authors concluded that hypothermia was beneficial for patients who suffered out-of-hospital cardiac arrest, but they emphasized that this intervention would need to be studied in other settings.

For further details, refer to the original abstract, available at: http://onlinelibrary.wiley.com/doi/10.1002/14651858.CD004128.pub4/epdf.

Emergency intubation for acutely ill and injured patients

This review[14] aimed to assess endotracheal intubation (ETI) among acutely ill and injured patients (children and adults) who were unable to maintain adequate airways. The intention was to compare ETI with other airway management techniques. Three RCTs (n = 1,177) were included in a qualitative synthesis.

One RCT included 830 children (71% with non-traumatic cardiac arrest) and compared out-of-hospital ETI with bag-valve-mask ventilation and subsequent emergency department ETI. There was no difference regarding survival until hospital discharge (OR 0.82; 95% CI 0.61 to 1.11; one RCT; 830 participants) or good neurological outcome (OR 0.87; 95% CI 0.62 to 1.22; one RCT; 830 participants).

Another RCT evaluated ETI versus use of an esophageal gastric tube and included 175 patients who suffered out-of-hospital non-traumatic cardiac arrest. There was also no difference between the groups regarding survival until discharge (RR 0.86; 95% CI 0.39 to 1.90; one RCT; 175 participants).

The last RCT included 172 patients and compared ETI with use of a combi-tube among adults who suffered out-of-hospital non-traumatic cardiac arrest. There was also no difference between the groups regarding survival until hospital discharge (RR 0.43; 95% CI 0.09 to 1.99; one RCT; 172 participants).

The authors concluded that the efficacy of emergency intubation had not been rigorously studied, despite its widespread use in current practice. Further studies would be needed to evaluate this intervention among cardiac arrest patients.

For further details, refer to the original abstract, available at: http://onlinelibrary.wiley.com/doi/10.1002/14651858.CD001429.pub2/full.

DISCUSSION

This review included nine Cochrane systematic reviews that assessed interventions among patients who suffered cardiac arrest. The interventions included related to the use of compression techniques or devices (three SRs), defibrillation (two SRs) and other interventions (two SRs regarding hypothermia interventions, one regarding airway management and one regarding pharmacological intervention).

Although cardiac arrest is a very common cause of death, this condition has not been greatly studied through RCTs, i.e. using the gold-standard primary research design for evaluating the efficacy and safety of interventions. This may have happened partially because it is more difficult and very costly to perform RCTs under emergency conditions, and even more so during management of cardiac arrest. These interventions are commonly delivered by more than one person, which requires more training and elevates the clinical diversity between studies. Even the concept of "controlled" is challenged under these conditions, since most of the interventions are implemented in out-of-hospital settings, sometimes by an untrained person. This difficulty may be partly resolved by conducting clinical trials using nested designs, such as clustered designs, rather than using the widely used parallel design. However, this may lead to higher risk of bias and should be considered in planning further studies.

Regarding clinical implications, high-quality evidence was found in two systematic reviews as follows: (a) survival until hospital discharge is increased with continuous compression, when compared to interrupted chest compression, both administered by an untrained person and (b) there was no difference regarding the return of spontaneous circulation of bradyasystolic patients under cardiac arrest, comparing aminophylline and placebo. For all other comparisons and related outcomes, only very low to moderate evidence quality was found. Thus, clinical practice may be guided from the results presented in **Table 2** and from those obtained through other study designs (especially well-performed comparative observational studies), but most of these findings may be subject to change in the light of data from future studies.

Regarding the implications for further research, it is highly necessary to ensure that any future RCT on interventions relating to cardiac arrest should be planned. Such studies should only assess clinically relevant outcomes. The reporting of such studies needs to rigorously follow the guidelines of the CONSORT[18] statement, in order to enhance transparency and reproducibility.

CONCLUSION

Most of the nine Cochrane systematic reviews assessing CPR found no evidence or only provided limited evidence to allow any practical recommendation. High-quality evidence was found by two systematic reviews as follows: (a) survival until hospital discharge was increased with continuous compression, when compared to interrupted chest compression, both administered by an untrained person; and (b) there was no difference regarding the return of spontaneous circulation of bradyasystolic patients under cardiac arrest, comparing aminophylline and placebo. Further studies are needed in order to reach solid conclusions.

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Leiomyoma of the breast parenchyma: a case report and review of the literature

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KEY WORDS:
Breast.
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ABSTRACT

INTRODUCTION: Benign tumors are often seen in breast screening examinations. However, the differential diagnosis is not always simple because of radiological similarity between the different benign lesions.

CASE REPORT: We present a rare case report of leiomyoma of the breast parenchyma in a 68-year-old asymptomatic patient. The mammographic and ultrasonographic findings were similar to those observed in benign lesions.

CONCLUSION: The histopathological diagnosis requires careful differentiation from lesions that have smooth muscle proliferation, especially leiomyosarcoma. The most commonly performed treatment is resection of the lesion with free margins. Although breast leiomyoma is rare, it should be considered among the differential diagnoses for breast nodules of benign appearance. Resection with safety margins proved to be the only treatment needed.

INTRODUCTION

Leiomyoma is considered to be the rarest non-epithelial tumor of the breast.[1] It occurs more frequently in the retroareolar region because of the greater amount of smooth muscle in this location.[2] Its presence in the mammary parenchyma is extremely rare, with fewer than 30 cases reported so far in the literature.[3] The clinical, radiological and pathological characteristics do not differ markedly from those observed in the most frequent benign lesions. We report a case of leiomyoma in the breast parenchyma that was seen in our service and conducted a review of the literature, with special attention to radiological features that have been described so far.

CASE REPORT

A 68-year-old woman was seen at the Division of Mastology, Department of Gynecology of the Federal University of São Paulo (Universidade Federal de São Paulo, UNIFESP) with a non-palpable tumor that had been detected through screening mammography. The patient presented controlled hypertension and minor degenerative osteoarticular alterations. She reported having had three pregnancies and two deliveries, with thirty months of breastfeeding. She said that she did not have any other symptoms such as papillary flow or cutaneous lesions. She reported having had routine annual mammograms and that she had not had any previous surgery or biopsies. The mammogram performed two years earlier did not show any abnormalities. The physical examination was unremarkable, with no evidence of any palpable mass, skin changes or axillary lymphadenopathy.

Imaging findings

Mammographic images showed an isodense circumscribed oval mass measuring 1.8 x 1.0 cm that was located at the junction of the upper quadrants of the left breast. Sonographic images of the left breast showed a hypoechoic homogenous oval mass measuring 1.4 x 0.7 cm that

was horizontal and parallel to the skin. It had two lobulations and circumscribed margins, and was coincident with the location described through mammography (**Figure 1**). The lesion did not present any posterior acoustic shadow, hyperechoic halo or other associated abnormal features. The mass was classified as being in Breast Imaging-Reporting and Data System (BI-RADS) category 4.

Histopathological findings

An ultrasound-guided breast core biopsy with a 12-gauge needle was performed and five fragments were obtained. The pathological evaluation showed a mesenchymal neoplasm with muscle differentiation. The patient underwent surgical excision of the lesion. The histological findings revealed a circumscribed lesion with a pattern of fusiform proliferation and formation of interlaced bundles and fascicles (**Figure 2**). No cellular atypia, necrosis or mitotic figures was found. Immunohistochemical stains for CD34 and S100 were positive, and negative for desmin and smooth muscle actin. A diagnosis of smooth muscle tumor, and specifically mammary parenchyma leiomyoma, was established. There was no recurrence of the lesion after follow-up of 60 months.

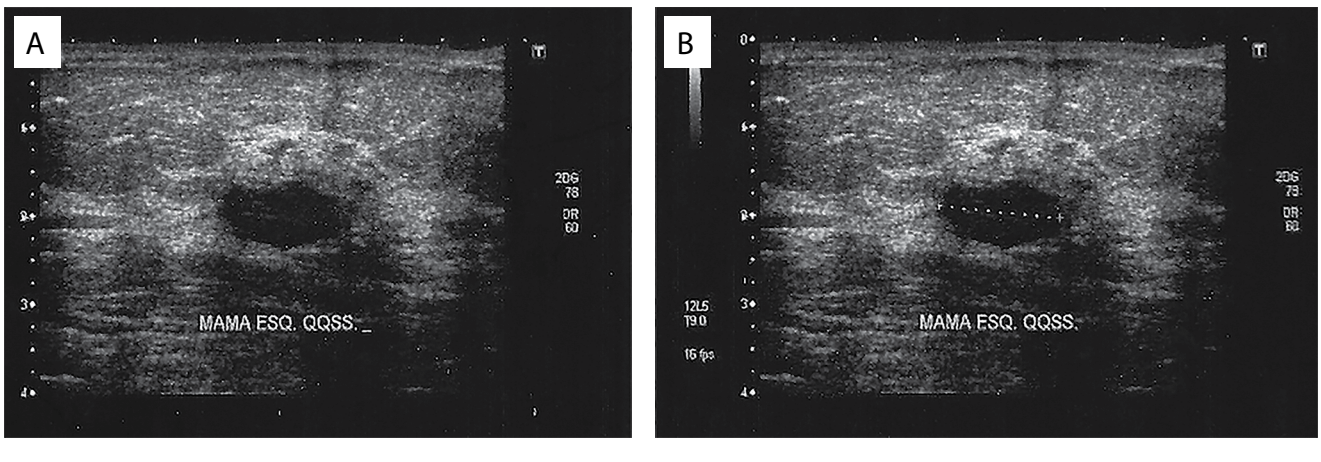

Figure 1. Sonographic findings in breast leiomyoma, demonstrating a hypoechoic oval mass that was predominantly circumscribed but sometimes showed microlobulated margins, and which was parallel to the breast skin. It was classified via ultrasonography in Breast Imaging-Reporting and Data System (BI-RADS) category 4.

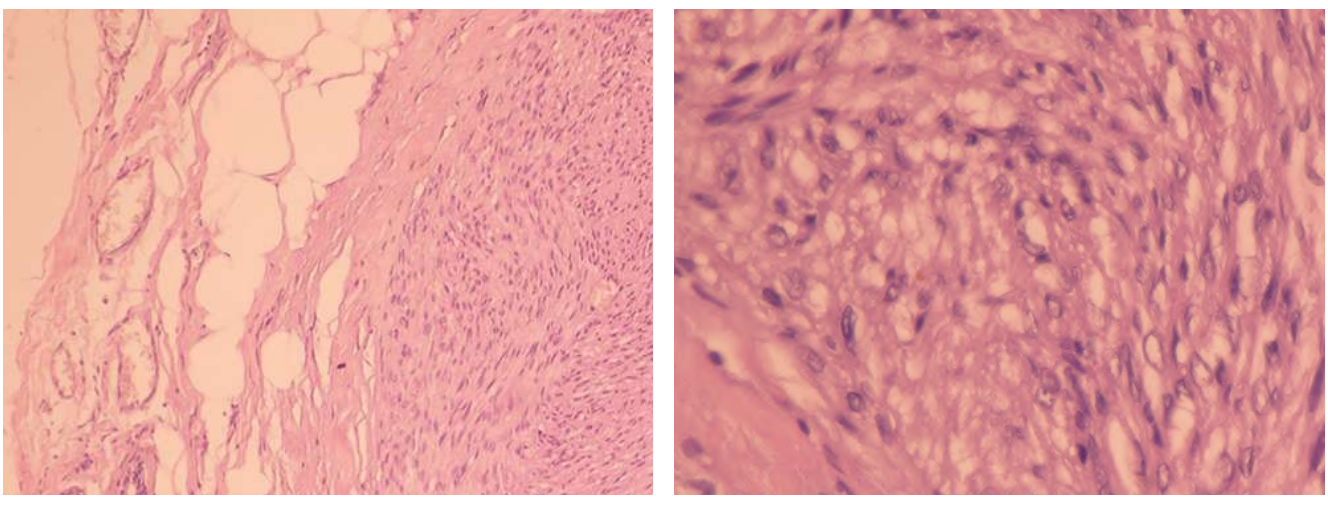

Figure 2. Histological sections revealing circumscribed appearance of the lesion, with proliferation of fusiform pattern and lack of atypical forms. Staining with hematoxylin and eosin (10 x and 40 x).

DISCUSSION

Even though Strong's first paper on breast leiomyoma was published in 1913, knowledge of the etiology of this condition remains uncertain.[4] It has been taken to originate from smooth-muscle angiomatous cells, given the "angiocentric" proliferation of smooth muscle that is observed. This theory is reinforced through the observation that blood vessels are present at locations showing defects or artefacts of histological fixation.[5] Current immunohistochemical findings rule out teratogenic origins. Uncertainty remains regarding theories of embryological displacement of smooth muscle cells of the areola, and regarding an origin from multipotent mesenchymal cells. These were proposed in the first half of the twentieth century by Melnick[6] and Shauder.[7]

Breast leiomyoma occurs predominantly in women, with only one case reported in a man.[2] The age of highest incidence is between 40 and 60 years. It presents as an isolated tumor of slow growth, with similar characteristics to the most common benign tumors.[8-10] The presence of pain was observed in only three cases, being more frequent in tumors of areolar location due to the contraction of neoplastic muscle cells.[11]

Physical examination usually reveals a mobile nodule with well-defined limits and fibroelastic consistency, although sometimes it has been reported to have hardened consistency.[12-14] Mammographic images have been described as showing an isodense or hyperdense oval mass, with outlines that are most often circumscribed (**Table 1**).[1,13,15-21] Microcalcifications relating to leiomyoma have never been described.[15,16,22,23]

The effectiveness of mammography is limited in relation to lesions measuring less than 1.0 cm and breasts with predominant glands. Sonography frequently shows a hypoechoic mass with well-defined limits and oval shape.[17] Presence of lobulations has frequently been observed. Growth parallel to the skin has been observed in 100% of the cases. No well-defined posterior acoustic shadowing has been described.[18]

Magnetic resonance imaging findings were first reported by Minami et al. They described a circumscribed oval nodule, with hypersignal in T1 and T2, and homogeneous enhancement after gadolinium infusion. They pointed out that presence of degeneration can influence the signal pattern in different sequences, as noted in leiomyoma in other regions of the body.[16]

The differential diagnosis should be done in relation to lesions that have smooth muscle proliferation in the absence of epithelial or ductal structures. In this context, the lesions that comprise the differential diagnosis are angioleiomyoma, fibroadenoma and malignant phyllodes tumor.[24-26] Because mature adipose tissue is needed to identify cases of hamartoma, this lesion does not provide difficulties in the differential diagnosis.[5] In cases of lesions suggestive of leiomyoma, leiomyosarcoma is the main situation that needs to be ruled out.[19,27]

Presence of 2-16 mitotic figures per 10 high-power figures is the main feature for diagnosing leiomyosarcoma. According to Pourbagher, presence of 1-3 mitotic figures might be considered to represent an intermediate category because of the higher risk of local recurrence and, therefore, treatment that is more radical.[15] Boscaino et al. reported local recurrence in two cases initially diagnosed as leiomyoma. Histological reevaluation of the lesions found presence of increased mitotic activity, and the lesions were reclassified as smooth-muscle neoplasms of undetermined prognosis.[28] In patients with a confirmed diagnosis of breast leiomyoma, no cases of local recurrence have been reported to date.[11-19,22-27]

We reviewed the literature in MEDLINE and Lilacs using the English keywords "leiomyoma", "fibroid tumors", "benign tumor", "benign neoplasms", "breast tumor", "breast neoplasms" and "ultrasonography". We found 30 case reports that described patients with leiomyoma in the breast parenchyma (**Table 2**).

In reviewing treatments that have been implemented, a wide range of interventions can be identified, from lumpectomy to radical mastectomy (**Table 3**).[1,2,4-10,13,15-21,24,29] However, since the report by Lauwers in 1990, the standard treatment has been resection with free margins.[20,21]

Table 1. Radiological findings from 10 cases of mammary leiomyoma.

Author	Year	Radiological findings
Lauwers et al.[20]	1990	MMG: Well-defined focal asymmetry; benign appearance without calcifications or loss of contours US: None
Nazário et al.[13]	1995	MMG: Hyperdense, homogeneous image with defined regular margins. US: None
Kaufman and Hirsch[1]	1996	MMG: Dense breast without identifiable abnormalities. US: None
Son et al.[18]	1998	MMG: Oval nodule with well-defined margins US: Isoechoic oval nodule; slightly lobulated with well-defined margins
Sidoni et al.[17]	1999	MMG: Bulky oval mass, with circumscribed margins. US: Hypoechoic oval mass, with well-defined margins.
Pourbagher et al.[15]	2005	MMG: Nodule with well-defined margins without calcifications. US: Circumscribed hypoechoic solid oval mass, with well-defined margins.
Ende et al.[19]	2007	MMG: Isodense oval nodule with indistinct margins. US: Not viewed.
Minami et al.[16]	2011	MMG: Hyperdense oval nodule with indistinct margins, without spicules or microcalcifications. US: Hypoechoic nodule, with well-defined margins.
Shah et al.[30]	2013	MMG: Circumscribed isodense oval nodule. US: None
Brandão et al. (present case)	2015	MMG: Circumscribed isodense oval nodule. US: Circumscribed hypoechoic oval nodule with rare lobulations.

MMG = mammogram. US = ultrasonography

Table 2. Search of the literature in medical databases for case reports on leiomyoma in the breast parenchyma. The search was conducted on December 5, 2016

Database	Search strategies	URL	Papers found	Related papers
MEDLINE (via PubMed)	(("leiomyoma"[MeSH Terms] OR "leiomyoma"[All Fields]) OR "fibroid tumors"[All Fields] OR ("leiomyoma"[MeSH Terms] OR "leiomyoma"[All Fields] OR "fibromyoma"[All Fields]) OR "benign tumor"[All Fields] OR "benign neoplasms"[All Fields] OR "benign tumor"[All Fields]) AND ("breast/pathology"[Mesh Terms] OR "breast neoplasms"[MeSH Terms] OR "breast cancer"[All Fields] OR "breast tumor"[All Fields] OR "mammary cancer"[All Fields] OR "cancer of breast"[All Fields]) AND ("ultrasonography"[MeSH Terms] AND ("diagnostic imaging"[Subheading] OR ("diagnostic"[All Fields] AND "imaging"[All Fields]) OR "diagnostic imaging"[All Fields] OR "ultrasonography"[All Fields] OR "ultrasonography"[MeSH Terms]) OR ("diagnostic imaging"[Subheading] OR ("diagnostic"[All Fields] AND "imaging"[All Fields]) OR "diagnostic imaging"[All Fields] OR "ultrasound"[All Fields] OR "ultrasonography"[MeSH Terms] OR "ultrasonography"[All Fields] OR "ultrasound"[All Fields] OR "ultrasonics"[MeSH Terms] OR "ultrasonics"[All Fields]) OR ("ultrasonography, mammary"[MeSH Terms] OR ("ultrasonography"[All Fields] AND "mammary"[All Fields]) OR "mammary ultrasonography"[All Fields] OR ("mammary"[All Fields] AND "ultrasonography"[All Fields]))))	http://bit.ly/2mCc4uj	117	24
LILACS (via Bireme)	mh: leiomyoma OR tw:leiomyoma OR tw:"fibroid tumors" OR tw:fibromyoma OR tw:"benign tumor" OR tw:"benign neoplasms" OR tw:"benign tumor")) AND (tw:(("breast/pa" OR mh:c04.588.180 OR mh:c17.800.090.500 OR mh:"breast neoplasms" OR tw:"breast cancer" OR tw:"mammary cancer" OR tw:"breast neoplasms"))) AND (tw:ultrasound OR tw:ultrasonography)) AND (instance:"regional") AND (db:("LILACS"))) AND (instance:"regional") AND (mj:("Mama"))	https://goo.gl/HbOEvW	42	6

Table 3. Clinical findings from 20 cases of breast leiomyoma

Author	Year	Sex	Race	Age (years)	Symptoms	Location	Size (cm)	Therapy
Strong[4]	1913	F	W	46	Discomfort	UOQ R	6.0	-
Schauder[7]	1927	F	W	34	Discomfort	UOQ R	3.0	Nodulectomy
Melnick[6]	1932	F	W	45	Pain	JLI R	"small"	Total mastectomy
Leibowich and Lenz[8]	1940	F	W	58	Discomfort	Midline	13.8	Total mastectomy
Stein[9]	1943	F	W	54	Discomfort	UIQ R	4.0	Radical mastectomy
Craig[10]	1947	F	B	40	Pain	LOQ L	10	Nodulectomy
Libcke[247]	1969	F	W	50	Hardening	JUQ R	0.5	Nodulectomy
Haagensen[29]	1971	F	-	52	None	Midline	2.5	Nodulectomy
Diaz-Arias et al.[5]	1989	F	W	69	None	UOQ R	2.0	Nodulectomy
Lauwers et al.[20]	1990	F	B	43	Mammographic finding	JUQ L	0.5	Resection with free margins
Nazario et al.[13]	1995	F	B	53	Nodule	UIQ L	10	Resection with free margins
Kaufman and Hirsch[1]	1996	F	W	48	Nodule	Midline R	1.0	Resection with free margins
Son et al.[18]	1998	F	A	50	Pain	UOQ R	1.0	Resection with free margins
Sidoni et al.[17]	1999	F	-	48	Nodule	UOQ L	4.0	Resection with free margins
Pourbagher et al. [15]	2005	F	-	47	Mammographic finding	JIQ L	2.5	Resection with free margins
Ende et al.[19]	2007	F	-	48	Mammographic finding	JIQ L	1.2	Resection with free margins
Minami et al.[16]	2011	F	A	63	Mammographic finding	UIQ R	1.6	Excisional biopsy
Shah et al.[21]	2013	F	W	27	Nodule	UIQ L	2.0	Excisional biopsy
Strader et al.[2]	2013	M	W	70	Nodule	JOQ L	7.0	Resection with free margins
Brandão et al. (current case)	2015	F	W	68	Mammographic finding	JUQ L	1.4	Resection with free margins

F = female; M = male; W = white; B = black; A = Asian; R = right; L = left; UOQ = upper outer quadrant; UIQ = upper inner quadrant; JIQ = junction of inner quadrants; JOQ = junction of outer quadrants; JUQ = junction of upper quadrants; JLI = junction of lower quadrants; LOQ = lower outer quadrant.

CONCLUSION

In conclusion, it can be said that leiomyoma in mammary tissue is an extremely rare condition. The clinical presentation does not differ from that observed in the most common benign tumors of the breast. The radiological findings are characteristically benign, which helps rule out the hypothesis of cancer. In histopathological evaluations, it is important to pay attention to the differential diagnosis of leiomyosarcoma. The standard recommended treatment is local resection with free margins. In this situation, the risk of local recurrence is practically zero.

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Bariatric surgery as a treatment for pseudotumor *cerebri:* case study and narrative review of the literature

Cirurgia bariátrica como tratamento para pseudotumor *cerebri*: estudo de caso e revisão narrativa de literatura

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KEY WORDS:
Pseudotumor cerebri.
Obesity.
Bariatric surgery.
Gastric bypass.
Intracranial hypertension.

PALAVRAS-CHAVE:
Pseudotumor cerebral.
Obesidade.
Cirurgia bariátrica.
Derivação gástrica.
Hipertensão intracraniana.

ABSTRACT

CONTEXT: Pseudotumor *cerebri* occurs when there is an increase in intracranial pressure without an underlying cause, usually leading to loss of vision. It is most commonly observed in obese women of childbearing age.

CASE REPORT: A 46-year-old woman presented at our service with idiopathic intracranial hypertension that had been diagnosed two years earlier, which had led to chronic refractory headache and an estimated 30% loss of visual acuity, associated with bilateral papilledema. She presented partial improvement of the headache with acetazolamide, but the visual loss persisted. Her intracranial pressure was 34 cmH_2O. She presented a body mass index of 39.5 kg/m^2, also associated with high blood pressure. Computed tomography of the cranium with endovenous contrast did not show any abnormalities. She underwent Roux-en-Y gastric bypass with uneventful postoperative evolution. One month following surgery, she presented a 24% excess weight loss. An ophthalmological examination revealed absence of visual loss and remission of the papilledema. There were no new episodes of headache following the surgery. There was also complete resolution of high blood pressure. The intracranial pressure decreased to 24 cmH_2O, six months after the surgery.

CONCLUSION: Although the condition is usually associated with obesity, there are few reports of bariatric surgery among individuals with pseudotumor *cerebri*. In cases studied previously, there was high prevalence of resolution or improvement of the disease following bariatric surgery. There is no consensus regarding which technique is preferable. Thus, further research is necessary in order to establish a specific algorithm.

RESUMO

CONTEXTO: O pseudotumor *cerebri* ocorre quando há aumento na pressão intracraniana sem causa subjacente, comumente levando a perda visual. É mais comum em mulheres obesas em idade fértil.

RELATO DE CASO: Mulher de 46 anos, foi admitida com hipertensão intracraniana idiopática diagnosticada há dois anos, que levou a cefaleia refratária crônica e perda estimada de 30% da acuidade visual, associada a papiledema bilateral. Apresentou melhora parcial da cefaleia com acetazolamida, mas a perda visual persistiu. A pressão intracraniana era de 34 cmH_2O. Apresentava índice de massa corpórea de 39,5 kg/m^2, associado a hipertensão arterial. Tomografia computadorizada com contraste endovenoso de crânio não apresentou anormalidades. Foi submetida ao *bypass* gástrico em Y de Roux, com evolução pós-operatória sem intercorrências. Um mês após a cirurgia, apresentou perda de peso em excesso de 24%. Um exame oftalmológico demonstrou ausência de perda visual e remissão do papiledema; não houve novos episódios de cefaleia após a cirurgia. Houve também resolução completa da hipertensão arterial. A pressão intracraniana caiu para 24 cmH_2O após seis meses da cirurgia.

CONCLUSÃO: Embora a condição seja usualmente associada à obesidade, há escassos relatos de cirurgia bariátrica em indivíduos com pseudotumor *cerebri*. Nos casos previamente estudados, há alta prevalência de resolução ou de melhora da doença após a cirurgia bariátrica. Não há consenso sobre qual é a técnica cirúrgica de escolha. Portanto, mais estudos são necessários para estabelecer um algoritmo específico.

INTRODUCTION

Pseudotumor *cerebri* (PC), also known as benign or idiopathic intracranial hypertension (IIH), is a disorder of elevated intracranial pressure (ICP) that primarily affects obese women of childbearing age, but can also affect non-obese adults and children.[1,2] IIH occurs predominantly in women, especially in the age range from 20 to 45, who are four to eight times more likely than men to be affected.[1,2] The incidence is approximately 2/100,000 and, given the global obesity epidemic, is likely to rise further.[3] According to the Dandy criteria, as revised by Friedman and Jacobson, IIH is diagnosed when six criteria are fulfilled:

1. suggestive symptoms or cranial hypertension are present;
2. suggestive signs of cranial hypertension are present;
3. normal cerebrospinal fluid composition;
4. elevation of lumbar puncture opening pressure (> 20 cmH_2O in lean and > 25 cmH_2O in obese individuals);
5. no abnormalities on computed tomography or magnetic resonance scans; and
6. no other identifiable cause of intracranial pressure.

Papilledema is typically present.[2-5] The underlying pathophysiological mechanisms that lead to this disease remain unknown, and the best-accepted theories are that the change in cranial pressure is linked to increased abdominal pressure, hormonal changes and unrecognized disorders in the cerebral venous system and in relation to cerebrospinal fluid resorption.[4,5]

Headache is the most common symptom of PC and is present in over 90% of these patients.[6] Up to 86% develop some degree of visual impairment, which may be severe and even blinding in 10%.[7]

CASE REPORT

A 46-year-old woman presented at our service with previously diagnosed IIH that had been diagnosed two years earlier, which had led to chronic refractory headache and an estimated 30% loss of visual acuity, associated with bilateral papilledema. She presented partial improvement of the headache with acetazolamide, but the visual loss persisted. The intracranial pressure, measured by means of lumbar puncture, was 34 cmH_2O. Biochemical, cytological and microbiological assessments on the cerebrospinal fluid did not reveal any abnormalities. Contrast-enhanced computed tomography did not show any abnormalities either (**Figure 1a**). She has been obese for 20 years and, on admission, presented a body mass index (BMI) of 39.5 kg/m^2, also associated with high blood pressure that was controlled through use of enalapril maleate.

She underwent Roux-en-Y gastric bypass with uneventful postoperative evolution. One month after surgery, the patient reported a slight reduction in the frequency of her episodes of headache and improvement of her visual impairment; there was also complete resolution of her high blood pressure. She had lost 24% of her excess weight by then. Use of acetazolamide and enalapril maleate was discontinued at this point.

Six months after the surgery, she presented a 55% loss of excess weight, such that her BMI was 31.5 kg/m^2. An ophthalmological examination revealed absence of visual loss and remission of the papilledema. The patient reported that there had been a more significant reduction in the frequency and intensity of the episodes of headache since her previous postoperative report. Lumbar puncture was performed again and the opening pressure was found to have decreased to 24 cmH_2O. There were no abnormalities in the biochemical, cytological and microbiological assessments on cerebrospinal fluid. **Table 1** details the characteristics of the cerebrospinal fluid before and six months after surgery. Contrast-enhanced computed tomography showed that no abnormalities were present (**Figure 1b**).

DISCUSSION

There are several treatment options for IIH. They may aim towards providing headache prophylaxis through using propranolol, amitriptyline and topiramate, or towards alleviation of intracranial pressure and optic symptoms through using diuretics such as acetazolamide and furosemide. In refractory

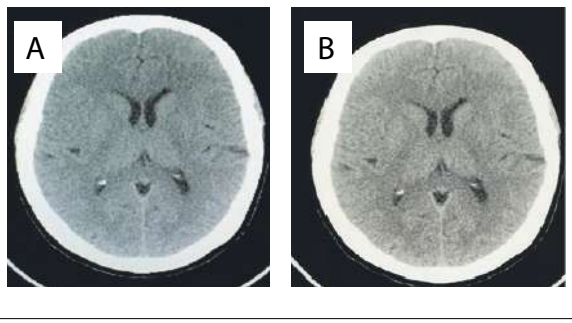

Figure 1. Computed tomography scans: 1A) preoperative; 1B) postoperative.

Table 1. General cerebrospinal fluid characteristics before and after surgery in a patient with pseudotumor *cerebri* who underwent bariatric surgery

	Preoperative	Postoperative
Protein (mg/dl)	26	23
Glucose (mg/dl)	62	55
pH	7.3	7.31
Red blood cells (cells/mm^3)	0	0
White blood cells (cells/mm^3)	2	1
Gram stain	Negative	Negative
Culture	Negative	Negative

cases, use of corticosteroids may be warranted. There is also the possibility of surgical interventions that aim to decrease the intracranial pressure (through lumbar or ventriculoperitoneal shunts) or alleviate the visual damage (through optic nerve sheath fenestration). The outcomes previously reported from these surgical procedures have been mixed and somewhat frustrating.[1-4,5-7]

Although usually associated with obesity, there are few reports of bariatric surgery among individuals with PC. A review of the literature was conducted through an online search for the MeSH terms "pseudotumor cerebri" and "bariatric surgery" in MEDLINE (via PubMed) and LILACS (via BVS) (**Table 2**).

There was significant overlap between the databases. After careful analysis, we selected three systematic reviews, one retrospective cohort study, two case series and nine case reports that evaluated bariatric surgery in individuals with PC, or that compared bariatric surgery with other treatment regimens. **Table 3**[8-22] summarizes the main articles selected and their respective levels of evidence according to the Oxford classification, and the results observed. **Figure 2** is a flow diagram showing the literature search and selection of articles.

Although two systematic reviews[10,13] were found, the majority of the studies that evaluated bariatric surgery as a treatment for IIH were case reports and case series. Thus, the quality of most of the evidence available so far is poor. The present report is only the second published case on pseudotumor *cerebri* that was treated by means of bariatric surgery in Brazil. The first case was reported by Fontes et al.,[21] who observed that complete resolution of PC-related symptoms was achieved in a 37-year-old female after RYGB. Nadkarni et al.[20] reported on two cases of obese women, both aged 42 years, who underwent gastric bypass and gastric stapling. Complete resolution of PC was observed at the one-year reevaluation. Soto et al.[18] described the case of a 30-year-old woman who presented complete resolution of headache, visual impairment and dizziness three months after undergoing laparoscopic RYGB. Levin et al.[11] reported the case of a 29-year-old obese woman with PC who presented dramatic improvement of headache four months after laparoscopic RYGB, and maintained this improvement one year after surgery. The case reported in our study also presented early improvement in PC-related symptoms, similar to the previously published evidence.

Roth et al.[9] compared individuals who underwent ventricular shunt surgery alone or in association with bariatric surgery. Their study revealed that, among shunted patients, bariatric surgery might not lead to resolution of PC-related symptoms and that these patients might remain shunt-dependent.

The systematic review conducted by Fridley et al.[13] identified a total of 62 individuals with PC who underwent bariatric surgery. They observed that the resolution rate for PC-related symptoms following bariatric surgery was 92%, with an average postoperative pressure decrease of 25.4 cmH_2O. These authors concluded that the class IV evidence published up to the time of their study suggested that bariatric surgery might be an effective treatment for PC among obese patients, but that prospective, controlled studies would be necessary for better elucidation of its role. A more recent systematic review by Handley et al.,[10] which enrolled 65 individuals, showed that there was an overall improvement in PC symptoms after bariatric surgery, in 60 of the 65 patients observed (92%). The postoperative lumbar puncture opening pressure was shown to decrease by an average of 189 mmH_2O in the patients for whom records of this pressure were available. A comprehensive systematic review conducted by Kalyvas et al.,[8] which also included studies that evaluated other treatment options, evaluated 32 individuals who underwent bariatric surgery. They observed that papilledema resolved in all patients and that headache improvement was documented in 96% of the patients, with no deterioration in any of the patients. However, these authors also emphasized that there was a higher degree of morbidity in the bariatric surgery group, compared with the other treatment regimens evaluated in other studies.

Despite the growing evidence of high rates of improvement and even resolution of PC achieved by means of bariatric surgery, the low quality of most of the available evidence means that no ultimate conclusions can be reached. Nonetheless, there is an increasing perception that obese individuals with increased

Table 2. Database search results for bariatric surgery among individuals with pseudotumor *cerebri*, on November 19, 2016

Electronic databases	Search strategies	Results
MEDLINE (PubMed)	((Pseudotumor cerebri) OR (Intracranial hypertension)) AND (Bariatric surgery)	3 systematic reviews 1 retrospective cohort study 2 case series 8 case reports
LILACS (BVS)	(((Pseudotumor cerebri) OR (Pseudotumor cerebral) OR (Seudotumor cerebral)) OR ((Intracranial hypertension) OR (Hipertensão Intracraniana) OR (Hipertensión Intracraneal))) AND ((Bariatric surgery) OR (Cirugia Bariátrica) OR (Cirurgia Bariátrica))	2 systematic reviews 1 retrospective cohort study 1 case series 4 case reports

Table 3. Main studies on bariatric surgery among individuals with pseudotumor *cerebri*

Study	Methods	N	Level of evidence	Treatment option	Main results
Kalyvas et al.[8]	Systematic review of case series and case reports	728	3a	341: optic nerve sheath fenestration 128: lumboperitoneal shunting 72: ventriculoperitoneal shunting 155: venous sinus stenting 32: bariatric surgery (29: gastric bypass; 2: gastroplasty; 1: gastric banding)	The studies were heterogeneous. No type of surgery proved to be clearly superior. Bariatric surgery presented a higher success rate among obese individuals but also a higher morbidity rate.
Roth et al.[9]	Case series	13 (6: shunting and bariatric surgery; 7: only shunting)	4	Bariatric surgery in individuals who previously underwent shunting procedures vs. only shunting (4: sleeve gastrectomy; 2: gastric banding)	Bariatric surgery is less effective and may lead to over-drainage symptoms in individuals who previously underwent shunting
Handley et al.[10]	Systematic review	65	3a	Bariatric surgery (48: gastric bypass; 6: gastric banding; 4: gastroplasty; 5: sleeve gastrectomy)	Overall improvement in 92% of the individuals; mean 18.9 cmH_2O decrease in lumbar puncture pressure
Levin et al.[11]	Case report	1	4	Gastric bypass	Improvement of headache and reversal of papilledema
Egan et al.[12]	Case series	4	4	Gastric banding	Total resolution or significant improvement of headache (mean improvement in pain score of 76.3/100 (range 55-95) on an analogue pain scale)
Fridley et al.[13]	Systematic review	62	3a	Bariatric surgery (55: gastric bypass; 4: gastroplasty; 3: gastric banding)	Resolution of headache in 92% of the individuals; mean 25.4 cmH_2O decrease in CSF pressure
Williams et al.[14]	Case report	1	4	Gastric banding	Complete resolution of headache and visual loss
Stangherlin et al.[15]	Case report	1	4	Gastric banding	Complete resolution of headache and CSF rhinorrhea
Leslie et al.[16]	Case report	1	4	Gastric bypass	Complete resolution of visual loss
Chandra et al.[17]	Case report	1	4	Gastric bypass	Complete resolution of visual loss
Soto et al.[18]	Case report	1	4	Gastric bypass	Complete resolution of headache, visual loss and dizziness
Lazcano-Herrera et al.[19]	Case report	1	4	Modified jejunocolic bypass	Complete resolution of headache and visual loss
Nadkarni et al.[20]	Case report	2	4	1: gastric bypass 1: gastric stapling	Complete resolution of headache and visual loss
Fontes et al.[21]	Case report	1	4	Gastric bypass	Complete resolution of headache and visual loss
Sugerman et al.[22]	Retrospective cohort	24	2b	23: gastric bypass 1: gastric banding	Resolution of visual loss in 100% and headache and tinnitus in 94.7% of the individuals

N = number of individuals; CSF = cerebrospinal fluid. Levels of evidence according to the Oxford classification - 1a = Systematic reviews (with homogeneity) of randomized controlled trials; 1b = Individual randomized controlled trials (with narrow confidence interval); 1c =: "All or none" randomized controlled trials; 2a = Systematic reviews (with homogeneity) of cohort studies; 2b = Individual cohort study or low-quality randomized controlled trials (e.g. < 80% follow-up); 2c = "Outcomes" research; ecological studies; 3a = Systematic review (with homogeneity) of case-control studies; 3b = Individual case-control study; 4 = Case series (and poor-quality cohort and case-control studies); 5 = Expert opinion without explicit critical appraisal, or based on physiology, bench research or "first principles".

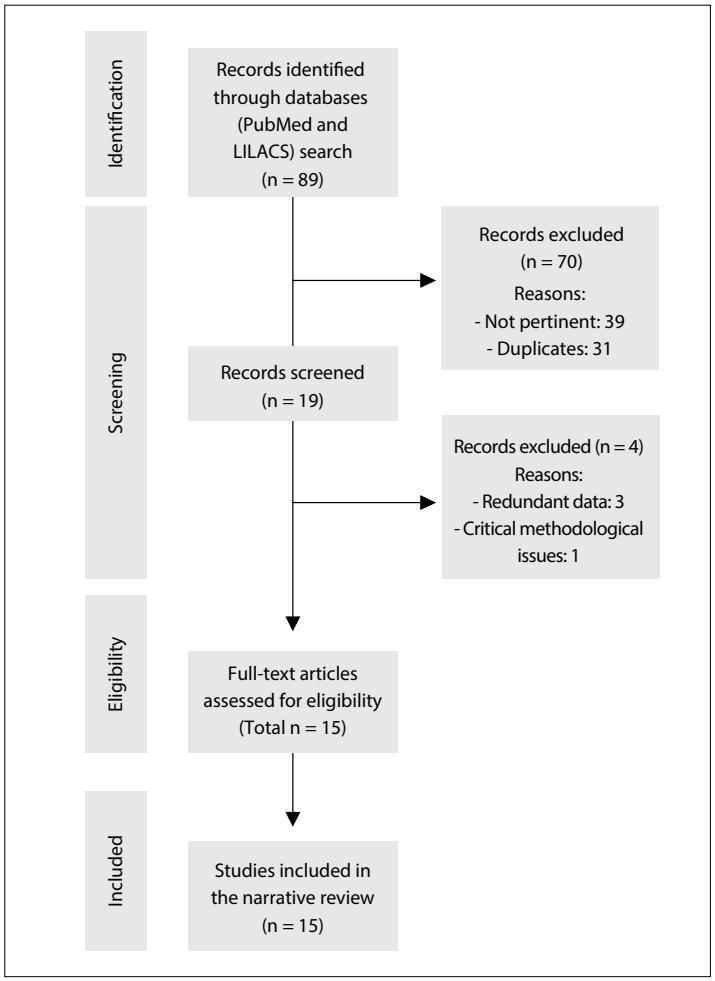

Figure 2. Flow diagram of the narrative review of the literature.

intracranial hypertension may significantly benefit from bariatric surgery. Hence, individuals who fulfill the current indications for bariatric surgery should at least be offered this type of treatment.

CONCLUSION

Bariatric surgery led to early improvement in the PC-related symptoms in this report, and this was comparable with evidence published previously.

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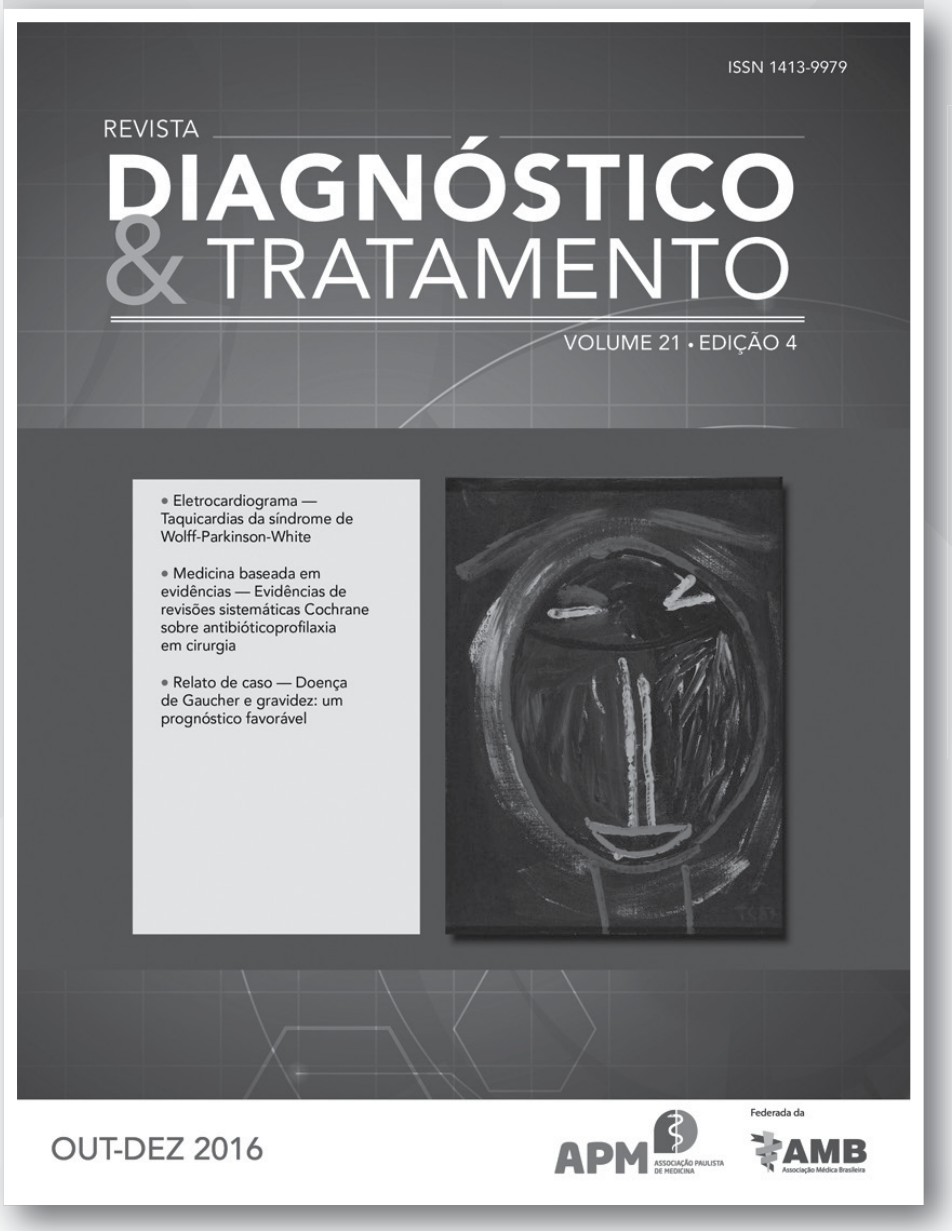

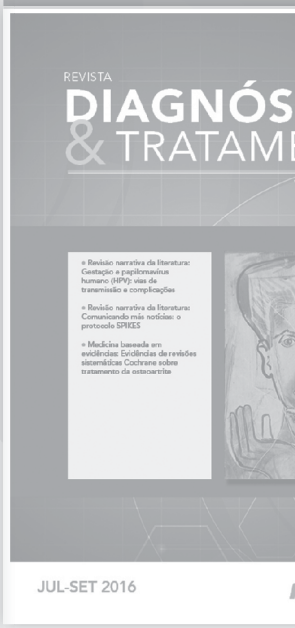

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