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December 3 - Volume 138 - Number 6

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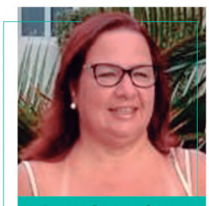

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What editors, reviewers, researchers and librarians need to know about the PRESS, MECIR, PRISMA and AMSTAR instruments with regard to improving the methodological quality of searches for information for articles

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The question that people involved in scientific information and publishing keep asking is "What can we do to further improve the quality of scientific publications?"

Scientific publications contain text that reports on the steps taken within scientific research. The published text is the end product from this work, which deserves to be reported properly and in detail.

Evaluative instruments through which syntheses and synopses of evidence are made add rigor and methodological quality to published studies at all stages, so that the final product will have reliable and reproducible results.

Therefore, in answer to the initial question, we can survey the instruments available to aid in searching for information. A search for information forms an important methodological stage in any scientific investigation, and not just in studies that have the aim of producing a synthesis of the evidence.

The structured tools that are used in assessments and in producing certain types of study such as systematic reviews, technological healthcare evaluations, scoping reviews, rapid systematic reviews, overviews, integrative reviews, and so on, may form instruments that guide editors, reviewers, researchers and librarians. One such instrument was specifically created to guide librarians in evaluating and conducting high-sensitivity search strategies.

Four instruments fall into this category, as follows:

- **MECIR** - Methodological Expectations for Cochrane Intervention Reviews;
- **PRISMA** - Preferred Reporting Items for Systematic Reviews and Meta-Analyses;
- **AMSTAR** - Assessing the Methodological Quality of Systematic Reviews;
- **PRESS** - Peer Review of Electronic Search Strategies.[1-9]

In **Table 1**, we present these four instruments for conducting sectional assessments and analyses, specifically for searching for information and developing a search strategy. Through this, it can be seen that the PRESS and MECIR instruments provide more detail for conducting searches than do PRISMA and AMSTAR, including provision of detailed guidance for this stage and greater rigor.[1-9]

MECIR

The librarian of the Cochrane Collaboration, who has the title of Cochrane Information Specialist (CIS), has the task of **designing and implementing search strategies**. This involves the entire process of defining the question, identifying the vocabulary that covers this question, transcribing the question into a search strategy, selecting the databases, transcribing the strategy for all the databases that were selected (mandatory, specialized and recommended databases), testing the performance of the strategy, adjusting it and running it in all the databases selected for the question. The librarian assists in saving and guiding the management of results obtained

Table 1. Instruments used for conducting sectional syntheses of evidence and assessing their quality, in order to evaluate search strategies and select databases[1-9]

MECIR – METHODOLOGICAL EXPECTATIONS FOR COCHRANE INTERVENTION REVIEWS - https://methods.cochrane.org/methodological-expectations-cochrane-intervention-reviews. This instrument is used by the Cochrane Collaboration to ensure the rigor and quality of its publications.
What is MECIR? It consists of methodological standards to which all Cochrane protocols, reviews and updates must adhere, and rules for conducting them and making reports, etc.

Searching for studies (C24-C38)

C24. Searching in general bibliographic databases (MEDLINE, Embase) and CENTRAL – **Mandatory**

C25. Searching in specialized bibliographic databases (CINAHL, LILACS, PsycINFO) – **Highly desirable**

C26. Searching for different types of evidence: specific eligibility criteria regarding the design of the study, to address adverse effects, economic issues or qualitative research issues – **Mandatory**

C27. Searching for trial registrations: Investigation of registration of studies and repositories of results, when relevant to the topic, through ClinicalTrials.gov, the WHO International Clinical Trial Registration Portal (ICTRP) and other sources as appropriate – **Mandatory**

C28. Searching the grey literature: Investigation of relevant sources of grey literature, such as reports, dissertations, theses, databases and conference abstract databases – **Highly desirable**

C29. Searching for other comments: Investigation of previous analyses on the same topic – **Highly desirable**

C30. Searching reference lists: Verification of reference lists in the studies included and any relevant systematic reviews that were identified – **Mandatory**

C31. Investigation of contacts with relevant individuals and organizations: Contacts with relevant individuals and organizations to obtain information on studies that are unpublished or in progress – **Highly desirable**

C32. Structuring of search strategies for bibliographic databases: The structure of the search strategies in bibliographic databases around the main concepts of the review should be informed, using appropriate elements from PICO (problem-intervention-comparison-outcome) and the study design. In structuring the investigation, sensitivity should be maximized while seeking reasonable precision. Correct use of the operators "AND" and "OR" should be ensured – **Mandatory**

C33. Development of research strategies for bibliographic databases: Appropriate controlled vocabulary needs to be identified (for example, MeSH or Emtree, including "exploded" terms), along with free-text terms (for example, considering spelling variations, synonyms, acronyms, stem operators and proximity) – **Mandatory**

C34. Use of search filters: Specially designed and tested search filters should be used when appropriate, including highly sensitive Cochrane search strategies for identifying randomized clinical trials in MEDLINE. However, filters should not be used in prefiltered databases. For example, randomized trial filters should not be used in CENTRAL and systematic review filters should not be used in DARE – **Highly desirable**

C35. Restrictions on database searches: The use of any restrictions in search strategies regarding publication date and publication format needs to be justified – **Mandatory**

C36. Documenting the search process: The search process should be documented with sufficient detail to ensure that it can be reported correctly in the review – **Mandatory**

C37. Doing searches again: The searches in all the relevant databases should be done again within the last 12 months before the review is published or updated, to check for any results from potentially eligible studies – **Mandatory**

C38. Incorporation of discoveries from repeated searches: Any studies identified through repeating or updating the search within the last 12 months before the review is published or updated should be incorporated in full – **Highly desirable**

PRISMA – Preferred Reporting Items for Systematic Reviews and Meta-Analyses - http://www.prisma-statement.org/. This is a checklist for the main recommendations and items to be included in reporting on a systematic review. It relates only to information searches.

Information sources:

ITEM 7: Describe all the information sources in the search (for example: database with dates of coverage or contact with authors to identify additional studies) and the date of the last search.

ITEM 8. Present a complete electronic search strategy for at least one database, including any limits used, so that it can be repeated.

- Detailed description of the information flow in the different phases of the systematic review (PRISMA flow diagram).

AMSTAR 2 – ASSESSING THE METHODOLOGICAL QUALITY OS SYSTEMATIC REVIEW - https://amstar.ca/Publications.php. This is a critical assessment tool that is used to evaluate the quality of systematic reviews on randomized studies and also, in this version 2, non-randomized healthcare intervention studies.

Question 4. Did the review authors use a comprehensive strategy for searching the literature?

- They searched at least two databases (that were relevant to the research question)
- They supplied keywords and/or search strategies
- They justified any publication restrictions (for example, language)
- They investigated reference lists or bibliographies in the studies included
- They investigated registers of trials and studies
- They included or consulted specialists within the field
- They investigated the grey literature when this was relevant
- They did a search within 24 months after concluding the review

PRESS 2015 – Guidelines and recommendations for librarians' practices[8]
Here, we highlight the recommendations for librarians, in addition to those in **Table 3**, which shows the simplified list of PRESS.

Continue...

Table 1. Continuation

1. Translation of the research question: Assess whether the research question was translated correctly, within the research concepts.	Ideally, the primary search strategy should be submitted to peer review to ensure conceptual precision. The research question, which is normally formatted in accordance with some variation of PICO and fine points about how the research was informed by the reference interview, should be sent with the research strategy.
2. Boolean and proximity operators: Assess whether the elements relating to the research question were combined correctly using Boolean and/or proximity operators.	Look again at the search regarding any instances of errors in Boolean operators. For example, OR may have been accidently replaced by AND (or vice versa), or AND may have been used to link phrases or words (for example, as a conjunction) instead of as a Boolean operator. Note that where NOT was used, there is the possibility of unintentional exclusions, and another device (for example, use of a subject title, verification label or limit) may produce an equivalent result. Check that any use of nesting between square brackets is logical and has been applied as necessary. Also, note whether use of a proximity operator (adjacent, near, within) instead of AND might increase the precision. If proximity operators have been used, consider whether the width chosen is narrow enough to capture all the foreseen instances of the search terms, which may vary depending on whether the database investigated does or does not recognize stop words. Consider whether the width is too broad. If there are restrictions (for example, human populations or elderly populations), check whether an appropriate construction was used.
3. Subject headers (specific for the database): Assess whether there is enough scope in selecting subject headers for the recall to be optimized.	Examine the following elements used in subject titles: absent or incorrect titles, relevance or irrelevance of terms and correct use of explosion for including more restrictive relevant terms. Consider using floating subtitles: in most cases, this is preferable to using subtitles attached to specific subject titles (for example, in MEDLINE, "Neck Pain/and su.fs." instead of "Neck Pain/su"). Note that subject titles and subtitles are specific to databases.
4. Search for text words (free text): Assess whether the search terms without adequate coverage of the subject title are well represented by free-text terms and whether additional synonyms and antonyms (opposites) and related terms are needed.	Free-text terms are normally used to cover subject headers of absent databases. Consider whether elements using free text might be too narrow or too broad, what the relevance of these terms is and whether synonyms and antonyms have been included.
5. Spelling, syntax and line number: Assess the correctness of the spelling and syntax and the implementation of correct searches.	Review the search strategy for words with spelling mistakes and system syntax errors that are not easily found through spellcheckers. Check each line number and combinations of line numbers to ensure that the logic of the search has been correctly implemented.
6. Limits and filters: Assess whether the limits used (including filters) are appropriate and have been correctly applied.	Review the search strategy to see whether limits that are not relevant for the eligible study designs or for the clinical question were applied, since this could introduce epidemiological bias. Check whether the methodological filters for the search were applied correctly: for example, to ensure that systematic reviews of economic evaluations are not restricted to clinical trials.

through automated systems for selecting and identifying duplicated studies.[1,2]

The CIS has to ensure that the research methods are documented in accordance with the MECIR standards. These also serve as a compass for the CIS in conducting the whole process.[1,2]

Involvement of this specialist adds significantly to improvement of the reporting of the research methods and also to evaluation of the general quality of the development process and presentation of the review.

Information specialists' involvement in traditional research tasks is always recommendable as a central methodological tenet for producing high-quality systematic reviews. However, these professionals' experience is increasingly being implemented in new ways.

In 2014, The Lancet, one of the world's most important medical journals, published a series of articles on how to improve research and reduce waste within it. These articles are available with open access and are listed in the following **Table 2**.[10-17]

Furthermore, a campaign in 2014 that aimed to reduce waste within research, named **REWARD** (REduce research Waste And ***Reward*** Diligence), to which The Lancet subscribed, highlighted the central role of information specialists in helping to reduce waste within research. Journal editorial teams and funding bodies were brought into biomedical research centers to examine the rigor of research processes, assess the extent of uncertainty and identify relevant research that was in progress (**Figure 1**). When information specialists at the Cochrane Collaboration decided to rename

their positions, as Trial Search Coordinators, this was in recognition of these evolving functions.[18]

PRESS

This instrument was conceived and created with the aim of conducting and evaluating search strategies for syntheses of evidence. It can be used to initiate the bibliographic search process of any research and publication project with the aim of augmenting the quality and general coverage of research.

Table 2. Lancet Reward (REduce research Waste And Reward Diligence) Publications

Comments
• How should medical science change?[10]
• Biomedical research: increasing value, reducing waste.[11]
Series (2014)
• How to increase value and reduce waste when research priorities are set.[12]
• Increasing value and reducing waste in research design, conduct, and analysis.[13]
• Increasing value and reducing waste in biomedical research regulation and management.[14]
• Increasing value and reducing waste: addressing inaccessible research.[15]
• Reducing waste from incomplete or unusable reports of biomedical research.[16]
Point of view (2014)
• This series related to an article published by The Lancet in 2009: Avoidable waste in the production and reporting of research evidence.[17]

Table 3 presents an evidence-based verification list of guidelines for PRESS 2015.[8]

This instrument provides descriptions of six elements for use as guidelines for librarians' practices. Moreover, for editors, this can serve as an instrument for general methodological assessment of reviews.

It is important that editors and reviewers should adopt or establish peer review strategies for evaluating articles submitted for publication that involve input from a specialist librarian.[9]

The ideal is that all of this search process should be done at the start of the research, so as to avoid perpetuating errors, not just at the end of the study but throughout its course. There is no doubt that as soon as peer review practices for search strategies are implemented by editors and everyone involved in publication processes, authors will start to conduct searches with adequate criteria from the outset.

The idea would be to make it clear in the instructions for authors what criteria should be used for descriptions of methodologies and what instrument or combination of instruments the journal will be using for assessing the quality of studies that are submitted to it.

From the information in **Table 1**, a template of options for description can be created so that all studies submitted, and also those already conducted, can have better methodological descriptions and quality. MECIR and PRESS provide broad descriptions

Figure 1. Editors engaged in REWARD – Reduce research Waste And Reward Diligence.

Table 3. Evidence-based verification list from the guidelines of PRESS 2015[8]

Translation of the research question	Does the search strategy correspond to the research question and PICO? Are the search concepts clear? Have many or few PICO elements been included? Are the search concepts too restrictive or too broad? Does the search recover many or few records? (Please show the number of occurrences per line.) Have unconventional or complex strategies been explained?
Boolean and proximity operators (these vary according to the search service)	Have Boolean or proximity operators been used correctly? Is the use of nesting with square brackets adequate and effective for the search? If NOT was used, is it likely that this has resulted in some undesired exclusion? Could the precision be improved by using proximity operators (for example, adjacent, near or within) or search for phrases instead of using AND? Is the width of the proximity operators appropriate? (For example, would adj5 get more variants than adj2?)
Subject headers (specific to the database)	Are the subject headers relevant? Are any relevant subject headers missing? For example, any previous index terms? Are any subject titles too broad or too narrow? Have the subject headers been exploded when necessary and vice versa? Have main titles been used ("starring" or restrictive in focus)? If so, is there adequate justification? Are subtitles missing? Are the subtitles attached to the subject headers? (Floating subtitles may be preferred.) Are the floating subtitles relevant and appropriately used? Have both subject headers and free-text terms (see below) been used for each concept?
Search for text words (free text)	Does the search include all spelling variants in free text (for example, British spelling versus American spelling)? Does the search include all synonyms or antonyms (for example, opposites)? Does the search capture relevant stems (i.e. is the stemming in the right place)? Is the stemming too broad or too narrow? Are the acronyms or abbreviations used appropriately? Do they pick up any irrelevant material? Have the complete terms also been included? Are the keywords sufficiently specific or too broad? Are too many or too few keywords used? Are stop words used? Have appropriate fields been searched? For example, was it appropriate to choose text word fields (.tw.) or all fields (.af.)? Are there any other fields to be included or excluded (specific to the database)? Should any long strings be divided into several shorter search declarations?
Spelling, syntax and line numbers	Are there any spelling mistakes? Are there any errors in the system syntax? For example, use of a stem symbol for a different search interface? Are there any incorrect combinations of lines or orphan lines? (In other words, are there any lines that are not mentioned in the final summary that might indicate an error in an AND or OR instruction?
Limits and filters	Have all the limits and filters been used appropriately and are they relevant for the research question? Have all the limits and filters been used appropriately and are they relevant for the database? Are any potentially useful limits or filters missing? Are the limits or filters too broad or too narrow? Could any limits or filters be added or removed? Have the sources for the filters used been cited?

and rigor for use in all research. It is also important to note that PRESS will shortly be available in Portuguese.

There is a clear need to improve the adequacy of search strategies for systematic reviews and for reviews in general. The presence of a search specialist, with experience in developing strategies throughout the research process has become essential for ensuring transparency and reproducibility of research methods, thus benefiting the quality of the reviews produced.

It is important that the reviewer using the search strategy and the information specialist who designed the strategy should be supported by a national forum for search specialists and should have access to teams that could review their strategies. Furthermore, they should also use the use the verification list of PRESS, which summarizes the main potential errors made in search strategies.[9]

All efforts exerted towards improving the quality of all research and reviews are valid.

With the material that is made available, along with the tools and instruments, the next step is to work put a route along which editors can better assess search strategies that are submitted for publication.

REFERENCES

1. Higgins JPT, Lasserson T, Chandler J, Tovey D, Churchill R. Methodological Expectations of Cochrane Intervention Reviews. Version 1.02. London: Cochrane; 2016. Available from: http://community.cochrane.org/sites/default/files/uploads/MECIR%20PRINTED%20BOOKLET%20FINAL%20v1.02.pdf. Accessed in 2020 (Nov 25).
2. Higgins J, Churchill R, Lasserson T, Chandler J, Tovey D. Update from the Methodological Expectations of Cochrane Intervention Reviews (MECIR) project. Cochrane Methods. Cochrane DB Syst Rev. 2012;Suppl 1:1-56. Available from: http://citeseerx.ist.psu.edu/viewdoc/download?doi=10.1.1.471.1712&rep=rep1&type=pdf#page=8. Accessed in 2020 (Nov 25).
3. Moher D, Liberati A, Tetzlaff J, Altman DG; PRISMA Group. Preferred reporting items for systematic reviews and meta-analyses: the PRISMA statement. PLoS Med. 2009;6(7):e1000097. PMID: 19621072; https://doi.org/10.1371/journal.pmed.1000097.
4. Tricco AC, Lillie E, Zarin W, et al. PRISMA Extension for Scoping Reviews (PRISMA-ScR): Checklist and Explanation. Ann Intern Med. 2018;169(7):467-73. PMID: 30178033; https://doi.org/10.7326/M18-0850.
5. Shea BJ, Grimshaw JM, Wells GA, et al. Development of AMSTAR: a measurement tool to assess the methodological quality of systematic reviews. BMC Med Res Methodol. 2007;7:10. PMID: 17302989; https://doi.org/10.1186/1471-2288-7-10.
6. Shea BJ, Bouter LM, Peterson J, et al. External validation of a measurement tool to assess systematic reviews (AMSTAR). PLoS One. 2007;2(12):e1350. PMID: 18159233; doi: 10.1371/journal.pone.0001350.
7. Shea BJ, Reeves BC, Wells G, et al. AMSTAR 2: a critical appraisal tool for systematic reviews that include randomised or non-randomised studies of healthcare interventions, or both. BMJ. 2017;358:j4008. PMID: 28935701; https://doi.org/10.1136/bmj.j4008.
8. McGowan J, Sampson M, Salzwedel DM, et al. PRESS Peer Review of Electronic Search Strategies: 2015 Guideline Statement. J Clin Epidemiol. 2016;75:40-6. PMID: 27005575; https://doi.org/10.1016/j.jclinepi.2016.01.021.
9. Lefebvre C, Duffy S. Peer reviewing search strategies. HTAi Vortal, 2018. Available from: http://vortal.htai.org/index.php?q=book/export/html/918. Accessed in 2020 (Nov 23).
10. Kleinert S, Horton R. How should medical science change? Lancet. 2014;383(9913):197-8. PMID: 24411649; https://doi.org/10.1016/S0140-6736(13)62678-1.
11. Macleod MR, Michie S, Roberts I, et al. Biomedical research: increasing value, reducing waste. Lancet. 2014;383(9912):101-4. PMID: 24411643 https://doi.org/10.1016/S0140-6736(13)62329-6.
12. Chalmers I, Bracken MB, Djulbegovic B, et al. How to increase value and reduce waste when research priorities are set. Lancet. 2014;383(9912):156-65. PMID: 24411644; https://doi.org/10.1016/S0140-6736(13)62229-1.
13. Ioannidis JP, Greenland S, Hlatky MA, et al. Increasing value and reducing waste in research design, conduct, and analysis. Lancet. 2014;383(9912):166-75. PMID: 24411645; https://doi.org/10.1016/S0140-6736(13)62227-8.
14. Al-Shahi Salman R, Beller E, Kagan J, et al. Increasing value and reducing waste in biomedical research regulation and management. Lancet. 2014;383(9912):176-85. PMID: 24411646; https://doi.org/10.1016/S0140-6736(13)62297-7.
15. Chan AW, Song F, Vickers A, et al. Increasing value and reducing waste: addressing inaccessible research. Lancet. 2014;383(9913):257-66. PMID: 24411650; https://doi.org/10.1016/S0140-6736(13)62296-5.
16. Glasziou P, Altman DG, Bossuyt P, et al. Reducing waste from incomplete or unusable reports of biomedical research. Lancet. 2014;383(9913):267-76. PMID: 24411647; https://doi.org/10.1016/S0140-6736(13)62228-X.
17. Chalmers I, Glasziou P. Avoidable waste in the production and reporting of research evidence. Lancet. 2009;374(9683):86-9. PMID: 19525005; https://doi.org/10.1016/S0140-6736(09)60329-9.
18. THE REWARD THE LANCET – The Lancet REWARD (REduce research Waste And Reward Diligence) Campaign invites everyone involved in biomedical research to critically examine the way they work to reduce waste and maximise efficiency. Available from: https://www.thelancet.com/campaigns/efficiency. Accessed in 2020 (Jul 7).

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Evidence of association between the use of drugs and community-dwelling older people frailty: a cross-sectional study

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ABSTRACT

BACKGROUND: The scientific literature has shown that an association between polypharmacy and frailty exists. However, few studies have also considered drug interactions and the use of potentially inappropriate medications.

OBJECTIVE: To evaluate the association between the use of drugs and frailty among community-dwelling older people.

DESIGN AND SETTING: Cross-sectional study carried out among 580 older people in Uberaba (MG).

METHODS: Data were collected at these older people's homes using instruments validated in Brazil. Descriptive, bivariate and binary logistic regression analyses were performed ($P < 0.05$).

RESULTS: Most of these individuals were classified as pre-frail (55.7%), while 13.1% were frail. It was found that 31.7% of them presented polypharmacy, 41.7% had drug interactions and 43.8% were using potentially inappropriate medications. In the initial model, polypharmacy (odds ratio, OR = 1.91; confidence interval, CI = 1.27-2.86) and use of potentially inappropriate medications (OR = 2.45; CI = 1.68-3.57) increased the chance that these older people would be pre-frail or frail. In the final adjusted model, use of potentially inappropriate drugs remained associated with the outcome (OR = 2.26; CI = 1.43-3.57).

CONCLUSION: Use of potentially inappropriate medications was the independent variable that explained the occurrence of frailty in a representative sample of community-dwelling older adults.

INTRODUCTION

Frailty syndrome among older people is related to changes that occur through the human aging process, such as sarcopenia, neuroendocrine dysregulation and immune system dysfunction.[1] Frail individuals are at increased risk of adverse events and injuries due to falls, which, together with various comorbidities, can cause higher rates of institutional care, hospitalizations and mortality.[1,2]

The aging process can promote physiological changes that cause older people to exhibit distinctive pharmacokinetics, such that they may become more sensitive both to the therapeutic effects and to the toxic effects of drug therapy.[3] Furthermore, multimorbid conditions require the use of multiple drugs, which is characterized as polypharmacy. This, together with the physiological changes of aging can increase the chances of adverse events among older people.[3-6] These include the increased levels of pathogenesis within frailty syndrome, as highlighted in the International Frailty Consensus.[7]

There are several concepts of polypharmacy, although most of them consider it to be the concomitant use of five or more drugs.[8] This was the concept used in the present investigation. It is important to note that polypharmacy increases the risk of drug interactions (DI), as well as the use of potentially inappropriate medications (PIMs) among older people.[3] Polypharmacy, therefore, cannot be considered to be the only marker for assessing the quality of drug prescriptions,[9] which requires consideration of DIs and use of PIMs for clinical care among older people.

DIs consist of clinically significant changes to the effect of a given drug caused by administration of another drug. Such changes may lead to modification of the absorption capacity to bind to proteins, or of the metabolic or excretion rate of one or even two of the medications involved in the interaction concerned.[10,11] Faced with considerable increases in the proportion

of drug prescriptions issued to older people and the consequent increased risk of adverse events among these individuals, there is concern regarding identification and prevention of undesirable combinations and use of PIMs.

It is known that PIMs increase the chances of adverse outcomes among older adults and that these are exacerbated when frailty syndrome is present.[9,13,14] Nevertheless, studies in the scientific literature on this topic have focused on demonstrating the association between polypharmacy and frailty,[15,16] but without including evaluations of DIs and PIMs. It is also worth mentioning that older people, including frail individuals, experience reduced efficacy of medications, in addition to higher risk of adverse effects.[17] The possible explanations for this phenomenon include impaired physiological systems that combat frailty, drug interactions, drug-disease interactions and reduced adherence to medication. Additionally, adverse reactions to medications go unnoticed and can lead to other prescriptions.[17]

The existence of this gap in knowledge emphasizes the need for clarifications regarding the relationship of these variables with frailty syndrome among community-dwelling older people. Better knowledge of the implications arising from variables relating to use of drugs can improve preventive clinical approaches towards the embrittlement process among older people. This could lead to significant differences in quality of life during the aging process.

OBJECTIVE

The objective of this study was to evaluate the association between the use of drugs and frailty among community-dwelling older people.

METHODS

Design

This cross-sectional study consisted of a household survey conducted among older people living in the urban area of the city of Uberaba, Minas Gerais, in the southeastern region of Brazil. This study followed the guidelines of the Checklist for Reporting Results of Internet E-Surveys and the guidelines for Strengthening the Reporting of Observational Studies in Epidemiology (STROBE).

Sample

The sample size calculation considered a prevalence of frailty of 12.8%,[6] accuracy of 2.7% and a 95% confidence interval for a finite population of 36,703 older people. From this, the sample size was determined as 579 subjects. However, allowance was made for a sampling loss of 20% and therefore it was calculated that the maximum number of individuals to be approached would be 724 elderly people. To define the study population, a multistage cluster sampling process was used, considering census tracts, with information on neighborhoods and streets provided by the Brazilian Institute for Geography and Statistics. Tracts were drawn in order to subsequently select older people living in these tracts.

Older adults aged 60 or older, who were living in the urban area of the municipality and who were able to walk, were included in the study. It needs to be highlighted that, in Brazil, people aged 60 years or over are considered to be older adults, according to the current legislation.[18]

Subjects were excluded from this study in the following situations: presentation of cognitive decline, as assessed using the Mini Mental State Examination (MMSE);[19] failure to locate the individual after three visits; hospitalization and/or institutionalization; and inability to undergo the assessment of frailty. This assessment because impossible if the subject presented inability to walk, severe sequelae from stroke, localized loss of strength and aphasia, or a severe or unstable stage of Parkinson's disease and associated severe impairment of motility, speech or cognition.

In the end, a total of 768 older people were approached, taking into account both the inclusion criteria and the losses, which comprised 154 due to cognitive decline and 34 due to incomplete tests for frailty evaluation. Hence, 580 patients were assessed in the present study.

Data collection

The interviews took place in the older people's homes, in the period from March to June 2016. They were conducted by trained interviewers with previous experience in collecting data. Five supervisors, who had previously been selected, checked the interviews to verify the filling out and consistency of the items, in order to ensure quality control.

Explanatory and adjustment variables

The explanatory and adjustment variables were collected using a structured questionnaire that sought the following information: (1) socioeconomic: age (numerical variable) and/or age group in years (60 to 69, 70 to 79 and 80 or older); gender (male or female); marital status (with or without a partner); schooling, in years (no education, 1 to 4 years and 5 years or more); individual monthly income, in minimum wages (no income, ≤ 1 minimum wage and > 1 minimum wage); and (2) number of self-reported morbidities (0, 1 to 4 and 5 or more), as described in a previous study.[20]

Frailty syndrome (dependent variable)

Presence of frailty syndrome, which was taken to be the dependent variable, was identified through the five items that were proposed as components of the frailty phenotype by Fried et al.:[1]

1. Unintentional weight loss: assessed through the question: "In the last year, did you lose more than 4.5 kg without intention (that is, without dieting or exercise)?".
2. Self-report of exhaustion and/or fatigue: assessed through two questions from the Brazilian version of the Center for Epidemiological Studies (CES-D) depression scale, i.e. item 7 ("Did you feel you had to make an effort to cope with your usual tasks?") and item 20 ("Were you unable to carry on with your things?"). The elderly people with a score of 2 or 3 in either of these questions met the frailty criterion for this item.[21]
3. Decreased muscle strength, as assessed from handgrip strength using a manual hydraulic dynamometer (Model SH5001, SAEHAN, São Paulo, Brazil) and adopting the cutoff points proposed by Fried et al.[1]
4. Slow gait speed, obtained from the gait time (in seconds) that was needed to cover a distance of 4.6 meters, using the cutoff points proposed by Fried et al.[1]
5. Low level of physical activity, as ascertained from the long version of the International Physical Activity Questionnaire (IPAQ), adapted for older people.[22] The classification used for this component considered older people to be inactive if they had 0-149 minutes of physical activity per week.[23]

The older people who were positive for three or more of these items were classified as frail and those who were positive for one or two items were classified as pre-frail. Those who were negative in all the tests were considered to be robust or non-frail.[1]

Drug use (independent variables)

To assess the variables relating to drug use, the older subjects were first asked: "Could you show me the medications you are currently using?" Thus, they were asked about their medical prescriptions and the packaging of the drugs that were being used at the time of data collection. The following were recorded: the pharmaceutical form of the medicinal products, the amounts consumed and the number of applications per day. Based on these data, situations of polypharmacy, DIs and PIMs were evaluated, as described below.

Polypharmacy was checked by counting the number of medications used by each older individual. When these older people reported using five or more medications, they were deemed to present polypharmacy.[8]

Occurrences of DIs were also assessed through the Micromedex Drug Reax System (Greenwood Village, Colorado, USA), using its online access platform,[24] which contains evidence-based information on drugs and diseases. This tool allowed identification of the DIs that occurred (drug-drug) and ranked them according to severity (severe, moderate or mild). It is worth noting that this tool is widely recognized worldwide for use by healthcare professionals, including pharmacists, to obtain unbiased data. The value of this tool has been sustained through systematic reviews on the subject.[24]

Use of PIMs was classified in accordance with the criteria established in the Brazilian Consensus on Potentially Inappropriate Drugs for Older People.[12] To analyze this variable, the subjects were divided between: "Using PIMs", when it was found that they were using at least one drug classified as inappropriate; and "Not using PIMs" when they did not use any of these drugs.

Data analysis

The data were entered into an electronic spreadsheet in the Excel software, in duplicate, in order to identify any possible inconsistencies from data entry. Subsequently, the data were imported into the Statistical Package for the Social Sciences (SPSS) software, version 22.0 (New Orchard Road, Armonk, New York, USA), to carry out the analyses.

A descriptive statistical analysis was conducted by distributing absolute and percentage frequencies. The bivariate analysis on the socioeconomic characteristics and variables relating to use of drugs according to frailty condition was done using the chi-square test. To assess associations among use of polypharmacy, PIMs and DIs in relation to the frailty syndrome, the logistic regression model was adopted. In this model, the outcome variable was recategorized so as to become dichotomous (frail/pre-frail versus non-frail). In the final adjusted model, the independent variables were included (polypharmacy, use of PIMs and DIs), along with other potential confounding variables such as gender, age, education and number of self-reported morbidities. For all analyses, the tests were considered significant when $P < 0.05$.

Ethical considerations

This study was approved by the human-research ethics committee of the Federal University of Triângulo Mineiro (Universidade Federal do Triângulo Mineiro, UFTM), under protocol no. 493,211, dated December 13, 2013.

RESULTS

Out of the total number of participants (n = 768), 154 older people were excluded because they presented cognitive decline and 34 because of inability to perform the comprehensive evaluation of the components of the frailty phenotype. Thus, the final sample consisted of 580 older adults.

In comparing the older people who were excluded with those who participated in the study, it was found that for both groups, the majority were female (70.7% versus 68.1%; P = 0.418); were living without a partner (71.3% versus 52.4%; P = 0.353); had had one to four years of schooling (56.4 versus 52.6%; P = 0.352); had a

monthly income of less than or equal to two minimum salaries (88.2% versus 81.6%; P = 0.979); and had five or more self-reported morbidities (64.7% versus 62.4%; P = 0.493). Regarding the age groups, older people aged 70 to 79 years (30.9%) predominated among the excluded individuals; while older adults aged 60 to 69 years (44.1%) predominated among those who participated in the study. However, there was no significant difference regarding age groups (P = 0.645).

Based on the final sample (n = 580), the frailty status among the subjects was as follows: 13.1% (n = 76) were frail; 55.7% (n = 323) were pre-frail; and 31.2% (n = 181) were non-frail.

It was found that most of the participants were female (68.1%); were between 60 and 69 years old (44.1%); were living without a partner (52.4%); had had one to four years of schooling (52.6%); and had a monthly income of two minimum wages (46.0%), followed by ≤ 1 minimum wage (44.7%). In analyzing the sociodemographic variables according to the frailty classification, a higher percentage of older people aged 70 to 79 years (P < 0.001) and with no education (P = 0.008) was observed in the frail and pre-frail groups, compared with the non-frail group. It was also observed A higher proportion of older people with five or more frail and pre-frail morbidities was also observed, in relation to the non-frail ones (P = 0.013) (**Table 1**).

Presence of polypharmacy was found in 31.7% (n = 184) of the older people. It was found that 41.7% (n = 242) had at least one DI and 43.8% (n = 254) were using PIMs. Occurrence of these events was more common among the frail older people, among whom 51.3% (n = 39) presented polypharmacy (P < 0.001), 60.5% (n = 46) had DIs (P = 0.001) and 53.9% (n = 41) had PIM use (P < 0.001), in comparison with the other groups (**Figure 1**).

In logistic regression analysis, it could be seen in the initial model that presence of polypharmacy (odds ratio, OR = 1.91; confidence interval, CI = 1.27-2.86) and use of PIMs (OR = 2.45; CI = 1.68-3.57) increased the odds of occurrence of frailty/pre-frailty among these community-dwelling older people. Evaluation of the final adjusted model showed that use of PIMs remained associated with increased chances of occurrence of frailty/pre-frailty (OR = 2.33, CI = 1.47-3.70), regardless of gender, age group, number of self-reported morbidities, education or other variables relating to use of medications (polypharmacy and DIs). It is noteworthy that age was also an explanatory variable for occurrences of frailty (**Table 2**).

DISCUSSION

The data from this study highlight that frailty among older people is a serious public health problem, given that significant prevalence (13.1%) of this event among elderly individuals living in their own homes was demonstrated. This finding was similar to what has been found in other studies conducted in Brazil and worldwide that also used Fried's phenotype: 12.8%,[6] 14.8%,[25] 10%[26] and 14%.[27] However, it differed from others that have identified higher prevalences (47%[28] and 65.25%[29]) through using the Tilburg Frailty Indicator (TFI) concept and instrument.

This divergence of results was expected, given that the prevalence of frailty may vary according to the diagnostic instrument,

Table 1. Absolute and percentage frequency distributions of the sociodemographic and health variables of the elderly subjects, according to their frailty phenotype classification; Brazil, 2016

Variables		Frailty phenotype			Total % (n)	P*
		Non-frail % (n)	Pre-frail % (n)	Frail % (n)		
Gender	Male	30.4 (55)	34.4 (111)	25.0 (19)	31.9 (185)	0.252
	Female	69.6 (126)	65.6 (212)	75.0 (57)	68.1 (395)	
Age group (in years)	60 to 69	59.1 (107)	39.3 (127)	28.9 (22)	44.1 (256)	< 0.001
	70 to 79	35.4 (64)	42.4 (137)	38.2 (29)	39.7 (230)	
	80 or older	5.5 (10)	18.3 (59)	32.9 (25)	16.2 (94)	
Marital status	Companion	48.1 (87)	52.6 (170)	47 (61.8)	304 (52.4)	0.130
	No companion	51.9 (94)	47.4 (153)	29 (38.2)	276 (47.6)	
Education (years of schooling)	No education	11.6 (21)	16.1 (52)	23.7 (18)	15.7 (91)	0.008
	1 to 4	47.5 (86)	55.7 (180)	51.3 (39)	52.6 (305)	
	5 or more	40.9 (74)	28.2 (91)	25.0 (19)	31.7 (184)	
Monthly income	No income	11.6 (21)	9.0 (29)	5.3 (4)	9.3 (54)	0.132
	≤ 1 minimum wage	39.8 (72)	44.6 (144)	56.6 (43)	44.7 (259)	
	> 2 minimum wages	48.6 (88)	46.4 (150)	38.2 (29)	46.0 (267)	
Number of morbidities	0	4.4 (8)	1.3 (4)	0 (0)	2.1 (12)	0.013
	1 to 4	37.6 (68)	36.8 (119)	25.0 (19)	35.5 (206)	
	5 or more	58.0 (105)	61.9 (200)	75.0 (57)	62.4 (362)	

*Chi-square test.

methodological standardization, plurality of existing concepts and variability of sample composition.[30] A systematic review by Collard et al. showed that there was marked variation in the prevalence of frailty among community-dwelling older people, from 4.0% to 59.1%.[31] These data emphasize the need for these differences to be considered not only by healthcare professionals in evaluating older

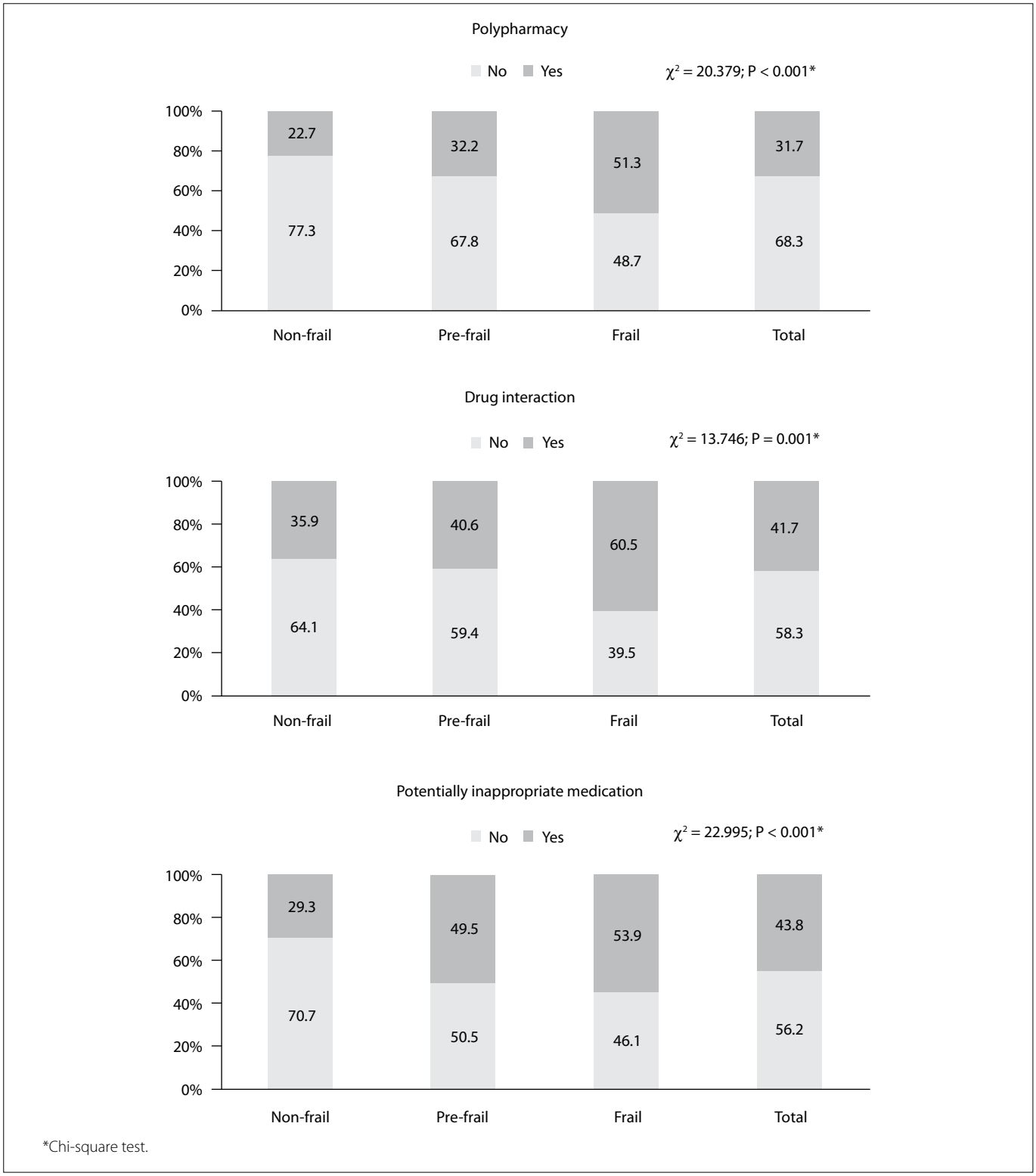

Figure 1. Occurrences (%) of polypharmacy, drug interaction and use of potentially inappropriate medication for elderly people, according to the frailty phenotype classification; Brazil, 2016.

people within clinical practice but also by managers in formulating public health policies.[31]

Since drug prescription is a participant in the frailty process, its quality requires special attention from healthcare professionals. The aging process makes older people more susceptible to developing chronic conditions, which eventually leads to use of several medications concomitantly.[9] This, together with the pharmacokinetic and pharmacodynamic changes that occur with advancing age, results in exacerbated adverse effects, especially when the frailty syndrome is present.[9,32]

These results converge with findings that were highlighted by other researchers, through demonstration of the association between polypharmacy and frailty in the initial logistic regression model.[15,16,33] According to the International Frailty Consensus, polypharmacy is a possible cause of increased pathogenesis of frailty. Hence, reduction of the use of drugs for older people is recommended, among other clinical guidelines.[7] A longitudinal study on Japanese older people found that those who used six or more drugs were at higher risk of developing frailty, in relation to the others, over a six-year period.[34] It is worth considering, however, that polypharmacy did not remain associated with an increased chance of frailty in the adjusted model of the present study, and this was also seen in other studies.[29,35] These data highlight the importance of including other variables associated with evaluation of the quality of drug use among older people within clinical practice.

The relationship between DI and frailty was also analyzed in the present study but no significant association was found, either in the initial logistic regression model or in the adjusted model. Pagno et al. found that 52.2% of the older people were exposed to DIs, which was a result similar to that of the present study. They also found that most older people with DIs were classified as frail (68.2%) and demonstrated that exposure of older people to DIs increased the chance of this outcome. However, they did not carry out multivariate analysis with adjustment for other variables.[33] It is important to note that most of the researchers who have evaluated DIs among older people did not consider frailty to be a factor associated with this event, as seen in an integrative review of the literature conducted by Rodrigues and Oliveira.[3] Hence, there is a need for further clarification of this relationship through additional studies.

In the current study, use of PIMs was the independent variable that explained the increased chances of occurrence of frailty, thus confirming other findings that have been described in the literature.[33,36-39] The hypotheses that might contribute towards understanding this association include the following:

a) Use of PIMs can worsen older people's clinical state, thereby interfering with their quality of life and increasing the magnitude of adverse health outcomes;[12,33] and these occurrences are exacerbated when frailty syndrome is present.[9,13,14]
b) Among the adverse outcomes relating to use of PIMs, a strong association with functional decline has been shown;[36] this is significantly correlated with frailty syndrome, as shown by Fried et al.[1]
c) PIMs can affect the components that are measured in the frailty phenotype, such as weakness, low gait speed or low levels of physical activity.[1,36]

The findings of the current study demonstrated that use of PIMs was highly prevalent among these community-dwelling

Table 2. Logistic regression models to verify associations among polypharmacy, drug interaction and use of potentially inappropriate medications in relation to the elderly frailty phenotype, Brazil, 2016

		Pre-frail/frail		Pre-frail/frail	
		Initial model		Adjusted final model	
		OR	CI	OR	CI
Polypharmacy	No	1	1	1	1
	Yes	**1.91‡**	**1.27-2.86‡**	1.23	0.69-2.19
DI	No	1	1	1	1
	Yes	1.42	0.99-2,04	0.77	0.46-1.28
PIM	No	1	1	1	1
	Yes	**2.45‡**	**1.68-3.57‡**	**2.33‡**	**1.47-3.70‡**
Gender	Female	-	-	1	1
	Male	-	-	0.79	0.52-1.21
Age	-	-	-	**1.08‡**	**1.05-1.11‡**
Education	No education				
	1 to 4 years			0.79	0.58-1.04
Number of diseases	-	-	-	1.04	0.98-1.11

Reference category = non-frail; ‡P < 0.001; 1 = reference category.
OR = odds ratio; CI = confidence interval; DI = drug interactions.

older people and that its presence was associated with occurrences of frailty. These findings are concordant with the clinical guidance for management of frailty, in which reduction or deprescription of potentially inappropriate medication for older adults is strongly recommended.[40] Curtin et al. used the STOPPFrail criteria and demonstrated that this is a tool that removes an important barrier against deprescription of medications through explicitly highlighting the circumstances in which commonly used medications can be safely deprescribed among older people with advanced frailty.[41]

Professionals working within primary healthcare are in closer contact with community-dwelling older people and, therefore, should incorporate evaluation of use of PIMs in their overall routine for geriatric assessment. In this regard, the International Frailty Consensus recommends use of the Beers and STOPPFrail criteria within clinical practice. When use of PIMs is identified, the older individuals presenting this usage should be referred for medical evaluation, in order to optimize their medication treatment and, therefore, prevent frailty syndrome. Lavan et al. found that almost 65% of their patients awaiting long-term care were eligible for application of the STOPPFrail criteria, such that over 90% of these had been prescribed at least one PIM. They concluded that the transition to nursing-home care represented an opportunity to review the therapeutic appropriateness and goals of the medications that had been prescribed for these individuals.[42]

Although use of PIMs was the only explanatory independent variable for frailty syndrome in the present study, the importance of evaluating polypharmacy and DIs cannot be overlooked. It is known that both the presence of PIM and the presence of polypharmacy tend to make frail older people more prone to negative events, such as increased risk of adverse effects, mostly coming from DIs. These relationships can be explained in terms of the changes and features present in frail older people that make them more vulnerable to manifestations of DIs and health problems arising from them.[33,43,44]

In addition, several studies have shown that use of multiple medications is associated with use of PIMs.[38,45-51] Other authors have shown, however, that the risk of using PIMs is greater among individuals with higher numbers of morbidities and who, thus, have to use more drugs.[48,52,53] Pagno et al. also identified that the prevalence of frailty was higher in the presence of PIMs that were involved in DIs.[33] Moreover, Lorenzo-López et al. confirmed the dynamics of frailty and the bidirectional nature of frailty transitions, thus indicating the need for prevention and treatment of these conditions in later life, in order to minimize the burden of frailty.[54]

The findings from the present study need to be considered cautiously due to its cross-sectional nature, which did not allow cause-and-effect relationships to be established among the variables. Moreover, it needs to be borne in mind that a self-report questionnaire was used to investigate morbidities, which meant that some of the information found may have been underestimated or overestimated. Therefore, use of cohort studies among community-dwelling older people is suggested, in order to assess the effect of interactions among the variables of DI, PIM and polypharmacy, regarding occurrences of frailty syndrome.

CONCLUSION

It was found that use of inappropriate medications was the independent variable that explained the occurrences of frailty in this representative sample of community-dwelling older people in a Brazilian municipality. However, this study showed that there is a need for research with a longitudinal design, in order to assess the causality of these conditions in relation to frailty.

Nevertheless, the data obtained in this study constitute an advance in this field of knowledge, since they indicate the need for advanced practices, with application of explicit methods for evaluation of drug use within primary healthcare, with a view to improving the quality of life of older people living in their own homes. Thus, in clinical practice, accurate analysis with the use of validated tools and technologies for monitoring and recognition of polypharmacy, potential drug interactions and inappropriate use of drugs can optimize the adequacy of prescription and hence minimize problems relating to these medications, thereby diminishing the onset of frailty.

REFERENCES

1. Fried LP, Tangen CM, Walston J, et al. Frailty in older adults: evidence for a phenotype. J Gerontol. 2001;56(3):M146-56. PMID: 11253156; doi: 10.1093/gerona/56.3.M146.
2. Fabrício-Wehbe SC, Rodrigues RA, Haas VJ, et al. Association of frailty in hospitalized and institutionalized elderly in the community-dwelling. Rev Bras Enferm. 2016;69(4):691-6. PMID: 27508474; doi: 10.1590/0034-7167.20166904l1i.
3. Rodrigues MCS, Oliveira CD. Drug-drug interactions and adverse drug reactions in polypharmacy among older adults: an integrative review. Rev Lat Am Enfermagem. 2016;24:e2800. PMID: 27598380; doi: 10.1590/1518-8345.1316.2800.
4. Davies EA, O'Mahony MS. Adverse drug reactions in special populations – the elderly. Br J Clin Pharmacol. 2015;80(4):796-807. PMID: 25619317; doi: 10.1111/bcp.12596.
5. Lana LD, Schneider RH. The frailty syndrome in elderly: a narrative review. Rev Bras Geriatr Gerontol. 2014;17(3):673-80. doi: 10.1590/1809-9823.2014.12162.
6. Pegorari MS, Tavares DMS. Fatores associados à síndrome de fragilidade em idosos residentes em área urbana. Rev Latino-Am Enfermagem. 2014;22(5):874-82. doi: 10.1590/0104-1169.0213.2493.

7. Morley JE, Vellas B, Van Kan GA, et al. Frailty consensus: a call to action. J Am Med Dir Assoc. 2013;14(6):392-7. PMID: 23764209; doi: 10.1016/j.jamda.2013.03.022.
8. Hovstadius B, Petersson G. Factors leading to excessive polypharmacy. Clin Geriatr Med. 2012;28(2):159-72. PMID: 22500536; doi: 10.1016/j.cger.2012.01.001.
9. Poudel A, Peel NM, Nissen LM, et al. Adverse Outcomes in Relation to Polypharmacy in Robust and Frail Older Hospital Patients. J Am Med Dir Assoc. 2016;17(8):767.e9-767.e13. PMID: 27373672; doi: 10.1016/j.jamda.2016.05.017.
10. Gnjidic D, Hilmer SN. Use of potentially inappropriate medications in the care of frail older people. Aging Health. 2010;6(6):705-16. doi: 10.2217/ahe.10.78.
11. Oates JA. The science of drug therapy. In: Brunton LL. Goodman & Gilman's The pharmacological basis of therapeutics**.** 11th ed. New York: McGraw-Hill; 2006. p. 77.
12. Oliveira MG, Amorim WW, Oliveira CRB, et al. Consenso brasileiro de medicamentos potencialmente inapropriados para idosos [Brazilian consensus of potentially inappropriate medication for elderly people]. Geriatr Gerontol Aging. 2016; 10(4): 168-181; doi: 10.5327/z2447-211520161600054.
13. Lavan AH, O'Mahony D, Gallagher P. STOPPFrail (Screening Tool of Older Persons' Prescriptions in Frail adults with a limited life expectancy) criteria: application to a representative population awaiting long-term nursing care. Eur J Clin Pharmacol. 2019;75(5):723-31. PMID: 30685856; doi: 10.1007/s00228-019-02630-3.
14. Granas AG, Stendal Bakken M, Ruths S, Taxis K. Deprescribing for frail older people - Learning from the case of Mrs. Hansen. Res Social Adm Pharm. 2018;14(6):612-6. PMID: 28733142; doi: 10.1016/j.sapharm.2017.07.003.
15. Saum KU, Schöttker B, Meid AD, et al. Is Polypharmacy Associated with Frailty in Older People? Results from the ESTHER Cohort Study. J Am Geriatr Soc. 2016;65(2):e27-e32. PMID: 28024089; doi: 10.1111/jgs.14718.
16. Veronese N, Stubbs B, Noale M, et al. Polypharmacy is associated with higher frailty risk in older people: an 8-year longitudinal cohort study. J Am Med Dir Assoc. 2017;18(7):624-8. PMID: 28396180; doi: 10.1016/j.jamda.2017.02.009.
17. Woodford HJ, Fisher J. New horizons in deprescribing for older people. Age Ageing. 2019;48(6):768-75. PMID: 31595290; doi: 10.1093/ageing/afz109.
18. Brasil. Lei nº 10.741 de 01 de outubro de 2003. Dispõe sobre o Estatuto do Idoso e dá outras providências. Diário Oficial da União, Brasília. Available from: http://www.planalto.gov.br/ccivil_03/leis/2003/l10.741.htm. Accessed in 2020 (Jul 2).
19. Bertolucci PHF, Brucki SMD, Campacci SR, et al. O Mini-Exame do Estado Mental em uma população geral: impacto da escolaridade [The Mini-Mental State Examination in an outpatient population: influence of literacy]. Arq Neuro-Psiquiatr. 1994;52(1):01-07. doi: 10.1590/S0004-282X1994000100001.
20. Tavares DMDS, Pelizaro PB, Pegorari MS, Paiva MM, Marchiori GF. Prevalência de morbidades autorreferidas e fatores associados entre idosos comunitários de Uberaba, Minas Gerais, Brasil [Prevalence of self-reported morbidities and associated factors among community-dwelling elderly in Uberaba, Minas Gerais, Brazil]. Cien Saude Colet. 2019;24(9):3305-3313. doi: 10.1590/1413-81232018249.31912017.
21. Batistoni SST, Neri AL, Cupertino APFB. Validade da escala de depressão do Center for Epidemiological Studies entre idosos brasileiros [Validity of the Center for Epidemiological Studies Depression Scale Among Brazilian Elderly]. Rev Saude Publica. 2007;41(4):598-605. PMID: 17589758; doi: 10.1590/S0034-89102007000400014.
22. Mazo GZ, Benedetti TRB. Adaptação do questionário internacional de atividade física para idosos [Adaptation of the international physical activity questionnaire for the elderly]. Rev Bras Cineantropom Desempenho Hum**.** 2010;12(6):480-4. doi: 10.1590/S1980-00372010000600013.
23. Pate RR, Pratt M, Blair SN, et al. Physical activity and public health. A recommendation from the Centers for Disease Control and Prevention and the American College of Sports Medicine. JAMA. 1995;273(5):402-7. PMID: 7823386; doi: 10.1001/jama.1995.03520290054029.
24. Micromedex Health care Series [Internet]. Greenwood Village: Thomson Reuters (Healthcare); 2011. Available from: https://www.micromedexsolutions.com/home/dispatch. Accessed in 2020 (Jul 27).
25. Herr M, Sirven N, Grondin H, Pichetti S, Sermet C. Frailty, polypharmacy, and potentially inappropriate medications in old people: findings in a representative sample of the French population. Eur J Clin Pharmacol. 2017;73(9):1165-72. PMID: 28601963; doi: 10.1007/s00228-017-2276-5.
26. Yamada Y, Nanri H, Watanabe Y, et al. Prevalence of Frailty Assessed by Fried and Kihon Checklist Indexes in a Prospective Cohort Study: Design and Demographics of the Kyoto-Kameoka Longitudinal Study. J Am Med Dir Assoc. 2017;18(8):733.e7-733.e15. PMID: 28501417; doi: 10.1016/j.jamda.2017.02.022.
27. Gale CR, Cooper C, Sayer AA. Prevalence of frailty and disability: findings from the English Longitudinal Study of Ageing. Age Ageing. 2015;44(1):162-5. PMID: 25313241; doi: 10.1093/ageing/afu148.
28. Gobbens RJ, Van Assen MA, Luijkx KG, Wijnen-Sponselee MT, Schols JM. Determinants of Frailty. J Am Med Dir Assoc. 2010;11(5):356-64. PMID: 20511103; doi: 10.1016/j.jamda.2009.11.008.
29. Neves AQ, Silva AMC, Cabral JF, et al. Prevalence of and factors associated with frailty in elderly users of the Family Health Strategy. Rev Bras Geriatr Gerontol. 2018;21(6):680-90. doi: 10.1590/1981-22562018021.180043.
30. Carneiro JA, Ramos GC, Barbosa AT, et al. Prevalência e fatores associados à fragilidade em idosos não institucionalizados [Prevalence and factors associated with frailty in non-institutionalized older adults]. Rev. Bras. Enferm**.** 2016;69(3):435-42. PMID: 27355291; doi: https://doi.org/10.1590/0034-7167.2016690304i.

31. Collard RM, Boter H, Schoevers RA, Oude Voshaar RC. Prevalence of frailty in community-dwelling older persons: a systematic review. J Am Geriatr Soc. 2012; 60(8):1487-92. PMID: 22881367; doi: 10.1111/j.1532-5415.2012.04054.x.
32. Hubbard RE, O'Mahony MS, Woodhouse KW. Medication prescribing in frail older people. Eur J Clin Pharmacol, 2013;69(3):319-26. PMID: 22965651; doi: 10.1007/s00228-012-1387-2.
33. Pagno AR, Gross CB, Gewehr DM, et al. A terapêutica medicamentosa, interações potenciais e iatrogenia como fatores relacionados à fragilidade em idosos [Drug therapy, potential interactions and iatrogenesis as factors related to frailty in the elderly]. Rev Bras Geriatr Gerontol. 2018;21(5):588-96. doi: 10.1590/1981-22562018021.180085.
34. Yuki A, Otsuka R, Tange C, et al. Polypharmacy is associated with frailty in Japanese community-dwelling older adults. Geriatr Gerontol Int. 2018;18(10):1497-500. PMID: 30168240; doi: 10.1111/ggi.13507.
35. Santiago LM, Mattos IE. Prevalência e fatores associados à fragilidade em idosos institucionalizados das regiões Sudeste e Centro-Oeste do Brasil [Prevalence and factors associated to frailty in institutionalized elderly of Southeastern and Middle-Western Brazil]. Rev Bras Geriatr Gerontol. 2014;17(2):327-37. doi: 10.1590/S1809-98232014000200010.
36. Muhlack DC, Hoppe LK, Stock C, et al. The associations of geriatric syndromes and other patient characteristics with the current and future use of potentially inappropriate medications in a large cohort study. Eur J Clin Pharmacol. 2018;74(12):1633-44. PMID: 30159676; doi: 10.1007/s00228-018-2534-1.
37. Cullinan S, O'Mahony D, O'Sullivan D, Byrne S. Use of a frailty index to identify potentially inappropriate prescribing and adverse drug reaction risks in older patients. Age Ageing. 2016;45(1):115-20. PMID: 26683048; doi: 10.1093/ageing/afv166.
38. Cassoni TC, Corona LP, Romano-Lieber NS, et al. Uso de medicamentos potencialmente inapropriados por idosos do Município de São Paulo, Brasil: Estudo SABE [Use of potentially inappropriate medication by the elderly in São Paulo, Brazil: SABE Study]. Cad. Saude Publica. 2014;30(8):1708-20. PMID: 25210910; doi: 10.1590/0102-311x00055613.
39. Bolina AF, Gomes NC, Marchiori GF, Pegorari MS, Tavares DMDS. Potentially inappropriate medication use and frailty phenotype among community-dwelling older adults: A population based study. J Clin Nurs. 2019;28(21-22):3914-22. PMID: 31240751; doi: 10.1111/jocn.14976.
40. Dent E, Lien C, Lim WS, et al. The Asia-Pacific clinical practice guidelines for the management of frailty [published correction appears in J Am Med Dir Assoc. 2018 Jan;19(1):94]. J Am Med Dir Assoc. 2018;18(7):564-75. PMID: 28648901; doi: 10.1016/j.jamda.2017.04.018.
41. Curtin D, Dukelow T, James K, et al. Deprescribing in multi-morbid older people with polypharmacy: agreement between STOPPFrail explicit criteria and gold standard deprescribing using 100 standardized clinical cases. Eur J Clin Pharmacol. 2019;75(1):427-32. PMID: 30421220; doi: 10.1007/s00228-018-2598-y
42. Lavan AH, Gallagher P, Parsons C, O'Mahony D. STOPPFrail (Screening Tool of Older Persons Prescriptions in Frail adults with limited life expectancy): consensus validation. Age Ageing. 2017;46(4):600-7. PMID: 28119312; doi: 10.1093/ageing/afx005.
43. Secoli SR. Polifarmácia: interações e reações adversas no uso de medicamentos por idosos [Polypharmacy: interaction and adverse reactions in the use of drugs by elderly people]. Rev Bras Enferm. 2010;63(1):136-40. PMID: 20339769; doi: 10.1590/S0034-71672010000100023.
44. Vieira RA, Guerra RO, Giacomin KC, et al. Prevalência de fragilidade e fatores associados em idosos comunitários de Belo Horizonte, Minas Gerais, Brasil: dados do estudo FIBRA. [Prevalence of frailty and associated factors in community-dwelling elderly in Belo Horizonte, Minas Gerais State, Brazil: data from the FIBRA study] [published correction appears in Cad Saude Publica. 2013 Nov;29(11):2357]. Cad Saude Publica. 2013;29(8):1631-43. PMID: 24005928; doi: 10.1590/0102-311X00126312.
45. Baldoni Ade O, Ayres LR, Martinez EZ, et al. Factors associated with potentially inappropriate medications use by the elderly according to Beers criteria 2003 and 2012. Int J Clin Pharm. 2014; 36(2):316-24. PMID: 24271923; doi: 10.1007/s11096-013-9880-y.
46. Buck MD, Atreja A, Brunker CP, et al. Potentially inappropriate medication prescribing in outpatient practices: prevalence and patient characteristics based on electronic health records. Am J Geriatr Pharmacother. 2009;7(2):84-92. PMID: 19447361; doi: 10.1016/j.amjopharm.2009.03.001.
47. Gallagher PF, Barry PJ, Ryan C, Hartigan I, O'Mahony D. Inappropriate prescribing in an acutely ill population of elderly patients as determined by Beers' Criteria. Age Ageing, 2008;37(1):96-101. PMID: 17933759; doi: 10.1093/ageing/afm116.
48. Gallagher P, Lang PO, Cherubini A, et al. Prevalence of potentially inappropriate prescribing in an acutely ill population of older patients admitted to six European hospitals. Eur J Clin Pharmacol. 2011;67(11):1175-88. PMID: 21584788; doi: 10.1007/s00228-011-1061-0.
49. Gavilán ME, Morales Suárez-Varela MT, Hoyos Esteban JA, Pérez Suanes AM. Polimedicación y prescripción de fármacos inadecuados en pacientes ancianos inmovilizados que viven en la comunidad [Inappropriate multiple medication and prescribing of drugs in immobile elderly patients living in the community]. Aten Primaria. 2006;38(9):476-82. PMID: 17194349; doi: 10.1157/13095047.
50. Holguín-Hernández E, Orozco-Díaz JG. Medicación potencialmente inapropiada en ancianos en un hospital de primer nivel, Bogotá 2007 [Potentially inappropriate medication in elderly in a first level hospital, Bogota 2007]. Rev Salud Publica (Bogota). 2010;12(2):287-99. PMID: 21031239; doi: 10.1590/s0124-00642010000200012.
51. Oliveira MG, Amorim WW, de Jesus SR, Rodrigues VA, Passos LC. Factors associated with potentially inappropriate medication use by the elderly in the Brazilian primary care setting. Int J Clin Pharm. 2012;34(4):626-32. PMID: 22692715; doi: 10.1007/s11096-012-9656-9.

52. Blalock SJ, Byrd JE, Hansen RA, et al. Factors associated with potentially inappropriate drug utilization in a sample of rural community-dwelling older adults. Am J Geriatr Pharmacother. 2005;3(3):168-79. PMID: 16257819; doi: 10.1016/S1543-5946(05)80023-6
53. Rozenfeld S, Fonseca MJ, Acurcio FA. Drug utilization and polypharmacy among the elderly: a survey in Rio de Janeiro City, Brazil. Rev Panam Salud Publica, 2018;23(1):34-43. PMID: 18291071; doi: 10.1590/s1020-49892008000100005.
54. Lorenzo-López L, López-López R, Maseda A, et al. Changes in frailty status in a community-dwelling cohort of older adults: The VERISAÚDE study. Maturitas, 2019;119:54-60. PMID: 30502751; doi: 10.1016/j.maturitas.2018.11.006.

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Inequalities in mammography and Papanicolaou test coverage: a time-series study

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ABSTRACT

BACKGROUND: Cancer is a serious public issue problem worldwide. In Brazil, breast cancer is the most common type and cervical cancer is the third most frequent among women.

OBJECTIVE: To analyze the temporal trend of coverage of mammography and cervical oncotic cytological testing, between 2007 and 2018.

DESIGN AND SETTING: Time-series study conducted in the 26 Brazilian state capitals and in the Federal District.

METHODS: A linear regression model was used to estimate trends in coverage of mammography and cervical oncotic cytological testing over the period. The data collection system for Surveillance of Risk and Protection Factors for Chronic Diseases by Telephone Survey (Vigitel) was used.

RESULTS: A significant increase in mammography coverage was observed, from 71.1% in 2007 to 78.0% in 2018. There was a trend towards an increase among women with 0 to 8 years of schooling, in all regions of Brazil. Regarding cervical oncotic cytological testing coverage, there was a trend towards stability during the period analyzed, reaching 81.7% in 2018. On the other hand, there was a significant increase in the northern region.

CONCLUSIONS: There was an improvement in the coverage of these screening examinations, especially regarding mammography. However, it is still necessary to expand their provision, quality and surveillance, aimed towards women's health.

INTRODUCTION

Cancer is a serious public health issue worldwide. In Brazil, among women, the most common type is breast cancer (29.7%) and cervical cancer is the third most frequent (7.4%).[1] In 2017, there were 16,724 deaths from breast cancer and 6,385 from cervical cancer.[1] They were responsible, respectively, for the losses of 551,306.08 and 59,498.97 million disability-adjusted life years (DALYs).[2] There are also great variations in the magnitude and types of cancer across the different regions of Brazil.[1]

Brazil is expected to have 66,280 cases of breast cancer diagnosed per year between 2020 and 2022, corresponding to a rate of 61.6 diagnoses per 100,000 women. The number of new cervical cancer cases expected for the same period would be 16,590, corresponding to a rate of 15.43 per 100,000 women.[1]

Cervical and breast cancer incidence, mortality and morbidity may be reduced through effective control strategies. These should include screening programs, health promotion actions, prevention, early diagnosis, treatment, rehabilitation and palliative care, when necessary.[3]

The Brazilian National Health System (Sistema Único de Saúde, SUS) guarantees universal free access to mammography examinations and cervical cytological testing, also known as the Papanicolaou test. The Brazilian Ministry of Health recommends screening mammography for women aged 50 to 69, to be done every two years.[4]

The screening method for cervical cancer and its precursor lesions is oncotic cytological testing. Screening should start at the age of 25 for women who have already had sexual activity and periodic examinations must continue until they are 64 years old. The first two examinations should be performed at an annual interval and, if both results presented satisfactory samples and were negative for malignancy, subsequent examinations should be performed every three years.[5]

To promote development and implementation of effective, integrated, sustainable and evidence-based public policies, the federal government launched the Strategic Action Plan for Confronting Chronic Noncommunicable Diseases in Brazil, 2011-2022. Among the proposed national targets were increases in mammography coverage among women between 50 and 69 years old to 70% and in Papanicolaou test coverage among women from 25 to 64 years old to 85%; promotion of improved quality of screening tests; and treatment of 100% of women diagnosed with precursor cancer lesions. Among the actions to speed up the diagnosis, there were investments in diagnostic capacity and infrastructure, especially in the northern and northeastern regions of Brazil.[6,7]

OBJECTIVE

Thus, the objective of the present study was to analyze the temporal trends of mammography and cervical oncotic cytological test coverage, between the years 2007 and 2018.

METHODS

Study design and data collection

This study analyzed the trends in coverage of mammography and cervical oncotic cytological tests using data covering the years between 2007 and 2018 that were collected from the Surveillance of Risk and Protection Factors for Chronic Diseases by Telephone Survey (Vigitel).

Vigitel is a survey conducted through telephone calls in the Brazilian population, which annually monitors the main chronic noncommunicable diseases (NCDs) and their risk and protection factors. This survey is conducted on a representative sample of the adult population in Brazil (≥ 18 years old) living in households with at least one fixed telephone line, in each of the 26 Brazilian state capitals and in the Federal District. Every year, approximately 2,000 people answer the survey questions and, over the years in which Vigitel has been conducted, 382,255 adult women have been interviewed. Survey professionals have applied some adjustment procedures that have taken sex, age and education levels into account, with the aim of reducing the non-representation bias inherent to telephone interviews and seeking to make the sample distribution similar to the sociodemographic characteristics of the adult population of each state capital.[8] Details on the sampling and data collection process can be found in the published Vigitel results.[8,9]

Indicator definition

The mammography and cervical oncotic cytological testing coverage indicators used in the study were obtained through the following Vigitel questions:[8]

- **Percentage of women (50 to 69 years old) who underwent mammography examinations over the last two years:** a measurement of the number of women between 50 and 69 years old who underwent mammography over the last two years, derived from the number of women between these ages who were interviewed. This was in answer to the questions: "Did you ever have a mammogram breast x-ray?" and "How long ago did you have a mammogram?". These questions were only applied to women between 50 and 69 years of age because this is the age range within which breast cancer screening through mammography is recommended.
- **Percentage of women (25 to 64 years old) who underwent a Papanicolaou test for cervical cancer over the last three years:** a measurement of the number of women between 25 and 64 years old who underwent an oncotic cytological examination over the last three years, derived from the number of women between these ages who were interviewed. This was in answer to the questions: "Did you ever have a Papanicolaou test/cervical cancer screening?" and "How long has it been since you took a Papanicolaou test?"

Statistical analysis

The indicators were stratified according to schooling level (0 to 8; 9 to 11; and ≥ 12 years), Brazilian state capitals and regions (North, Northeast, Southeast, South and Center-West) and age groups for the Papanicolaou test (25 to 34; 35 to 44; 45 to 54; and 55 to 64 years) and mammography (50 to 59; and 60 to 69 years).

The dependent variables were the prevalences of mammography and cervical cytological test coverage and the independent variable was the year of the survey.

A linear regression model was used to estimate trends over the period. Significant linear trends were considered to exist when the slope of the model was different from zero for a P-value ≤ 0.05. The adjusted R^2 value was used as a measurement of model fit.

The analyses were performed using the Stata software (Stata Corp LP, College Station, United States), version 13.0. Quantum GIS (QGIS) version 3.12.0 (QGIS.org (2020); QGIS Geographic Information System; Open Source Geospatial Foundation Project) was used to build the maps.

The Vigitel data is available for public access and use. The National Commission for Research Ethics of the Ministry of Health approved collection of these survey data on human beings (number: 355.590; date: June 26, 2013). Informed consent was obtained orally, at the time of telephone contact with the interviewees.

RESULTS

Over the entire time period of the present study, there was an increase in mammography coverage performed within the last two years from 71.1% in 2007 to 78% in 2018. This represented

a growth rate of 0.741 per year (P < 0.001). Stratified according to the number of years of schooling, there was a linear trend of progression among women with 0 to 8 years of schooling, from 66.1% to 73.5% (P < 0.001), while the coverage among the other schooling-level ranges remained static. There was a tendency towards significant increases in coverage for all age groups, from 73.4% to 78.6% among women aged 50 to 59 years and from 67.2% to 76.9% for those aged 60 to 69 years. In all regions of Brazil, the trend was upward, and the northern region had the fastest growth rate (β = 1.613) among all the regions (**Table 1**).

The coverage of cervical oncotic cytological testing performed within the last three years remained static, with 82.0% in 2007 and 81.7% in 2018. There were declining trends in coverage among women with 12 or more years of schooling (β = -0.463; P < 0.001) and among those aged 25 to 34 years (β = -0.356; P = 0.003). On the other hand, there was an increase in coverage among women aged 55 to 64 years (β = 0.402; P < 0.001). For all regions of Brazil, the coverage remained static (**Table 2**).

Figures 1 and **2** show maps of the distribution of mammography and cervical cytological testing coverage in all the Brazilian state capital cities and the Federal District. Mammography coverage above 70%, considering the entire period (2007 to 2018), was found in Aracaju, Belo Horizonte, Campo Grande, Curitiba, Florianópolis, Goiânia, Porto Alegre, Salvador, São Paulo, Teresina and Vitória (**Figure 1**). Regarding cervical oncotic cytological testing, coverage above 85% was only found in Curitiba, Palmas, Porto Alegre and São Paulo (**Figure 2**).

Table 1. Temporal trends of mammography coverage among women (50 to 69 years old) over the last two years in the Brazilian state capitals and in the Federal District, according to sociodemographic characteristics. Vigitel; 2007 to 2018 (n = 385,255)

	Variables	2007	2008	2009	2010	2011	2012	2013	2014	2015	2016	2017	2018	P-value	Angular coefficient (β)
	Total	71.1	71.7	72.4	73.4	74.4	77.4	78.0	77.8	78.1	78.2	78.5	78.0	< 0.001	0.741
Education (years)	0-8	66.1	66.5	66.4	67.5	67.8	71.4	72.9	71.8	71.9	71.2	72.3	73.5	< 0.001	0.709
	9-11	77.3	77.6	79.4	77.3	80.5	81.8	81.4	80.9	81.5	82.4	81.9	77.6	0.075	0.297
	≥ 12	87.6	88.8	87.9	87.8	87.6	90	88.3	91.8	89.3	90.5	87.3	87.9	0.457	0.092
Age range	50-59	73.4	74.2	74.1	75.9	77.3	79.7	79.6	78.8	79.8	78.0	79.9	78.6	< 0.001	0.558
	60-69	67.2	67.3	69.8	69.3	69.9	73.7	75.3	76.3	75.6	78.5	76.1	76.9	< 0.001	1.046
Region	North	60.2	59.0	60.3	63.7	64.4	70.7	70.9	70.9	72.6	77.5	72.4	74.4	< 0.001	1.613
	Northeast	71.6	71.6	70.9	71.9	72.6	76.9	77.1	76.4	77.4	77.6	78.3	76.2	< 0.001	0.688
	Center-West	72.3	70.0	69.6	79.2	72.9	73.4	79.6	78.2	79.6	79.2	79.6	75.6	0.014	0.748
	Southeast	70.9	73.0	74.5	73.4	75.7	78.2	78.3	78.4	78.3	77.8	78.9	79.2	< 0.001	0.700
	South	79.2	76.2	76.3	79.9	81.7	84.5	82.7	83.4	81.6	81.2	80.5	82.0	0.050	0.404

Table 2. Temporal trends of cervical oncotic cytological testing coverage among women (25 to 64 years old) over the last three years in the Brazilian state capitals and the Federal District, according to sociodemographic characteristics. Vigitel; 2007 to 2018 (n = 385,555)

	Variables	2007	2008	2009	2010	2011	2012	2013	2014	2015	2016	2017	2018	P-value	Angular coefficient (β)
	Total	82.0	83.3	82.2	82.2	81.8	82.3	82.9	81.4	81.0	82.0	82.8	81.7	0.329	-0.055
Education (years)	0-8	78.6	80	77.7	78.7	77.6	78.3	78.3	77	77.8	76.7	79.5	79.3	0.692	-0.035
	9-11	83.7	83.7	83.1	81.3	81.6	81.7	83.7	81.1	80.1	82.6	83.0	80.1	0.086	-0.192
	≥ 12	87.9	90.2	89.2	89.7	88.5	88.5	87.3	86.2	84.9	85.9	85.4	84.8	< 0.001	-0.463
Age range	25-34	77.6	80.2	78.2	78.1	78.4	78.2	78.8	76.8	75.1	75.9	76.6	74.5	0.003	-0.356
	35-44	86.0	86.5	85.2	83.9	83.9	84.3	85.2	82.5	83.9	86.1	85.7	84.9	0.586	-0.057
	45-54	85.6	85.6	84.6	87.2	85.0	85.0	86.5	85.7	83.9	85.8	87.1	85.7	0.683	0.035
	55-64	78.2	80.5	81.7	80.5	80.5	83.5	81.8	82.5	83.3	82	83.8	84.1	< 0.001	0.402
Region	North	78.6	79.9	78.1	80.0	77.0	78.4	81.2	79.3	81.9	81.7	82.9	82.1	0.006	0.384
	Northeast	75.7	78.2	75.3	76.5	75.3	75.5	76.5	75.4	75	75.8	76.1	74.7	0.148	-0.114
	Center-West	80.3	79.3	80.8	78.3	78.6	81.5	79.5	79.1	77.6	79.8	80.2	79.4	0.645	-0.045
	Southeast	85.5	87.1	86.3	85.6	86.1	86.5	86.8	84.5	83.9	84.9	86.5	85.5	0.241	-0.099
	South	87.5	87.6	87.6	88.8	88.0	86.4	88.3	89.2	87.6	89.5	87.4	86.8	0.889	0.012

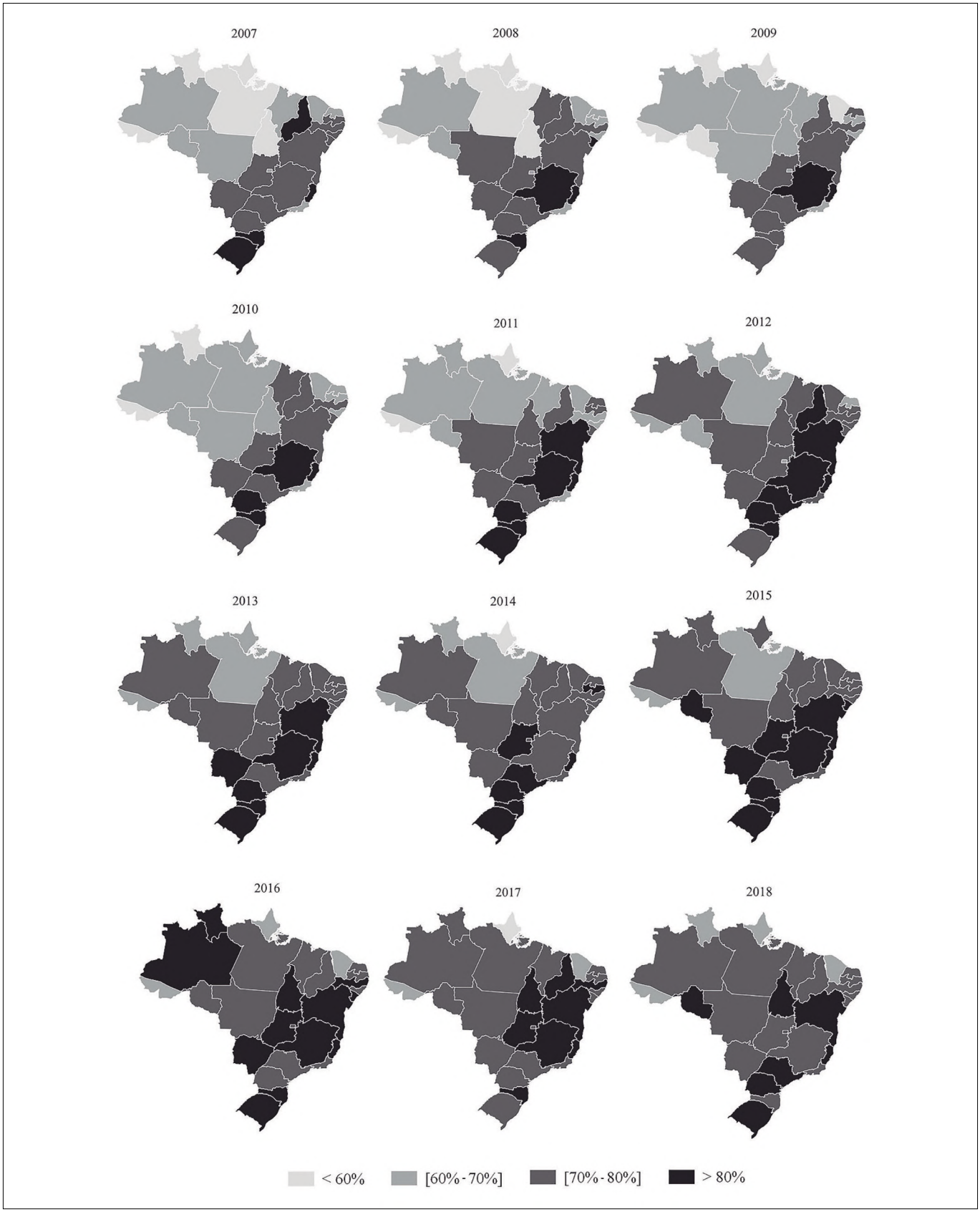

Figure 1. Frequencies of mammography coverage among women (50 to 69 years old) over the last two years in the Brazilian state capitals and in the Federal District. Vigitel; 2007 to 2018 (n = 385,555).

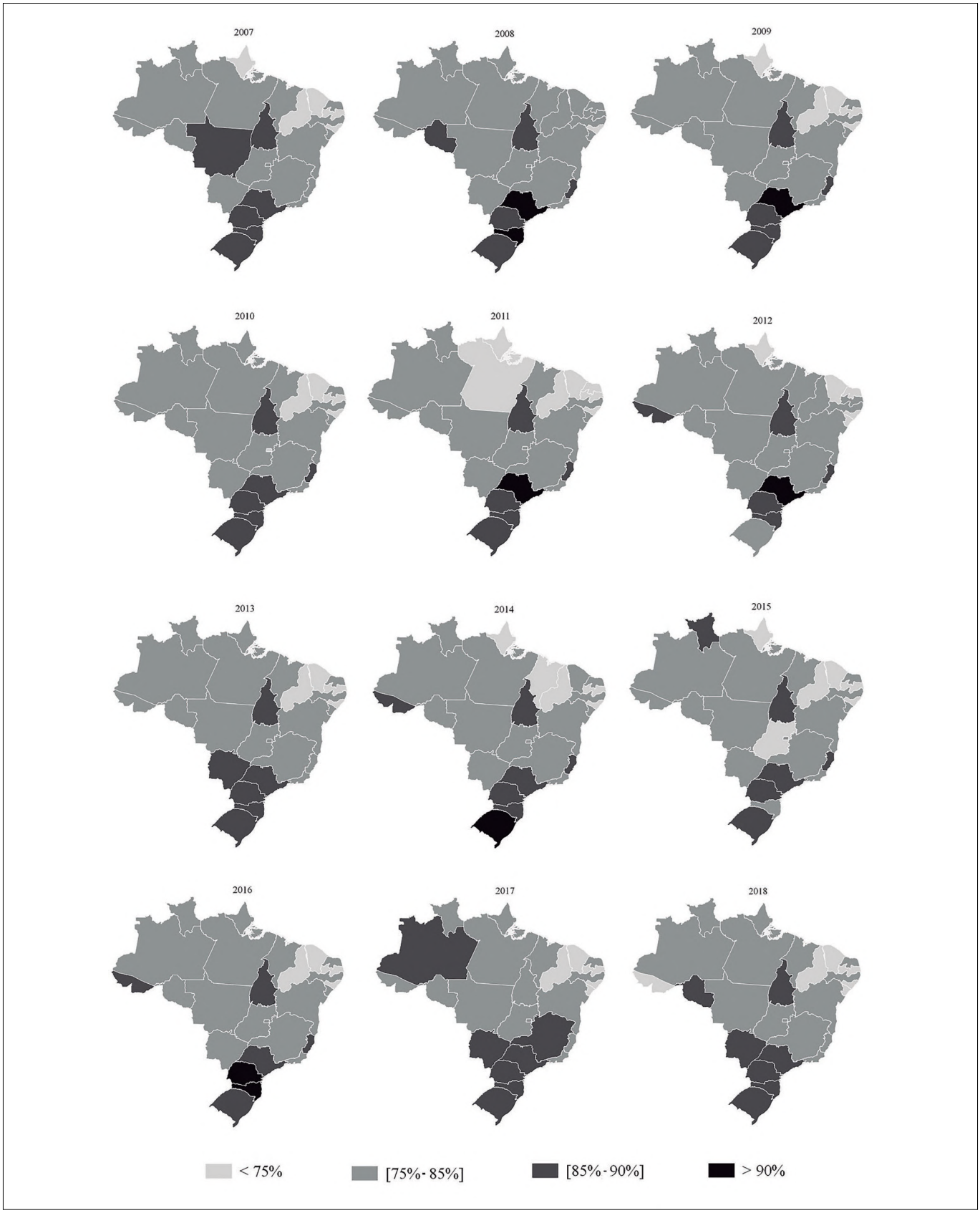

Figure 2. Frequencies of cervical oncotic cytological testing coverage among women (25 to 64 years old) over the last three years in the Brazilian state capitals and the Federal District. Vigitel; 2007 to 2018 (n = 385,255).

DISCUSSION

This study showed that there were increases in mammography coverage between 2007 and 2018 among women with less education, for all age groups and regions of Brazil. Regarding cervical oncotic cytological testing, the tendency was for static coverage when considering the entire period. There were declining trends among women with 12 or more years of schooling and aged 25 to 34 years. The trends were upward among women aged 55 to 64 years and static for all regions.

The World Health Organization (WHO) advocates strategies for screening and early detection of cancer among women.[10] Implementation of population-based breast cancer screening programs in developed countries has resulted in a 20% reduction in breast cancer morbidity and mortality.[10] The Brazilian guidelines indicate mammography only for women aged 50 to 69 years, with two-year frequency.[1] Mammography conducted among women aged 40 to 49 years presents lower detection sensitivity because of higher breast density at these ages, thus generating a greater number of false-positive results, with unnecessary exposure to radiation, surgical procedures and other events such as psychological distress and invasive examinations.[1] Thus, the Brazilian Ministry of Health and the National Cancer Institute (INCA) contraindicate mammography in this age group, in the belief that the risks outweigh the benefits.[4]

There is no consensus regarding this contraindication among different countries and medical associations. In Brazil, the Brazilian Federation of Gynecology and Obstetrics (Federação Brasileira das Associações de Ginecologia e Obstetrícia, FEBRASGO) recommends that this screening test should be done annually in the 40 to 69 age group, which could explain the high number of women undergoing mammography under 50 years of age.[11] On the other hand, the Swiss Medical Council does not recommend any mammographic screening program in any age group because it considers that the benefit is small and questionable.[4]

It is also noteworthy that the most recent evidence does not recommend breast self-examination, since its effectiveness has not been proven and health risks associated with this practice have been demonstrated.[1] Analysis on data from the Global Burden of Disease study indicated that mortality remained stable from 1990 to 2015 in Brazil and its states. There was no significant increase in any of the states in the northern and northeastern regions.[12] The increase in mammography coverage may explain the stability in mortality rates, but attention needs to be drawn to the worse performance in the northern and northeastern regions. Coverage was also lower in these regions and this resulted from uneven geographical distribution of mammography devices and the lower operational capacity in these locations.

Healthcare inequalities generate different exposures to factors that determine health, illness and death.[13] It is important to advance in interventions on social determinants of health that require multisectoral and coordinated actions on the various aspects of life in different societies.[13]

Inequalities in the coverage of screening tests according to schooling level are socioeconomic determinants that can influence both the perception of risk and the behavioral factors that influence the decision to seek healthcare services. Such inequalities are of relevance with regard to access to these examinations.[14]

Although there were differences in mammography and Papanicolaou test coverage according to region and schooling level, these coverage levels were close to the targets set out in the national plan for combating noncommunicable diseases, i.e. 75 and 85% respectively.[7] These findings are a reflection of the implementation of several policies, programs, actions and strategies by the Ministry of Health over the last decade, with emphasis on the National Policy for Comprehensive Care for Women's Health, the National Policy for Oncological Care and the Plan for Strengthening the Cancer Prevention, Diagnosis and Treatment Network, which included the National Cervical and Breast Cancer Control Program and the Strategic Action Plan for Combating Chronic Noncommunicable Diseases in Brazil, 2011-2022.[15] The expansion of primary care actions and the More Doctors Program (Programa Mais Médicos) were essential for expanding the provision of actions relating to women's health and controlling cervical and breast cancers.[12]

The importance of advancing communicative and preventive actions, especially among women with lower schooling and income levels in the poorest state capitals of the country needs to be highlighted. Such actions have the aim of increasing the frequency with which women undergo examinations and their adherence to examination programs.[3] These programs, policies and actions aimed at improving women's health, together with the expansion of primary care, have also enabled greater access and knowledge of these tests for all women, regardless of income, schooling and race, thus also reducing healthcare inequalities.[3] Therefore, expanding investment in SUS is one of the solutions for reducing social disparities, and this can be understood to be a policy for reducing inequities.[17]

The results from this study present some limitations. Self-reported data collected through telephone interviews are subject to the potential for information bias. Moreover, the Vigitel results refer to the adult population living in the 26 Brazilian state capitals and the Federal District and, therefore, these results cannot be extrapolated to the entire Brazilian population. Another limitation relates to the concept of Papanicolaou test coverage. The samples need to be satisfactory and, for the coverage to be considered adequate, the initial screening must take place with two negative examinations with a one-year interval between them, so that it becomes possible to move on to examinations every three years. These data regarding the sample and two negative

results with a one-year interval were not addressed in the Vigitel questions during the telephone interview because of the specificity of the desired responses. In Brazil, obtaining access to the information needed for cervical cancer screening to be considered ideal is a challenge, given that there are no adequate surveillance mechanisms and no monitoring of the coverage of these tests. Papanicolaou examinations in Brazil are conducted in an opportunistic manner, and not through an organized scheme of surveillance and monitoring.

CONCLUSION

There was a trend of increasing mammography coverage among women aged 50 to 69 years and a static trend regarding cervical oncotic cytological testing among women aged 25 to 64 years living in Brazilian state capitals and the Federal District. However, differences in prevalence were observed, such that it was higher among better educated women and among women living in the southern and southeastern regions. Therefore, there is still a need to expand the provision, quality and availability of actions and services aimed at improving women's health and, above all, to prioritize investments in the regions that had the least coverage of these tests.

REFERENCES

1. Ministério da Saúde. Instituto Nacional de Câncer José Alencar Gomes da Silva. Estimativa 2020: incidência de câncer no Brasil. Rio de Janeiro: INCA; 2019. Available from: https://www.inca.gov.br/sites/ufu.sti.inca.local/files/media/document/estimativa-2020-incidencia-de-cancer-no-brasil.pdf. Accessed in 2020 (Jun 1).
2. Institute for Health Metrics and Evaluation. GBD Compare Data Visualization. Seattle: IHME; 2017. Available from: https://vizhub.healthdata.org/gbd-compare//. Accessed in 2020 (Jun 1).
3. Brasil. Ministério da Saúde. Secretaria de Atenção à Saúde. Departamento de Atenção Básica. Controle dos cânceres do colo do útero e da mama. 2ª ed. Brasília: Ministério da Saúde; 2013. Available from: http://bvsms.saude.gov.br/bvs/publicacoes/controle_canceres_colo_utero_2013.pdf. Accessed in 2020 (Jun 1).
4. Ministério da Saúde. Instituto Nacional de Câncer José Alencar Gomes da Silva. Diretrizes para detecção precoce do Câncer de Mama no Brasil. Rio de Janeiro: INCA; 2015. Available from: https://www.inca.gov.br/sites/ufu.sti.inca.local/files//media/document//diretrizes_deteccao_precoce_cancer_mama_brasil.pdf. Accessed in 2020 (Jun 1).
5. Ministério da Saúde. Instituto Nacional de Câncer José Alencar Gomes da Silva. Coordenação de Prevenção e Vigilância. Divisão de Detecção Precoce e Apoio à Organização de Rede. Diretrizes brasileiras para o rastreamento do câncer do colo do útero. 2ª ed. Rio de Janeiro: INCA; 2016. Available from: http://www.citologiaclinica.org.br/site/pdf/documentos/diretrizes-para-o-rastreamento-do-cancer-do-colo-do-utero_2016.pdf. Accessed in 2020 (Jun 1).
6. Brasil. Ministério da Saúde. Secretaria de Vigilância em Saúde. Departamento de Análise de Situação de Saúde. Plano de ações estratégicas para o enfrentamento das doenças crônicas não transmissíveis (DCNT) no Brasil 2011-2022. Brasília: Ministério da Saúde; 2011. Available from: http://bvsms.saude.gov.br/bvs/publicacoes/plano_acoes_enfrent_dcnt_2011.pdf. Accessed in 2020 (Jun 1).
7. Malta DC, Morais Neto OL, Silva Junior JB. Presentation of the strategic action plan for coping with chronic diseases in Brazil from 2011 to 2022. Epidemiol Serv Saúde. 2011;20(4):425-38. doi: 10.5123/S1679-49742011000400002.
8. Brasil. Ministério da Saúde. Secretaria de Vigilância em Saúde. Departamento de Análise em Saúde e Vigilância de Doenças não Transmissíveis. Vigitel Brasil 2018: vigilância de fatores de risco e proteção para doenças crônicas por inquérito telefônico: estimativas sobre frequência e distribuição sociodemográfica de fatores de risco e proteção para doenças crônicas nas capitais dos 26 estados brasileiros e no Distrito Federal em 2018. Brasília: Ministério da Saúde; 2019. Available from: https://portalarquivos2.saude.gov.br/images/pdf/2019/julho/25/vigitel-brasil-2018.pdf. Accessed in 2020 (Jun 1).
9. Bernal RTI, Iser BPM, Malta DC, Claro RM. Sistema de Vigilância de Fatores de Risco e Proteção para Doenças Crônicas por Inquérito Telefônico (Vigitel): mudança na metodologia de ponderação [Surveillance System for Risk and Protective Factors for Chronic Diseases by Telephone Survey (Vigitel): changes in weighting methodology]. Epidemiol Serv Saude. 2017;26(4):701-12. PMID: 29211136; doi: 10.5123/S1679-49742017000400003.
10. World Health Organization. Breast cancer: prevention and control. 2020. Available from: https://www.who.int/cancer/detection/breastcancer/en/index3.html. Accessed in 2020 (Jun 1).
11. Filassi JR, Ricci MD. Rastreamento e propedêutica do câncer de mama. São Paulo: Federação Brasileira das Associações de Ginecologia e Obstetrícia (FEBRASGO); 2018. (Protocolo FEBRASGO - Ginecologia, no. 79/Comissão Nacional Especializada em Mastologia).
12. Guerra MR, Bustamente-Teixeira MT, Corrêa CSL, et al. Magnitude e variação da carga da mortalidade por câncer no Brasil e Unidades da Federação, 1990 e 2015 [Magnitude and variation of the burden of cancer mortality in Brazil and Federation Units, 1990 and 2015]. Rev Bras Epidemiol. 2017;20(Suppl 1):102-15. PMID: 28658376; doi: 10.1590/1980-5497201700050009.
13. Barreto ML. Desigualdades em Saúde: uma perspectiva global [Health inequalities: a global perspective]. Cienc Saude Colet. 2017;22(7):2097-108. PMID: 28723991; doi: 10.1590/1413-81232017227.02742017.
14. de Oliveira EX, Pinheiro RS, Melo EC, Carvalho MS. Condicionantes socioeconômicos e geográficos do acesso à mamografia no Brasil, 2003-2008 [Socioeconomic and geographic constraints to access mammography in Brasil, 2003-2008]. Cienc Saude Colet. 2011;16(9):3649-64. PMID: 21987309; doi: 10.1590/s1413-81232011001000002.

15. Malta DC, Oliveira TP, Santos MA, Andrade SS, Silva MM. Avanços do Plano de Ações Estratégicas para o Enfrentamento das Doenças Crônicas não Transmissíveis no Brasil, 2011-2015 [Progress with the Strategic Action Plan for Tackling Chronic Non-Communicable Diseases in Brazil, 2011-2015]. Epidemiol Serv Saude. 2016;25(2):373-90. PMID: 27869955; doi: 10.5123/S1679-49742016000200016.
16. Barros MBA. Social inequality in health: revisiting moments and trends in 50 years of publication of RSP. Rev Saude Publica. 2017;51(17):1-8. PMID: 28355334; doi: 10.1590/S1518-8787.2017051000156.

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Prostate examination among adult and elderly subjects in southern Brazil: a cross-sectional population-based study

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ABSTRACT

BACKGROUND: Population-wide screening for prostate cancer remains a controversial topic, given the need for an individualized approach to patients regarding the risks and benefits of prostate-specific antigen testing and digital rectal examination.

OBJECTIVE: The aim of this study was to investigate the prevalence of, and factors associated with, prostate examination among men aged 45 or older.

DESIGN AND SETTING: Cross-sectional population-based study developed in the city of Rio Grande (RS), Brazil.

METHODS: The outcome of interest was a history of prostate examination (prostate-specific antigen testing or digital rectal examination). The following independent variables were analyzed: age group, skin color, marital status, schooling, economic level, leisure-time physical activity, smoking habits, excessive alcohol consumption, overweight, health insurance, visits to the doctor during the preceding year, hypertension and diabetes. After a two-stage sampling process, the final sample consisted of 281 male individuals.

RESULTS: The prevalence of a history of prostate-specific antigen testing or digital rectal examination was 68.3% (95% confidence interval (CI): 62.2 to 74.5). The highest prevalence rates were observed among men aged 70 years or older (88%) and the lowest among smokers (36%). The following characteristics were found to be associated with the outcome: advanced age; marital status other than single; more schooling and higher economic status; practicing physical activity; non-smoking habits; overweight; having health insurance; and having visited a doctor during the preceding year.

CONCLUSION: Approximately two thirds of the study population had been screened for prostate examination, mostly older individuals, with higher socioeconomic status and a healthier lifestyle.

INTRODUCTION

Population-wide screening for prostate cancer remains a controversial topic, given the need for an individualized approach to patients regarding the risks and benefits of prostate-specific antigen testing and digital rectal examination. Treatment of prostate cancer may prove challenging because of matters such as biopsy procedures, which may lead to local complications (e.g. infection); and also because of the possibility of sexual impotence and urinary incontinence secondary to treatment.[1,2]

The combination of prostate-specific antigen testing and digital rectal examination has been considered to be an effective approach, since 18% to 45% of tumors would not have been diagnosed, had one of these two methods not been performed.[3] The American Cancer Society advises that, among men whose life expectancy exceeds 10 years, screening should be done annually, through informed consent. This should be started at the age of 50 years for those at moderate risk; at the age of 45 for those at high risk (afro-descendants and individuals with a history of prostate cancer in first-degree family members at ages younger than 65 years); and at the age of 40 for those at very high risk (multiple family members diagnosed with prostate cancer before the age of 65).[4]

In an official note, in 2017, the Brazilian Society of Urology advised that from the age of 50 years onwards, the male population should seek a specialist annually, for assessment and discussion of the risks and benefits of prostate cancer screening. The Brazilian Society of Urology recommends that men aged 45 who present risk factors should undergo screening for prostate cancer; but for individuals aged 75 and older, this is valid only for those with life expectancy greater than 10 years.[2]

In guidelines issued in 2013, the American Urological Association was in favor of screening for prostate cancer among individuals aged 55 to 69 years, if they so desired, and suggested that a two-year interval between examinations would preserve the benefits and reduce overdiagnosis and false positives.[5] In 2018, the United States Preventive Services Task Force also indicate screening for the age group from 55 to 69, based on an analysis of risks versus benefits.[6]

However, like the Australian Federal Department of Health and the National Screening Committee in the United Kingdom, the Brazilian Ministry of Health does not recommend routine screening and advises that individuals in the male population who are spontaneously willing to get tested should be widely informed about the associated risks and benefits.[7,8]

In this study, we determined the profile and sociodemographic context of individuals undergoing screening for prostate cancer, along with their level of awareness regarding prostate health.

OBJECTIVES

The aim of this study was to investigate the prevalence of, and factors associated with, prostate examination among men aged 45 years or older in the city of Rio Grande (RS), Brazil.

METHODS

This was a cross-sectional population-based study, which formed part of a larger project named "Health of the population of Rio Grande". The questionnaire from this project was applied by nine trained interviewers, who were supervised by ten postgraduate students. This interview process was coordinated by two professors of postgraduate programs at the Fundação Universidade Federal do Rio Grande (FURG). The criteria for interviewer selection were the following: female sex; at least high-school education completed; available in the evenings and on the weekends; attendance at training; and approval in tests during the training. It was decided to select only female interviewers because the potential subjects were more likely to receive them and feel safer to open their houses for them. During the data collection, four interviewers continued to work until the end of the data collection and conducted about 80% out of all the interviews.

Demographic census data indicated that the target population for the study comprised 138,996 individuals aged at least 18 years.[9] The parameters used for the prevalence outcome calculation were the following: an estimated prevalence of 10% with a range of error of two percentage points and a 95% confidence interval, thus totaling 860 individuals. To this, 50% was added to account for the design effect. In relation to associated factors, the calculation was as follows: an estimated prevalence outcome of 10% with a 95% confidence interval and power of 80%. Furthermore, a prevalence ratio of 2,0 and exposure frequency range from 20% to 60% were used, thus totaling 784 subjects. To this, 50% was added to account for the design effect, which was considered to be 1.5; and, to this, another 15% was added with the aim of minimizing confounding factors. In this manner, a total sample size of 1,294 individuals was reached. To this, another 10% was added to account for possible missing of interviews or refusal to participate. Hence, the final sample size became 1,423 eligible subjects.

The sampling process was carried out in two stages, considering firstly census tracts and secondly households and individuals. Seventy-two out of the 293 eligible census tracts (25%) were systematically selected, and an average of 10 households per tract was then selected. An average of two individuals aged at least 18 years was estimated per household. Hence, the total number of 1,423 individuals corresponded to an estimate of 710 households. To minimize the design effect, more census tracts and fewer households were preferred. Further methodological details can be found elsewhere.[9]

Out of the 1,423 individuals who were found to be eligible to be included in the survey "Health of the population of Rio Grande" after the sampling process, 1,300 were interviewed. Thus, the sample loss was around 10%.

In the present study, the data analysis was restricted to eligible male individuals aged 45 years or older, living in the urban area of Rio Grande (n = 281). Those among the 1,423 individuals in the original sample who were institutionalized in nursing homes, hospitals or prisons, or who were physically and/or cognitively unable to answer the questionnaire, were excluded from the analysis.[9]

The main dependent variable was a self-reported history of prostate examination at least once in a lifetime. The secondary outcome was a history of prostate-specific antigen testing and digital rectal examination. The following independent variables were analyzed: age group, skin color, marital status, schooling, economic status, leisure-time physical activity, smoking habits, excessive alcohol consumption, overweight, health insurance, visits to the doctor during the preceding year, hypertension and diabetes. The study participants' economic status was assessed through an asset index that was determined by means of analysis on the main components of specific household goods. This index took into consideration the participants' possession of specific household goods and their household characteristics. Data on leisure-time physical activity were collected through the International Physical Activity Questionnaire and were dichotomized into "yes" or "no".[10] Excessive alcohol consumption was defined as ingestion of five or more standard drinks for men and four or more standard drinks for women on a single occasion.[11] Excess weight was defined as having a body mass index above 24.9 kg/m², based on self-reported weight and height data. Information on hypertension and diabetes was collected based on a self-reported medical diagnosis.

For data quality control, some key questions from the questionnaire were applied again to 10.5% of the sample, in order to

verify whether the interviews were really conducted. From this process, an average kappa index value of 0.80 was obtained. The questionnaires were then coded, reviewed and entered twice into the Epi-Data 3.1 software (EpiData Association, Odense, Denmark). Subsequently, the data were transferred to the Stata 11.2 statistical software package (Stata Press, College Station, Texas, United States) for exploratory analysis, transformation and categorization of variables. A univariate analysis was performed using absolute and relative frequencies. Bivariate and multivariate analyses were performed using Poisson regression, to take the effect of the sample design into consideration. The significance level was taken to be 5% in all two-tailed statistical tests.

This research project had previously been approved by the local public university research ethics committee, under the number 20/2016, dated March 18, 2016. The study volunteers signed an informed consent form to authorize their participation, or consented to this by fingerprinting the form after it had been read aloud to them.

RESULTS

The final sample size consisted of 281 male individuals aged 45 years or older (mean: 59.3 years; standard deviation (SD): 10.6; maximum age: 96 years). The sample design effect for the prostate examination variable was 1.23 (intraclass correlation coefficient = 0.02).

Most of these individuals were white (86%); were married, divorced or widowed (76%); had 0 to 8 years of schooling (56%); and were not practicing leisure-time physical activity (65%). One fifth (21%) of them were smokers; 14% had consumed alcohol in excess within the previous 30 days; 62% were overweight; 52% had health insurance; three quarters (75%) had visited a doctor during the preceding year; and 39% reported a medical diagnosis of hypertension and 12%, diabetes (**Table 1**).

The prevalence of men who had undergone prostate-specific antigen testing or digital rectal examination in their lifetimes was 68.3% (95% confidence interval (CI): 62.2 to 74.5). Of these, 45.3% (n = 87) had been tested through both methods (prostate-specific antigen testing and digital rectal examination). The highest prevalence rates of for prostate examination were observed among men aged 70 years or older (88.2%) and the lowest among smokers (36.2%) (**Table 2**). The following characteristics were found to be associated with the outcome: advanced age; being married, divorce, or widowed; having 12 or more years of schooling; having higher economic status; practicing leisure-time physical activity; non-smoking habits; overweight; having health insurance; having visited a doctor during the preceding year; and having a diagnosis of hypertension and/or diabetes (**Table 2**). However, through the adjusted analysis, the association between the outcome and hypertension and diabetes ceased to be statistically significant.

Table 1. Description of the sample of male individuals aged 45 years or older, living in the urban area of Rio Grande (RS), who either had or had not undergone prostate examinations, surveyed in 2016

Variable	n	Had undergone prostate examination (%)	Had not undergone prostate examination (%)
Age groups (years)			
45-49	60	51.7	48.3
50-59	98	66.3	33.7
60-69	72	70.8	29.2
≥ 70	51	88.2	11.8
Skin color			
White	241	69.3	30.7
Others	40	62.5	37.5
Marital status			
Single	68	47.1	52.9
Married, widowed, separated or divorced	213	75.1	24.9
Schooling (years)			
0-8	158	62.0	38.0
9-11	65	73.3	26.7
≥ 12	57	82.5	17.5
Economic status (in terciles)			
Poorest	94	54.3	45.7
Intermediate	82	73.3	26.7
Richest	105	82.5	17.5
Leisure-time physical activity			
No	183	59.6	40.4
Yes	97	85.6	14.4
Smoking habit			
No	223	76.7	23.3
Yes	58	32.6	67.4
Excessive alcohol consumption			
No	242	69.0	31.0
Yes	38	63.2	36.8
Overweight			
No	105	55.2	44.8
Yes	173	75.7	24.3
Health insurance			
No	134	52.2	47.8
Yes	147	83.0	17.0
Visit to a doctor during the preceding year			
No	71	43.7	56.3
Yes	210	76.7	23.3
Hypertension			
No	172	62.2	37.8
Yes	109	78.0	22.0
Diabetes			
No	248	66.5	33.5
Yes	33	81.8	18.2
Total	**281**		

Table 2. Prevalence of prostate examination among male individuals aged 45 years or older who were living in the urban area of Rio Grande (RS), surveyed in 2016 (n = 281)

Variable	Crude analysis PR (95% CI)	Adjusted analysis PR (95% CI)
Age groups (years)		
45-49	1.00	1.00
50-59	1.28 (0.99-1.67)	1.24 (0.98-2.59)
60-69	**1.37 (1.02-1.85)**§	**1.35 (1.02-1.78)**§
≥ 70	**1.71 (1.28-2.27)**§	**1.68 (1.29-2.19)**§
Skin color		
White	1.11 (0.88-1.40)	1.07 (0.85-1.36)
Others	1.00	1.00
Marital status		
Single	1.00	1.00
Married, widowed, separated or divorced	**1.60 (1.26-2.02)**§	**1.38 (1.09-1.74)**§
Schooling (years)		
0-8	1.00	1.00
9-11	1.17 (0.96-1.41)	1.06 (0.88-1.28)
≥ 12	**1.33 (1.13-1.57)**§	**1.24 (1.02-1.51)**§
Economic status (in terciles)		
Poorest	1.00	1.00
Intermediate	1.21 (0.94-1.58)	1.19 (0.91-1.57)
Richest	**1.53 (1.23-1.89)**§	**1.36 (1.07-1.74)**§
Leisure-time physical activity		
No	1.00	1.00
Yes	**1.44 (1.25-1.65)**§	**1.22 (1.08-1.37)**§
Smoking habits		
No	**2.11 (1.54-2.91)**§	**1.58 (1.18-2.12)**§
Yes	1.00	1.00
Excessive alcohol consumption		
No	1.09 (0.86-1.40)	0.92 (0.72-1.17)
Yes	1.00	1.00
Overweight		
No	1.00	1.00
Yes	**1.37 (1.15-1.64)**§	**1.31 (1.10-1.55)**§
Health insurance		
No	1.00	1.00
Yes	**1.59 (1.33-1.89)**§	**1.35 (1.14-1.60)**§
Visit to a doctor during the preceding year		
No	1.00	1.00
Yes	**1.76 (1.35-2.29)**§	**1.44 (1.15-1.80)**§
Hypertension		
No	1.00	1.00
Yes	**1.25 (1.07-1.46)**§	0.98 (0.86-1.12)
Diabetes		
No	1.00	1.00
Yes	**1.23 (1.01-1.50)**§	1.04 (0.87-1.24)

§Statistically significant (P < 0.05); PR = prevalence ratio; CI = confidence interval.

Among the 68% who had been screened (n = 192), our findings showed that older individuals with higher economic status were more likely to have been tested using both methods (versus only using one of them). Analysis on the likelihood of having been tested using both methods (prostate-specific antigen testing and digital rectal examination) versus not having been tested, the associated factors were the same as those for having been tested using one of these two methods (data not shown).

DISCUSSION

This study reports the factors associated with prostate-specific antigen testing and digital rectal examination among men aged 45 years and older. Our findings indicated that seven in every ten individuals reported a history of having undergone prostate examination in their lifetimes. After adjustment for possible confounders, the following characteristics remained associated with the outcome: advanced age; marital status other than single; more schooling; being in the upper tercile of economic status; practicing physical activity; non-smoking habits; overweight; having health insurance; and having visited a doctor during the preceding year.

The prevalence rate of prostate-specific antigen testing observed in our study (33.1%) was similar to, or greater than, the rates that have been reported in developed countries. A study carried out in Milan, Italy, between 1999 and 2000, revealed that over 300,000 men had been tested for prostate-specific antigen, which corresponded to a prevalence rate of 26.9%. When only individuals younger than 50 years were considered, the prevalence rate of prostate-specific antigen testing increased to 34%, which the authors of that study considered to be high coverage of the population.[12]

An analysis on data gathered through the Behavioral Risk Factor Surveillance System (BRFSS) in the United States in 2012 and 2014, on a population of 158,103 men aged 40 to 64 years who had been tested for prostate-specific antigen in the previous year, indicated that the prevalence rates of prostate examinations in 2011 and 2013 were 24.4% and 22.3%, respectively.[13] In addition, a study on data from the Dominican Republic Demographic and Health Survey (DRDHS, 2013), on a population of 3,272 men aged 40 to 60 years old, found that 30.6% of them had been screened preventively for prostate cancer (prostate-specific antigen testing or digital rectal examination) at some point in their lifetimes.[14] That prevalence rate was less than half of the rate found in our study (68.3%).

In Brazil, three cross-sectional studies were carried out between 2001 and 2007 to determine the coverage of prostate examinations (prostate-specific antigen testing or digital rectal examination) in the city of São Paulo, the coastal region around Santos (Baixada Santista) and the remainder of the state of São Paulo. The studies had heterogeneous designs: two of them were population-based surveys and the third used a research instrument that had been designed specifically for that study. The findings from these studies were as follows:

- In the city of São Paulo, the prevalence rate of prostate examination in the city of São Paulo was 47%, based on a sample of 540 men older than 18 years. Although significant, that prevalence was lower than what we observed in our study. Furthermore, a high proportion of non-coverage among individuals under 50 years of age was expected, as shown in our results, which was close to one in every two individuals.[15]
- The Multicenter Health Survey of the State of São Paulo (Inquérito de Saúde no Estado de São Paulo, ISA-SP) indicated that 55.6% out of 992 men aged at least 50 years had been screened for prostate cancer. Of these, 73% had undergone prostate-specific antigen testing, 62% digital rectal examination and 22% both examinations. Among all the examinations, 50% had been performed in the previous year, probably due to the predominance of individuals aged over 60 in the sample.[3]
- In the Baixada Santista, a study conducted among 927 respondents aged 40 years or older showed that 56.5% of them had been tested for prostate-specific antigen at least once in their lifetimes.[16]

The risk factors for development of prostate cancer include the following:

1) Age – in Brazil, out of every ten diagnoses, nine are among men older than 55 years, particularly those older than 65 years (85%). In contrast, the American Cancer Society has estimates that six out of every ten diagnoses occur in men aged at least 65 years.[1,14,17]
2) Ethnicity – Afro-descendants.[14,17]
3) Family history of prostate cancer – defined as a father or sibling diagnosed before the age of 60.[1]
4) Overweight and obesity.[1]

On the other hand, the main protective factors against prostate cancer are the following: healthy eating, physical activity practice, adequate body weight, non-smoking habits and no alcohol consumption.[1]

In the present study, the group of men aged at least 70 years had been more frequently screened for prostate cancer through prostate-specific antigen testing or digital rectal examination. Importantly, one in every two men had been tested by means of both prostate-specific antigen testing and digital rectal examination. These findings are in line with the tendency shown in the ISA-SP survey, which reported that the prevalence was around 70% for this age group.[18] Due to comorbidities resulting from aging, individuals aged 70 and older are more frequently in contact with healthcare services and, therefore, are more likely to undergo preventive examinations. In addition, aging has also been associated with benign prostatic hyperplasia, which gives rise to a need for prostate-specific antigen testing and digital rectal examination.[18]

The Dominican Republic Demographic and Health Survey (DRDHS, 2013) indicated a trend towards a higher frequency of prostate examinations with aging,[14] but only from the age of 60 years onwards. Conversely, Americans aged 50 to 59 years were screened approximately 2.5 times more frequently for prostate cancer than were older individuals.[19]

In our study, there was a significant association between marital status other than single (married, divorced or widowed) and higher prevalence of preventive screening for prostate cancer. This was in line with the findings from a study conducted in the Caribbean region.[14] We further observed that this did not occur only in relation to prostate-specific antigen testing, unlike what was reported in studies carried out in São Paulo and in the United States.[13,16] These last two studies also showed a positive association with prostate examination among individuals who had a steady partner or a casual partner, or who were widowed or divorced.[13,16] In the same way, in our study population, the lowest prevalence rates for the outcome were observed among single individuals. Conversely, in another study, it was reported that Americans who had never married or were single underwent more preventive examinations for prostate cancer.[19]

Factors such as more schooling, higher income, having health insurance and having visited a doctor during the preceding year are well established in the literature as predictive of undergoing prostate examination.[13,14,16,18,19] In our study, more schooling and higher income were positively associated with undergoing screening for prostate cancer, while having not visited a doctor during the preceding year proved to be an important negative factor for prostate examination (prostate-specific antigen testing and digital rectal examination), as expected.

Consistent with the findings from the ISA-SP survey, non-smoking men had been screened for prostate cancer more often,[18] while lower prevalence rates were observed among smokers. In our study, overweight was also significantly associated with the outcome. We reasoned that the higher prevalence of prostate examinations among overweight or obese men was because they sought healthcare on a frequent basis through awareness that their condition was a risk factor for prostate cancer.[1] In contrasting studies, one carried out in the United States demonstrated that not being overweight was a factor associated with being screened for prostate cancer, while another conducted nationwide in Brazil showed that this characteristic was not statistically significant.[18,19]

Our study has important limitations that need to be considered, namely:

1) It was impossible to establish a causal relationship due to the cross-sectional study design, and because of biases of memory and information regarding self-reported data. However, it is important to note that such an approach has been considered effective for population-wide surveys, to monitor cancer-related knowledge and preventive practices.[20]

2) Because of the scope of the base study ("Health of the population of Rio Grande"), it was not possible to provide any details concerning the clinical outcomes that led to use of prostate-specific antigen testing and digital rectal examination, or to scrutinize the results further.
3) This study only reflected the situation of a small area in the state of Rio Grande do Sul. Therefore, the capacity to generalize these results to the metropolitan regions of Brazil or to the entire country is limited.

To our knowledge, this is one of the few population-wide studies in the literature to have investigated the prevalence of, and factors associated with, prostate cancer screening. To date, there are no international guidelines in this field, in contrast to the situation regarding mammography and cervical screening among women. Hence, the advisory level for the recommendation that the male population should undergo preventive prostate screening is only at Grade C level, i.e. that this should be discussed individually.[5]

CONCLUSION

Approximately two thirds of the study population had been screened for prostate cancer. These individuals were mostly older, with higher socioeconomic status, healthier lifestyle and frequent use of healthcare services.

REFERENCES

1. Instituto Nacional de Câncer José Alencar Gomes da Silva. Câncer de próstata: vamos falar sobre isso? Rio de Janeiro: INCA; 2017. Available from: http://portal.saude.pe.gov.br/sites/portal.saude.pe.gov.br/files/2017_inca_cancer_de_prostata_vamos_falar_sobre_isso_cartilha.pdf. Accessed in 2020 (Jun 30).
2. Sociedade Brasileira de Urologia. Novembro Azul 2017 – URO ONCOL LITORAL 2017. Nota Oficial 2017 - Rastreamento do Câncer de Próstata. Available from: http://sbu-sp.org.br/medicos/noticias/nota-oficial-2017-rastreamento-do-cancer-de-prostata/. Accessed in 2020 (Sep 3).
3. Almeida JRC, Pedrosa NL, Leite JB, et al. Marcadores Tumorais: Revisão de Literatura [Tumor Markers: a Literature Review]. Revista Brasileira de Cancerologia. 2007;53(3):305-16. Available from: https://rbc.inca.gov.br/site/arquivos/n_53/v03/pdf/revisao1.pdf. Accessed in 2020 (Jun 30).
4. Smith RA, Andrews KS, Brooks D, et al. Cancer Screening in the United States, 2018: A Review of Current American Cancer Society Guidelines and Current Issues in Cancer Screening. CA Cancer J Clin. 2018;68(4):297-316. PMID: 29846940; doi: 10.3322/caac.21446.
5. Carter HB, Albertsen PC, Barry MJ, et al. Early Detection of Prostate Cancer: AUA Guideline. J Urol. 2013;190(2):419-26. PMID: 23659877; doi: 10.1016/j.juro.2013.04.119.
6. Fenton JJ, Weyrich MS, Durbin S, et al. Prostate-Specific Antigen-Based Screening for Prostate Cancer: Evidence report and Systematic Evidence Review for the US Preventive Services Task Force. JAMA. 2018;319(18):1914-31. PMID: 29801018; doi: 10.1001/jama.2018.3712.
7. Instituto Nacional de Câncer José Alencar Gomes da Silva. Rastreamento do Câncer de Próstata. Rio de Janeiro: INCA; 2013. Available from: https://www.inca.gov.br/sites/ufu.sti.inca.local/files/media/document/rastreamento-prostata-2013.pdf. Accessed in 2020 (Jun 30).
8. Instituto Nacional de Câncer José Alencar Gomes da Silva. Informativo Detecção precoce – Monitoramento das ações de controle do câncer de próstata. Rio de Janeiro: INCA; 2014. v. 5. n. 2. Available from: https://www.inca.gov.br/sites/ufu.sti.inca.local/files//media/document//informativo-deteccao-precoce-2-2014.pdf. Accessed in 2020 (Jun 30).
9. Dumith SC, Paulitsch RG, Carpena MX, et al. Planejamento e execução de um inquérito populacional de saúde por meio de consórcio de pesquisa multidisciplinar [Planning and execution of a population health survey by means of a multidisciplinary research consortium]. Sci Med. 2018;28(3):ID30407. doi: 10.15448/1980-6108.2018.3.30407.
10. Craig CL, Marshall AL, Sjöström M, et al. International physical activity questionnaire: 12-country reliability and validity. Med Sci Sports Exer. 2003;35(8):1381-95. PMID: 12900694; doi: 10.1249/01.MSS.0000078924.61453.FB.
11. World Health Organization. Global Status Report on Alcohol and Health 2014. Geneva: WHO; 2014. Available from: https://www.who.int/substance_abuse/publications/alcohol_2014/en/. Accessed in 2020 (Jun 30).
12. Russo A, Autelitano M, Bellini A, Bisanti L. Estimate of population coverage with the prostate specific antigen (PSA) test to screen for prostate cancer in a metropolitan area of northern Italy. J Med Screen. 2002;9(4):179-80. PMID: 12518009; doi: 10.1136/jms.9.4.179.
13. Sammon JD, Serrell EC, Karabon P, et al. Prostate Cancer Screening in Early Medicaid Expansion States. J Urol. 2018;199(1):81-8. PMID: 28765069; doi: 10.1016/j.juro.2017.07.083.
14. Kangmennaang J, Luginaah I. The Influences of Health Insurance and Access to Information on Prostate Cancer Screening among Men in Dominican Republic. J Cancer Epidemiol. 2016;2016:7284303. PMID: 27034669; doi: 10.1155/2016/7284303.
15. Segri NJ, Cesar CL, Barros MB, et al. Health survey: comparison of interviewees according to ownership of a residential telephone line. Rev Saude Publica. 2010;44(3):503-12. PMID: 20464258; doi: https://doi.org/10.1590/s0034-89102010005000012.
16. Acesso aos serviços de saúde em Municípios da Baixada Santista. Temas em Saúde Coletiva, n. 8. Escuder MML, Monteiro PHN, Pupo LR, editors. São Paulo: Instituto de Saúde; 2008. Available from: http://www.saude.sp.gov.br/resources/instituto-de-saude/homepage/temas-saude-coletiva/pdfs/temas08.pdf. Accessed in 2020 (Jun 30).
17. American Cancer Society. Cancer Facts & Figures 2019. Atlanta: American Cancer Society; 2019. Available from: https://www.cancer.org/content/dam/cancer-org/research/cancer-facts-and-statistics/annual-cancer-facts-and-figures/2019/cancer-facts-and-figures-2019.pdf. Accessed in 2020 (Jun 30).

18. Amorim VM, Barros MB, César CL, et al. Fatores associados à realização dos exames de rastreamento para o câncer de próstata: um estudo de base populacional [Factors associated with prostate cancer screening: a population-based study]. Cad. Saude Publica. 2011;27(2):347-56. PMID: 21359471; doi: 10.1590/S0102-311X2011000200016.
19. Garg V, Raisch DW, Selig JP, Thompson TA. Health disparities in clinical practice patterns for prostate cancer screening by geographic regions in the United States: a multilevel modeling analysis. Prostate Cancer Prostatic Dis. 2013;16(2):193-203. PMID: 23399779; doi: 10.1038/pcan.2013.3.
20. Rauscher GH, Johnson TP, Cho YI, Walk JA. Accuracy of self-reported cancer-screening histories: a meta-analysis. Cancer Epidemiol Biomarkers Prev. 2008;17(4):748-57. PMID: 18381468; doi: 10.1158/1055-9965.EPI-07-2629.

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Clinical characteristics and outcomes among Brazilian patients with severe acute respiratory syndrome coronavirus 2 infection: an observational retrospective study

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ABSTRACT

BACKGROUND: Since February 2020, data on the clinical features of patients infected by severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) and their clinical evolution have been gathered and intensively discussed, especially in countries with dramatic dissemination of this disease.

OBJECTIVE: To assess the clinical features of Brazilian patients with SARS-CoV-2 and analyze its local epidemiological features.

DESIGN AND SETTING: Observational retrospective study conducted using data from an official electronic platform for recording confirmed SARS-CoV-2 cases.

METHODS: We extracted data from patients based in the state of Pernambuco who were registered on the platform of the Center for Strategic Health Surveillance Information, between February 26 and May 25, 2020. Clinical signs/symptoms, case evolution over time, distribution of confirmed, recovered and fatal cases and relationship between age group and gender were assessed.

RESULTS: We included 28,854 patients who were positive for SARS-CoV-2 (56.13% females), of median age 44.18 years. SARS-CoV-2 infection was most frequent among adults aged 30-39 years. Among cases that progressed to death, the most frequent age range was 70-79 years. Overall, the mortality rate in the cohort was 8.06%; recovery rate, 30.7%; and hospital admission rate (up to the end of follow-up), 17.3%. The average length of time between symptom onset and death was 10.3 days. The most commonly reported symptoms were coughing (42.39%), fever (38.03%) and dyspnea/respiratory distress with oxygen saturation < 95% (30.98%).

CONCLUSION: Coughing, fever and dyspnea/respiratory distress with oxygen saturation < 95% were the commonest symptoms. The case-fatality rate was 8.06% and the hospitalization rate, 17.3%.

INTRODUCTION

The ongoing pandemic caused by the novel severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) has been associated with a greater number of deaths occurring more rapidly than had been observed among previously leading causes of mortality, such as unintentional injuries, stroke and heart diseases. As of July 6, 2020, more than 11,495,412 confirmed cases have been reported, along with more than 535,185 officially notified deaths.[1] In developing countries, specific data regarding incidence, local clinical manifestations, radiological and laboratory abnormalities and requirements for establishment of differential diagnoses considering local peculiarities still remain obscure and are often insufficient. In Brazil, as of June 15, 2020, 1,603,055 cases and 64,867 deaths had been legally counted.[1]

So far, according to studies conducted in developed countries, the typical signs and symptoms of the novel 2019 coronavirus are fever, coughing (with or without sputum), sore throat, and shortness of breath (with or without associated respiratory distress comprising oxygen saturation < 95.0%).[2,3] However, new symptomatic profiles are being described in the literature, almost on a daily basis. Manifestations such as acute olfactory disorders, acute hyposmia and anosmia, dysgeusia and dermatological complaints might also be present with the onset of coronavirus disease (COVID-19).[4-7]

Although several studies have already described symptom profiles for patients in European and Asian-Pacific countries, at present there is no study providing detailed information within the Brazilian populational setting. Indeed, few papers on COVID-19 symptom profiles

have been published in developing and poor or middle-income countries. Additionally, the studies relating to the settings of developing countries have been either case series, typically with fewer than 100 patients, or case reports, which do not necessarily describe the real epidemiological status of either low or middle-income countries.[8-10] None of these studies assessed the most common clinical presentations of the novel coronavirus in Brazilian patients. Nor did they attempt to investigate differences in clinical presentation or underlying diseases among patients infected with this novel virus.

OBJECTIVE

In this study, we aimed to assess the clinical features of Brazilian patients infected with SARS-CoV-2 and to analyze patient mortality and the need for hospital admission.

METHODS

Study design

This was an observational retrospective study, based on individual data from Brazilian patients that were collected from the Center for Strategic Health Surveillance Information of the Health Secretariat of the Brazilian Ministry of Health. This government branch targets early detection through establishing continuous monitoring, in order to deliver adequate solutions for public healthcare emergencies such as COVID-19. Ethical approval was obtained from a local ethics committee (reference number 30350820.5.0000.0008), which was granted on April 13, 2020. The study authors did not have any contact with the patients described here, and did not deliver any pharmacological or non-pharmacological intervention to them.

Settings

All the confirmed patients included in this study were admitted to primary care centers, private clinics or hospital facilities in the state of Pernambuco, in northeastern Brazil. According to official governmental reports, as of June 10, 2020, Pernambuco had the seventh largest number of confirmed cases in Brazil (41,010 accumulated cases).[11] Overall, with a total area of 98,311 square kilometers, Pernambuco has around 8.8 million inhabitants, and in 2017 was considered to have a medium human development index (0.67).[12,13] However, because of regional discrepancies within this state regarding access to education, life expectancy and per capita income, it should be noted that several municipalities in the state have low human development indexes (< 0.50).

Participants

All patients, regardless age, who presented to any healthcare facility (public or private) with suspected SARS-CoV-2 infection between February 26 and May 25, 2020, and who were registered on the government's online platform for suspected cases were eligible for inclusion in this study. At the platform interface, patients are enrolled as "suspected cases – under investigation" and as soon the laboratory result has been shared with the requesting healthcare center, the designated medical provider can update the patients' status to "negative for SARS-CoV-2 infection" or "positive for SARS-CoV-2 infection", based on the report from the real-time quantitative polymerase chain reaction (RT-qPCR). There is also the possibility of providing results relating to alternative causes of infection that might be investigated (such as influenza A or B).

In our study, only patients with confirmed SARS-CoV-2 were included in the descriptive analysis. Therefore, patients were excluded if their laboratory result was negative for SARS-CoV-2. All the infected patients included in the present study had tested positive for SARS-CoV-2 through use of RT-qPCR on samples from nasopharyngeal or oropharyngeal specimens. The eligibility criterion for a positive diagnosis of SARS-CoV-2 infection was that at least one gene region was recognized and amplified as positive for viral proteins (nucleocapsid and open reading frame).

Informed consent was not required because we used secondary data from an official database. The RT-qPCR assay was performed either in the Central Public Health Laboratory (LACEN) or in private diagnostic laboratories.

Variables and outcomes

The main primary variable of the study was clinical manifestation of SARS-CoV-2 infection among the patients, along with categorization of these patients according to the outcome at the end of the follow-up period (i.e. on May 25, 2020). Thus, the patients who had been enrolled were classified into five outcome groups. Patients with a definitive clinical status were stratified as "Recovered" (patients who after medical assessment were considered not to present active infection) or "Died" (patients who progressed to death) and were compared with each other. Similarly, individuals with a transient clinical status (i.e. awaiting case improvement or worsening) were categorized as "Domestic quarantine" (patients who had been directed to place themselves in isolation at home), "Admitted to hospital care" (patients who, on May 25, 2020, were in a hospital, either in an isolation ward or in an ordinary hospital bed) or "Admitted to intensive care unit (ICU)" (patients who, on May 25, 2020, were hospitalized in an ICU).

Exploratory variables such as the case distribution according to age group and gender, temporal distribution of included cases, time elapsed between notification and death and time elapsed between symptom onset and death were also analyzed.

Data sources and measurements

In Brazil, a country with both single and multi-payer systems (public and private healthcare systems, respectively), notification of all confirmed SARS-CoV-2 cases (clinically classified as influenza-like syndrome or severe acute respiratory syndrome) has become mandatory since March 2020. These cases are registered in online servers and the records are subsequently processed. The notification and data registration are performed by healthcare personnel and once the laboratory result has been disclosed to the medical facility, the designated medical provider can update the diagnosis status in the system.

Influenza-like illness is defined as febrile sensation or fever, associated with coughing or sore throat or running nose or shortness of breath. Severe acute respiratory syndrome is defined as influenza-like symptoms with dyspnea/respiratory distress or persistent thoracic pressure or oxygen saturation < 95% in ambient air or peripheral cyanosis.

For non-hospitalized patients, such as patients attended in the primary care sector or at private clinics, the "e-SUS VE" is the final online host system for all suspected cases. On the other hand, cases of severe acute respiratory syndrome and deaths need to be notified through the Information System for Influenza Epidemiological Surveillance (Sistema de Informação de Vigilância Epidemiológica da Gripe, SIVEP-Gripe). In the state of Pernambuco, which is potentially the most transparent state in Brazil with regard to data sharing and epidemiological surveillance, reports from both systems are periodically integrated and compiled into a single online platform.[13]

All data associated with clinical symptoms and signs, previous health history and epidemiological features were extracted from the electronic panel of cases of novel coronavirus infection in the state of Pernambuco, Brazil. Two experienced medical research specialists reviewed and abstracted the data. After initial processing, the data were entered into a computerized database (Microsoft SQL Server, version 2019, United States) and were cross-checked.

Study size and statistics

No formal sample size calculation was carried out, because of the observational and convenience-sampling nature of the study. The statistical evaluation included descriptive analysis on the study population and comparisons between groups using the chi-square test. We defined differences as statistically significant if the P-value was < 0.05. Categorical variables were expressed as the number and its respective percentage. The Statistical Package for the Social Sciences (SPSS), version 20.0 (IBM, New York, United States) was used to obtain mathematical evaluations.

RESULTS

Participants' characteristics

Overall, the cases of 54,235 patients were retrieved from the governmental database up to May 25, 2020. Of these, 28,854 patients had a confirmed laboratory diagnosis of SARS-CoV-2, 22,034 were negative for virus detection and 3,347 were waiting for laboratory results.

In the study sample (infected patients; n = 28,854), the median age was 44.18 years and 56.13% were female, with a male to female ratio of 0.78. The largest proportion of the infected patients was aged between 30 and 39 years (n = 6,949; 24.08%). Information on underlying diseases was not reported for all patients, and it was not possible to know which patients did not have underlying diseases, or in which cases some variables were missing. Among the patients with any descriptions of preexisting comorbidities, hypertension (n = 863), diabetes (n = 533), obesity (n = 110), chronic renal failure (n = 90), history of stroke (n = 85) and asthma (n = 63) were the most prevalent ones. Among all the patients included, 22 (0.07%) were classified as having an additional ongoing viral coinfection (either influenza A or influenza B) at the time of the notification.

Descriptive data

After distribution of the patients into definitive outcomes, 8,863 patients (30.7%) were considered to have recovered of the infection, while 2,328 (8.06%) died due to complications from the infection. Male patients were more likely to progress to death (55.0%) (**Table 1**). For both genders, the majority of fatalities occurred in the group of patients older than 60 years. Among females, the majority of deaths were among individuals older than 80 years, while among male individuals, patients aged between 60 and 69 years progressed to death more frequently. Female patients recovered more frequently than did males (62.63%).

Regarding transient outcomes, 4,771 individuals (16.5%) were admitted to an isolation ward, 1,442 (5.0%) were directed to place themselves in domestic quarantine and 227 (0.78%) were hospitalized in an intensive care unit. For 10,996 patients with confirmed SARS-CoV-2 infection (38%), the final outcome was not available or not declared.

In the overall cohort of confirmed patients, the median length of time from symptom onset to regulatory notification was 7.0 days (interquartile range, IQR 4.0-10.0). Among patients who progressed to death, the median length of time between symptom onset and notification was 5.0 days (IQR 3.0-8.0), while the median length of time between symptom onset and death was 8.0 days (IQR 5.0-14.0).

Analysis on the clinical characteristics of confirmed cases of SARS-CoV-2

A summary of the clinical manifestations of the 28,854 confirmed cases of SARS-CoV-2 infection is shown in **Table 2**. Overall, signs or symptoms of some type were registered in relation to 17,631 patients (61.10%). Thus, notifications were made in the cases of 38.9% (n = 11,223) of the confirmed patients and these cases were registered in the database. However, none of the clinical information was precisely inserted.

The main clinical manifestations observed among the patients comprised coughing (with or without sputum) (42.39%), fever (38.03%), dyspnea or respiratory distress with oxygen saturation lower than 95% (30.98%), sore throat or odynophagia (16.79%), myalgia (4.90%) and headache (3.63%). Less common symptoms such as anosmia (2.77%), adynamia or asthenia (1.88%), dysgeusia or loss of taste (1.6%) and hyporexia (0.047%) were also reported.

Comparison between the patients who recovered and those who died showed that dyspnea or respiratory distress with oxygen saturation < 95% (29.0% versus 88.0%) and fever (59.0% versus 64.0%) were significantly more frequent among the patients who died. Sore throat was more frequent among the patients who recovered (39.0% versus 9.0%). Comparison between patients hospitalized in an isolation ward and patients in an ICU showed that fever (67.0 versus 60.0%) was significantly more frequently observed among the patients in an isolation ward. Among the patients admitted to an ICU, there was higher frequency of manifestation of dyspnea than among those in an isolation ward (74.0 versus 87.0%).

Hypertension, diabetes and obesity were more frequently reported among patients admitted to an ICU and among the patients who died. A complete description of underlying diseases observed among the patients included, along with comparisons between patients who progressed to death (case-fatalities) and patients who recovered and between patients who were admitted to an isolation ward and those who were admitted to an ICU, for each symptom and comorbidity, is shown in **Table 2**.

DISCUSSION

Over the last few weeks, Brazil has become the epicenter of the novel coronavirus pandemic.[14-16] With the global impact of the novel coronavirus, it is important to highlight that different populations can manifest different clinical symptoms and can progress differently over the natural course of the infection. Overall, the most commonly reported clinical features consisted of coughing (with or without sputum) (42.39%), fever (38.03%) and dyspnea or respiratory distress with oxygen saturation lower than 95% (30.44%).

Our results showed slightly lower prevalences for most observed clinical features and comorbidities, compared with previous studies.[3] Severe illness (defined as patients requiring hospitalization) occurred in 17.3% of the patients. Indeed, fever and dyspnea were remarkably more frequently reported among fatalities. In addition, dyspnea and oxygen saturation < 95% were shown to be contributing factors for admission to an ICU.

With regard to underlying diseases, the comorbidities most often registered were hypertension, diabetes, obesity and chronic renal failure. Additionally, taking into account underlying pathological conditions, we observed that there was an association between the presence of comorbidities and worse progression of the disease. Regarding coexistence of underlying conditions, we perceived that the frequency of comorbidities was slightly lower among the cases reported here than in previously published data.[2] However, this may have been mainly caused by the singularities of the hospital environment and the features of the emergency department. In emergency departments, it is very frequently impossible to obtain a detailed medical history.

Table 1. Age distribution among the patients described in the data retrieved

Age groups	Confirmed cases (n = 28,854) n (%)		Recovered cases (n = 8,863) n (%)		Case-fatalities (deaths) (n = 2,328) n (%)	
	Female	Male	Female	Male	Female	Male
0 to 9 years	444 (1.53)	373 (1.29)	156 (1.76)	140 (1.56)	6 (0.25)	5 (0.21)
10 to 19 years	178 (0.61)	143 (0.49)	42 (0.47)	36 (0.40)	4 (0.17)	4 (0.17)
20 to 29 years	2,018 (6.99)	1,262 (4.36)	764 (8.62)	408 (4.60)	14 (0.60)	15 (0.64)
30 to 39 years	4,171 (14.45)	2,778 (9.62)	1,768 (19.95)	926 (10.43)	24 (1.03)	54 (2.32)
40 to 49 years	3,717 (12.88)	2,861 (9.91)	1,509 (17.02)	882 (9.94)	60 (2.57)	127 (5.46)
50 to 59 years	2,552 (8.84)	2,098 (7.26)	886 (9.99)	546 (6.15)	150 (6.44)	179 (7.69)
60 to 69 years	1,325 (4.59)	1,376 (4.75)	237 (2.68)	208 (2.34)	246 (10.57)	315 (13.54)
70 to 79 years	947 (3.28)	1,059 (3.66)	102 (1.16)	98 (1.10)	258 (11.09)	312 (13.40)
> 80 years	846 (2.93)	706 (2.43)	87 (0.98)	68 (0.75)	286 (12.29)	269 (11.56)
Total	**16,198 (56.13)**	**12,656 (43.87)**	**5,551 (62.63)**	**3,312 (37.37)**	**1,048 (45.01)**	**1,280 (54.99)**

During the analyzed period, there were 22 confirmed co-infection of influenza A or influenza B. In addition, there were 54,235 cases registered in the database (including suspected, confirmed and negative cases).

Even though disease profiling for COVID-19 has been replicated and implemented in several countries, this was the first study to describe its main clinical characteristics and outcome distribution in Brazil using a substantial number of patients. Brazil is a country with continental geographical proportions and has a wide spectrum of tropical infectious diseases (most of them neglected), such as Chagas disease, leishmaniasis and dengue. However, to date, no previous diseases has had the impact of abruptly increasing the number of patients seeking medical consultations.[17] In association with Brazil's large territorial proportions, it is also a country with social and economic inequalities, which consequently influences the health status of its inhabitants.[18] Thus, as the novel coronavirus has disseminated across the country, the impact of the disease on low-income populations has been increasing substantially, thus resulting in serious negative effects among these citizens.

Table 2. Clinical data from confirmed cases of SARS-CoV-2 infection in the state of Pernambuco, Brazil (data up to May 25, 2020)

Clinical presentation of confirmed patients (n = 17,631)	Domestic quarantine (n = 1,442) n (%)	Recovered (n = 8,863) n (%)	Case-fatalities (n = 2,328) n (%)	Admitted to isolation ward (n = 4,771) n (%)	Admitted to ICU (n = 227) n (%)	Comparison between recovered and case-fatality patients (P-value)	Comparison between patients admitted to isolation ward and ICU (P-value)
Coughing (n = 12,232)	874 (0.60)	6,124 (0.69)	1,574 (0.67)	3,512 (0.73)	148 (0.65)	0.169	0.005
Fever (n = 10,976)	853 (0.59)	5,256 (0.59)	1,493 (0.64)	3,236 (0.67)	138 (0.60)	< 0.001	0.027
Dyspnea or respiratory distress with SpO_2 < 95% (n = 8,941)	507 (0.35)	2,619 (0.29)	2,057 (0.88)	3,559 (0.74)	199 (0.87)	< 0.001	< 0.001
Sore throat or odynophagia (n = 4,847)	460 (0.31)	3,470 (0.39)	216 (0.09)	664 (0.13)	37 (0.16)	< 0.001	0.313
Myalgia (n = 1,416)	460 (0.31)	333 (0.03)	99 (0.04)	513 (0.10)	11 (0.04)	0.270	0.005
Vomiting or nausea or diarrhea (n = 1,293)	186 (0.12)	316 (0.03)	191 (0.08)	582 (0.12)	18 (0.07)	< 0.001	0.053
Headache (n = 1,049)	277 (0.19)	352 (0.03)	51 (0.02)	361 (0.07)	8 (0.03)	< 0.001	0.023
Anosmia (n = 801)	223 (0.15)	284 (0.03)	31 (0.01)	257 (0.05)	6 (0.02)	< 0.001	0.070
Adynamia or asthenia (n = 545)	55 (0.03)	120 (0.01)	77 (0.02)	287 (0.06)	6 (0.02)	< 0.001	0.035
Dysgeusia or loss of taste (n = 490)	170 (0.11)	218 (0.02)	20 (< 0.01)	77 (0.01)	5 (0.02)	< 0.001	0.495
Hyporexia (n = 138)	10 (< 0.01)	10 (< 0.01)	31 (0.01)	85 (0.01)	2 (< 0.01)	< 0.001	0.311
Abdominal pain (n = 88)	7 (< 0.01)	13 (< 0.01)	19 (< 0.01)	48 (0.01)	1 (< 0.01)	< 0.001	0.398
Sneezing (n = 46)	9 (< 0.01)	27 (< 0.01)	1 (< 0.01)	9 (< 0.01)	-	0.025	0.512
Eye pain (n = 20)	5 (< 0.01)	16 (< 0.01)	2 (< 0.01)	3 (< 0.01)	-	0.724	0.705
Chest pain (n = 12)	3 (< 0.01)	4 (< 0.01)	1 (< 0.01)	4 (< 0.01)	-	0.965	0.663
Running nose (n = 9)	4 (< 0.01)	154 (0.01)	19 (< 0.01)	2 (< 0.01)	-	< 0.001	0.758
Asymptomatic (n = 9)	1 (< 0.01)	5 (< 0.01)	1 (< 0.01)	2 (< 0.01)	-	0.803	0.758
Not declared or not available (n = 1,339)	279 (0.19)	704 (0.07)	107 (0.04)	239 (0.05)	10 (0.04)	< 0.001	0.683
Comorbidities							
Hypertension (n = 863)	17 (0.01)	63 (< 0.01)	643 (0.27)	126 (0.02)	14 (0.06)	< 0.001	0.002
Diabetes (n = 533)	1 (< 0.01)	182 (0.02)	309 (0.13)	35 (< 0.01)	6 (0.02)	< 0.001	0.002
Obesity (BMI > 25 kg/m^2) (n = 110)	1 (< 0.01)	6 (< 0.01)	86 (0.03)	14 (< 0.01)	3 (0.01)	< 0.001	0.009
Chronic renal failure (any stage) (n = 90)	-	2 (< 0.01)	76 (0.03)	11 (< 0.01)	1 (< 0.01)	< 0.001	0.528
History of stroke (n = 85)	-	2 (< 0.01)	72 (0.03)	10 (< 0.01)	1 (< 0.01)	< 0.001	0.468
Asthma (n = 63)	-	12 (< 0.01)	35 (0.01)	14 (< 0.01)	2 (< 0.01)	< 0.001	0.126
Chronic obstructive pulmonary disease (n = 48)	-	5 (< 0.01)	36 (0.01)	4 (< 0.01)	3 (0.01)	< 0.001	< 0.001
Any neoplasia (n = 33)	-	3 (< 0.01)	26 (0.01)	4 (< 0.01)	-	< 0.001	0.663
History of myocardial infarction (n = 32)	-	1 (< 0.01)	27 (0.01)	3 (< 0.01)	1 (< 0.01)	< 0.001	0.049
Chronic liver disease or hepatitis (n = 11)	-	1 (< 0.01)	5 (< 0.01)	5 (< 0.01)	-	< 0.001	0.626
HIV infection (under control or not) (n = 9)	-	3 (< 0.01)	4 (< 0.01)	2 (< 0.01)	-	0.018	0.758
Transplanted (n = 3)	-	-	2 (< 0.01)	1 (< 0.01)	-	0.006	0.827
Alcoholism (n = 1)	-	-	1 (< 0.01)	-	-	0.051	-
Without comorbidities or not declared or not available (n = 8,308)	866 (0.60)	3,640 (0.41)	767 (0.32)	2,882 (0.60)	153 (0.67)	< 0.001	0.035

ICU = intensive care unit; BMI = body mass index; HIV = human immunodeficiency virus.

It is important to state that the comparison shown above relates to: 1) Comparison between patients who progressed to death (case-fatalities) and patients who recovered; and 2) Comparison between patients who were admitted to an isolation ward and those admitted to an ICU. Therefore, for each symptom and comorbidity category, we performed statistical analysis to check whether there was any group-to-group significant difference.

The extensive spectrum of reported symptoms during admission (with several body systems involved), together with the wide range of severity (from asymptomatic cases to severely ill patients), may potentially cause an initial misdiagnosis, especially for patients whose first RT-qPCR is negative.[4] We found that the frequency of reports on anosmia/hyposmia and other minor symptoms as dermatological manifestations was low. However, considering that the reporting of these symptoms only started in mid-April, medical care for these manifestations in our cohort within a Brazilian setting may have been delayed or been given less attention. Nevertheless, several studies have already reported that these particular symptoms are highly sensitive for diagnosing the disease.[4] In addition, developing countries like those in Latin America and Africa have their own endemic diseases that are currently presenting increasing incidence. This increases the challenge involved in reaching a conclusive final diagnostic hypothesis.[19]

Fever was more prevalent among the patients who died than among those who required hospital admission. However, we hypothesized that this may have been due to lack of completion of the reporting questionnaire. Patients who needed hospital care may have less frequently filled out the entire questionnaire.

In our study, the majority of the symptoms were associated with alternative infections, such as influenza, rhinovirus, dengue fever or gastroenteritis. Therefore, we highlight the fact that in areas in which concomitant outbreaks may have been occurring in parallel, use of differential diagnosis should always be borne in mind. Through this, presence of potential secondary pathogens can be ruled out and clinical management of greater accuracy can be implemented for patients for whom a differential diagnosis could not yet be established.

In our study, 8% (n = 2,328) of the patients with SARS-CoV-2 infection progressed to death (in less than three months). The mortality rate in the state of Pernambuco was also slightly higher than the Brazilian national average, possibly because of the economic peculiarities of the region and because of lack of hospital infrastructure for severe cases.[20] In addition, the explanations for this higher mortality rate may relate to delayed diagnosis of the disease, fundamentally caused by limitations on the availability of laboratory tests and trained medical personnel. The explanations may even relate to patients' fear of seeking medical care in the early stage of the disease. This would consequently favor greater severity of clinical condition at the time of late hospital admission.

Furthermore, in the state of Pernambuco, a significant number of municipalities face either geographical or structural difficulties with regard to accessing appropriate medical treatment. One compelling example of these challenges is that, by the end of the period analyzed (May 25, 2020), 98% of the beds available for COVID-19 patients (in isolation wards or ICUs) were occupied. Thus, especially in settings where social and economic discrepancies prevail, this disease is of extreme importance, considering its social, economic or public health-related impacts.

Although the total number of individuals infected with SARS-CoV-2 may have been underestimated, this disease is an important public healthcare issue in Brazil and in developing countries across the globe. Taking into account the entire year of 2018 (when the total number of deaths in the state of Pernambuco was 62,011), the current number of fatalities resulting from SARS-CoV-2-related infections corresponds to the same mortality rate for all other infectious diseases aggregated (including flu, tuberculosis, all forms of hepatitis and HIV).[20] In relation to the body of literature, the mortality rate observed in our study was slightly higher than rates seen in other settings such as China and Italy.[20-23]

Our data suggested that the mortality rate among male Brazilian subjects was higher than the rate among females. This had also been observed in previous studies.[3] Even though it was perceived that female patients accounted for 56.0% of the total number of confirmed cases of infection, there was a higher mortality rate among male patients (55.0%).

There are different hypotheses to explain this fact. Initially, it was suggested that women might be less susceptible to viral infections than men due to higher production of circulating antibodies along with prolonged levels of these biomarkers.[22,23] Additionally, another factor that might explain the lower susceptibility of female patients to the novel coronavirus infection is their production of estrogen and immune factors linked to X chromosomes.[24] In women, the double X chromosome affects the immune system with regard to expression of several elements, such as the expression of toll-like receptor 7 (TLR7).[25] Since TLRs are expressed at higher levels in women and their expression leads to higher immune responses, it has been suggested that these two associated factors might therefore increase resistance to viral infections. Another cell-related explanation for the higher immunoprotection among female patients than among male patients relates to CD4+ T cells.[26] Expression of these cells is higher in women and, thus, a state of higher immune response may be achieved in females than in males, which also would provide a more protected status.[25,26] Lastly, but not least, cultural features can also account for the imbalanced mortality rate between male and female patients.

In Brazil, promotion of healthcare policies for women has brought this population closer to healthcare facilities, both for elective medical procedures and for emergencies.[27,28] In addition, especially in traditional areas like northeastern Brazil, the stereotype of the masculine image, depicted as the family progenitor who never gets sick, can also be related to this sociocultural feature.[20,30] Thus, even with the observed disparity of confirmed cases between males and females, male patients are at higher risk of a fatal outcome than are female patients.

The main strength of the current study was that laboratory data on more than 28,000 confirmed cases were examined. Patients who only had a clinical diagnosis and thus might have been infected with other diseases instead were excluded. Moreover, we included patients from different municipalities in the state of Pernambuco, which provided us with a more heterogeneous dataset, as well as more representative and less biased sample selection.

Essentially, the main limitation of the study related to patient admission, which could be either to isolation wards or to intensive care units. Furthermore, at the time of admission via an emergency department, the notification sheet might not have been completely filled out. This would be due to high demand (several patients arriving hourly), insufficiency of medical personnel and presence of severe cases that required more attention. Additionally, data entry done from multiple locations by many different professionals would lead to inherent contrasts regarding the use of medical terms and descriptions, which would also result in heterogeneity of form-filling. Thus, it was sometimes impossible to obtain complete and accurate medical histories, including information about underlying diseases and a more detailed description of symptoms. Nonetheless, we believe that for healthcare decision-makers and medical researchers, a description of the Brazilian framework of the current pandemic is of utmost importance, in order to understand more specifically the scenario in this country.

CONCLUSION

The novel coronavirus has been dramatically affecting developing countries like Brazil. In this country, the disease has been shown to have a broad range of symptoms and severity, including common symptoms such as coughing, fever, dyspnea and sore throat. Given the overall all-cause mortality rate of 8.06%, it is important that preventive non-pharmacological interventions should be endorsed by healthcare authorities until such time that a safe and universally available vaccine has been produced. In view of the statistical difference between patients who progressed to death and those who recovered, regarding the presence of dyspnea or respiratory distress with oxygen saturation < 95% and fever, medical providers should consider the presence of these conditions to be important prognostic factors.

We emphasize the importance of mandatory reporting systems in terms of enabling better understanding of the distribution and evolution of infectious diseases in Brazil. We therefore recommend that better and more complete investigation of medical histories and better reporting should be implemented in medical units across the country. At the present time, researchers around the world should focus their efforts on undertaking high-quality studies to assess the effectiveness of the most-used pharmacological and non-pharmacological interventions, in addition to the multiple ongoing immunization therapy trials.

REFERENCES

1. Johns Hopkins, Coronavirus Resource Center. COVID-19 Dashboard of the Center for Systems Science and Engineering (CSSE) at Johns Hopkins University (JHU). Available from: https://coronavirus.jhu.edu/map.html. Accessed in 2020 (Jul 3).
2. Guan WJ, Ni ZY, Hu Y, et al. Clinical Characteristics of Coronavirus Disease 2019 in China. N Engl J Med. 2020;382(18):1708-20. PMID: 32109013; doi: 10.1056/NEJMoa2002032.
3. Borges do Nascimento IJ, Cacic N, Abdulazeem HM, et al. Novel Coronavirus Infection (COVID-19) in Humans: A Scoping Review and Meta-Analysis. J Clin Med. 2020;9(4):941. PMID: 32235486; doi: 10.3390/jcm9040941.
4. Vaira LA, Salzano G, Deiana G, De Riu G. Anosmia and Ageusia: Common Findings in COVID-19 Patients. Laryngoscope. 2020;130(7):1787. PMID: 32237238; doi: 10.1002/lary.28692.
5. Gilani S, Roditi R, Naraghi M. COVID-19 and anosmia in Tehran, Iran. Med Hypotheses. 2020;141:109757. PMID: 32344276; doi: 10.1016/j.mehy.2020.109757.
6. Joob B, Wiwanitkit V. COVID-19 can present with a rash and be mistaken for dengue. J Am Acad Dermatol. 2020;82(5):e177. PMID: 32213305; doi: 10.1016/j.jaad.2020.03.036.
7. Sociedade Brasileira de Dermatologia. Manifestações na pele devido à COVID-19 causadas pelo vírus SARS-CoV-2: fatos e fotos até 17 de abril de 2020. Available from: https://www.sbd.org.br/mm/cms/2020/04/21/artigo-manifestacoes-pele-dr-paulo-criado-revisado-final.pdf. Accessed in 2020 (Jul 3).
8. Muniz BC, Milito MA, Marchiori E. COVID-19 – Computed tomography findings in two patients in Petrópolis, Rio de Janeiro, Brazil. Rev Soc Bras Med Trop. 2020;53:e20200147. PMID: 32321099; doi: 10.1590/0037-8682-0147-2020.
9. Chate RC, Fonseca EKUN, Passos RBD, et al. Presentation of pulmonary infection on CT in COVID-19: initial experience in Brazil. J Bras Pneumol. 2020;46(2):e20200121. PMID: 32294718; doi: 10.36416/1806-3756/e20200121.
10. Bastos LS, Niquini RP, Lana RM, et al. COVID-19 e hospitalizações por SRAG no Brasil: uma comparação até a 12ª semana epidemiológica de 2020 [COVID-19 and hospitalizations for SARI in Brazil: a comparison up to the 12th epidemiological week of 2020]. Cad Saude Publica. 2020;34(4):e00070120. PMID: 32321075; doi: 10.1590/0102-311X00070120.
11. Ministério da Saúde. Brasil. Painel Coronavirus. Available from: https://covid.saude.gov.br. Accessed in 2020 (Jul 3).
12. Governo do Estado do Pernambuco. Geografia de Pernambuco. Available from: http://www.pe.gov.br/conheca/geografia/. Accessed in 2020 (Jul 3).
13. Ministério da Economia. Brasil. Radar IDHM: evolução do ISHM e de seus índices componentes no período de 2012 a 2017. Brasília: IPEA, PNUD, FJP; 2019. Available from: http://atlasbrasil.org.br/2013/data/rawData/Radar%20IDHM%20PNADC_2019_Book.pdf. Accessed in 2020 (Jul 3).
14. Secretaria do Planejamento e Gestão, Secretaria de Saúde, Agência Estadual de Tecnologia da Informação. Painel de casos de doença pelo coronavirus 2019 (COVID-19) em Pernambuco, no Brasil e no Mundo. Available from: https://dados.seplag.pe.gov.br/apps/corona.html. Accessed in 2020 (Jul 3).

15. Menezes PL, Garner DM, Valenti VE. Brazil is projected to be the next global COVID-19 pandemic epicenter. medRxiv preprint. doi: 10.1101/2020.04.28.20083675.
16. Darlington S, Crespo G, John T. Latin America is now the "epicenter of the outbreak," says health official. CNN. Available from: https://edition.cnn.com/2020/05/26/americas/latin-america-coronavirus-toll-intl/index.html. Accessed in 2020 (Jul 3).
17. Lindoso JA, Lindoso AA. Neglected tropical diseases in Brazil. Rev Inst Med Trop Sao Paulo. 2009;51(5):247-53. PMID: 19893976; doi: 10.1590/s0036-46652009000500003.
18. Barros MB. Social inequality in health: revisiting moments and trends in 50 years of publication of RSP. Rev Saude Publica. 2017;51(0):17. PMID: 28355334; doi: 10.1590/S1518-8787.2017051000156.
19. TelessaúdeRS. Universidade Federal do Rio Grande do Sul. Quais são os diagnósticos diferenciais da COVID-19? 2020. Available from: https://www.ufrgs.br/telessauders/perguntas/quais-sao-os-diagnosticos-diferenciais-da-covid-19/. Accessed in 2020 (Jul 3).
20. Ministério da Saúde. Secretaria de Vigilância em Saúde. Sistema de Informação sobre Mortalidade – SIM. Available from: http://tabnet.datasus.gov.br/cgi/tabcgi.exe?sim/cnv/obt10uf.def. Accessed in 2020 (Jul 3).
21. Lippi G, Mattiuzzi C, Sanchis-Gomar F, Henry BM. Clinical and demographic characteristics of patients dying from COVID-19 in Italy vs China. [published online ahead of print, 2020 Apr 10]. J Med Virol. 2020;10.1002/jmv.25860. PMID: 32275075; doi: 10.1002/jmv.25860.
22. Li LQ, Huang T, Wang YG, et al. COVID-19 patients' clinical characteristics, discharge rate, and fatality rate of meta-analysis. J Med Virol. 2020;92(6):577-83. PMID: 32162702; doi: 10.1002/jmv.25757.
23. Bernardi S, Toffoli B, Tonon F, et al. Sex Differences in Proatherogenic Cytokine Levels. Int J Mol Sci. 2020;21(11):3861. PMID: 32485823; doi: 10.3390/ijms21113861.
24. Ter Horst R, Jaeger M, Smeekens SP, et al. Host and Environmental Factors Influencing Individual Human Cytokine Responses. Cell. 2016;167(4):1111-24. PMID: 27814508; doi: 10.1016/j.cell.2016.10.018.
25. Arnold AP. The organizational-activational hypothesis as the foundation for a unified theory of sexual differentiation of all mammalian tissues. Horm Behav. 2009;55(5):570-8. PMID: 19446073; doi: 10.1016/j.yhbeh.2009.03.011.
26. Conti P, Younes A. Coronavirus COV-19/SARS-CoV-2 affects women less than men: clinical response to viral infection. J Biol Regul Homeost Agents. 2020;34(2):10.23812. Available from: https://pesquisa.bvsalud.org/controlecancer/resource/pt/mdl-32253888. Accessed in 2020 (Jul 3).
27. Qureshi S, Medzhitov R. Toll-like receptors and their role in experimental models of microbial infection. Genes Immun. 2003;4(2):87-94. PMID: 12618855; doi: 10.1038/sj.gene.6363937.
28. De Oliveira MM, Daher DV, Da Silva JL, Andrade SS. Men's health in question: seeking assistance in primary health care. Cienc Saude Colet. 2015;20(1):273-8. PMID: 25650621; doi: 10.1590/1413-81232014201.21732013.
29. Gomes R. Sexualidade Masculina, Gênero e Saúde. Rio de Janeiro: Fiocruz; 2008.
30. Gomes R, Nascimento EF, Araújo FC. Por que os homens buscam menos os serviços de saúde do que as mulheres? As explicações de homens com baixa escolaridade e homens com ensino superior [Why do men use health services less than women? Explanations by men with low versus higher education]. Cad Saude Publica 2007;23(3):565-74. PMID: 17334571; doi: 10.1590/s0102-311x2007000300015.

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SARS-CoV-2 and arbovirus infection: a rapid systematic review

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ABSTRACT

BACKGROUND: The numbers of cases of arboviral diseases have increased in tropical and subtropical regions while the coronavirus disease (COVID-19) pandemic overwhelms healthcare systems worldwide. The clinical manifestations of arboviral diseases, especially dengue fever, can be very similar to COVID-19, and misdiagnoses are still a reality. In the meantime, outcomes for patients and healthcare systems in situations of possible syndemic have not yet been clarified.

OBJECTIVE: We set out to conduct a systematic review to understand and summarize the evidence relating to clinical manifestations, disease severity and prognoses among patients coinfected with severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) and arboviruses.

METHODS: We conducted a rapid systematic review with meta-analysis, on prospective and retrospective cohorts, case-control studies and case series of patients with confirmed diagnoses of SARS-CoV-2 and arboviral infection. We followed the Cochrane Handbook recommendations. We searched EMBASE, MEDLINE, Cochrane Library, LILACS, Scopus and Web of Science to identify published, ongoing and unpublished studies. We planned to extract data and assess the risk of bias and the certainty of evidence of the studies included, using the Quality in Prognosis Studies tool and the Grading of Recommendations Assessment.

RESULTS: We were able to retrieve 2,407 citations using the search strategy, but none of the studies fulfilled the inclusion criteria.

CONCLUSION: The clinical presentations, disease severity and prognoses of patients coinfected with SARS-CoV-2 and arboviruses remain unclear. Further prospective studies are necessary in order to provide useful information for clinical decision-making processes.

PROTOCOL REGISTRATION NUMBER IN THE PROSPERO DATABASE: CRD42020183460

INTRODUCTION

Since the novel severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) emerged, the coronavirus disease (COVID-19) has spread worldwide. On March 11, 2020, the World Health Organization declared the outbreak of the COVID-19 disease to be a pandemic event and a Public Health Emergency of International Concern. In the meantime, its epidemiological picture has been constantly changing. Up to July 9, 2020, almost 12 million cases had been confirmed, with 545,481 deaths, in 213 countries and territories around the world, as reported to the World Health Organization (WHO).[1,2]

Amidst this pandemic, the world still needs to deal with the burden of various other diseases that present overlapping occurrences. Whether these are communicable or non-communicable, much remains to be learned regarding how to manage them all, so as to simultaneously mitigate issues relating to healthcare system saturation. In particular, countries located in tropical and subtropical regions, where arboviral diseases occur abundantly, are still dealing with these old endemics, which for some countries are epidemic diseases.[3-6] Individuals affected by these various diseases may present clinical features that range from subclinical to severe forms, such as encephalitic or hemorrhagic forms, with very significant fatality rates.[5] It has been estimated that more than two billion people live in environments suitable for arbovirus dissemination.[7]

Throughout the world, epidemiologists have been warning of temporal coincidence between endemic peaks and outbreaks relating to arboviruses and COVID-19.[8,9] The constantly evolving knowledge of COVID-19 and its characteristics suggests that it and arboviral diseases share similarities with regard to clinical manifestations and laboratory findings.[4,7] So far, dengue fever

is the arboviral disease that has been found to share the largest number of clinical features with COVID-19, including the excessive systemic inflammatory response that is induced by both diseases.[4] The effects of these diseases when a patient is infected with only one of them is already known, albeit more so with regard to arboviral diseases than to COVID-19. However, there still is a lack of information on the impact of coinfection with these diseases on patients' clinical manifestations, the potential for severe disease and the prognosis. This knowledge is of vital importance for enabling adequate medical approaches towards these types of cases and, consequently, for applying the most appropriate treatment.

OBJECTIVE

The aim of this rapid systematic review was to summarize the evidence that exists concerning the impact of coinfection relating to SARS-CoV-2 and arboviruses, with regard to clinical features, disease severity and prognoses among coinfected patients.

METHODS

Protocol and registration

The protocol for this rapid systematic review was registered within the PROSPERO (International Prospective Register of Systematic Reviews) platform, under the protocol number CRD42020183460. Additionally, we developed and published a protocol on the SciELO preprints platform (https://preprints.scielo.org/index.php/scielo/preprint/view/346).

This study was developed at the Cochrane Brazil Center and it followed the Cochrane methodology.[10]

Eligibility criteria

Types of studies

Cohort studies, case-control studies and case series that described the clinical presentation, severity or prognosis of patients coinfected with SARS-CoV-2 and arboviruses were deemed to be eligible for inclusion.

Types of participants

Patients of any age who tested positive for SARS-CoV-2 infection and positive for any type of arboviral infection were included.

Types of comparators

Patients mono-infected with SARS-CoV-2 were used as comparators.

Outcome measurements

The primary outcomes evaluated were mortality rate, length of hospital stay and disease severity.

The secondary outcomes evaluated were clinical characteristics, length of intensive care unit stay, need for invasive mechanical ventilation, hospitalization rate and time taken to achieve clinical improvement.

Information sources and search strategy

We developed a search strategy (**Appendix 1**) to retrieve eligible studies from the following databases: MEDLINE, EMBASE, the Cochrane Central Register of Controlled Trials, BVS Portal, Scopus, Web Of Science, SciELO and LILACS (Literatura Latino-Americana e do Caribe em Ciências da Saúde). Additional COVID-19 specific databases such as Epistemonikos COVID-19 L·OVE platform, ClinicalTrial.gov and the World Health Organization International Clinical Trials Registry Platform (WHO ICTRP) were also searched for ongoing studies.

To improve the range of studies that we identified, we applied specific search strategies within large open-source databases, such as Mendeley Data and Figshare. Lastly, we applied the snowballing technique, in which the reference lists of the studies selected were also screened to identify possible published papers for inclusion in this review. There were no restrictions relating to languages or publication site. All studies published before May 18, 2020 were considered within this search strategy.

Study selection and data extraction

The titles and abstracts of citations identified through the search strategy described above were screened for eligibility by one author of this review. When duplicated citations were found, only one of them was considered for inclusion. If reports using the same participants but with different outcome measurements or different assessment time points were found, these reports would be considered as parts of only one study. Studies that clearly did not fulfill the eligibility criteria would be excluded and the remaining articles would be fully read and assessed by two authors for inclusion in the review. Disagreements between the authors, relating to this matter, would be resolved by a third author. To optimize the screening process and selection of studies, the Rayyan QCRI[11] software was used.

We planned that two authors of this review would independently conduct the data extraction from the studies included. After that, they would together discuss any conflicts found among their results or discrepancies within this process. If necessary, a third author would mediate and resolve any conflicts. The data would be extracted through a Microsoft Excel file and would comprise information relating to study design and setting, demographic and clinical characteristics, time points used for the assessments, epidemiological characteristics, outcomes, numbers of participants, means, standard deviations, standard errors, medians, interquartile ranges, minimums, maximums, 95% confidence intervals (CI) (for continuous outcomes) and p-values, among other information.

Risk of bias in individual studies and risk of bias across studies

We planned to perform critical appraisals on the studies included, using the Quality in Prognosis Studies (QUIPS) tool,[12] and to assess the certainty of evidence using the GRADE approach (Grading of Recommendations Assessment, Development and Evaluation).[8,13,14]

Summary measurements and synthesis of results

We planned to assess the possibility of pooling the results from the studies included into meta-analyses when at least two studies were sufficiently homogeneous in terms of design, participants and outcome measurements. If insufficient information or heterogeneous studies were found, we planned to summarize the results through a qualitative synthesis.

If the response of interest was provided by a continuous variable, we planned to perform the analysis in terms of the mean difference (MD) or the standardized mean difference (SMD; via Hedge's g and Cohen's d). Hazard ratios (unadjusted crude or adjusted) or odds ratios (OR) were to be pooled in cases of a dichotomous response, for hospital admission, intensive care unit admission and/or respiratory support and mortality. All the other parameters, such as standard deviations (for MD or SMD), numbers of events, relative risks or odds ratios, were planned to be pooled. In all cases, we planned to use the generic inverse variance method with a random-effects model.

Dealing with missing data

For studies that did not provide the mean and the associated standard deviation (SD) parameters, we planned to use the information and results reported in the text or tables and to provide an inference from those findings. Additionally, we planned to contact the principal investigators of the studies included, to ask for additional data or to clarify specific concerns relating to the studies. In the absence of any response from those authors, we planned to present the data in a descriptive manner, so as to avoid making undue inferences.

Assessment of heterogeneity

We planned to use Cochran's Q test to assess the presence of heterogeneity. We took P-values < 0.1 to be the threshold for indicating that heterogeneity was present. In addition, we planned to assess statistical heterogeneity by examining the Higgins I^2 statistic, following these thresholds: < 25%, no heterogeneity; 25% to 49%, low heterogeneity; 50% to 74%, moderate heterogeneity; and ≥ 75%, high heterogeneity.

RESULTS

The search strategy developed retrieved 2,407 records (**Figure 1**). After removal of duplicates and screening of the citations, we were not able to find a single study that fulfilled the eligibility criteria of this systematic review.

DISCUSSION

This rapid systematic review was the first of its kind, i.e. with the aim of summarizing the evidence relating to clinical features, disease severity and prognoses among patients coinfected with SARS-CoV-2 and arboviruses. While extraordinary attention has been given to finding effective interventions for treating patients with COVID-19, this review highlights that no significant efforts have been made to look at situations of coinfection with SARS-CoV-2 and the arboviral diseases that are already endemic in tropical and subtropical regions, and present in some temperate regions.[6]

Among over 2,000 records screened through the perspective of our search strategy, there were no studies of either observational or experimental design that had been fully performed to address any of the important aspects of coinfection between SARS-CoV-2 and arboviruses. Thus, our findings revealed an absence of published papers or other research that addressed this subject.

The limitations of this review with regard to finding eligible studies could have various explanations. Major gaps in the response to COVID-19 characterized the beginning of the pandemic.[15] It is very likely that any initial COVID-19 patients who may have actually been coinfected were treated as presenting the COVID-19 disease only. Once a test result positive for SARS-CoV-2 had been obtained, the diagnosis would have been established and other infections may not have been considered. The opposite could also be true: if patients presented test results positive for an arboviral disease and did not progress to worsening of their health condition or symptoms, COVID-19 might not have been considered.

Part of the problem is a lack of adequate testing, for both conditions. In Brazil, for example, it has been estimated that only 23% of dengue fever cases are tested on a daily basis.[16] However, this reality is not exclusive to the Brazilian context; the majority of the diagnoses of arboviral diseases in endemic regions, which are distinguished mostly as low-income countries, are defined through clinical-epidemiological assessment, due to lack of resources relating to the availability of testing.[17-19]

It is possible that the natural learning curve generated through responding to and managing COVID-19, including adjustment of healthcare services to the new routine, will lead to production of more reports relating to occurrences of arboviral diseases diagnosed simultaneously with COVID-19. Given that the response to the COVID-19 pandemic is still evolving, the gaps in knowledge still to be filled need to include understanding the development of coinfections between SARS-CoV-2 and arboviruses. This is critically important for development of appropriate treatment planning, in order to avoid worsening clinical status among coinfected cases.

Because of the similarities between the clinical and laboratory features of COVID-19 and arboviral diseases, differentiating between them can be a challenge,[17,20,21] unless specific testing can be conducted. These similarities can lead to misdiagnosis of these diseases, and thus contribute to delayed treatment, thereby increasing the chances of development of greater severity of such cases and ultimately leading to death.[20,22,23]

It is noteworthy that presence of skin rashes and exanthema has been well established as having high predictive value as signs and symptoms for COVID-19.[24-27] Skin rashes and exanthema are also present within the development of some arboviral diseases, especially dengue fever. A study conducted in Pakistan[21] reported a misdiagnosed COVID-19 case: after two serologically negative tests for SARS-CoV-2, antibody testing for dengue fever showed positive immunoglobulin M (IgM) titers and borderline NS1 antigen results. On the other hand, a study conducted in Thailand[22] reported a case that was initially misdiagnosed as dengue fever due to the presence of a skin rash with petechiae, which was later correlated with the COVID-19 disease. In the same way, two cases reported from Singapore[20] were initially misdiagnosed as dengue fever through rapid tests for dengue fever that provided false-positive results. As the health condition of these patients gradually worsened, they were tested for SARS-CoV-2 and confirmed as positive cases of COVID-19.

Unfortunately, most cases of arboviral diseases relate to individuals living in low-income countries, where access to the healthcare system is difficult and of poor quality, due to lack of resources. Even worse, this scenario is faced within situations in which the healthcare system is in a fragile state, which is the reality for the majority of tropical countries.[8,28]

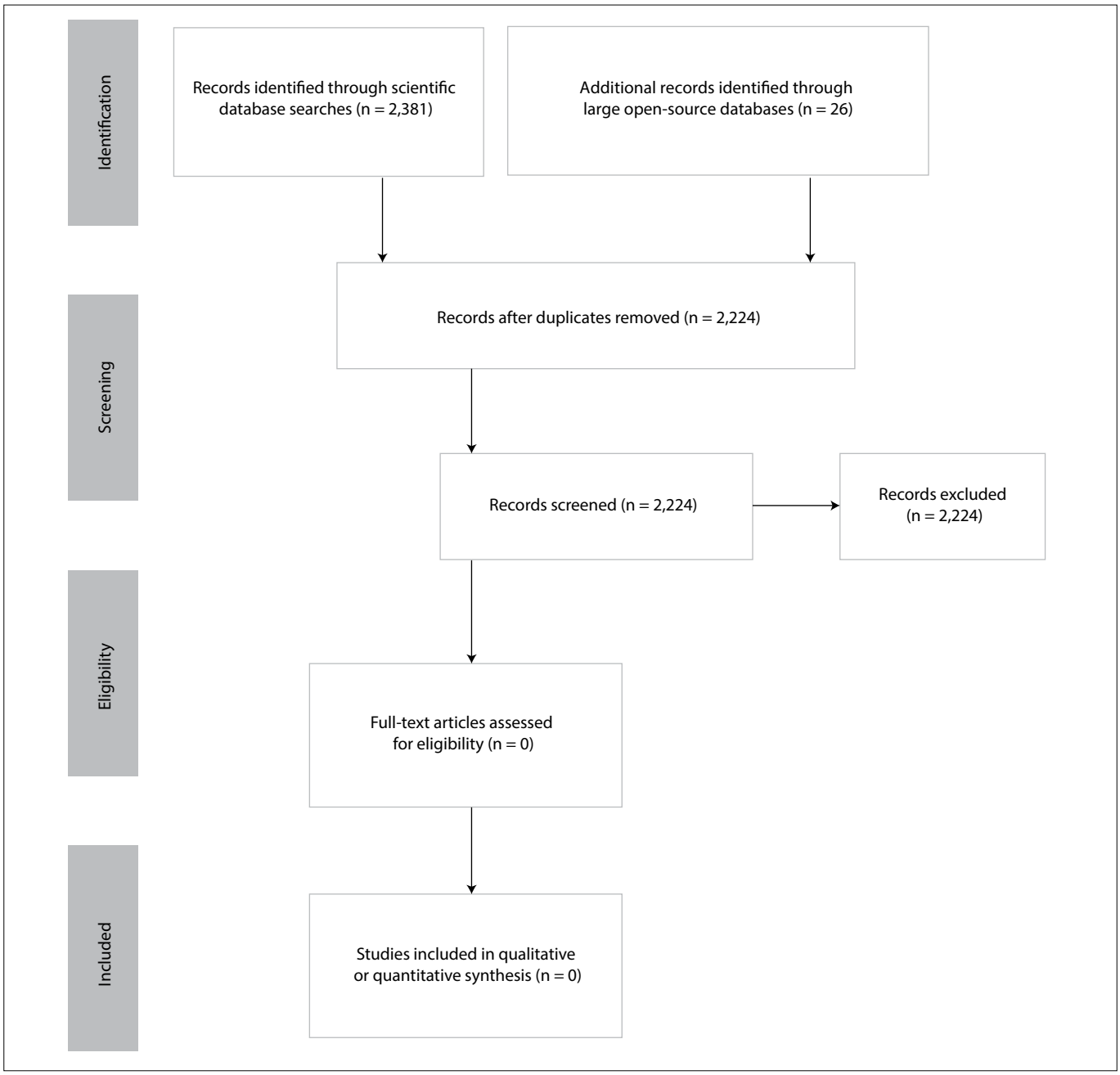

Figure 1. Flow diagram of the study selection process, conducted on June 20, 2020.

Ideally, rapid, sensitive, accurate and accessible tools for diagnosing the different types of arboviral diseases and COVID-19 should be considered vital. Moreover, allocation of resources to manage and respond adequately to the pandemic should be well balanced.[29,30]

Nevertheless, knowledge of the impact of this type of coinfection on patients is still unclear at best. Much remains in the realm of the unknown. Overlapping of these diseases would affect the healthcare system, which is already overwhelmed. The expression of these diseases among patients and healthcare systems in the form of a possible syndemic[31,32] remains unclear. Therefore, we undertook a systematic search of the literature to look for outcomes from coinfection between SARS-CoV-2 and arboviruses, including their clinical presentations, disease severity and prognoses, in order to provide support for decision-makers in future scenarios of a possible syndemic.

Thinking about this matter is of vital importance, for several reasons. One of these is that there remains a need to understand what impact these types of coinfections have on the clinical manifestations, disease severity and prognoses of coinfected patients. It has already been established that both COVID-19 and dengue fever induce cytokine storms, multi-organ failure and shock.[33] How the immune system responds to simultaneous occurrence of these diseases is a matter that has not been clarified yet.

Given the lack of evidence found, we call on researchers to conduct studies on arboviral infections within the context of the COVID-19 pandemic. Prospective cohort studies are strongly recommended within this scenario. Our research has revealed a possibly substantial public health threat that needs to be addressed. This also highlights the importance for healthcare professionals who are on the front line of providing care for patients to consider the possibility of coinfection of SARS-CoV-2 and arboviruses, especially in tropical and subtropical regions. We hope that this review may help healthcare professionals to broaden their approach to diagnosis and treatment, and that this may stimulate more vital research, in a timely manner.

CONCLUSION

The clinical presentation, disease severity and prognoses of patients coinfected with SARS-CoV-2 and arboviruses remain unclear. Given that no eligible studies have been found to date through this systematic review, no conclusions relating to this research question can be drawn. Since this study is an ongoing systematic review, we hope to find evidence that can fill the gap in scientific information, in our subsequent publication updates.

REFERENCES

1. World Health Organization. WHO Coronavirus Disease (COVID-19) Dashboard. Geneva: WHO; 2020. Available from: https://covid19.who.int/. Accessed in 2020 (Aug 18).
2. World Health Organization. Events as they happen. Rolling updates on coronavirus disease (COVID-19). Geneva: WHO; 2020. Available from: https://www.who.int/emergencies/diseases/novel-coronavirus-2019/events-as-they-happen. Accessed in 2020 (Aug 18).
3. World Health Organization. Dengue and Severe Dengue. Geneva; WHO; 2020. Available from: http://www.who.int/mediacentre/factsheets/fs117/en/. Accessed in 2020 (Jul 7).
4. Saavedra-Velasco M, Chiara-Chilet C, Pichardo-Rodriguez R, Grandez-Urbina A, Inga-Berrospi F. Coinfección entre dengue y COVID-19: Necesidad de abordaje en zonas endémicas [Coinfection between dengue and covid-19: need for approach in endemic zones]. Revista de la Facultad de Ciencias Medicas de Cordoba. 2020;77(1):52-4. doi: 10.31053/1853.0605.v77.n1.28031.
5. Huang YS, Higgs S, Vanlandingham DL. Emergence and re-emergence of mosquito-borne arboviruses. Curr Opin Virol. 2019;34:104-9. PMID: 30743191; doi: 10.1016/j.coviro.2019.01.001.
6. Liang G, Gao X, Gould EA. Factors responsible for the emergence of arboviruses; strategies, challenges and limitations for their control. Emerg Microbes Infect. 2015;4(3):e18. PMID: 26038768; doi: 10.1038/emi.2015.18.
7. Martinez JD, Garza JAC, Cuellar-Barboza A. Going viral 2019: Zika, chikungunya, and dengue. Dermatol Clin. 2019;37(1):95-105. PMID: 30466692; doi: 10.1016/j.det.2018.07.008.
8. Lorenz C, Azevedo TS, Chiaravalloti-Neto F. COVID-19 and dengue fever: A dangerous combination for the health system in Brazil. Travel Med Infect Dis. 2020;35:101659. PMID: 32278756; doi: 10.1016/j.tmaid.2020.101659.
9. Cimerman S, Chebabo A, Cunha CAD, Rodríguez-Morales AJ. Deep impact of COVID-19 in the healthcare of Latin America: the case of Brazil. Braz J Infect Dis. 2020;24(2):93-5. PMID: 32335078; doi: 10.1016/j.bjid.2020.04.005.
10. Higgins JPT, Green S. Cochrane handbook for systematic reviews of interventions. Chichester (UK): John Wiley & Sons; 2011.
11. Ouzzani M, Hammady H, Fedorowicz Z, Elmagarmid A. Rayyan-a web and mobile app for systematic reviews. Syst Rev. 2016;5(1):210. PMID: 27919275; doi: 10.1186/s13643-016-0384-4.
12. Hayden JA, van der Windt DA, Cartwright JL, Côté P, Bombardier C. Assessing bias in studies of prognostic factors. Ann Intern Med. 2013;158(4):280-6. PMID: 23420236; doi: 10.7326/0003-4819-158-4-201302190-00009.
13. Guyatt GH, Oxman AD, Vist GE, et al. GRADE: an emerging consensus on rating quality of evidence and strength of recommendations. BMJ. 2008;336(7650):924-6. PMID: 18436948; doi: 10.1136/bmj.39489.470347.AD.
14. Guyatt G, Oxman AD, Akl EA, et al. GRADE guidelines: 1. Introduction-GRADE evidence profiles and summary of findings tables. J Clin Epidemiol. 2011;64(4):383-94. PMID: 21195583; doi: 10.1016/j.jclinepi.2010.04.026.
15. Chersich MF, Gray G, Fairlie L, et al. COVID-19 in Africa: care and protection for frontline healthcare workers. Global Health. 2020;16(1):46. PMID: 32414379; doi: 10.1186/s12992-020-00574-3.
16. Genovese G, Colonna C, Marzano AV. Varicella-like exanthem associated with COVID-19 in an 8 year old girl: A diagnostic clue? Pediatr Dermatol. 2020;37(3):435-6. PMID: 32315079; doi: 10.1111/pde.14201.
17. Yan G, Pang L, Cook AR, et al. Distinguishing Zika and dengue viruses through simple clinical assessment, Singapore. Emerg Infect Dis. 2018;24(8):1565-8. PMID: 30016242; doi: 10.3201/eid2408.171883.

18. Magalhaes T, Chalegre KDM, Braga C, Foy BD. The Endless Challenges of Arboviral Diseases in Brazil. Trop Med Infect Dis. 2020;5(2):75. PMID: 32397512; doi: 10.3390/tropicalmed5020075.
19. Rahman MT, Sobur MA, Islam MS, Toniolo A, Nazir KHMNH. Is the COVID-19 pandemic masking dengue epidemic in Bangladesh? J Adv Vet Anim Res. 2020;7(2):218-9. PMID: 32607352; doi: 10.5455/javar.2020.g412.
20. Yan G, Lee CK, Lam LTM, et al. Covert COVID-19 and false-positive dengue serology in Singapore. Lancet Infect Dis. 2020;20(5):536. PMID: 32145189; doi: 10.1016/S1473-3099(20)30158-4.
21. Bokhari SMMA, Mahmood F, Bokhari SMSA. Case Report: Diagnosis of COVID-19 versus Tropical Diseases in Pakistan. Am J Trop Med Hyg. 2020;103(1):77-8. PMID: 32372752; doi: 10.4269/ajtmh.20-0356.
22. Joob B, Wiwanitkit V. COVID-19 can present with a rash and be mistaken for Dengue. J Am Acad Dermatol. 2020;82(5):e177. PMID: 32213305; doi: 10.1016/j.jaad.2020.03.036.
23. Joob B, Wiwanitkit V. COVID-19 in medical personnel: observation from Thailand. J Hosp Infect 2020;104(4):453. PMID: 32114054; doi: 10.1016/j.jhin.2020.02.016.
24. Marzano AV, Genovese G, Fabbrocini G, et al. Varicella-like exanthem as a specific COVID-19–associated skin manifestation: Multicenter case series of 22 patients. J Am Acad Dermatol. 2020;83(1):280-5. PMID: 32305439; doi: 10.1016/j.jaad.2020.04.044.
25. Ortega-Quijano D, Jimenez-Cauhe J, Burgos-Blasco P, Jimenez-Gomez N, Fernandez-Nieto D. Reply to "Varicella-like exanthem as a specific COVID-19-associated skin manifestation: multicenter case series of 22 patients": Discussing specificity. J Am Acad Dermatol. 2020;83(1):e87. PMID: 32380215; doi: 10.1016/j.jaad.2020.04.156.
26. Sachdeva M, Gianotti R, Shah M, et al. Cutaneous manifestations of COVID-19: Report of three cases and a review of literature. J Dermatol Sci. 2020;98(2):75-81. PMID: 32381430; doi: 10.1016/j.jdermsci.2020.04.011.
27. Recalcati S. Cutaneous manifestations in COVID-19: a first perspective. J Eur Acad Dermatol Venereol. 2020;34(5):e212-e213. PMID: 32215952; doi: 10.1111/jdv.16387.
28. Rodriguez-Morales AJ, Gallego V, Escalera-Antezana JP, et al. COVID-19 in Latin America: The implications of the first confirmed case in Brazil. Travel Med Infect Dis. 2020;35:101613. PMID: 32126292; doi: 10.1016/j.tmaid.2020.101613.
29. Ribeiro VST, Telles JP, Tuon FF. Arboviral diseases and COVID-19 in Brazil: Concerns regarding climatic, sanitation and endemic scenario [published online ahead of print, 2020 May 28]. J Med Virol. 2020;10.1002/jmv.26079. PMID: 32462677; doi: 10.1002/jmv.26079.
30. Navarro JC, Arrivillaga-Henríquez J, Salazar-Loor J, Rodriguez-Morales AJ. COVID-19 and dengue, co-epidemics in Ecuador and other countries in Latin America: Pushing strained health care systems over the edge [published online ahead of print, 2020 Apr 5]. Travel Med Infect Dis. 2020;101656. PMID: 32268196; doi: 10.1016/j.tmaid.2020.101656.
31. Singer M. Introduction to syndemics: A critical systems approach to public and community health. San Francisco, CA: John Wiley & Sons; 2009. ISBN: 978-0-470-47203-3.
32. Singer M, Bulled N, Ostrach B, Mendenhall E. Syndemics and the biosocial conception of health. Lancet. 2017;389(10072):941-50. PMID: 28271845; doi: 10.1016/S0140-6736(17)30003-X.
33. Suwanmanee S, Luplertlop N. Dengue and Zika viruses: lessons learned from the similarities between these Aedes mosquito-vectored arboviruses. J Microbiol. 2017;55(2):81-9. PMID: 28120186; doi: 10.1007/s12275-017-6494-4.

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Milby KM: conceptualization, methodology, selection of the studies, formal analysis, discussion of the results, validation, writing of the whole text and of the original draft and review and approval of the final draft; Atallah AN: discussion of the results, drafting of the final text and review and approval of the final draft; Rocha-Filho CR: drafting of the text, selection of studies, discussion of the results, writing the discussion and review and approval of the final draft; Pinto ACPN: conceptualization, methodology, selection of the studies, formal analysis, validation, discussion of the results, writing of the original draft and review and approval of the final draft; Rocha AP: drafting of the methodology, discussion of the results and review and approval of the final draft; Reis FSA: drafting of the methodology, discussion of the results and review and approval of the final draft; Carvas Junior N: drafting of the statistical analysis, discussion of the results and review and approval of the final draft; Civile VT: drafting of the statistical analysis, discussion of the results and review and approval of the final draft; Santos RRP: drafting of the statistical analysis, methodology, formal analysis, discussion of the results and review and approval of the final draft: Ferla LJ: selection of the studies, methodology, discussion of the results and review and approval of the final draft; Trevisani GFM: selection of the studies, discussion of the results and review and approval of the final draft; Ramalho GS: selection of the studies, methodology, discussion of the results and review and approval of the final draft; Puga MES: search strategy, discussion of the results and review and approval of the final draft; and Trevisani VFM: discussion of the results, drafting of the final text and review and approval of the final draft

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APPENDIX 1. Search strategies

COCHRANE LIBRARY

#1 (COVID 19) OR (COVID-19) OR (2019-nCoV) OR (nCoV) OR (Covid19) OR (SARS-CoV) OR (SARSCov2 or ncov*) OR (SARSCov2) OR (2019 coronavirus*) OR (2019 corona virus*) OR (Coronavirus (COVID-19)) OR (2019 novel coronavirus disease) OR (COVID-19 pandemic) OR (COVID-19 virus infection) OR (coronavirus disease-19) OR (2019 novel coronavirus infection) OR (2019-nCoV infection) OR (coronavirus disease 2019) OR (2019-nCoV disease) OR (COVID-19 virus disease) OR "severe acute respiratory syndrome coronavirus 2" [Supplementary Concept] OR (Wuhan coronavirus) OR (Wuhan seafood market pneumonia virus) OR (COVID19 virus) OR (COVID-19 virus) OR (coronavirus disease 2019 virus) OR (SARS-CoV-2) OR (SARS2) OR (2019-nCoV) OR (2019 novel coronavirus)

EMBASE

#1 'covid 19'/exp OR (COVID 19) OR (COVID-19) OR (2019-nCoV) OR (nCoV) OR (Covid19) OR (SARS-CoV) OR (SARSCov2 or ncov*) OR (SARSCov2) OR (2019 coronavirus*) OR (2019 corona virus*) OR (Coronavirus (COVID-19)) OR (2019 novel coronavirus disease) OR (COVID-19 pandemic) OR (COVID-19 virus infection) OR (coronavirus disease-19) OR (2019 novel coronavirus infection) OR (2019-nCoV infection) OR (coronavirus disease 2019) OR (2019-nCoV disease) OR (COVID-19 virus disease) OR (severe acute respiratory syndrome coronavirus 2) OR (Wuhan coronavirus) OR (Wuhan seafood market pneumonia virus) OR (COVID19 virus) OR (COVID-19 virus) OR (coronavirus disease 2019 virus) OR (SARS-CoV-2) OR (SARS2) OR (2019-nCoV) OR (2019 novel coronavirus)

WEB OF SCIENCE

#1 (COVID 19) OR (COVID-19) OR (2019-nCoV) OR (nCoV) OR (Covid19) OR (SARS-CoV) OR (SARSCov2 or ncov*) OR (SARSCov2) OR (2019 coronavirus*) OR (2019 corona virus*) OR (Coronavirus (COVID-19)) OR (2019 novel coronavirus disease) OR (COVID-19 pandemic) OR (COVID-19 virus infection) OR (coronavirus disease-19) OR (2019 novel coronavirus infection) OR (2019-nCoV infection) OR (coronavirus disease 2019) OR (2019-nCoV disease) OR (COVID-19 virus disease) OR (severe acute respiratory syndrome coronavirus 2) OR (Wuhan coronavirus) OR (Wuhan seafood market pneumonia virus) OR (COVID19 virus) OR (COVID-19 virus) OR (coronavirus disease 2019 virus) OR (SARS-CoV-2) OR (SARS2) OR (2019-nCoV) OR (2019 novel coronavirus)

SCOPUS

#1 (COVID 19) OR (COVID-19) OR (2019-nCoV) OR (nCoV) OR (Covid19) OR (SARS-CoV) OR (SARSCov2 or ncov*) OR (SARSCov2) OR (2019 coronavirus*) OR (2019 corona virus*) OR (Coronavirus (COVID-19)) OR (2019 novel coronavirus disease) OR (COVID-19 pandemic) OR (COVID-19 virus infection) OR (coronavirus disease-19) OR (2019 novel coronavirus infection) OR (2019-nCoV infection) OR (coronavirus disease 2019) OR (2019-nCoV disease) OR (COVID-19 virus disease) OR (severe acute respiratory syndrome coronavirus 2) OR (Wuhan coronavirus) OR (Wuhan seafood market pneumonia virus) OR (COVID19 virus) OR (COVID-19 virus) OR (coronavirus disease 2019 virus) OR (SARS-CoV-2) OR (SARS2) OR (2019-nCoV) OR (2019 novel coronavirus)

PORTAL REGIONAL BVS

MH:"Infecções por Coronavirus" OR (Infecções por Coronavirus) OR (Infecciones por Coronavirus) OR (Coronavirus Infections) OR (COVID-19) OR (COVID 19) OR (Doença pelo Novo Coronavírus (2019-nCoV)) OR (Doença por Coronavírus 2019-nCoV) OR (Doença por Novo Coronavírus (2019-nCoV)) OR (Epidemia de Pneumonia por Coronavirus de Wuhan) OR (Epidemia de Pneumonia por Coronavírus de Wuhan) OR (Epidemia de Pneumonia por Coronavírus de Wuhan de 2019-2020) OR (Epidemia de Pneumonia por Coronavírus em Wuhan) OR (Epidemia de Pneumonia por Coronavírus em Wuhan de 2019-2020) OR (Epidemia de Pneumonia por Novo Coronavírus de 2019-2020) OR (Epidemia pelo Coronavírus de Wuhan) OR (Epidemia pelo Coronavírus em Wuhan) OR (Epidemia pelo Novo Coronavírus (2019-nCoV)) OR (Epidemia pelo Novo Coronavírus 2019) OR (Epidemia por 2019-nCoV) OR (Epidemia por Coronavírus de Wuhan) OR (Epidemia por Coronavírus em Wuhan) OR (Epidemia por Novo Coronavírus (2019-nCoV)) OR (Epidemia por Novo Coronavírus 2019) OR (Febre de Pneumonia por Coronavírus de Wuhan) OR (Infecção pelo Coronavírus 2019-nCoV) OR (Infecção pelo Coronavírus de Wuhan) OR (Infecção por Coronavirus 2019-nCoV) OR (Infecção por Coronavírus 2019-nCoV) OR (Infecção por Coronavírus de Wuhan) OR (Infecções por Coronavírus) OR (Pneumonia do Mercado de Frutos do Mar de Wuhan) OR (Pneumonia no Mercado de Frutos do Mar de Wuhan) OR (Pneumonia por Coronavírus de Wuhan) OR (Pneumonia por Novo Coronavírus de 2019-2020) OR (Surto de Coronavírus de Wuhan) OR (Surto de Pneumonia da China 2019-2020) OR (Surto de Pneumonia na China 2019-2020) OR (Surto pelo Coronavírus 2019-nCoV) OR (Surto pelo Coronavírus de Wuhan) OR (Surto pelo Coronavírus de Wuhan de 2019-2020) OR (Surto pelo Novo Coronavírus (2019-nCoV)) OR (Surto pelo Novo Coronavírus 2019) OR (Surto por 2019-nCoV) OR (Surto por Coronavírus 2019-nCoV) OR (Surto por Coronavírus de Wuhan) OR (Surto por Coronavírus de Wuhan de 2019-2020) OR (Surto por Novo Coronavírus (2019-nCoV)) OR (Surto por Novo Coronavírus 2019) OR (Síndrome Respiratória do Oriente Médio) OR (Síndrome Respiratória do Oriente Médio (MERS)) OR (Síndrome Respiratória do Oriente Médio (MERS-CoV)) OR (Síndrome Respiratória do Oriente Médio por Coronavírus) OR MH:C01.925.782.600.550.200$

Environmental cleaning to prevent COVID-19 infection. A rapid systematic review

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KEY WORDS (MeSH terms):
COVID-19 [supplementary concept].
Coronavirus infections.
Environmental monitoring.
Disinfection.
Sterilization.

AUTHORS' KEY WORDS:
SARS-CoV-2.
Ambiance cleaning.
Ambiance hygiene.
Environmental cleaning.
Environment hygiene.
Cleaning.

ABSTRACT

BACKGROUND: Faced with a pandemic, all healthcare actions need to reflect best practices, in order to avoid high transmissibility, complications and even hospitalizations. For hospital environments, the products recommended and authorized by regulatory institutions for environmental cleaning and disinfection need to be highly effective.

OBJECTIVE: To identify, systematically evaluate and summarize the best available scientific evidence on environmental cleaning to prevent COVID-19 infection.

DESIGN AND SETTING: A systematic review of studies analyzing cleaning products that inactivate coronavirus, conducted within the evidence-based health program of a federal university in São Paulo (SP), Brazil.

METHODS: A systematic search of the relevant literature was conducted in the PubMed, EMBASE, Cochrane Library, CINAHL and LILACS databases, for articles published up to May 27, 2020, relating to studies evaluating cleaning products that inactivate coronavirus in the environment.

RESULTS: Seven studies were selected. These analyzed use of 70% alcohol, detergent, detergent containing iodine, household bleach, sodium hypochlorite, hydrogen peroxide, chlorine dioxide, glutaraldehyde, ultraviolet irradiation and plasma air purifier. The effectiveness of treating sewage with sodium hypochlorite and chlorine dioxide was also evaluated.

CONCLUSION: Disinfection of environments, especially those in ordinary use, such as bathrooms, needs to be done constantly. Viral inactivation was achieved using chlorine-based disinfectants, alcohol, detergents, glutaraldehyde, iodine-containing detergents, hydrogen peroxide compounds and household bleaches. Alcohol showed efficient immediate activity. In sewage, sodium hypochlorite had better action than chlorine dioxide.

REGISTRATION NUMBER: DOI: 10.17605/OSF.IO/YC5P4 in the Open Science Framework.

INTRODUCTION

Severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2), which is an emerging respiratory pathogen, causes the COVID-19 disease. Some issues regarding its main epidemiological, clinical and virological characteristics, and particularly its capacity for dissemination, are being discovered. Evidence from other coronavirus diseases, for example severe acute respiratory syndrome (SARS) and Middle East respiratory syndrome (MERS), and the experiences from control and prevention of COVID-19 adopted so far, suggests that it is transmitted through droplets and contact. Thus, COVID-19 can be spread through aerosols relating to procedures that produce aerosolization, such as swab sample collection, intubation and aspiration, among others.[1,2]

Prevention and control measures for the new coronavirus need to include hand hygiene, disinfection of surfaces (notably those that are very frequently touched), respiratory etiquette, avoidance of touching one's face and use of masks. When all these measures are combined, they are efficient for prevention of human-human transmission of COVID-19.[3,4] With the emergence of SARS caused by the new coronavirus, the world has seen the consequences of respiratory transmission between people. It acknowledges that the incubation period is 2 to 10 days, which facilitates its propagation on inanimate surfaces.[4,5]

Information relating to specific inactivation of COVID-19 has recently emerged. Current studies demonstrate that for human coronaviruses to be inactivated (for example SARS coronavirus, MERS coronavirus or endemic human coronavirus (HCoV)), use of products such as ethanol,

hydrogen peroxide or sodium hypochlorite, in addition to other biocidal agents used in chemical disinfection, like benzalkonium chloride or chlorhexidine digluconate, is effective.[5,6] Therefore, early containment and prevention of further spread will be crucial in order to stop the ongoing outbreak and control this new infectious disease.

The presence and persistence of COVID-19 in clinical settings and on surfaces are being extensively researched. Experiments performed under controlled laboratory conditions have provided some indications of the ability of the virus to survive under different environmental conditions. This transmission can develop if there is inadequate waste management and inappropriate handling of personal protective equipment (PPE) in developing countries.[5]

Research conducted specifically on COVID-19 has indicated that the new coronavirus may survive for at least 72 hours, and that it is more stable on the plastic or stainless steel substrates commonly found in operating rooms.[5-7] Persistence of the virus in the environment is known to be a means for transmission of infection. Contact with contaminated fomites is one of the pathways involved in spreading the infection of SARS-CoV-2.[7] The virus is most frequently transmitted through inhalation of respiratory droplets or their deposition in the mucosa (mouth, nose and eyes).[8]

Faced with a pandemic, all healthcare actions need to reflect best practices, in order to avoid high transmissibility, complications and even hospitalizations. For hospital environments, the products recommended and authorized by regulatory bodies for environmental cleaning and disinfection need to be highly effective. The Centers for Disease Control (CDC) have published guidelines for patients with suspected or actual infection with SARS-CoV-2 who are seen at healthcare services. The guidelines mention the importance of having a protocol to guide the team for cleaning the environment and equipment.[9,10]

Within this scenario, it can also be highlighted that it is important to draw up protocols for a gradual return to everyday activities in order to ease social distancing.

OBJECTIVES

The aim of this study was to identify, systematically evaluate and summarize the best available scientific evidence on environmental cleaning to prevent COVID-19 infection.

METHODS

Study model

This study was a rapid systematic review. The research protocol was registered in the Open Science Framework.

Inclusion criteria

The search was performed in accordance with the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) guidelines. Given the limited number of studies on environmental cleaning to prevent COVID-19 infection that might have been published so far, the purpose of this review was to map the knowledge that currently existed on this subject and identify the designs of these studies according to their level of evidence. There was no restriction in relation to origin, language or publication status of the study.

Phenomena of interest

The phenomena of interest for this review comprised cleaning practices performed in healthcare services with the aim of cleaning environments that had possibly become contaminated with suspected or confirmed COVID-19 infection.

Type of intervention

Use of products recommended and authorized by regulatory bodies that presented safety and efficiency with regard to cleaning the environment comprised the intervention.

Type of outcomes

The outcomes selected were effectiveness of disinfection, use of products for cleaning the environment and elimination of environmental contamination.

Selection of studies and data extraction

Identification of eligible studies followed a two-stage process accomplished by two independent reviewers. Any disagreement was resolved by reaching a consensus. In the first stage, after exclusion of duplications, the titles and abstracts of the references identified through the search strategy were evaluated and the potentially eligible studies were pre-selected. In the second stage, a full-text evaluation of the pre-selected studies was carried out to confirm their eligibility. The selection process was performed through the Rayyan platform (https://rayyan.qcri.org).[11]

Research methods for selecting studies

The search strategy was elaborated in accordance with the following research question: Is there any evidence that it is important to use cleaning and disinfection products against SARS-CoV-2?

The searches were elaborated using health science descriptors and adapted for use in each of the databases selected: Cochrane Library (Wiley); Embase (Elsevier); VHL Portal; Medical Literature Analysis and Retrieval System Online (MEDLINE, PubMed); CINAHL; Web of Science; Scopus; and Opengrey (https://opengrey.eu). These descriptors were as follows: "severe acute respiratory syndrome coronavirus 2"[Supplementary Concept] OR "severe acute respiratory syndrome coronavirus 2"[All Fields] OR "sars cov 2"[All Fields]) AND ("environment"[MeSH Terms]

OR "environment"[All Fields]) AND ("disinfection"[MeSH Terms] OR "disinfection"[All Fields]).

A manual search was conducted in the references of the primary and secondary studies that were identified through the electronic search. The search strategies developed and used for each electronic database were performed between April 29, 2020 and May 27, 2020. They are presented in **Table 1**. There were no restrictions on languages or forms of publication.

RESULTS

Studies selected

The systematic review yielded 641 papers; 30 of them were duplicates. After the titles and abstracts had been read by two independent evaluators through the Rayyan online platform, 45 articles were included for the full text to be read. Through this, seven studies were included. The Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) flowchart is shown in **Figure 1**. The years of publication ranged from 2000 to 2020. These studies were conducted in Italy, Canada, Peru, Australia, Germany and China (two studies). The details of the seven studies selected are shown in **Table 2**.[7,12-17]

Characteristics of the studies included

One case-control study and one experimental study were carried out in hospital settings. Another five studies were laboratory tests.

Table 1. Search strategy according to the corresponding databases

Database	Search strategy
Cochrane Library	#1 MeSH descriptor: [SARS Virus] explode all trees #2 MeSH descriptor: [Coronavirus Infections] explode all trees #3 MeSH descriptor: [Environmental Monitoring] explode all trees #4 MeSH descriptor: [Housekeeping] explode all trees #5 MeSH descriptor: [Housekeeping, Hospital] explode all trees #6: #1 OR #2 AND #3 OR #4 OR #5
MEDLINE	#1: "Coronavirus Infections"[MeSH] OR (Coronavirus Infection) OR (Infection, Coronavirus) OR (Infections, Coronavirus) OR (Middle East Respiratory Syndrome) OR (MERS (Middle East Respiratory Syndrome)) OR "COVID-19 [Supplementary Concept]"[MeSH] OR (2019 novel coronavirus infection) OR (COVID19) OR (coronavirus disease 2019) OR (coronavirus disease-19) OR (2019-nCoV disease) OR (2019 novel coronavirus disease) OR (2019-nCoV infection) OR "SARS Virus"[MeSH] OR (Severe Acute Respiratory Syndrome Virus) OR (SARS-Related Coronavirus) OR (Coronavirus, SARS-Related) OR (SARS Related Coronavirus) OR (SARS-CoV) OR (Urbani SARS-Associated Coronavirus) OR (Coronavirus, Urbani SARS-Associated) OR (SARS-Associated Coronavirus, Urbani) OR (Urbani SARS Associated Coronavirus) OR (SARS Coronavirus) OR (Coronavirus, SARS) OR (Severe acute respiratory syndrome-related coronavirus) OR (Severe acute respiratory syndrome related coronavirus) OR (SARS-Associated Coronavirus) OR (Coronavirus, SARS-Associated) OR (SARS Associated Coronavirus) #2: "Environmental Monitoring"[MeSH] OR (Monitoring, Environmental) OR (Environmental Surveillance) OR (Surveillance, Environmental) OR "Housekeeping"[MeSH] OR (Housework) OR "Housekeeping, Hospital"[MeSH] OR (Hospital Housekeeping) OR (Hospital Housekeepings) OR (Housekeepings, Hospital) #3: #1 AND #2
EMBASE (OvidSP)	#1: 'covid 19'/exp OR 'SARS coronavirus'/exp OR 'Coronavirus infection'/exp #2: Environmental Monitoring/ exp or Housekeeping/ exp or Hospital service/ exp #3: #1 AND #2
LILACS	#1: "Vírus da Sars" or (Virus del SRAS) or (SARS Virus) or (CoV-SARS) or (CoV-SRAG) or (Coronavirus Associado a SARS) or (Coronavirus Relacionado à Síndrome Respiratória Aguda Grave) or (SARS-CoV) or (SRAG-CoV) or (Vírus SARS) or (Vírus da Pneumonia Asiática) or (Vírus da Síndrome Respiratória Aguda Grave) or (Vírus da Síndrome Respiratória Aguda Severa) or (mh:B04.820.504.540.150.113.937$) #2: "Monitoramento Ambiental" or (Monitoreo del Ambiente) or (Environmental Monitoring) or (Combate à Poluição) or (Controle Ambiental) or (Controle da Contaminação Ambiental) or (Monitoramento Ecológico) or (Prevenção da Poluição) or (Redução da Poluição) or (mh:N06.850.460.350.080$) or (mh:N06.850.780.375$) or (mh:SP2.001.030.040$) or (mh:SP2.036.010.008$) or (mh:SP4.102.072.092.693.364$) or (mh:SP4.102.072.573.954$) or (mh:SP4.127.413.629.885$) or (mh:SP5.006.067.100.150$) or (mh:SP8.473.654.412.052.005.030.050.010$) or (mh:VS4.001.001$) or "Serviço de Limpeza" or (Servicio de Limpieza) or (Housekeeping) or (Limpeza) or (mh:N02.508$) or "Serviço Hospitalar de Limpeza" or (Servicio de Limpieza en Hospital) or (Housekeeping, Hospital) or (mh:N02.278.216.500.968.412$) or (mh:N02.508.472$) or (mh:N04.452.442.452.422.412$) or (mh:VS3.002.001.001.011.001$) #3 #1 AND #2
CINAHL	#1: (Sars virus) OR (Coronavirus infections) OR (covid-19 or coronavirus or 2019-ncov) #2: (environmental monitoring) OR (Housekeeping) OR (Housekeeping, Hospital) #3: #1 AND #2

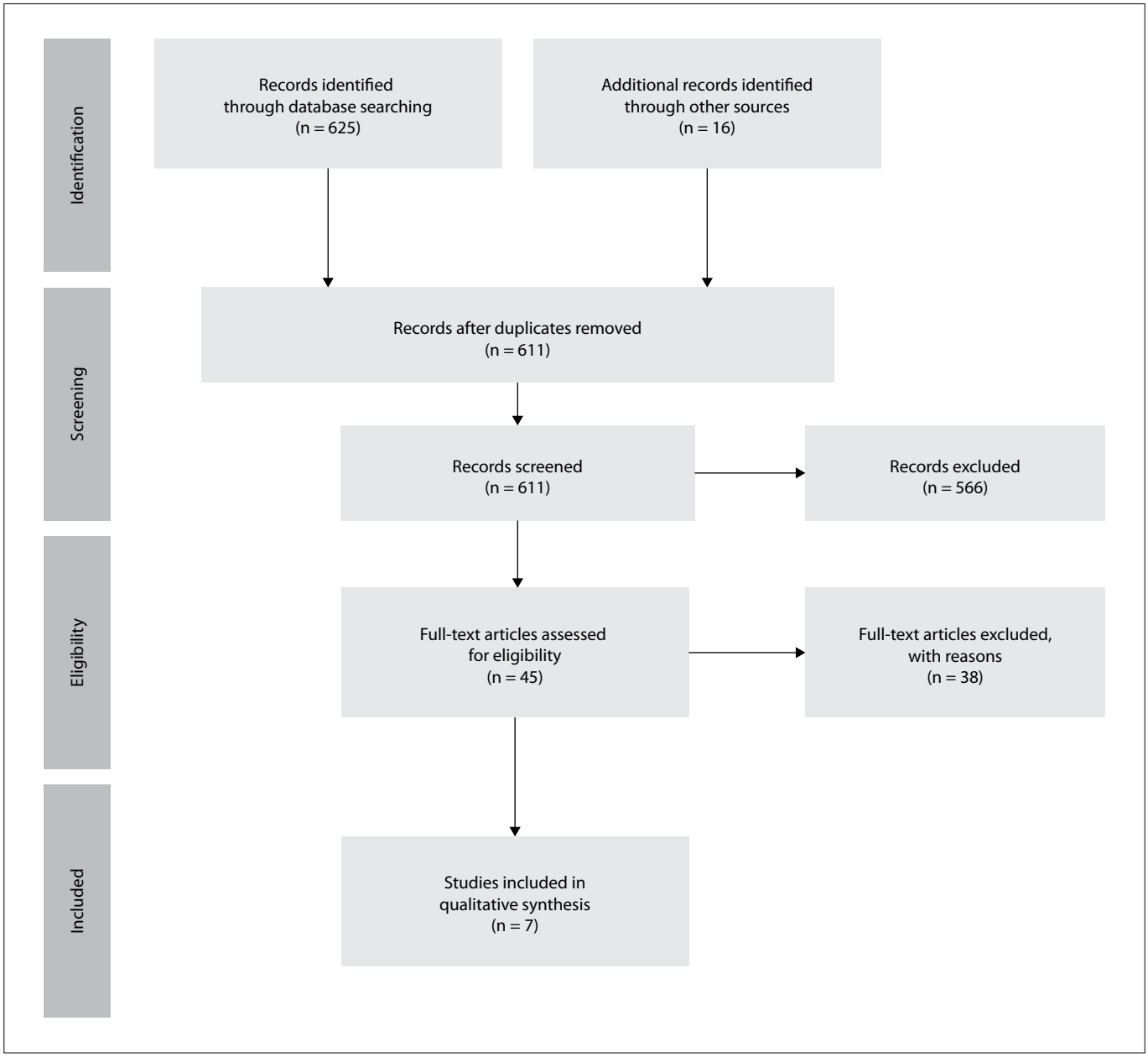

Figure 1. Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) flow diagram for study selection.

Products analyzed

Sodium hypochlorite at dilutions of 0.1 to 0.5%

Lai et al.[12] analyzed paper samples, waterproof disposable cloaks and fabric cloak (cotton). Sodium hypochlorite significantly reduced the viral load after five minutes of incubation.

In the study by Wang J et al.,[13] tissues impregnated with hypochlorite were used for cleaning and disinfecting surfaces in hospitals and personal protective equipment (PPE). Inpatient units with patients undergoing treatment for COVID-19 were selected. After this cleaning, the polymerase chain reaction (PCR) was performed on samples collected from the environment, and no presence of SARS-CoV-2 was observed. The PPE used by professionals who provided care in these environments also yielded the same results through PCR analysis.

In the study by Wang XW et al.,[14] conducted in Wuhan, China, the presence of SARS-CoV was observed in wastewater samples containing feces and urine from a hospital and in domestic sewage and in tap water. The persistence of the virus between different types of water treatment (chlorinated or not chlorinated) was

Table 2. Analysis on the articles included in the study

Study	Study design	Environment/ surface studied	Cleaning and disinfection methods/products	Results and conclusion
Sizun et al.[16]	Laboratory	Aluminum, sterile latex surgical gloves and sterile sponges.	Several common disinfectant agents were evaluated: 70% (v/v) ethanol; detergent containing 0.75% free iodine; 1.5% freshly prepared (v/v) household bleach; and soap. 12 aluminum pieces of 1 cm in diameter were washed with tap water and disinfected with 70% ethanol for 30 minutes, followed by further disinfection through heating.	The free iodine detergent reduced the degree of infection of the virus by at least 50%. HCoV-OC43 was more sensitive to free iodine detergent than was HCoV-229E, since it was neutralized with a lower concentration of this chemical disinfectant. Use of soap and ethanol is believed to be effective, since alcohol and detergents destabilize the lipid bilayer of viruses.
Booth et al.[15]	Laboratory	Hospital environment. Environmental samples were collected from 19 inpatient rooms for patients infected with SARS.	Air samples and patient room surfaces, handrails, telephones, televisions, remote controls, switches, medical records, beds, bathroom furniture and utensils, corridors adjacent to rooms, hand sanitizing stations, personal protective equipment and nursing rooms. The cleaning protocol of the hospitals included consisted of cleaning and disinfection of surfaces, equipment and floors with products based on hydrogen peroxide. Detection of SARS-CoV by means of RT-PCR.	The study data showed that an environmental cleaning protocol with well-designed routines was effective. The environments were disinfected twice a day, as also were the frequently touched surfaces. In this study, only two surfaces were positive: the refrigerator at the nursing station and the television remote control in the patients' rooms.
Lai et al.[12]	Laboratory	Examination request paper, waterproof disposable cloak and non-disposable cotton cloak.	Sodium hypochlorite, household detergent and a hydrogen peroxide compound.	The risk of infection from contact with contaminated droplets on paper was small. The three products reduced the viral load after five minutes of incubation. Regarding the type of cloak, those made with higher-absorption material such as cotton were preferable to those made of non-absorbent materials. The virus was easily inactivated using common disinfectants.
Rabenau et al.[7]	Case control	Hospital.	Test of the eight products most used in Germany, with exposures of 30 seconds, 30 minutes and 60 minutes to evaluate the effectiveness of SARS. The products used were aldehyde, formaldehyde, active oxygen and aldehyde for instruments and alcohol for hand hygiene. Evaluations were done with minimum organic load reduction factors (RFs): 0.3% serum albumin (BSA), 10% fetal calf serum (FCS) and 0.3% BSA with 0.3% sheep erythrocytes.	All were effective for SARS-CoV inactivation.
Wang et al.[14]	Laboratory	Feces, urine and water.	Sodium hypochlorite and chlorine dioxide. Detection of SARS-CoV by means of RT-PCR.	Free chlorine inactivated SARS-CoV better than chlorine dioxide. Free residual chlorine over 0.5 mg/L for chlorine or 2.19 mg/L for chlorine dioxide in wastewater ensured complete inactivation of SARS-CoV. The product concentration was inverse to the time taken for SARS-CoV inactivation.
Walker et al.[17]	Laboratory	Experimental chamber.	250 nm ultraviolet irradiation. Viruses were aerosolized in the experiment and were found to be susceptible to UV radiation, with significant reductions in viral load. The coronavirus demonstrated high sensitivity: only 12% of the virus survived exposure to 599 μW-s/cm^2 of UV-C.	Air disinfection through an association of HEPA filter with 254 nm UV-C can be an effective tool for inactivating viral aerosols. Among the viruses examined, adenovirus was the most resistant to 254 nm UV-C and needed to be exposed to high doses of UV for complete inactivation.
Wang et al.[13]	Laboratory	Hospital inpatient areas used by contaminated patients.	Plasma air purifies the environment. Disinfection is achieved through using a tissue moistened with chlorine on surfaces that have been touched by patients affected by SARS-CoV-2 and by professionals who treated these patients. The environment samples were collected four hours after cleaning and were evaluated by means of RT-PCR.	The importance of hand hygiene and cleaning the environment to prevent the transmission of SARS-CoV-2 was shown.

v/v = volume per volume; HCoV = human coronavirus; SARS = severe acute respiratory syndrome; SARS-CoV = severe acute respiratory syndrome coronavirus; RT-PCR = reverse-transcription polymerase chain reaction; nm = nanometers; UV = ultraviolet; UV-C = ultraviolet-C; HEPA = high-efficiency particulate arrestance.

analyzed. It was found that the virus persisted in residual water with no chlorine treatment for up to three days; in feces for 14 days; and in urine for 17 days. Also, a difference in the persistence of SARS-CoV was observed at lower temperatures. When treatments with sodium hypochlorite and chlorine dioxide were implemented, the virus was inactivated.

Peroxygen compounds

Lai et al.[12] evaluated the use of peroxygen compounds through cell cultures. They found that these compounds reduced the viral load of SARS-CoV after five minutes of incubation. The surfaces tested were paper samples, waterproof disposable cloaks and fabric cloaks (cotton).

Hydrogen peroxide

Booth et al.[15] used hydrogen peroxide-based products to clean and disinfect the air and different surfaces such as handrails, telephones, televisions, remote controls, switches, charts, beds, furniture and bathroom utensils, in the bedrooms of patients infected with SARS-CoV. They also applied these products in corridors adjacent to these rooms, at hand sanitation stations, on personal protective equipment and in nursing rooms. The environments were disinfected twice a day, in addition to the surfaces frequently touched. According to the data from this study, environmental cleaning protocols with well-designed routines are effective. It is worth noting that only two surfaces were positive in reverse-transcription polymerase chain reaction (RT-PCR) tests: the refrigerator at the nursing station and the television remote control in the patients' rooms. These findings highlight that environmental control measures need to be applied alongside adherence to hand hygiene among all personnel.

Household detergents

Lai et al.[12] found that household detergent was able to reduce the viral load of SARS-CoV after five minutes of incubation. This was observed in relation to paper samples, waterproof disposable covers and fabric covers (cotton).

Product combination: 70% alcohol, glutaraldehyde, iodine detergent and household bleach

Rabenau et al.[7] studied products for surface cleaning and the exposure time needed for each product. In this study, products with an active ingredient based on alcohol, glutaraldehyde, detergent with iodine and household bleach were used. Elimination of SARS-CoV-2 from the environment was observed, independent of the length of exposure of the surface to the product.

In a study on various types of coronavirus by Sizun et al.,[16] 12 pieces of aluminum were cleaned with running water and disinfected with 70% alcohol for 30 minutes. The results from this study suggested that presence of the virus on the surface of materials may be the main sources of hospital infections. The use of povidone-iodine and 70% alcohol showed efficacy in eliminating the virus (SARS-CoV-2, SARS and MERS-CoV) in all the environments evaluated.

Ultraviolet C germicide

Walker et al.[17] conducted an experiment in which irradiation using ultraviolet (UV)-C light through a high-efficiency particulate arrestance (HEPA) filter was correlated with the effect of UV radiation alone at 250 nanometers (nm). The murine hepatitis virus (MHV) coronavirus was found to be sensitive to the action of germicidal UV at 254 nm; only 12% of the aerosolized virus survived UV exposure at a rate of 599 microwatt-seconds (μW-sec) per square centimeter (cm^2). The viral aerosols tested showed higher susceptibility to UV than did a liquid suspension. It was concluded that disinfection of the air using 254 nm UV-C ("germicidal" ultraviolet radiation) could be an effective tool for inactivation of viral aerosols. Among the viruses examined, adenovirus was the most resistant to 254 nm UV-C, and it needed to be exposed to high doses of UV for complete inactivation.

Plasma for air purification

Wang J et al.[13] investigated plasma treatment for air purification in areas where patients were hospitalized, in association with environmental care for surfaces. The samples from this environment were negative except for three samples of pre-processed sewage and one sample after disinfection and pre-processing.

DISCUSSION

The main reason for this review, regardless of the specific characteristics of the viruses, was to investigate the possibility that human coronavirus might be transmitted indirectly. The virus remains active on different types of surfaces, and infection can arise after the virus has come into contact with human mucosal surfaces.[18] The present study complements the guidelines for prevention and control of COVID-19, with the aim of ensuring that the best evidence is used in managing the environment. Focusing on products and techniques that are applied consistently in communities, homes, schools, markets and healthcare facilities will help prevent transmission of the virus that causes COVID-19.

For contaminated surfaces to play a role in transmission, the respiratory pathogens need to be expelled into the environment and subsequently survive on these surfaces. These pathogens then need to be transferred to hands or to other materials at a viral load that is considered to be infectious. In addition, the pathogens need to have the ability to start an infection through contact with the eyes, nose or mouth.[19]

The cleaning process consists of removing microorganisms mechanically and chemically, thereby reducing the microbial load in this environment. Therefore, undertaking cleaning in association with disinfection is essential for obtaining significant reductions in the microbial load.[20] The disinfection process does not eliminate bacterial spores, but it does eradicate most of the microbial agents in an environment or on a surface. Sterilization is the process that destroys microbial life in an object or on a surface through heat, pressure or chemical methods.[21,22]

The best way to prevent the spread of SARS-CoV-2 in the environment is to encourage cleaning and disinfection in places and surfaces that are touched very frequently. This is usually done together with implementation of individual non-pharmacological prevention measures such as hand hygiene, avoidance of touching the face and using masks.[4]

The seven studies included in this review presented analyses on disinfection products and techniques in order to investigate coronavirus inactivation. The analyses addressed the use of 70% alcohol, detergent, detergent containing iodine, household bleach, sodium hypochlorite, hydrogen peroxide, chlorine dioxide, glutaraldehyde, ultraviolet irradiation and plasma air purifier.[7,12-17] These studies were mostly carried out in laboratories (five studies). This makes it possible to develop more accurate tests on product action and viral inactivation. On the other hand, studies conducted in a hospital environment with an observational design make it possible to compare the techniques and effectiveness of institutional protocols.

Sizun et al.[16] and Lai et al.[12] analyzed the use of different materials: aluminum, sterile latex surgical gloves, gauze, paper, sterile sponges and types of aprons. They analyzed the activity of the following products in relation to the materials: detergent, detergent containing iodine, household bleach, alcohol soap, hypochlorite sodium and a compound containing hydrogen peroxide. Among all the materials tested, these products were efficient for inactivating the coronavirus. The surfaces analyzed by these authors were sufficiently diversified to demonstrate the effectiveness and action of the products described, especially given the findings of persistent capacity of coronaviruses to survive on different surfaces that have been shown in several studies.[6,12,23]

Booth et al.,[15] Wang et al.[13] and Rabenau et al.[7] analyzed the most-touched surfaces, i.e. handrails, televisions, beds, furniture, bathroom utensils, remote controls and switches, among other surfaces in the patients' rooms, along with areas relating to direct care, such as the health center. These areas have been described during the pandemic as important related sites at which SARS-CoV-2 has been detected during this period.[24,25] The products tested were wipes containing chlorine, alcohol, glutaraldehyde and a product based on hydrogen peroxide. All of them were effective against the coronavirus. Rabenau et al.[7] suggests that alcohol and hypochlorite should be applied to surfaces and floors. They also recommend that glutaraldehyde should be applied to equipment that is used within care, such as for disinfection of bronchoscopes.

Ong et al.[25] analyzed the presence of SARS-CoV-2 in hospital environments before and after the cleaning process. Sixteen out of 26 samples were positive for SARS-CoV-2. Positive results were obtained from these samples in 13 (87%) of the 15 locations inside the room (including exhaust fans) and in three (60%) of the five bathroom locations (i.e. toilet, sink and door handle). In that study, there was a significant degree of environmental contamination from patients with SARS-CoV-2, through respiratory droplets and fecal leakage. This suggested that the environment was a potential means of transmission.

Viral inactivation through use of chlorine-based disinfectants, alcohol, detergents, glutaraldehyde, iodine-containing detergents, hydrogen peroxide compounds and household bleaches has been demonstrated.[7,12,15,16] These substances are easily accessible for use in hospital environments and domestic environments. Alcohols have immediate efficient activity.[6,26]

The present review also warns about viral aerosols that might be found in environments that are commonly used, such as bathrooms and stores. Due to lack of ventilation, these environments allow the virus to remain in suspension. There is no certainty about the viral load that may influence this transmission, but it is known that the virus particles can remain suspended in the air for hours.

Liu et al. reported that the SARS-CoV-2 outbreak could be correlated with transmission through at least three means:[27]

- Inhalation of liquid droplets produced by infected people or by their contacts.
- Presence of the pathogen as aerosols in confined areas.
- Contact with surfaces contaminated with SARS-CoV-2.

In that study,[27] research was carried out on the environment in a hospital dedicated to patients with SARS-CoV-2. The places with the greatest presence of the virus were the room in which personal protective equipment (PPE) was removed and the mobile toilet used in the hospital. In this way, the importance of frequent cleaning of the environment is evident.

Environmental control measures implemented in association with disinfection techniques such as the use of laminar flow ventilation with UV-C and plasma treatment are considered feasible.[8,13,17,27] In an experimental study, Walker et al.[17] showed the benefits of using UV-C light in association with a laminar flow device, for viral inactivation in the air treatment system. However, the data provided did not allow any guarantee of effectiveness in relation to different types of coronavirus and to the capacity of the technique, according to the flow and air passage of each system. Wang et al.[13] demonstrated that use of an environmental surface cleaning protocol in association with air treatment with plasma

was suitable for an environmental contamination test to screen for SARS-CoV-2.

In a study by Van Doremalen et al.,[8] it was observed that use of laminar flow ventilation for the place where healthcare professionals remove their PPE was a favorable alternative for prevention of proliferation of the virus in the environment. A high concentration of the virus was observed in toilets and changing rooms without this type of ventilation, in their study.

It needs to be borne in mind that SARS-CoV-2 can be active on inanimate surfaces for up to nine days at temperatures of 30 °C. Therefore, environmental cleaning needs to be intensified, especially for the areas that are most touched.[5-7] The resistance of the virus on inanimate surfaces is influenced by the following factors:[12,23,28]

- The type of surface.
- The temperature of the environment.
- The relative humidity of the air.

Surfaces like plastic show viral activity for long periods, and this can last for up to 20 days. Low temperatures and low relative humidity enable persistence of human coronaviruses for longer periods. At lower temperatures, greater stability of the virus is observed.

Regarding the persistence of the virus at different temperatures, which was much discussed at the beginning of the pandemic, Wang et al.[13] pointed out that at lower temperatures, longer survival of this virus in the environment is observed. Hence, these authors considered that lower temperatures would be ideal for its dissemination. On the other hand, in a study conducted by Wang et al.[14] in a public sauna of 300 square meters (m^2) at a temperature between 25 and 41 °C and relative humidity of approximately 60%, an outbreak of SARS-CoV-2 was observed among seven patients who had used the same space within a one-week period. All the patients had clinical symptoms and positive results.

The way in which sewage is treated in different countries is also relevant. Wang et al.[13] compared the effectiveness of treating sewage with sodium hypochlorite and chlorine dioxide as a control measure against SARS-CoV-2, to avoid water contamination. Sodium hypochlorite was observed to have better action than chlorine dioxide. Moreover, the time taken to reach virus inactivation was inversely proportional to the concentration of the product. These findings provide a warning about the importance of sewage treatment, even though there is little evidence so far to support this route as a potential means of infection. It was also found in that study that other human coronaviruses survived for about two days in dechlorinated tap water and hospital wastewater at 20 °C.

Wang et al.[14] found that places where there was no effective sewage treatment had viral loads that potentially posed a risk of transmission of the virus. Only limited studies on waste management have been conducted but, nonetheless, evidence is emerging that viral fragments are present in untreated excrement and sewage.[14,20] Provision of good drinking water, sanitation and hygiene conditions is essential for protecting human health in all outbreaks of infectious diseases, including COVID-19.

During the current pandemic, through fear, some people have been increasing the concentrations of cleaning products that they use at home. We would warn about the importance of not increasing the concentrations of these products and about the undesirability of making homemade preparations. Depending on the substance used, higher concentrations may give rise to chemical reactions that could cause poisoning of the person who is performing this manipulation. Studies have shown that since the beginning of the SARS-CoV-2 pandemic, there has been an increase in the number of cases of exogenous poisoning seen in urgent and emergency services in the United States.[9,10,29]

Given the public health challenges relating to social issues and the need for a gradual and programmed return to activities, we suggest that measures to improve hand hygiene, social distancing, use of masks, cleaning and environmental disinfection among the population should be considered as nonpharmacological strategies towards prevention of COVID-19.

One of the limitations of our study was that data on the effectiveness of various types of disinfection against SARS-CoV were scarce. Nonetheless, even though the outbreak of this disease is very recent, it was possible to ascertain the action and efficiency of the most usual and accessible disinfectants and products, at the concentrations and exposure times used, and to demonstrate that their activity was reproducible, even with different types of organic load.

Unfortunately, we did not find any data on certain substances and materials that are widely publicized and even commercialized, such as ozone, in the articles that we were able to assess. Moreover, it also needs to be taken into account that not all of the studies cited the time taken for the substance to have its effect, with regard to elimination of the virus.

We can highlight that the present study demonstrates that a variety of products and techniques enable efficient elimination of SARS-CoV-2 in the environment. These can be used in public, domestic and hospital environments, in a way that is accessible for the population, in terms of both management and product costs. In addition, we showed that cleaning measures implemented within the infrastructure of toilets and changing rooms are essential for preventing the spread of the virus in the environment to employees, especially when they are removing their PPE.

The studies presented showed the importance of highlighting the survival time of SARS-CoV-2 in the environment, and demonstrated to its relationship with temperature variation and air humidity. The implication of these findings for the pandemic is that the products described here are essential for effective cleaning and disinfection of inanimate areas.

Development of protocols for attending cases of SARS-CoV-2 infection needs to include not only clinical conduct but also use of personal protective equipment for care and cleaning, and disinfection of equipment, surfaces and the environment. The infrastructure for patient and population care is extremely important: it is essential that, in attending these cases, the professionals involved and hence the general population are not exposed to an imminent risk of contamination.

CONCLUSION

Disinfection of environments, especially those in ordinary use, such as bathrooms, needs to be done constantly. Viral inactivation was seen to occur through using chlorine-based disinfectants, alcohol, detergents, glutaraldehyde, iodine-containing detergents, hydrogen peroxide compounds and household bleaches. Alcohol showed efficient immediate activity. In sewage, sodium hypochlorite was observed to have better action than chlorine dioxide.

REFERENCES

1. Luo C, Yao L, Zhang L, et al. Possible Transmission of Severe Acute Respiratory Syndrome Coronavirus 2 (SARS-CoV-2) in a Public Bath Center in Huai'an, Jiangsu Province, China. JAMA Netw Open. 2020;3(3):e204583. PMID: 32227177; doi: 10.1001/jamanetworkopen.2020.4583.
2. Fathizadeh H, Maroufi P, Momen-Heravi M, et al. Protection and disinfection policies against SARS-CoV-2 (COVID-19). Infez Med. 2020;28(2):185-91. PMID: 32275260.
3. To KK, Tsang OT, Chik-Yan Yip C, et al. Consistent detection of 2019 novel coronavirus in saliva. Clin Infect Dis. 2020. Published online ahead of print. PMID: 32047895; doi: 10.1093/cid/ciaa149.
4. Taminato M, Mizusaki-Imoto A, Saconato H, et al. Máscaras de tecido na contenção de gotículas respiratórias – revisão sistemática. Acta Paul Enferm. 2020;33:1-11. doi: 10.37689/acta-ape/2020AR0103.
5. Centers for Disease Control and Prevention (CDC). Coronavirus disease. Considerations for Wearing Masks: Help Slow the Spread of COVID-19. National Center for Immunization and Respiratory Diseases (NCIRD), Division of Viral Diseases; 2020. Available from: https://www.cdc.gov/coronavirus/2019-ncov/prevent-getting-sick/cloth-face-cover-guidance.html. Accessed in 2020 (Jul 28).
6. Kampf G, Todt D, Pfaender S, Steinmann E. Persistence of coronaviruses on inanimate surfaces and their inactivation with biocidal agents. J Hosp Infect. 2020;104(3):246-51. PMID: 32035997; doi: 10.1016/j.jhin.2020.01.022.
7. Rabenau HF, Kampf G, Cinatl J, Doerr HW. Efficacy of various disinfectants against SARS coronavirus. J Hosp Infect. 2005;61(2):107-11. PMID: 15923059; doi: 10.1016/j.jhin.2004.12.023.
8. van Doremalen N, Bushmaker T, Munster VJ. Stability of Middle East respiratory syndrome coronavirus (MERS-CoV) under different environmental conditions. Euro Surveill. 2013;18(38):20590. PMID: 24084338; doi: 10.2807/1560-7917.es2013.18.38.20590.
9. European Centre for Disease Prevention and Control. Disinfection of environments in healthcare and non-healthcare settings potentially contaminated with SARS-CoV-2. 2020. Available from: https://www.ecdc.europa.eu/sites/default/files/documents/Environmental-persistence-of-SARS_CoV_2-virus-Options-for-cleaning2020-03-26_0.pdf. Accessed in 2020 (Jul 28).
10. Centers Disease Control and Prevention. Cleaning and Disinfection for Households. 2020. Available from: https://www.cdc.gov/coronavirus/2019-ncov/prevent-getting-sick/cleaning-disinfection.html. Accessed in 2020 (Jul 28).
11. Ouzzani M, Hammady H, Fedorowicz Z, Elmagarmid A. Rayyan-a web and mobile app for systematic reviews. Syst Rev. 2016;5(1):210. PMID: 27919275; doi: 10.1186/s13643-016-0384-4.
12. Lai MYY, Cheng PKC, Lim WWL. Survival of severe acute respiratory syndrome coronavirus. Clin Infect Dis. 2005;41(7):e67-71. PMID: 16142653; doi: 10.1086/433186.
13. Wang J, Feng H, Zhang S, et al. SARS-CoV-2 RNA detection of hospital isolation wards hygiene monitoring during the Coronavirus Disease 2019 outbreak in a Chinese hospital. Int J Infect Dis. 2020;94:103-6. PMID: 32311449; doi: 10.1016/j.ijid.2020.04.024.
14. Wang XW, Li JS, Jin M, et al. Study on the resistance of severe acute respiratory syndrome-associated coronavirus. J Virol Methods. 2005;126(1-2):171-7. PMID: 15847934; doi: 10.1016/j.jviromet.2005.02.005.
15. Booth TF, Kournikakis B, Bastien N, et al. Detection of airborne severe acute respiratory syndrome (SARS) coronavirus and environmental contamination in SARS outbreak units. J Infect Dis. 2005;191(9):1472-7. PMID: 15809906; doi: 10.1086/429634.
16. Sizun J, Yu MW, Talbot PJ. Survival of human coronaviruses 229E and OC43 in suspension and after drying on surfaces: a possible source of hospital-acquired infections. J Hosp Infect. 2000;46(1):55-60. PMID: 11023724; doi: 10.1053/jhin.2000.0795.
17. Walker CM, Ko G. Effect of ultraviolet germicidal irradiation on viral aerosols. Environ Sci Technol. 2007;41(15):5460-5. PMID: 17822117; doi: 10.1021/es070056u.
18. World Health Organization. Coronavirus disease (COVID-19) advice for the public. Available from: https://www.who.int/emergencies/diseases/novel-coronavirus-2019/advice-for-public. Accessed in 2020 (Jul 28).
19. World Health Organization. Modes of transmission of virus causing COVID-19: implications for IPC precaution recommendations. 2020. Available from: https://www.who.int/news-room/commentaries/detail/modes-of-transmission-of-virus-causing-covid-19-implications-for-ipc-precaution-recommendations. Accessed in 2020 (Jul 28).
20. Lénès D, Deboosere N, Ménard-Szczebara F, et al. Assessment of the removal and inactivation of influenza viruses H5N1 and H1N1 by drinking water treatment. Water Res. 2010;44(8):2473-86. PMID: 20149404; doi: 10.1016/j.watres.2010.01.013.

21. Centers for Disease Control and Prevention. Cleaning – Guideline for Disinfection and Sterilization in Healthcare Facilities (2008). Available from: https://www.cdc.gov/infectioncontrol/guidelines/disinfection/cleaning.html. Accessed in 2020 (Jul 28).
23. Kampf G. Potential role of inanimate surfaces for the spread of coronaviruses and their inactivation with disinfectant agents. Infection Prevention in Practice. 2020;2(2):100044. doi: 10.1016/j.infpip.2020.100044.
24. Chia PY, Coleman KK, Tan YK, et al. Detection of air and surface contamination by SARS-CoV-2 in hospital rooms of infected patients. Nat Commun. 2020;11(1):2800. PMID: 32472043; doi: 10.1038/s41467-020-16670-2.
25. Ong SWX, Tan YK, Chia PY, et al. Air, Surface Environmental, and Personal Protective Equipment Contamination by Severe Acute Respiratory Syndrome Coronavirus 2 (SARS-CoV-2) From a Symptomatic Patient. JAMA. 2020;323(16):1610-12. PMID: 32129805; doi: 10.1001/jama.2020.3227.
26. Hota B. Contamination, disinfection, and cross-colonization: are hospital surfaces reservoirs for nosocomial infection? Clin Infect Dis. 2004;39(8):1182-9. PMID: 15486843; doi: 10.1086/424667.
27. Liu Y, Ning Z, Chen Y, et al. Aerodynamic analysis of SARS-CoV-2 in two Wuhan hospitals. Nature. 2020;582(7813):557-60. PMID: 32340022; doi: 10.1038/s41586-020-2271-3.
28. Chan KH, Peiris JSM, Lam SY, et al. The effects of temperature and relative humidity on the viability of the SARS coronavirus. Adv Virol. 2011;2011:734690. PMID: 22312351; doi: 10.1155/2011/734690.
29. Centers for Disease Control and Prevention. Interim Infection Prevention and Control Recommendations for Patients with Suspected or Confirmed Coronavirus Disease 2019 (COVID-19) in Healthcare Settings. 2020. Available from: https://www.cdc.gov/coronavirus/2019-ncov/hcp/guidance-home-care.html. Accessed in 2020 (Jul 28).

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COVID-19 and patients with immune-mediated inflammatory diseases undergoing pharmacological treatments: a rapid living systematic review

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ABSTRACT

BACKGROUND: Patients with immune-mediated inflammatory diseases (IMID) are at increased risk of infection.

OBJECTIVE: To assess whether patients undergoing pharmacological treatment for IMID present higher risk of worse outcomes when diagnosed with COVID-19.

DESIGN AND SETTING: Rapid systematic review conducted in the medical school of the Federal University of São Paulo (SP), Brazil.

METHODS: We searched CENTRAL, MEDLINE, EMBASE, LILACS, SCOPUS, Web of Science, L·OVE, ClinicalTrials.gov and WHO-ICTRP for studies evaluating patients diagnosed with COVID-19 who were undergoing pharmacological treatment for IMID. Two authors selected studies, extracted data and assessed risk of bias and certainty of evidence, following the Cochrane recommendations.

RESULTS: We identified 1,498 references, from which one cohort study was included. This compared patients with and without rheumatic diseases (RD) who all had been diagnosed with COVID-19. Those with RD seemed to have higher chances of hospitalization and mortality, but no statistical difference was detected between the groups: hospitalization: odds ratio (OR) 1.17; 95% confidence interval (CI) 0.6 to 2.29; mortality rate: OR 1.53; 95% CI 0.33 to 7.11 (very low certainty of evidence). Patients with RD were three times more likely to require admission to intensive care units (ICUs), with invasive mechanical ventilation (IMV), than those without RD: OR 3.72; 95% CI 1.35 to 10.26 (for both outcomes; very low certainty of evidence).

CONCLUSION: Patients undergoing pharmacological treatment for IMID seem to present higher chances of requiring admission to ICUs, with IMV. Additional high-quality studies are needed to analyze the effects of different treatments for IMID.

INTRODUCTION

In response to the current coronavirus disease (COVID-19) outbreak, many physicians and researchers have been concerned about patients with immune-mediated inflammatory diseases (IMID).[1-4] Through immunosuppressive treatment regimens, these patients may be more prone to infections with poor evolution of outcomes.[5] Although Favalli et al.[3] showed that the incidence of COVID-19 was quite similar between rheumatic disease patients and individuals in the general population in Lombardy, Italy (0.62% versus 0.66%, respectively), a previous study showed that the most prevalent comorbidity among patients under 40 years old who had been diagnosed with COVID-19 and admitted to ICUs was IMID.[6]

Immunomodulatory therapies have been tested for treating patients with COVID-19. The biological reason for using these drugs is that they mitigate excessive inflammatory responses (cytokine storms), which can cause severe disease and worse prognosis among patients with COVID-19. Therefore, it has also been hypothesized that immunomodulatory therapies have a potential protective effect.[7] However, neither this therapy nor the protective hypothesis has been proven to be effective.

Although the therapeutic effect of immunomodulatory drugs for treating COVID-19 has been exhaustively explored, the protective effect remains poorly investigated. The protective

hypothesis is particularly concerning, since patients under immunomodulatory therapies may neglect preventive measures, including social distancing and the use of personal protective equipment. Analysis on this hypothesis may help decision-makers and healthcare organizations to develop guidelines for management of patients with IMID and identify high-risk individuals during the pandemic.

OBJECTIVE

To assess whether patients undergoing pharmacological treatment for IMID are at higher risk of worse outcomes when diagnosed with COVID-19.

METHODS

We used abbreviated systematic review methods, and therefore we did not perform any independent screening of abstracts and did not search the grey literature.[8] As this was a rapid review, it will be continuously updated (i.e. through monthly searches) and, when any important new evidence is identified, we will analyze the data and update the results.

The protocol for this systematic review was registered on the PROSPERO "International Prospective Register of Systematic Reviews" platform (CRD42020179863).

Design and setting

The rapid systematic review methodology used here followed the recommendations proposed in the Cochrane Collaboration Handbook. This review was conducted in the medical school of a public university in São Paulo (SP), Brazil.

Criteria for including reviews

Types of studies

We planned to include cohort and case-control studies, and if no better evidence were available, we planned to also consider case series and electronic health records for inclusion.

Types of participants

We included participants with IMID who were undergoing pharmacological treatments and who then received a confirmed diagnosis of severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) infection. Their pharmacological treatment for IMID could include any of the following drugs:

- Immunosuppressants (e.g. azathioprine, mycophenolate or cyclophosphamide);
- Immunomodulators (e.g. glucocorticoids or immunoglobulins);
- Immunobiological agents (e.g. tocilizumab, infliximab, adalimumab, etanercept, certolizumab, rituximab, secukinumab or ustekinumab);
- Synthetic disease-modifying anti-rheumatic drugs (methotrexate, leflunomide, chloroquine or sulfasalazine);
- Targeted synthetic disease-modifying anti-rheumatic drugs (e.g. apremilast, tofacitinib or baricitinib).

Types of outcomes

These were our prespecified outcomes:

- Primary outcomes
  - Mortality rate;
  - Length of hospital stay;
  - Adverse events.
- Secondary outcomes
  - Duration of invasive mechanical ventilation;
  - Time to viral clearance;
  - Time to clinical improvement;
  - Length of intensive care unit stay.

Search strategy

We conducted a systematic search of the literature on July 5, 2020, in the following databases: Medline via PubMed, Embase via Elsevier, Cochrane Library - Cochrane Central Register of Controlled Trials (CENTRAL), BVS Regional Portal (LILACS), Scopus and Web of Science using relevant descriptors and synonyms, with adaptation of the search to the specifications of each database, to identify published, ongoing and unpublished studies. We also searched the following COVID-19 specific databases: Epistemonikos COVID-19 L·OVE platform (https://app.iloveevidence.com/loves/5e6fdb9669c00e4ac072701d); ClinicalTrials.gov (https://ClinicalTrials.gov/ct2/results?cond=COVID-19); and World Health Organization International Clinical Trials Registry Platform (WHO-ICTRP). In addition, we searched the reference lists of the studies included. Studies published in any language since November 2019 were considered for inclusion. The search strategies for each database are presented in Appendix 1.

Two review authors selected the studies for inclusion, extracted data from these studies and assessed the risk of bias in these studies and the certainty of evidence for the outcomes. We planned to assess the possibility of pooling the results from the studies included, into meta-analyses when at least two studies were sufficiently homogeneous in terms of design, participants and outcome measurements. If insufficient information or heterogeneous studies were found, we planned to summarize the results only in a qualitative synthesis.

Modification of review protocol

In order to improve our rapid systematic review, we decided to perform a broader search strategy than what was presented in the review protocol. Therefore, we also searched for papers published in conference proceedings. Furthermore, to provide a more detailed assessment of the risk of bias, we decided to use Quality

Appraisal in Systematic Reviews of Prognosis Studies (QUIPS) rather than the Newcastle-Ottawa Scale.

RESULTS

Search results

We identified 1,498 reports through our searches in the selected databases and trial registries. After removing duplicates, we screened 1,258 citations, from which we excluded 1,238 reports that did not meet the inclusion criteria. We selected 20 full-text articles[9-28] but then we excluded 19 of these.[9-27] The reasons for exclusion are shown in the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) flow-chart (**Figure 1**).

Characteristics of the included study

We included one retrospective cohort study in our systematic review, which had been conducted in Massachusetts General Hospital and Brigham and Women's Hospital.[28] This study evaluated 52 patients (mean age 62.5 ± 15.1 years) with SARS-CoV-2 infection and the following rheumatic diseases: rheumatoid arthritis (19 patients), systemic lupus erythematosus (10), polymyalgia rheumatica (7), seronegative spondyloarthritis (7), myositis (3), giant cell arteritis (1), sarcoidosis (1), small vessel vasculitis (2), juvenile idiopathic arthritis (1) and Kikuchi's disease (1) and a control group of 104 participants (mean age 63.1 ± 14.9 years) without rheumatic diseases. In both groups, 69% of the participants were female. The participants in the rheumatic disease group (RDG) had the following comorbidities: hypertension (34 patients), diabetes (13), coronary artery disease (12), heart failure (4) and pulmonary disease (21); while the participants in the control group had hypertension (50 individuals), diabetes (29), coronary artery disease (10), heart failure (11) and pulmonary disease (28). The participants with rheumatic disease were under pharmacological treatment, including: hydroxychloroquine (9 patients), hydroxychloroquine monotherapy (5), tumor necrosis factor (TNF) inhibitor (7), interleukin 6 (IL-6) receptor inhibitor (1), belimumab (2), rituximab (3), interleukin 12/interleukin 23 (IL-12/IL-23) inhibitor (2), abatacept (1), tofacitinib (3), methotrexate (9), leflunomide (4), mycophenolate mofetil (3) and prednisone (5). The patients with rheumatic disease and SARS-CoV-2 infection were compared with the patients with SARS-CoV-2 who did not have rheumatic diseases (control group, CG), regarding comorbidities, age, race and gender.

Excluded studies

We read 20 full-text articles to assess the possibility of inclusion. We excluded 4 case series and 15 case-report studies,[9-27] because these study designs were not appropriate for assessing prognosis questions.

Risk of bias in the included study

We assessed the risk of bias in the retrospective cohort study using Quality Appraisal in Systematic Reviews of Prognosis Studies (QUIPS).[28,29] The study received two negative assessments, in relation to prognostic factor measurement and to confounding measurement and account criteria, because of multiple drug therapy used in the RDG (without adjustment for the confounders, for instance). We have summarized the risk of bias assessments in **Figure 2**.

Certainty of evidence

We rated the certainty of the evidence using the Grading of Recommendations Assessment, Development and Evaluation (GRADE) approach.[30] We found very low certainty of evidence for all the reported outcomes. We downgraded by one level in situations of study limitation (risk of bias), by one level in situations of indirectness (important differences in the severity of the different rheumatic diseases) and by one level in situations of imprecision of effect estimation.

Outcome results

Among the outcomes of interest, only hospitalization rate, length of hospital stay, ICU admission rate, need for invasive mechanical ventilation (IMV), duration of IMV support and mortality were evaluated in the study included in this review. The following outcomes were not reported: length of ICU stay, adverse events, time to viral clearance and time to clinical improvement. The results and certainty of evidence for each outcome measurement and the effect size (odds ratio and mean difference) are shown in the "Summary of findings" table (**Table 1**).

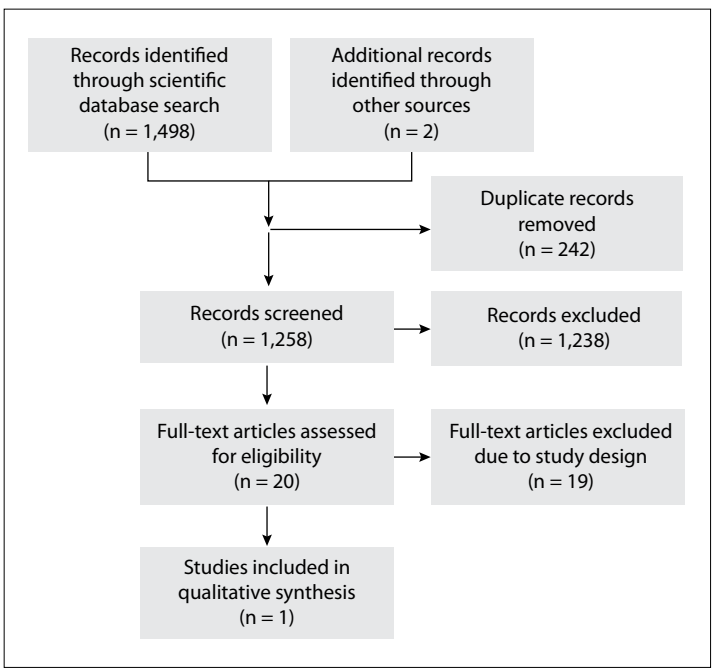

Figure 1. Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) flow diagram.

Hospitalization

Although the patients with RD seemed to have a higher chance of hospitalization, we could not detect any statistically significant difference between the groups. In the RDG, 23 patients were hospitalized versus 42 patients in the CG: odds ratio (OR) = 1.17; 95% confidence interval (CI) 0.6 to 2.29. The mean difference between the groups regarding the length of hospital stay was 1.30 days (95% CI 4.85 to 7.45).

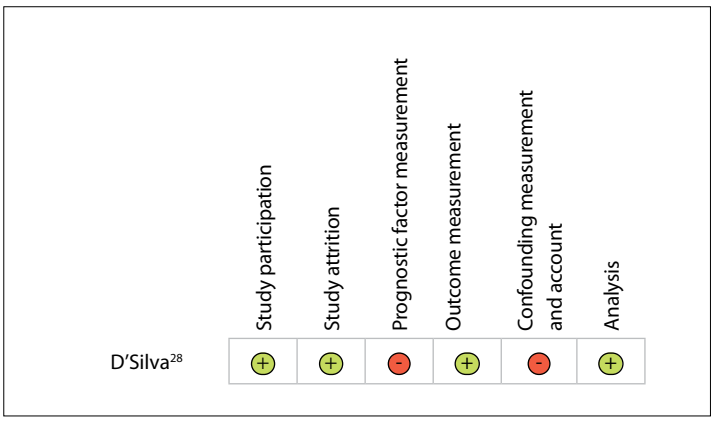

Figure 2. Risk of bias in the study included.

Intensive care unit (ICU) admission

The RDG presented three times more chance of being admitted to an ICU than participants in the CG (OR 3.72; 95% CI 1.35 to 10.26).

Invasive mechanical ventilation (IMV)

The number of patients who received IMV was statistically greater in the RDG (11 patients) than in the CG (7 patients) (OR 3.72; 95% CI 1.35 to 10.26). The mean difference between the two groups regarding mechanical ventilation was 3.14 days (95% CI 1.29 to 7.63).

Mortality

Although the patients in the RD group seemed to have a higher chance of mortality, we could not detect any statistically significant difference between the groups (OR 1.53; 95% CI 0.33 to 7.11).

Table 1. Summary of findings

Rheumatic patients undergoing treatments with immunosuppressants, immunobiological agents, synthetic DMARDs or targeted synthetic DMARDs, compared with participants without rheumatic diseases; both groups diagnosed with COVID-19			
Patient or population: Rheumatic patients using DMARDs, immunobiological agents, immunosuppressants or corticosteroid who were then diagnosed with COVID-19. **Comparison:** Participants without rheumatic diseases and not undergoing no drug treatment, who had been diagnosed with COVID-19. **Setting:** Tertiary-level care and community hospitals; and primary and specialty outpatient centers.			
Outcomes	**Relative effect (95% CI)**	**No. of participants (no. of studies)**	**Certainty of the evidence (GRADE)**
Hospitalization	**OR 1.1** (0.6 to 2.29)	156 (1 observational study)	⊕◯◯◯ VERY LOW [a,b,c]
Length of hospital stay	Mean difference in length of hospital stay between the groups was 1.3 (-4.85 to 7.34) days	65 (1 observational study)	⊕◯◯◯ VERY LOW [a,b,c]
ICU admission	**OR 3.72** (1.35 to 10.26)	156 (1 observational study)	⊕◯◯◯ VERY LOW [a,b,c]
Mechanical ventilation	**OR 3.72** (1.35 to 10.26)	156 (1 observational study)	⊕◯◯◯ VERY LOW [a,b,c]
Mortality	**OR 1.53** (0.33 to 7.11)	156 (1 observational study)	⊕◯◯◯ VERY LOW [a,b,c]
DMARDs = disease-modifying antirheumatic drugs; CI = confidence interval; OR = odds ratio; ICU: intensive care unit; length of hospital stay is expressed as the mean number of days (with standard deviation). **GRADE Working Group grades of evidence** **High certainty:** Further research is very unlikely to change our confidence in the estimate of effect. **Moderate certainty:** Further research is likely to have an important impact on our confidence in the estimate of effect and may change the estimate. **Low certainty:** Further research is very likely to have an important impact on our confidence in the estimate of effect and is likely to change the estimate **Very low certainty:** We are very uncertain about the estimate.			

Explanations

a. Downgraded by one level due to serious study limitations (risk of bias).

b. Downgraded by one level due to serious indirectness. Important differences in the severity of different rheumatic diseases.

c. Downgraded by one level due to serious imprecision. The 95% CI crossed the line of no effect and was also a wide interval around the estimate of the effect. Therefore, it was clinically irrelevant.

DISCUSSION

This was the first systematic review to evaluate whether patients with IMID undergoing pharmacological treatment with immunosuppressants, immunobiological agents, synthetic disease-modifying antirheumatic drugs (DMARDs) or targeted synthetic DMARDs have better or worse outcomes when infected by SARS-CoV-2. A single retrospective study[28] provided very low certainty of evidence that patients with IMID who were undergoing long-term pharmacological treatments seemed to have higher chances of hospitalization and mortality. However, comparison with patients without IMID and who were not undergoing treatments with immunosuppressants, immunobiological agents, synthetic DMARDs or targeted synthetic DMARDs did not show any statistically significant difference in these chances. There was also very low certainty of evidence from the same study that the chances of being admitted to an ICU and of needing IMV were higher in the RDG than among patients without IMID who were not receiving these long-term pharmacological treatments.

Several limitations of the study that was included in the present review need to be highlighted. Firstly, the RDG was composed of participants with several types of IMID and with different severities of disease. Secondly, the participants with IMID were under several drug treatments and no specific analyses taking into account the type of drug were conducted. Lastly, no information on drug dose and duration of drug treatment was provided. Therefore, we were unable to directly investigate the influence of each class of drugs on the course of COVID-19 in patients with IMID who were undergoing specific pharmacological treatments.

Our results are in line with those from a previous study that included 1,591 consecutive patients referred for ICU admission. That study showed that IMID was the most prevalent comorbidity in patients with laboratory confirmation as positive for SARS-CoV-2 who were admitted to ICUs.[6] The current systematic review also found one retrospective cohort study[28] suggesting that patients with IMID may be more likely to have worse evolution when infected by SARS-CoV-2. Although the latter study had a large sample, it was a retrospective case series and therefore it was excluded from the present review.

We took efforts to rapidly identify all the available evidence, through a broad and sensitive search. In spite of this, the studies identified were not appropriate for answering the clinical question of this review. We identified 19 studies (4 case series and 15 case reports) that discussed clinical and laboratory findings from patients with IMID, but several methodological limitations of the present review need to be taken into account. Firstly, the studies identified did not have control groups and we were unable to examine whether participants who were not under pharmacological treatment for IMID had better or worse outcomes. Secondly, we did not find any studies that evaluated potential adverse effects of long-term use of these drugs after the presence of SARS-CoV-2 infection had been diagnosed, or the time to viral clearance, time to clinical improvement or length of ICU stay. Lastly, none of the studies identified had been prospectively planned for evaluation of the question of this review.

Given that the current pandemic scenario has exposed shortages of professionals and resources, along with limitations to evidence-based clinical protocols, the outcomes of critical clinical importance would be those relating to the duration of usage of limited resources, such as the time taken to achieve clinical improvement, time to viral clearance and length of ICU stay. We are aware that the difficulties involved in designing and conducting studies during these times of pandemic have contributed to the dearth of high-quality studies. We are also conscious that the heterogeneous patient groups, multiple classes of drugs and multiple methodologies among the various studies conducted have added complications to standardized data extraction procedures, such as those required for systematic reviews and meta-analyses.

We believe that there is a great need for prospective cohorts to be conducted in the future with the aim of examining representative samples of patients with IMID undergoing pharmacological treatments who are then diagnosed with COVID-19. Adjustments will need to be made for confounding variables such as in relation to use of multiple drugs, administration route, disease severity, comorbidities and age. Through such studies, the level of confidence in the effect estimates can be improved.

The current evidence was assessed in the present review through methodological appraisal. Although this has provided scientifically rigorous data to inform further studies, the results reported here should be interpreted cautiously in analyses for decision-making processes.

CONCLUSION

To date, based on the results from a single retrospective cohort study, no protective effect from the drugs used for treating IMID, regarding the clinical course of COVID-19, has been demonstrated. On the contrary, patients with IMID seem to have higher chances of being admitted to ICUs and of requiring IMV. Furthermore, additional high-quality studies are needed in order to analyze the effects of different treatments for IMID, while considering the characteristics of the disease and the treatment administered on an individualized basis, among patients who also present infection with COVID-19.

REFERENCES

1. Venerito V, Lopalco G, Iannone F. COVID-19, rheumatic diseases and immunosuppressive drugs: an appeal for medication adherence. Rheumatol Int. 2020;40(5):827-8. PMID: 32232551; https://doi.org/10.1007/s00296-020-04566-9.

2. D'Antiga L. Coronaviruses and Immunosuppressed Patients: The Facts During the Third Epidemic. Liver Transpl. 2020;26(6):832-4. PMID: 32196933; https://doi.org/10.1002/lt.25756.
3. Favalli EG, Ingegnoli F, De Lucia O, et al. COVID-19 infection and rheumatoid arthritis: Faraway, so close! Autoimmun Rev. 2020;19(5):102523. PMID: 32205186; https://doi.org/10.1016/j.autrev.2020.102523.
4. Askanase AD, Khalili L, Buyon JP. Thoughts on COVID-19 and autoimmune diseases. Lupus Sci Med. 2020;7(1):e000396. PMID: 32341791; https://doi.org/10.1136/lupus-2020-000396.
5. Falagas ME, Manta KG, Betsi GI, Pappas G. Infection-related morbidity and mortality in patients with connective tissue diseases: a systematic review. Clin Rheumatol. 2007;26(5):663-70. PMID: 17186117; https://doi.org/10.1007/s10067-006-0441-9.
6. Grasselli G, Zangrillo A, Zanella A, el al. Baseline Characteristics and Outcomes of 1591 Patients Infected With SARS-CoV-2 Admitted to ICUs of the Lombardy Region, Italy. JAMA. 2020;323(16):1574-81. PMID: 32250385; https://doi.org/10.1001/jama.2020.5394.
7. Tufan A, Avanoğlu Güler A, Matucci-Cerinic M. COVID-19, immune system response, hyperinflammation and repurposing antirheumatic drugs. Turk J Med Sci. 2020;50(SI-1):620-32. PMID: 32299202; https://doi.org/10.3906/sag-2004-168.
8. Garritty C, Gartlehner G, Kamel C, et al. Cochrane Rapid Reviews Interim Guidance from the Cochrane Rapid Reviews Methods Group 2020. Available from: https://methods.cochrane.org/rapidreviews/sites/methods.cochrane.org.rapidreviews/files/public/uploads/cochrane_rr_-_guidance-23mar2020-v1.pdf. Accessed in 2020 (Jul 29).
9. Tomelleri A, Sartorelli S, Campochiaro C, Baldissera EM, Dagna L. Impact of COVID-19 pandemic on patients with large-vessel vasculitis in Italy: a monocentric survey. Ann Rheum Dis. 2020. Published online ahead of print. PMID: 32345617; https://doi/org/10.1136/annrheumdis-2020-217600.
10. Favalli EG, Ingegnoli F, Cimaz R, Caporali R. What is the true incidence of COVID-19 in patients with rheumatic diseases? Ann Rheum Dis. 2020. Published online ahead of print. PMID: 32321723; https://doi/org/10.1136/annrheumdis-2020-217615.
11. Gisondi P, Facheris P, Dapavo P, et al. The impact of COVID-19 pandemic on patients with chronic plaque psoriasis being treated with biologic therapy: the Northern Italy experience. Br J Dermatol. 2020;183(2):373-4. PMID: 32343839; https://doi/org/10.1111/bjd.19158.
12. Mathian A, Mahevas M, Rohmer J, et al. Clinical course of coronavirus disease 2019 (COVID-19) in a series of 17 patients with systemic lupus erythematosus under long-term treatment with hydroxychloroquine. Ann Rheum Dis. 2020;79(6):837-9. PMID: 32332072; https://doi/org/10.1136/annrheumdis-2020-217566.
13. Brenner EJ, Ungaro RC, Gearry RB, et al. Corticosteroids, but not TNF Antagonists, are Associated with Adverse COVID-19 Outcomes in Patients With Inflammatory Bowel Diseases: Results from an International Registry. Gastroenterology. 2020. Published online ahead of print. PMID: 32425234; https://doi/org/10.1053/j.gastro.2020.05.032.
14. Benhadou F, Del Marmol V. Improvement of SARS-CoV-2 symptoms following Guselkumab injection in a psoriatic patient. J Eur Acad Dermatol Venereol. 2020. Published online ahead of print. PMID: 32379925; https://doi/org/10.1111/jdv.16590.
15. Balestri R, Rech G, Girardelli CR. Occurrence of SARS-CoV-2 during mycophenolate mofetil treatment for pemphigus [published online ahead of print, 2020 May 2]. J Eur Acad Dermatol Venereol. 2020;10.1111/jdv.16578. PMID: 32359182; https://doi/org/10.1111/jdv.16578.
16. Conti A, Lasagni C, Bigi L, Pellacani G. Evolution of COVID-19 infection in four psoriatic patients treated with biological drugs. J Eur Acad Dermatol Venereol. 2020;34(8):e360-e361. PMID: 32379913; https://doi/org/10.1111/jdv.16587.
17. Damiani G, Pacifico A, Bragazzi NL, Malagoli P. Biologics increase the risk of SARS-CoV-2 infection and hospitalization, but not ICU admission and death: real-life data from a large cohort during red-zone declaration [published online ahead of print, 2020 May 1]. Dermatol Ther. 2020;e13475. PMID: 32356577; https://doi/org/10.1111/dth.13475.
18. Dousa KM, Malavade SS, Furin J, et al. SARS-CoV-2 infection in a patient on chronic hydroxychloroquine therapy: Implications for prophylaxis [published online ahead of print, 2020 Apr 27]. IDCases. 2020;20:e00778. PMID: 32341910; https://doi/org/10.1016/j.idcr.2020.e00778.
19. Duret PM, Sebbag E, Mallick A, et al. Recovery from COVID-19 in a patient with spondyloarthritis treated with TNF-alpha inhibitor etanercept [published online ahead of print, 2020 Apr 30]. Ann Rheum Dis. 2020;annrheumdis-2020-217362. PMID: 32354772; https://doi/org/10.1136/annrheumdis-2020-217362.
20. Guilpain P, Le Bihan C, Foulongne V, et al. Rituximab for granulomatosis with polyangiitis in the pandemic of covid-19: lessons from a case with severe pneumonia [published online ahead of print, 2020 Apr 20]. Ann Rheum Dis. 2020;annrheumdis-2020-217549. PMID: 32312768; https://doi/org/10.1136/annrheumdis-2020-217549.
21. Han Y, Jiang M, Xia D, et al. COVID-19 in a patient with long-term use of glucocorticoids: A study of a familial cluster. Clin Immunol. 2020;214:108413. PMID: 32276139; https://doi/org/10.1016/j.clim.2020.108413.
22. Jacobs J, Clark-Snustad K, Lee S. Case Report of a SARS-CoV-2 Infection in a Patient With Ulcerative Colitis on Tofacitinib. Inflamm Bowel Dis. 2020;26(7):e64. PMID: 32342098; https://doi/org/10.1093/ibd/izaa093.
23. Messina F, Piaserico S. SARS-CoV-2 infection in a psoriatic patient treated with IL-23 inhibitor. J Eur Acad Dermatol Venereol. 2020;34(6):e254-5. PMID: 32294258; https://doi/org/10.1111/jdv.16468.
24. Mihai C, Dobrota R, Schröder M, et al. COVID-19 in a patient with systemic sclerosis treated with tocilizumab for SSc-ILD. Ann Rheum Dis. 2020;79(5):668-9. PMID: 32241792; https://doi/org/10.1136/annrheumdis-2020-217442.
25. Song J, Kang S, Choi SW, et al. Coronavirus Disease 19 (COVID-19) complicated with pneumonia in a patient with rheumatoid arthritis receiving conventional disease-modifying antirheumatic drugs. Rheumatol Int. 2020;40(6):991-5. PMID: 32314010; https://doi/org/10.1007/s00296-020-04584-7.

26. Tursi A, Angarano G, Monno L, et al. COVID-19 infection in Crohn's disease under treatment with adalimumab. Gut. 2020;69(7):1364-5. PMID: 32312788; https://doi/org/10.1136/gutjnl-2020-321240.
27. Moutsopoulos HM. Anti-inflammatory therapy may ameliorate the clinical picture of COVID-19 [published online ahead of print, 2020 Apr 28]. Ann Rheum Dis. 2020;annrheumdis-2020-217562. PMID: 32345616; https://doi/org/10.1136/annrheumdis-2020-217562.
28. D'Silva KM, Serling-Boyd N, Wallwork R, et al. Clinical characteristics and outcomes of patients with coronavirus disease 2019 (COVID-19) and rheumatic disease: a comparative cohort study from a US 'hot spot' [published online ahead of print, 2020 May 26]. Ann Rheum Dis. 2020;annrheumdis-2020-217888. PMID: 32457048; https://doi/org/10.1136/annrheumdis-2020-217888.
29. Hayden A, Côté P, Bombardier C. Evaluation of the quality of prognosis studies in systematic reviews. Ann Inter Med. 2006;144(6):427-37. PMID: 16549855; https://doi/org/10.7326/0003-4819-144-6-200603210-00010.
30. Atkins D, Best D, Briss PA, et al. Grading quality of evidence and strength of recommendations. BMJ. 2004;328(7454):1490. PMID: 15205295; https://doi/org/10.1136/bmj.328.7454.1490.

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APPENDIX 1. Search strategies.

MEDLINE via PubMed.

"COVID-19" [Supplementary Concept OR (COVID 19) OR (COVID-19) OR (2019-nCoV) OR (nCoV) OR (Covid19) OR (SARS-CoV) OR (SARSCov2 or ncov*) OR (SARSCov2) OR (2019 coronavirus*) OR (2019 corona virus*) OR (Coronavirus (COVID-19)) OR (2019 novel coronavirus disease) OR (COVID-19 pandemic) OR (COVID-19 virus infection) OR (coronavirus disease-19) OR (2019 novel coronavirus infection) OR (2019-nCoV infection) OR (coronavirus disease 2019) OR (2019-nCoV disease) OR (COVID-19 virus disease) OR "severe acute respiratory syndrome coronavirus 2" [Supplementary Concept] OR (Wuhan coronavirus) OR (Wuhan seafood market pneumonia virus) OR (COVID19 virus) OR (COVID-19 virus) OR (coronavirus disease 2019 virus) OR (SARS-CoV-2) OR (SARS2) OR (2019-nCoV) OR (2019 novel coronavirus)

"Interleukin-6"[Mesh] OR interleukin 6 OR "IL 6" OR IL-6 OR IL6 OR "tocilizumab" [Supplementary Concept] OR Tocilizum* OR altizumab OR actemra OR RHPM-1 OR RG-1569 OR R-1569 OR MSB11456 OR MSB-11456 OR (monoclonal antibody, MRA) OR (RO-4877533) OR roactemra OR anti-IL-6 OR anti-interleukin-6 OR "siltuximab" [Supplementary Concept] OR CLLB8 OR (cCIB8 monoclonal antibody) OR Sylvant OR CNTO-328 OR (CNTO 328 monoclonal antibody) OR (monoclonal antibody CNTO328) OR "sarilumab" [Supplementary Concept] OR SAR-153191 OR SAR153191 OR Kevzara OR REGN-88 OR REGN88 OR "olokizumab" [Supplementary Concept] OR CDP-6038 OR CDP6038 OR elsilimomab OR BMS945429 OR ALD518 OR "sirukumab" [Supplementary Concept] OR (CNTO 136) OR CNTO-136 OR CPSI-2364 OR ALX-0061 OR "clazakizumab" [Supplementary Concept] OR ALD-518 OR ALD518 OR BMS-945429 OR "sarilumab" [Supplementary Concept] OR SAR-153191 OR SAR153191 OR Kevzara OR REGN-88 OR REGN88 OR "sirukumab" [Supplementary Concept] OR ARGX-109 OR FE301 OR FM101 OR "Tumor Necrosis Factor-alpha"[Mesh] OR TNF OR TNF-alpha OR TNF-α OR Anti-TNF OR "Infliximab"[Mesh] OR (Monoclonal Antibody cA2) OR (MAb cA2) OR Infliximab-abda OR Renflexis OR Infliximab-dyyb OR Inflectra OR Remicade OR "Etanercept"[Mesh] OR (TNFR-Fc Fusion Protein) OR (TNR 001) OR (TNT Receptor Fusion Protein) OR TNTR-Fc OR TNR-001 OR TNR001 OR Etanercept-szzs OR (TNF Receptor Type II-IgG Fusion Protein) OR (TNF Receptor Type II IgG Fusion Protein) OR Erelzi OR (Recombinant Human Dimeric TNF Receptor Type II-IgG Fusion Protein) OR (Recombinant Human Dimeric TNF Receptor Type II IgG Fusion Protein) OR Enbrel OR "Certolizumab Pegol"[Mesh] OR Certolizumab OR Cimzia OR CDP870 OR (CDP 870) OR "golimumab" [Supplementary Concept] OR CNTO-148 OR (CNTO 148) OR Simponi OR "Adalimumab"[Mesh] OR Humira OR Adalimumab-adbm OR Amjevita OR Adalimumab-atto OR Cyltezo OR (D2E7 Antibody) OR "Interleukin-1"[Mesh] OR IL-1 OR IL-1RA OR "IL 1" OR "canakinumab" [Supplementary Concept] OR ilaris OR ACZ-885 OR ACZ885 OR anti-IL-1 OR "rilonacept" [Supplementary Concept] OR ACZ885 OR anakinra OR "Interleukin-5"[Mesh] OR Anti-IL-5 OR "mepolizumab" [Supplementary Concept] OR Bosatria OR SB-240563 OR SB240563 OR Nucala OR "Interleukin-12"[Mesh] OR IL-12 OR "Ustekinumab"[Mesh] OR Stelara OR (CNTO 1275) OR CNTO-1275 OR "Interleukin-23"[Mesh] OR IL-23 OR "IL 23" OR "briakinumab" [Supplementary Concept] OR A-796874.0 OR BSF-415977 OR (BSF 415977) OR WAY-165772 OR LU-415977 OR (LU 415977) OR J-695 OR J695 OR ABT-874 OR (ABT-874 antibody, human) OR Anti-C5 OR "eculizumab" [Supplementary Concept] OR Alexion OR Soliris OR 5G1.1 OT (H5G1.1VHC+H5G1.1VLC) OR H5G1.1 OR H5G1-1 OR H5G11 OR "Abatacept"[Mesh] OR LEA29Y OR BMS224818 OR BMS-224818 OR (BMS 224818) OR Belatacept OR (BMS 188667) OR (BMS-188667) OR CTLA-4-Ig OR (Cytotoxic T Lymphocyte-Associated Antigen 4-Immunoglobulin) OR (Cytotoxic T Lymphocyte Associated Antigen 4 Immunoglobulin) OR CTLA4-Ig OR (CTLA4-Ig Immunoconjugate) OR (CTLA4 Ig Immunoconjugate) OR (Immunoconjugate, CTLA4-Ig) OR CTLA4-Fc OR Nulojix OR "Rituximab"[Mesh] OR (CD20 Antibody) OR (Rituximab CD20 Antibody) OR Mabthera OR (IDEC-C2B8 Antibody) OR (IDEC C2B8 Antibody) OR (IDEC-C2B8) OR (IDEC C2B8) OR GP2013 OR Rituxan OR "Antigens, CD20"[Mesh] OR (CD20 Antigen) OR (CD20 Antigens) OR "belimumab" [Supplementary Concept] OR (BEL-114333) OR BEL114333 OR HGS-1006 OR HGS1006 OR LymphoStat-B OR GSK-1550188 OR GSK1550188 OR Benlysta OR "secukinumab" [Supplementary Concept] OR "Interleukin-17"[Mesh] OR IL-17A OR IL-17 OR "IL 17" OR "ixekizumab" [Supplementary Concept] OR "brodalumab" [Supplementary Concept] OR "guselkumab" [Supplementary Concept] OR "tildrakizumab" [Supplementary Concept] OR "risankizumab" [Supplementary Concept] OR "apremilast" [Supplementary Concept] OR Otezla OR (CC 10004) OR CC10004 OR CC-10004 OR "tofacitinib" [Supplementary Concept] OR tasocitinib OR (tofacitinib citrate) OR Xeljanz OR (CP 690,550) OR CP690550 OR CP-690550 OR (CP 690550) OR CP-690,550 OR "baricitinib" [Supplementary Concept] OR LY3009104 OR Olumiant OR INCB028050 OR "Azathioprine"[Mesh] OR Azothioprine OR Imurel OR Imuran OR Immuran OR "Mycophenolic Acid"[Mesh] OR (Mycophenolate Mofetil) OR Cellcept OR (Mycophenolate Sodium) OR Myfortic OR (RS 61443) OR (RS-61443) OR RS61443 OR "Cyclophosphamide"[Mesh] OR Sendoxan OR B-518 OR (B 518) OR B518 OR Cytophosphane OR (Cyclophosphamide Monohydrate) OR Cytophosphan OR Cytoxan OR Endoxan OR Neosar OR NSC-26271 OR (NSC 26271) OR NSC26271 OR Procytox OR Cyclophosphane OR "Cyclosporine"[Mesh] OR Ciclosporin OR Cyclosporin OR Neoral OR (Sandimmun Neoral) OR (CyA-NOF) OR (CyA NOF) OR Sandimmune OR Sandimmun OR (CsA-Neoral) OR (CsA Neoral) OR CsANeoral OR (OL 27-400) OR (OL 27 400) OR (OL 27400) OR "Tacrolimus"[Mesh] OR Prograft OR FR-900506 OR (FR 900506) OR FR900506 OR (Anhydrous Tacrolimus) OR FK-506 OR (FK 506) OR FK506 OR "Hydroxychloroquine"[Mesh] OR (Hydroxychloroquine) OR Oxychlorochin OR Oxychloroquine OR Hydroxychlorochin OR Plaquenil OR Hidroxicloroquina OR Hydroxychloroquinum OR Oxichlorochine OR Oxicloroquine OR "Chloroquine"[Mesh] OR Chlorochin OR Cloroquina OR Cloroquine OR Chloroquine OR "Antimalarials"[Mesh] OR Antimalarials OR Anti-Malarials OR (Anti Malarials) OR Hydroquin OR Axemal OR Dolquine OR Quensyl OR Quinoric OR "Sulfasalazine"[Mesh] OR Salicylazosulfapyridine OR (Pyralin EN) OR Azulfadine OR Azulfidine OR Asulfidine OR (Colo-Pleon) OR (Colo Pleon) OR Pleon OR Ulcol OR Sulfasalazin OR Ucine OR Salazopyrin OR (ratio-Sulfasalazine) OR (ratio Sulfasalazine) OR "Methotrexate"[Mesh] OR Amethopterin OR Mexate OR "Leflunomide"[Mesh] OR (HWA 486) OR HWA-486 OR HWA486 OR SU101 OR Arava OR "Dapsone"[Mesh] OR DADPS OR Sulfonyldianiline OR Diaminodiphenylsulfone OR Diaphenylsulfone OR (4,4'-Diaminophenyl Sulfone) OR (4,4' Diaminophenyl Sulfone) OR Sulfona OR (Dapson-Fatol) OR Disulone OR Avlosulfone OR (Dapsoderm-X) OR "Glucocorticoids"[Mesh] OR Glucocorticoid OR "Immunoglobulins"[Mesh] OR Immunoglobulin OR Globulins

Publication date from 2019/11/01

#1 AND #2 AND #3

EMBASE

#1 'covid 19'/exp OR (COVID 19) OR (COVID-19) OR (2019-nCoV) OR (nCoV) OR (Covid19) OR (SARS-CoV) OR (SARSCov2 or ncov*) OR (SARSCov2) OR (2019 coronavirus*) OR (2019 corona virus*) OR (Coronavirus (COVID-19)) OR (2019 novel coronavirus disease) OR (COVID-19 pandemic) OR (COVID-19

Continue...

APPENDIX 1. Continuation.

virus infection) OR (coronavirus disease-19) OR (2019 novel coronavirus infection) OR (2019-nCoV infection) OR (coronavirus disease 2019) OR (2019-nCoV disease) OR (COVID-19 virus disease) OR (severe acute respiratory syndrome coronavirus 2) OR (Wuhan coronavirus) OR (Wuhan seafood market pneumonia virus) OR (COVID19 virus) OR (COVID-19 virus) OR (coronavirus disease 2019 virus) OR (SARS-CoV-2) OR (SARS2) OR (2019-nCoV) OR (2019 novel coronavirus)

#2 'interleukin 6'/exp OR 'interleukin 6' OR 'IL 6' OR interleukin-6 OR 'tocilizumab'/exp OR tocilizumab OR actemra OR atlizumab OR lusinex OR 'r 1569' OR r1569 OR roactemra OR 'sarilumab'/exp OR sarilumab OR kevzara OR 'regn 88' OR regn88 OR 'sar 153191' OR sar153191 OR 'tumor necrosis factor inhibitor'/exp OR 'tumor necrosis factor' OR 'TNF alpha' OR TNF-alpha OR TNF OR 'tumour necrosis factor' OR 'infliximab'/exp OR 'abp 710' OR abp710 OR avakine OR flixabi OR 'gp 1111' OR gp1111 OR inflectra OR infliximab-abda OR infliximab-dyyb OR infliximab-qbtx OR ixifi OR 'pf 06438179' OR 'pf 6438179' OR pf06438179 OR pf6438179 OR remicade OR remsima OR renflexis OR revellex OR 'ta 650' OR ta650 OR zessly OR 'etanercept'/exp OR etanercept OR avent OR benepali OR embrel OR enbrel OR enerceptan OR 'enia 11' OR enia11 OR erelzi OR etanercept-szzs OR etanercept-ykro OR eticovo OR 'gp 2015' OR gp2015 OR infinitam OR lifmior OR opinercept OR 'tnr 001' OR tnr001 OR tunex OR 'ylb 113' OR ylb113 OR 'certolizumab'/exp OR certolizumab OR 'golimumab'/exp OR 'cnto 148' OR cnto148 OR simponi OR 'golimumab'/exp OR golimumab OR 'cnto 148' OR cnto148 OR simponi OR 'adalimumab'/exp OR 'abp 501' OR abp501 OR 'abt d2e7' OR abtd2e7 OR adalimumab-adaz OR adalimumab-adbm OR adalimumab-atto OR adalimumab-bwwd OR adaly OR amgevita OR amjevita OR 'avt 02' OR avt02 OR 'bat 1406' OR bat1406 OR 'bax 2923' OR 'bax 923' OR bax2923 OR bax923 OR 'bi 695501' OR bi695501 OR 'chs 1420' OR chs1420 OR 'ct p17' OR ctp17 OR cyltezo OR 'da 3113' OR da3113 OR 'dmb 3113' OR dmb3113 OR exemptia OR 'fkb 327' OR fkb327 OR fyzoclad OR 'gp 2017' OR gp2017 OR hadlima OR halimatoz OR hefiya OR 'hlx 03' OR hlx03 OR hulio OR humira OR hyrimoz OR 'ibi 303' OR ibi303 OR idacio OR imraldi OR kromeya OR 'lu 200134' OR lu200134 OR 'm 923' OR m923 OR mabura OR 'monoclonal antibody D2E7' OR 'msb 11022' OR msb11022 OR 'ons 3010' OR ons3010 OR 'pf 06410293' OR 'pf 6410293' OR pf06410293 OR pf6410293 OR raheara OR 'sb 5' OR sb5 OR solymbic OR trudexa OR 'zrc 3197' OR zrc3197 OR 'interleukin 1'/exp OR 'interleukin 1' OR 'IL 1' OR IL-1 OR 'interleukin I' OR interleukin-1 OR 'canakinumab'/exp OR 'acz 885' OR acz885 OR ilaris OR 'rilonacept'/exp OR rilonacept OR arcalyst OR 'anakinra'/exp OR anakira OR kineret OR 'interleukin 5'/exp OR 'interleukin 5' OR 'il 5' OR interleukin-5 OR IL-5 OR 'mepolizumab'/exp OR mepolizumab OR bosatria OR nucala OR 'sb 240563' OR sb-240563 OR sb240563 OR 'interleukin 12'/exp OR 'interleukin 12' OR 'IL 12' OR il-12 OR interleukin-12 OR 'interleukin 23'/exp OR 'interleukin 23' OR 'IL 23' OR interleukin-23 OR 'ustekinumab'/exp OR ustekinumab OR 'cnto 1275' OR cnto1275 OR stelara OR 'eculizumab'/exp OR eculizumab OR 'monoclonal antibody 5G1.1' OR soliris OR 'abatacept'/exp OR abatacept OR 'bms 188667' OR bms188667 OR 'CTLA4 Ig' OR 'CTLA4 immunoglobulin' OR 'CTLA4 immunoglobulin G' OR CTLA4Ig OR orencia OR 'rituximab'/exp OR rituximab OR 'abp 798' OR 'abp798' OR blitzima OR 'ct p10' OR ctp10 OR 'gp 2013' OR gp2013 OR 'hlx 01' OR hlx01 OR 'idec 102' OR 'idec c2b8' OR idec102 OR idecc2b8 OR mabthera OR 'mk 8808' OR mk8808 OR 'monoclonal antibody idec c2b8' OR 'pf 05280586' OR 'pf 5280586' OR pf05280586 OR pf5280586 OR 'r 105' OR r105 OR reditux OR 'rg 105' OR rg105 OR ritemvia OR ritumax OR rituxan OR rituximab-abbs OR rituximab-pvvr OR rituxin OR rituzena OR rixathon OR riximyo OR 'ro 452294' OR ro452294 OR ruxience OR truxima OR tuxella OR 'belimumab'/exp OR belimumab OR benlysta OR 'lymphostat B' OR 'interleukin 17'/exp OR 'interleukin 17' OR 'il 17A' OR IL-17 OR 'interleukin 17A' OR interleukin-17 OR 'secukinumab'/exp OR secukinumab OR 'ain 457' OR ain457 OR cosentyx OR 'ixekizumab'/exp OR ixekizumab OR 'ly 2439821' OR ly2439821 OR taltz OR 'brodalumab'/exp OR brodalumab OR 'amg 827' OR amg827 OR kyntheum OR siliq OR 'guselkumab'/exp OR guselkumab OR 'cnto 1959' OR cnto1959 OR tremfya OR 'tildrakizumab'/exp OR tildrakizumab OR ilumetri OR ilumya OR 'mk 3222' OR 'mk3222' OR 'sch 900222' OR sch900222 OR 'sunpg 1622' OR 'sunpg 1623' OR sunpg1622 OR sunpg1623 OR 'tildrakizumab asmn' OR tildrakizumab-asmn OR 'risankizumab'/exp OR risankizumab OR 'abbv 066' OR abbv066 OR 'bi 655066' OR bi655066 OR 'risankizumab rzaa' OR risankizumab-rzaa OR skyrizi OR 'apremilast'/exp OR apremilast OR 'cc 10004' OR cc10004 OR otezla OR 'tofacitinib'/exp OR tofacitinib OR 'cp 690 550' OR 'cp 690, 550' OR 'cp 690550' OR 'cp 690550-10' OR 'cp690 550' OR 'cp690, 550' OR cp690550 OR cp690550-10 OR tasocitinib OR 'tofacitinib citrate' OR xeljanz OR 'xeljanz xr' OR 'baricitinib'/exp OR baricitinib OR 'incb 028050' OR 'incb 28050' OR incb028050 OR incb28050 OR 'ly 3009104' OR ly3009104 OR olumiant OR 'azathioprine'/exp OR azathioprine OR arathioprin OR arathioprine OR 'aza-q' OR azafalk OR azahexal OR azamedac OR azamun OR azamune OR azanin OR azapin OR azapress OR azaprine OR azarex OR azasan OR azathiodura OR azathiopine OR azathioprim OR azathioprin OR azathiopurine OR azathropsin OR azatioprina OR azatox OR azatrilem OR azopi OR azoran OR azothioprin OR azothioprine OR 'bw 57 322' OR 'bw 57-322' OR 'w 57322' OR bw57-322 OR bw57322 OR colinsan OR immuran OR immurel OR immuthera OR imunen OR imuprin OR imuran OR imurane OR imurek OR imurel OR imuren OR 'nsc 39084' OR nsc39084 OR thioazeprine OR thioprine OR transimune OR zytrim OR 'mycophenolate mofetil'/exp OR 'mycophenolate mofetil' OR 'cell cept' OR cellcept OR cellmune OR cellsept OR munoloc OR myclausen OR 'mycophenolic acid 2 morpholinoethyl ester' OR 'mycophenolic acid mofetil' OR myfenax OR 'rs 61443' OR 'rs 61443 190' OR rs61443 OR 'rs61443 190' OR 'cyclophosphamide'/exp OR cychophosphamide OR alkyroxan OR 'b 518' OR 'b 518 asta' OR b518 OR 'b518 asta' OR carloxan OR ciclofosfamida OR ciclolen OR cicloxal OR clafen OR cyclo-cell OR cycloblastin OR cycloblastine OR 'cyclofos amide' OR cyclofosfamid OR cyclofosfamide OR cyclophar OR cyclophosphamid OR 'cyclophosphamide isopac' OR cyclophosphamides OR cyclophosphan OR cyclophosphane OR cyclostin OR cycloxan OR cyphos OR cytophosphan OR cytophosphane OR cytoxan OR 'endocyclo phosphate' OR endoxan OR 'endoxan-asta' OR endoxana OR endoxon-asta OR enduxan OR genoxal OR ledoxan OR ledoxina OR mitoxan OR neosan OR neosar OR noristan OR 'nsc 26271' OR nsc2671 OR procytox OR procytoxide OR semdoxan OR sendoxan OR syklofosfamid OR 'cyclosporine'/exp OR cyclosporine OR 'adi 628' OR adi628 OR cequa OR 'cgc 1072' OR cgc1072 OR ciclomulsion OR cicloral OR ciclosporin OR ciclosporine OR cipol OR cipol-n OR consupren OR cyclasol OR cyclokat OR cyclosporin OR 'de 076' OR de076 OR deximune OR equoral OR gengraf OR ikervis OR iminoral OR implanta OR imusporin OR 'lx 201' OR lx201 OR 'mc2 03' OR mc203 OR 'mtd 202' OR mtd202 OR neoral OR neoral-sandimmun OR 'neuro-stat drug' OR 'neurostat drug' OR 'nm 0133' OR 'nm 133' OR nm0133 OR nm133 OR 'nova 22007' OR nova22007 OR 'ol 27400' OR ol27400 OR 'olo 400' OR olo500 OR 'opph 088' OR opph088 OR opsisporin OR 'otx 101' OR otx101 OR 'p 3072' OR p3072 OR padciclo OR papilock OR pulminiq OR restasis OR restaysis OR sanciclo OR sandimmun OR sandimmune OR sandimun OR sandimune OR 'sang 35' OR sang35 OR sangcya OR 'sp 14019' OR sp14019 OR 'sti 0529' OR sti0529 OR 't 1580' OR t1580 OR vekacia OR verkazia OR 'tacrolimus'/exp OR tacrolimus OR advagraf OR astagraf OR envarsus OR 'fk 506' OR fk-506 OR fk506 OR 'fr 900506' OR fr900506 OR fujimycin OR hecoria OR modigraf OR 'mustopic oint' OR prograf OR prograft OR protopic OR protopy OR tacforius OR 'tacrolimus hydrate' OR tsukubaenolide

Continue...

APPENDIX 1. Continuation.

#3 'hydroxychloroquine'/exp OR hydroxychloroquine OR 'chloroquinol'/exp OR chloroquinol OR 'ercoquin'/exp OR ercoquin OR 'hydrochloroquine'/exp OR hydrochloroquine OR 'hydrocloroquine'/exp OR hydrocloroquine OR 'oxychloroquine'/exp OR oxychloroquine OR 'quensyl'/exp OR quensyl OR 'sn 8137'/exp OR 'sn 8137' OR oxychlorochin OR hydroxychlorochin OR plaquenil OR hidroxicloroquina OR hydroxychloroquinum OR oxichloroquine OR 'chloroquine'/exp OR chloroquine OR a-cq OR amokin OR amokine OR anoclor OR aralan OR aralen OR aralene OR arechin OR arechine OR arequine OR arthrochin OR arthrochine OR arthroquine OR artrichin OR artrichine OR artriquine OR avloclor OR avoclor OR bemaphata OR bemaphate OR bemasulph OR bipiquin OR cadiquin OR chemochin OR chemochine OR chingamine OR chingaminum OR chloraquine OR chlorochin OR chlorochine OR chlorofoz OR chloroquin OR 'chloroquin phosphate' OR chloroquinesulphate OR 'chloroquini diphosphas' OR 'chloroquinum diphosphoricum' OR chlorquin OR chlorquine OR choloquine OR 'choroquine sulfate' OR 'choroquine sulphate' OR cidanchin OR 'clo-kit junior' OR clorichina OR clorichine OR cloriquine OR clorochina OR delagil OR delagyl OR dichinalex OR diclokin OR diquinalex OR diroquine OR emquin OR genocin OR gontochin OR gontochine OR gontoquine OR heliopar OR imagon OR iroquine OR klorokin OR klorokine OR klorokinfosfat OR lagaquin OR malaquin OR malarex OR malarivon OR malaviron OR maliaquine OR maquine OR mesylith OR mexaquin OR mirquin OR nivachine OR nivaquin OR nivaquine OR 'p roquine' OR quinachlor OR quingamine OR repal OR resochen OR resochene OR resochin OR 'resochin junior' OR resochina OR resochine OR resochinon OR resoquina OR resoquine OR reumachlor OR roquine OR 'rp 3377' OR rp3377 OR sanoquin OR sanoquine OR silbesan OR siragan OR sirajan OR 'sn 7618' OR sn7618 OR solprina OR solprine OR tresochin OR tresochine OR tresoquine OR trochin OR trochine OR troquine OR 'w 7618' OR w7618 OR 'win 244' OR win244 OR 'antimalarial agent'/exp OR 'antimalarial agent' OR 'anti malaria drug'/exp OR 'anti malaria drug' OR 'antimalaria agent'/exp OR 'antimalaria agent' OR 'antimalaria drug'/exp OR 'antimalaria drug' OR 'antimalaria drug, synthetic'/exp OR 'antimalarial'/exp OR antimalarial OR 'antimalarial drug'/exp OR 'antimalarial drug' OR 'antimalarials'/exp OR antimalarials OR 'antipaludean agent'/exp OR 'antipaludean agent' OR 'antiplasmodic agent'/exp OR 'antiplasmodic agent' OR 'synthetic antimalaria agent'/exp OR 'synthetic antimalaria agent' OR 'salazosulfapyridine'/exp OR salazosulfapyridine OR 'azlufidine en-tabs' OR azopyrin OR azopyrine OR azosulfidine OR azulfide OR azulfidina OR azulfidine OR 'azulfidine EN tabs' OR 'azulfidine en-tabs' OR 'azulfidine ra' OR azulfin OR benzosulfa OR 'colo pleon' OR colo-pleon OR colopleon OR disalazin OR gastropyrin OR 'pleon ra' OR 'pyralin en' OR rorasul OR rosulfant OR s.a.s.-500 OR salazine OR 'salazo sulfapyridine' OR salazodin OR salazopirina OR salazopyridin OR salazopyridine OR salazopyrin OR 'salazopyrin entabs' OR salazopyrin-en OR salazopyrina OR salazopyrine OR 'salazopyrine ec' OR 'salazosulfa pyridine' OR salazosulfpyridine OR 'salicyl azo sulfapyridine' OR salicylazosulfapyridin OR salicylazosulfapyridine OR salisulf OR salopyr OR saridine OR 'sas 500' OR sulcolon OR sulfasalazine OR sulfasalizine OR sulfosalazine OR sulphasalazine OR zopyrin OR 'methotrexate'/exp OR methotrexate OR '4 amino 10 methylfolic acid' OR '4 amino 10 methylpteroylglutamic acid' OR '4 amino n10 methylpteroylglutamic acid' OR 'a methopterine' OR abitrexate OR amethopterin OR amethopterine OR ametopterine OR antifolan OR biotrexate OR canceren OR 'cl 14377' OR cl14377 OR emtexateM OR emthexat OR emthexate OR emtrexate OR enthexate OR farmitrexat OR farmitrexate OR farmotrex OR folex OR ifamet OR imeth OR 'intradose MTX' OR jylamvo OR lantarel OR ledertrexate OR maxtrex OR metex OR methoblastin OR methohexate OR methotrate OR methotrexat OR methotrexato OR methoxtrexate OR methrotrexate OR methylaminopterin OR methylaminopterine OR meticil OR metoject OR metothrexate OR metotrexat OR metotrexate OR metotrexin OR metrex OR mexate OR mexate-aq OR 'mexate-aq preserved' OR 'mpi 5004' OR mpi5004 OR MTX OR neotrexate OR nordimet OR novatrex OR 'nsc 740' OR nsc740 OR otrexup OR 'otrexup pfs' OR rasuvo OR reumatrex OR rheumatrex OR 'rheumatrex dose pack' OR methotrexate OR texate OR texate-t OR texorate OR trexall OR xaken OR xatmep OR zexate OR 'leflunomide'/exp OR leflunomide OR 'alpha, alpha, alpha trifluoro 5 methyl 4 isoxazolecarboxy para toluidide' OR arabloc OR arava OR 'hwa 486' OR hwa486 OR repso OR 'rs 34821' OR rs34821 OR 'su 101' OR su101 OR 'dapsone'/exp OR dapsone OR '4 diaminodiphenylsulfone' OR '4 sulfonyldianiline' OR '4 diaminodiphenyl sulfone' OR '4 diaminodiphenylsulfone' OR '4 sulfonylbisbenzamine' OR '4 sulfonyldianiline' OR aczone OR atrisone OR avlosulfan OR avlosulfon OR avlosulfone OR '4 aminophenyl sulfone' OR 'bn 2405' OR bn2405 OR croysulfone OR dapsoderm-x OR dapson OR 'dapson-fatol' OR dapsona OR dds OR 'diamino diphenyl sulfone' OR 'diaminodiphenyl sulfone' OR diaminodiphenylosulfone OR diaminodiphenylsulfon OR diaminodiphenylsulfone OR diammodiphenylsulfone OR 'diaphenyl sulfone' OR diaphenylsulfon OR diaphenylsulfone OR diaphenylsulphone OR diphenason OR diphenasone OR diphone OR disulone OR dopsan OR dumitone OR eporal OR 'f 1358' OR f1358 OR lennon-dapsone OR lepravir OR novasulfon OR novophone OR 'nsc 6091' OR nsc6091 OR 'para sulfodianiline' OR servidapson OR servidapsone OR sulfadione OR sulfadoine OR sulfona OR 'sulfona mae' OR 'sulfone mere' OR udolac OR 'glucocorticoid'/exp OR glucocorticoid OR glucocorticoids OR glucocorticoidsteroid OR glucocorticosteroid OR glucocortoid OR glycocorticoid OR glycocorticosteroid OR 'immunoglobulin'/exp OR immunoglobulin OR 'antibody protein' OR endobulin OR 'flebogamma liquida' OR gamastan OR 'gamimmune n' OR gamimune OR 'gamma globulin' OR 'gamma globulins' OR 'gamma immunoglobulin' OR gamma-globulins OR gammagee OR gammaglobulin OR gammaglobuline OR gammar OR gammimune OR gamulin OR globuman OR 'glovenin i' OR Ig OR igam OR igc OR 'immune gamma globulin' OR 'immune globin' OR 'immune globulin' OR 'immune globuline' OR 'immune globulins' OR 'immune serum globulin' OR immuno OR 'immuno gamma globulin' OR 'immuno globulin' OR immunogammaglobulin OR immunoglobin OR 'immunoglobulin 17' OR 'immunoglobulin c' OR 'immunoglobulin c1' OR 'immunoglobulin chain' OR 'immunoglobulin gamma' OR 'immunoglobulin preparation' OR immunoglobulins OR 'immunoglobulins,intravenous' OR immunoprotein OR immunoproteins OR 'intraglobin f' OR isiven OR iveegam OR ivega OR ivig OR panglobulin OR sandoglobin OR tegelin OR tegeline OR veinoglobulin OR venoglobulin OR 'venoglobulin i' OR 'venoglobulin-i'

#4 #2 OR #3

#5 #1 AND #4

#6 #5 AND [embase]/lim NOT ([embase]/lim AND [medline]/lim) AND [1-11-2019]/sd

Cochrane

#1 MeSH descriptor: [Coronavirus] explode all trees

#2 MeSH descriptor: [Coronaviridae] explode all trees

Continue...

APPENDIX 1. Continuation.

#3 MeSH descriptor: [Betacoronavirus] explode all trees

#4 MeSH descriptor: [Coronavirus Infections] explode all trees

#5 (COVID 19) OR (COVID-19) OR (2019-nCoV) OR (nCoV) OR (Covid19) OR (SARS-CoV) OR (SARSCov2 or ncov*) OR (SARSCov2) OR (2019 coronavirus*) OR (2019 corona virus*) OR (Coronavirus (COVID-19)) OR (2019 novel coronavirus disease) OR (COVID-19 pandemic) OR (COVID-19 virus infection) OR (coronavirus disease-19) OR (2019 novel coronavirus infection) OR (2019-nCoV infection) OR (coronavirus disease 2019) OR (2019-nCoV disease) OR (COVID-19 virus disease) OR "severe acute respiratory syndrome coronavirus 2" OR (Wuhan coronavirus) OR (Wuhan seafood market pneumonia virus) OR (COVID19 virus) OR (COVID-19 virus) OR (coronavirus disease 2019 virus) OR (SARS-CoV-2) OR (SARS2) OR (2019-nCoV) OR (2019 novel coronavirus)

#6 #1 OR #2 OR #3 OR #4 OR #5

#7 MeSH descriptor: [Interleukin-6] explode all trees

#8 (interleukin 6) OR "IL 6" OR IL-6 OR IL6

#9 Tocilizum* OR altizumab OR actemra OR RHPM-1 OR RG-1569 OR R-1569 OR MSB11456 OR MSB-11456 OR (monoclonal antibody, MRA) OR (RO-4877533) OR roactemra OR anti-IL-6 OR anti-interleukin-6 OR siltuximab OR CLLB8 OR (cClB8 monoclonal antibody) OR Sylvant OR CNTO-328 OR (CNTO 328 monoclonal antibody) OR (monoclonal antibody CNTO328) OR sarilumab OR SAR-153191 OR SAR153191 OR Kevzara OR REGN-88 OR REGN88 OR olokizumab OR CDP-6038 OR CDP6038 OR elsilimomab OR BMS945429 OR ALD518 OR sirukumab OR (CNTO 136) OR CNTO-136 OR CPSI-2364 OR ALX-0061 OR clazakizumab OR ALD-518 OR ALD518 OR BMS-945429 OR sarilumab OR SAR-153191 OR SAR153191 OR Kevzara OR REGN-88 OR REGN88 OR sirukumab OR ARGX-109 OR FE301 OR FM101

#10 MeSH descriptor: [Tumor Necrosis Factors] explode all trees

#11 TNF OR TNF-alpha OR TNF-α OR Anti-TNF

#12 MeSH descriptor: [Tumor Necrosis Factor-alpha] explode all trees

#12 MeSH descriptor: [Infliximab] explode all trees

#13 Infliximab-dyyb OR Remicade OR Renflexis OR Inflectra OR Infliximab-abda OR (Monoclonal Antibody cA2) OR (MAb cA2) OR Infliximab-dyyb

#14 MeSH descriptor: [Etanercept] explode all trees

#15 (TNFR-Fc Fusion Protein) OR (TNR 001) OR (TNT Receptor Fusion Protein) OR TNTR-Fc OR TNR-001 OR TNR001 OR Etanercept-szzs OR Erelzi OR Etanercept-szzs OR (TNFR Fc Fusion Protein)

#16 MeSH descriptor: [Certolizumab Pegol] explode all trees

#17 Certolizumab OR CDP870 OR (CDP 870) OR Cimzia

#18 golimumab OR CNTO-148 OR (CNTO 148) OR Simponi

#19 MeSH descriptor: [Adalimumab] explode all trees

#20 Humira OR Adalimumab-adbm OR Amjevita OR Adalimumab-atto OR Cyltezo OR (D2E7 Antibody)

#21 MeSH descriptor: [Interleukin-1] explode all trees

#22 IL-1 OR IL-1RA OR (IL 1) OR canakinumab OR ilaris OR ACZ-885 OR ACZ885 OR anti-IL-1 OR rilonacept OR ACZ885 OR anakinra

#23 MeSH descriptor: [Interleukin-5] explode all trees

#24 IL-5 OR (IL 5) OR (interleukin 5) OR Anti-IL-5 OR mepolizumab OR Bosatria OR SB-240563 OR SB240563 OR Nucala

#25 MeSH descriptor: [Interleukin-23] explode all trees

#26 "IL-23" OR (Interleukin 23) OR guselkumab OR tildrakizumab OR risankizumab

#27 MeSH descriptor: [Interleukin-17] explode all trees

#28 (Interleukin 17F) OR IL-17F OR brodalumab OR secukinumab OR ixekizumab

#29 MeSH descriptor: [Abatacept] explode all trees

#30 LEA29Y OR BMS224818 OR BMS-224818 OR (BMS 224818) OR Belatacept OR (BMS 188667) OR BMS-188667 OR (CTLA4 Ig Immunoconjugate) OR Nulojix

#31 MeSH descriptor: [Rituximab] explode all trees

Continue...

APPENDIX 1. Continuation.

#32 (CD20 Antibody) OR (Rituximab CD20 Antibody) OR Mabthera OR (IDEC-C2B8 Antibody) OR (IDEC C2B8 Antibody) OR (IDEC-C2B8) OR (IDEC C2B8) OR GP2013 OR Rituxan OR (CD20 Antigen) OR (CD20 Antigens)

#33 belimumab OR (BEL-114333) OR BEL114333 OR HGS-1006 OR HGS1006 OR LymphoStat-B OR GSK-1550188 OR GSK1550188 OR Benlysta

#34 IL-17A OR IL-17 OR (IL 17)

#35 MeSH descriptor: [Interleukin-12] explode all trees

#36 MeSH descriptor: [Interleukin-23] explode all trees

#37 IL-23 OR (IL 23) OR (interleukin 23)

#38 MeSH descriptor: [Ustekinumab] explode all trees

#39 Stelara OR (CNTO 1275) OR CNTO-1275

#40 briakinumab OR A-796874.0 OR BSF-415977 OR (BSF 415977) OR WAY-165772 OR LU-415977 OR (LU 415977) OR J-695 OR J695 OR ABT-874 OR (ABT-874 antibody, human) OR Anti-C5 OR eculizumab OR Alexion OR Soliris OR H5G1.1 OR H5G1-1 OR H5G1

#41 Apremilast OR Otezla OR Tasocitinib OR (tofacitinib citrate) OR Xeljanz OR Baricitinib OR Olumiant

#42 Azathioprine OR Azothioprine OR Imurel OR Imuran OR Immuran

#43 MeSH descriptor: [Mycophenolic Acid] explode all trees

#44 (Mycophenolate Mofetil) OR (Mycophenolate Sodium) OR Myfortic

#45 MeSH descriptor: [Cyclophosphamide] explode all trees

#46 Sendoxan OR Cytophosphan OR Procytox OR Cyclophosphane OR Neosar OR Cytoxan OR Cytophosphane

#47 MeSH descriptor: [Cyclosporins] in all MeSH products

#48 (CsA Neoral) OR CsANeoral OR CsA-Neoral OR Neoral OR CyA-NOFM OR CyA NOF OR Cyclosporin OR Ciclosporin OR "Cyclosporine A" OR Sandimmune OR Sandimmun

#49 MeSH descriptor: [Tacrolimus] explode all trees

#50 Prograf OR Prograft

#51 MeSH descriptor: [Chloroquine] explode all trees

#52 Nivaquine OR Aralen OR Arechine OR Arequin OR Chlorochin OR Chingamin OR Khingamin

#53 MeSH descriptor: [Hydroxychloroquine] explode all trees

#54 Plaquenil OR Hydroxychlorochin OR Oxychlorochin OR Oxychloroquine

#55 MeSH descriptor: [Sulfasalazine] explode all trees

#56 Salicylazosulfapyridine OR Sulphasalazine OR Salazosulfapyridine OR (Colo Pleon) OR Pleon OR Colo-Pleon OR Azulfadine OR Azulfidine OR Asulfidine OR Sulfasalazin-Heyl OR Sulfasalazin OR Salazopyrin OR Ulcol OR Ucine OR "Pyralin EN"

#57 MeSH descriptor: [Methotrexate] explode all trees

#58 Methotrexate OR Mexate OR Amethopterin

#59 MeSH descriptor: [Leflunomide] explode all trees

#60 "N-(4-Trifluoromethyphenyl)-5-methylisoxazole-4-carboxamide" OR Arava OR (SU101) OR (HWA 486) OR HWA486 OR HWA-486

#61 MeSH descriptor: [Dapsone] explode all trees

#62 Sulfona OR "4,4'-Diaminophenyl Sulfone" OR Diaphenylsulfone OR DADPS OR "4,4' Diaminophenyl Sulfone" OR "Sulfone, 4,4'-Diaminophenyl" OR Diaminodiphenylsulfone OR Sulfonyldianiline OR Avlosulfone OR Disulone OR "Dapsoderm-X" OR "Dapson-Fatol"

#63 MeSH descriptor: [Glucocorticoids] explode all trees

#64 "Glucocorticoid Effect" OR Glucocorticoid

#65 MeSH descriptor: [Immunoglobulins] explode all trees

#66 Immunoglobulin OR Globulins

Continue...

APPENDIX 1. Continuation.

SCOPUS

#1 TITLE-ABS-KEY(coronavirus)

#2 TITLE-ABS-KEY(coronaviridae)

#3 TITLE-ABS-KEY("Coronavirus Infections")

#4 TITLE-ABS-KEY(betacoronavirus)

#5 (COVID 19) OR (COVID-19) OR (2019-nCoV) OR (nCoV) OR (Covid19) OR (SARS-CoV) OR (SARSCov2 or ncov*) OR (SARSCov2) OR (2019 coronavirus*) OR (2019 corona virus*) OR (Coronavirus (COVID-19)) OR (2019 novel coronavirus disease) OR (COVID-19 pandemic) OR (COVID-19 virus infection) OR (coronavirus disease-19) OR (2019 novel coronavirus infection) OR (2019-nCoV infection) OR (coronavirus disease 2019) OR (2019-nCoV disease) OR (COVID-19 virus disease) OR (severe acute respiratory syndrome coronavirus 2) OR (Wuhan coronavirus) OR (Wuhan seafood market pneumonia virus) OR (COVID19 virus) OR (COVID-19 virus) OR (coronavirus disease 2019 virus) OR (SARS-CoV-2) OR (SARS2) OR (2019-nCoV) OR (2019 novel coronavirus)

#6 #1 OR #2 OR #3 OR #4 OR #5

#7 TITLE-ABS-KEY(Interleukin-6)

#8 TITLE-ABS-KEY("Tumor Necrosis Factors")

#9 TITLE-ABS-KEY("Tumor Necrosis Factor-alpha")

#10 TITLE-ABS-KEY(Infliximab)

#11 TITLE-ABS-KEY(Etanercept)

#12 TITLE-ABS-KEY("Certolizumab Pegol")

#13 TITLE-ABS-KEY(Adalimumab)

#14 TITLE-ABS-KEY(Interleukin-1)

#15 TITLE-ABS-KEY(Interleukin-5)

#16 TITLE-ABS-KEY(Interleukin-23)

#17 TITLE-ABS-KEY(Interleukin-17)

#18 TITLE-ABS-KEY(Abatacept)

#19 TITLE-ABS-KEY(Rituximab)

#20 TITLE-ABS-KEY(Interleukin-12)

#21 TITLE-ABS-KEY(Interleukin-23)

#22 TITLE-ABS-KEY(Ustekinumab)

#23 TITLE-ABS-KEY("Mycophenolic Acid")

#24 TITLE-ABS-KEY(Cyclophosphamide)

#25 TITLE-ABS-KEY(Cyclosporins)

#26 TITLE-ABS-KEY(Tacrolimus)

#27 TITLE-ABS-KEY(Chloroquine)

#28 TITLE-ABS-KEY(Hydroxychloroquine)

#29 TITLE-ABS-KEY(Sulfasalazine)

#30 TITLE-ABS-KEY(Methotrexate)

#31 TITLE-ABS-KEY(Leflunomide)

#32 TITLE-ABS-KEY(Dapsone)

#33 TITLE-ABS-KEY(Glucocorticoids)

#34 TITLE-ABS-KEY(Immunoglobulins)

Continue...

APPENDIX 1. Continuation.

#35 (interleukin 6) OR "IL 6" OR IL-6 OR IL6 OR Tocilizum* OR altizumab OR actemra OR RHPM-1 OR RG-1569 OR R-1569 OR MSB11456 OR MSB-11456 OR (monoclonal antibody, MRA) OR (RO-4877533) OR roactemra OR anti-IL-6 OR anti-interleukin-6 OR siltuximab OR CLLB8 OR (cCIB8 monoclonal antibody) OR Sylvant OR CNTO-328 OR (CNTO 328 monoclonal antibody) OR (monoclonal antibody CNTO328) OR sarilumab OR SAR-153191 OR SAR153191 OR Kevzara OR REGN-88 OR REGN88 OR olokizumab OR CDP-6038 OR CDP6038 OR elsilimomab OR BMS945429 OR ALD518 OR sirukumab OR (CNTO 136) OR CNTO-136 OR CPSI-2364 OR ALX-0061 OR clazakizumab OR ALD-518 OR ALD518 OR BMS-945429 OR sarilumab OR SAR-153191 OR SAR153191 OR Kevzara OR REGN-88 OR REGN88 OR sirukumab OR ARGX-109 OR FE301 OR FM101 OR TNF OR TNF-alpha OR TNF-α OR Anti-TNF OR Infliximab-dyyb OR Remicade OR Renflexis OR Inflectra OR Infliximab-abda OR (Monoclonal Antibody cA2) OR (MAb cA2) OR Infliximab-dyyb OR (TNFR-Fc Fusion Protein) OR (TNR 001) OR (TNT Receptor Fusion Protein) OR TNTR-Fc OR TNR-001 OR TNR001 OR Etanercept-szzs OR Erelzi OR Etanercept-szzs OR (TNFR Fc Fusion Protein) OR Certolizumab Pegol OR Certolizumab OR CDP870 OR (CDP 870) OR Cimzia OR golimumab OR CNTO-148 OR (CNTO 148) OR Simponi OR Humira OR Adalimumab-adbm OR Amjevita OR Adalimumab-atto OR Cyltezo OR (D2E7 Antibody) OR IL-1 OR IL-1RA OR (IL 1) OR canakinumab OR ilaris OR ACZ-885 OR ACZ885 OR anti-IL-1 OR rilonacept OR ACZ885 OR anakinra OR IL-5 OR (IL 5) OR (interleukin 5) OR Anti-IL-5 OR mepolizumab OR Bosatria OR SB-240563 OR SB240563 OR Nucala OR "IL-23" OR (Interleukin 23) OR guselkumab OR tildrakizumab OR risankizumab OR (Interleukin 17F) OR IL-17F OR brodalumab OR secukinumab OR ixekizumab OR LEA29Y OR BMS224818 OR BMS-224818 OR (BMS 224818) OR Belatacept OR (BMS 188667) OR BMS-188667 OR (CTLA4 Ig Immunoconjugate) OR Nulojix OR (CD20 Antibody) OR (Rituximab CD20 Antibody) OR Mabthera OR (IDEC-C2B8 Antibody) OR (IDEC C2B8 Antibody) OR (IDEC-C2B8) OR (IDEC C2B8) OR GP2013 OR Rituxan OR (CD20 Antigen) OR (CD20 Antigens) OR belimumab OR (BEL-114333) OR BEL114333 OR HGS-1006 OR HGS1006 OR LymphoStat-B OR GSK-1550188 OR GSK1550188 OR Benlysta OR IL-17A OR IL-17 OR (IL 17) OR IL-23 OR (IL 23) OR (interleukin 23) OR Stelara OR (CNTO 1275) OR CNTO-1275 OR briakinumab OR A-796874.0 OR BSF-415977 OR (BSF 415977) OR WAY-165772 OR LU-415977 OR (LU 415977) OR J-695 OR J695 OR ABT-874 OR (ABT-874 antibody, human) OR Anti-C5 OR eculizumab OR Alexion OR Soliris OR H5G1.1 OR H5G1-1 OR H5G1 OR Apremilast OR Otezla OR Tasocitinib OR (tofacitinib citrate) OR Xeljanz OR Baricitinib OR Olumiant OR Azathioprine OR Azothioprine OR Imurel OR Imuran OR Immuran OR (Mycophenolate Mofetil) OR (Mycophenolate Sodium) OR Myfortic OR Sendoxan OR Cytophosphan OR Procytox OR Cyclophosphane OR Neosar OR Cytoxan OR Cytophosphane OR (CsA Neoral) OR CsANeoral OR CsA-Neoral OR Neoral OR CyA-NOFM OR CyA NOF OR Cyclosporin OR Ciclosporin OR "Cyclosporine A" OR Sandimmune OR Sandimmun OR Prograf OR Prograft OR Nivaquine OR Aralen OR Arechine OR Arequin OR Chlorochin OR Chingamin OR Khingamin OR Plaquenil OR Hydroxychlorochin OR Oxychlorochin OR Oxychloroquine OR Salicylazosulfapyridine OR Sulphasalazine OR Salazosulfapyridine OR (Colo Pleon) OR Pleon OR Colo-Pleon OR Azulfadine OR Azulfidine OR Asulfidine OR Sulfasalazin-Heyl OR Sulfasalazin OR Salazopyrin OR Ulcol OR Ucine OR "Pyralin EN" OR Methotrexate OR Mexate OR Amethopterin OR "N-(4-Trifluoromethyphenyl)-5-methylisoxazole-4-carboxamide" OR Arava OR (SU101) OR (HWA 486) OR HWA486 OR HWA-486 OR Sulfona OR "4,4'-Diaminophenyl Sulfone" OR Diaphenylsulfone OR DADPS OR "4,4' Diaminophenyl Sulfone" OR "Sulfone, 4,4'-Diaminophenyl" OR Diaminodiphenylsulfone OR Sulfonyldianiline OR Avlosulfone OR Disulone OR "Dapsoderm-X" OR "Dapson-Fatol" OR "Glucocorticoid Effect" OR Glucocorticoid OR Immunoglobulin OR Globulins

#36 #7 OR #8 OR #9 #10 OR #11 OR #12 OR #13 OR #14 OR #15 OR #16 OR #17 OR #18 OR #19 OR #20 OR #21 OR #22 OR #23 OR #24 OR #25 OR #26 OR #27 OR #28 OR #29 #30 OR #31 OR #32 OR #33 OR #34 OR #35

#37 #6 AND #36

#38 #37 AND (LIMIT-TO(PUBYEAR, 2020) OR LIMIT-TO(PUBYEAR, 2019))

WEB OF SCIENCE

TS=(COVID 19 OR COVID-19 OR 2019-nCoV OR nCoV OR Covid19 OR SARS-CoV OR SARSCov2 or ncov* OR 2019 coronavirus* OR 2019 corona virus* OR Coronavirus OR 2019 novel coronavirus disease OR COVID-19 pandemic OR COVID-19 virus infection OR coronavirus disease-19 OR 2019 novel coronavirus infection OR 2019-nCoV infection OR coronavirus disease 2019 OR 2019-nCoV disease OR COVID-19 virus disease OR severe acute respiratory syndrome coronavirus 2 OR Wuhan coronavirus OR Wuhan seafood market pneumonia virus OR COVID19 virus OR COVID-19 virus OR coronavirus disease 2019 virus OR SARS-CoV-2 OR SARS2 OR 2019 novel coronavirus) AND TS=(Interleukin-6 OR interleukin 6 OR IL 6 OR IL-6 OR IL6 OR Tocilizum* OR altizumab OR actemra OR RHPM-1 OR RG-1569 OR R-1569 OR MSB11456 OR MSB-11456 OR monoclonal antibody, MRA OR RO-4877533 OR roactemra OR anti-IL-6 OR anti-interleukin-6 OR siltuximab OR CLLB8 OR cCIB8 monoclonal antibody OR Sylvant OR CNTO-328 OR CNTO 328 monoclonal antibody OR monoclonal antibody CNTO328 OR sarilumab OR SAR-153191 OR SAR153191 OR Kevzara OR REGN-88 OR REGN88 OR olokizumab OR CDP-6038 OR CDP6038 OR elsilimomab OR BMS945429 OR ALD518 OR sirukumab OR CNTO 136 OR CNTO-136 OR CPSI-2364 OR ALX-0061 OR clazakizumab OR ALD-518 OR ALD518 OR BMS-945429 OR sarilumab OR SAR-153191 OR SAR153191 OR Kevzara OR REGN-88 OR REGN88 OR sirukumab OR ARGX-109 OR FE301 OR FM101 OR Tumor Necrosis Factors OR Tumor Necrosis Factor-alpha OR TNF OR TNF-alpha OR TNF-α OR Anti-TNF OR Infliximab-dyyb OR Remicade OR Renflexis OR Inflectra OR Infliximab OR Infliximab-abda OR Monoclonal Antibody cA2 OR MAb cA2 OR Infliximab-dyyb OR TNFR-Fc Fusion Protein OR TNR 001 OR TNT Receptor Fusion Protein OR TNTR-Fc OR TNR-001 OR TNR001 OR Etanercept OR Etanercept-szzs OR Erelzi OR Etanercept-szzs OR TNFR Fc Fusion Protein OR Certolizumab OR CDP870 OR CDP 870 OR Cimzia OR golimumab OR CNTO-148 OR CNTO 148 OR Simponi OR Humira OR Adalimumab OR Adalimumab-adbm OR Amjevita OR Adalimumab-atto OR Cyltezo OR D2E7 Antibody OR Interleukin-1 OR IL-1 OR IL-1RA OR IL 1 OR canakinumab OR ilaris OR ACZ-885 OR ACZ885 OR anti-IL-1 OR rilonacept OR ACZ885 OR anakinra OR Interleukin-5 OR IL-5 OR IL 5 OR interleukin 5 OR Anti-IL-5 OR mepolizumab OR Bosatria OR SB-240563 OR SB240563 OR Nucala OR Interleukin-23 OR IL-23 OR Interleukin 23 OR guselkumab OR tildrakizumab OR risankizumab OR Interleukin-17 OR Interleukin 17F OR IL-17F OR brodalumab OR secukinumab OR ixekizumab OR abatacept OR LEA29Y OR BMS224818 OR BMS-224818 OR BMS 224818 OR Belatacept OR BMS 188667 OR BMS-188667 OR CTLA4 Ig Immunoconjugate OR Nulojix OR CD20 Antibody OR Rituximab OR Rituximab CD20 Antibody OR Mabthera OR IDEC-

Continue...

APPENDIX 1. Continuation.

C2B8 Antibody OR IDEC C2B8 Antibody OR IDEC-C2B8 OR IDEC C2B8 OR GP2013 OR Rituxan OR CD20 Antigen OR CD20 Antigens OR belimumab OR BEL-114333 OR BEL114333 OR HGS-1006 OR HGS1006 OR LymphoStat-B OR GSK-1550188 OR GSK1550188 OR Benlysta OR IL-17A OR IL-17 OR IL 17 OR IL-23 OR Interleukin-12 OR Interleukin-23 OR IL 23 OR interleukin 23 OR Stelara OR CNTO 1275 OR CNTO-1275 OR ustekinumab OR briakinumab OR A-796874.0 OR BSF-415977 OR BSF 415977 OR WAY-165772 OR LU-415977 OR LU 415977 OR J-695 OR J695 OR ABT-874 OR ABT-874 antibody, human OR Anti-C5 OR eculizumab OR Alexion OR Soliris OR H5G1.1 OR H5G1-1 OR H5G1 OR Apremilast OR Otezla OR Tasocitinib OR tofacitinib citrate OR Xeljanz OR Baricitinib OR Olumiant OR Azathioprine OR Azothioprine OR Imurel OR Imuran OR Immuran OR Mycophenolic Acid OR Mycophenolate Mofetil OR Mycophenolate Sodium OR Myfortic OR Sendoxan OR Cyclophosphamide OR Cytophosphan OR Procytox OR Cyclophosphane OR Neosar OR Cytoxan OR Cytophosphane OR CsA Neoral OR CsANeoral OR CsA-Neoral OR Neoral OR CyA-NOFM OR CyA NOF OR Cyclosporins OR Cyclosporin OR Ciclosporin OR "Cyclosporine A" OR Sandimmune OR Sandimmun OR Tacrolimus OR Prograf OR Prograft OR Nivaquine OR Aralen OR Arechine OR Arequin OR Chloroquine OR Chlorochin OR Chingamin OR Khingamin OR Plaquenil OR Hydroxychloroquine OR Hydroxychlorochin OR Oxychlorochin OR Oxychloroquine OR Salicylazosulfapyridine OR Sulfasalazine OR Sulphasalazine OR Salazosulfapyridine OR Colo Pleon OR Pleon OR Colo-Pleon OR Azulfadine OR Azulfidine OR Asulfidine OR Sulfasalazin-Heyl OR Sulfasalazin OR Salazopyrin OR Ulcol OR Ucine OR Pyralin EN OR Methotrexate OR Mexate OR Amethopterin OR N-(4-Trifluoromethyphenyl)-5-methylisoxazole-4-carboxamide OR Arava OR SU101 OR HWA 486 OR HWA486 OR HWA-486 OR Sulfona OR 4,4'-Diaminophenyl Sulfone OR Diaphenylsulfone OR DADPS OR 4,4' Diaminophenyl Sulfone OR Sulfone, 4,4'-Diaminophenyl OR Diaminodiphenylsulfone OR Leflunomide OR Sulfonyldianiline OR Avlosulfone OR Disulone OR Dapsone OR Dapsoderm-X OR Dapson-Fatol OR Glucocorticoids OR Glucocorticoid Effect OR Glucocorticoid OR Immunoglobulins OR Immunoglobulin OR Globulins)

BVS regional portal – LILACS

MH:"Infecções por Coronavirus" OR (Infecções por Coronavirus) OR (Infecciones por Coronavirus) OR (Coronavirus Infections) OR (COVID-19) OR (COVID 19) OR (Doença pelo Novo Coronavírus (2019-nCoV)) OR (Doença por Coronavírus 2019-nCoV) OR (Doença por Novo Coronavírus (2019-nCoV)) OR (Epidemia de Pneumonia por Coronavirus de Wuhan) OR (Epidemia de Pneumonia por Coronavírus de Wuhan) OR (Epidemia de Pneumonia por Coronavírus de Wuhan de 2019-2020) OR (Epidemia de Pneumonia por Coronavírus em Wuhan) OR (Epidemia de Pneumonia por Coronavírus em Wuhan de 2019-2020) OR (Epidemia de Pneumonia por Novo Coronavírus de 2019-2020) OR (Epidemia pelo Coronavírus de Wuhan) OR (Epidemia pelo Coronavírus em Wuhan) OR (Epidemia pelo Novo Coronavírus (2019-nCoV)) OR (Epidemia pelo Novo Coronavírus 2019) OR (Epidemia por 2019-nCoV) OR (Epidemia por Coronavírus de Wuhan) OR (Epidemia por Coronavírus em Wuhan) OR (Epidemia por Novo Coronavírus (2019-nCoV)) OR (Epidemia por Novo Coronavírus 2019) OR (Febre de Pneumonia por Coronavírus de Wuhan) OR (Infecção pelo Coronavírus 2019-nCoV) OR (Infecção pelo Coronavírus de Wuhan) OR (Infecção por Coronavirus 2019-nCoV) OR (Infecção por Coronavírus 2019-nCoV) OR (Infecção por Coronavírus de Wuhan) OR (Infecções por Coronavírus) OR (Pneumonia do Mercado de Frutos do Mar de Wuhan) OR (Pneumonia no Mercado de Frutos do Mar de Wuhan) OR (Pneumonia por Coronavírus de Wuhan) OR (Pneumonia por Novo Coronavírus de 2019-2020) OR (Surto de Coronavírus de Wuhan) OR (Surto de Pneumonia da China 2019-2020) OR (Surto de Pneumonia na China 2019-2020) OR (Surto pelo Coronavírus 2019-nCoV) OR (Surto pelo Coronavírus de Wuhan) OR (Surto pelo Coronavírus de Wuhan de 2019-2020) OR (Surto pelo Novo Coronavírus (2019-nCoV)) OR (Surto pelo Novo Coronavírus 2019) OR (Surto por 2019-nCoV) OR (Surto por Coronavírus 2019-nCoV) OR (Surto por Coronavírus de Wuhan) OR (Surto por Coronavírus de Wuhan de 2019-2020) OR (Surto por Novo Coronavírus (2019-nCoV)) OR (Surto por Novo Coronavírus 2019) OR (Síndrome Respiratória do Oriente Médio) OR (Síndrome Respiratória do Oriente Médio (MERS)) OR (Síndrome Respiratória do Oriente Médio (MERS-CoV)) OR (Síndrome Respiratória do Oriente Médio por Coronavírus) OR MH:C01.925.782.600.550.200$

Filter: Publication year: 2019-2020

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Epidemiological profile of inflammatory bowel disease in Caxias do Sul, Brazil: a cross-sectional study

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KEY WORDS (MeSH terms):
Inflammatory bowel disease.
Crohn disease.
Colitis, ulcerative.
Infliximab.
Adalimumab.

AUTHORS' KEY WORDS:
Latin America.
South America.
Mesalamine.
Indeterminate colitis.
Epidemiology of inflammatory bowel disease.

ABSTRACT

BACKGROUND: Inflammatory bowel diseases affect mostly young patients and have a huge impact on their quality of life and growing treatment costs. Currently, there are few Brazilian studies concerning their epidemiological profile.

OBJECTIVE: The aim of this study was to describe the regional clinical and epidemiological profile of these pathological conditions in Caxias do Sul, Brazil.

DESIGN AND SETTING: Cross-sectional study in Caxias do Sul (RS), Brazil.

METHODS: A search for patients was conducted in the municipality's special medications pharmacy using the International Classification of Diseases, and medical records were manually reviewed for data collection. Sixty-seven patients were included.

RESULTS: The patients' mean age was 46.5 years and females predominated (71.6%). Ulcerative colitis was the most prevalent disease (70%) and Montreal E3 was the most prevalent presentation. The mean age at diagnosis was 39 years. Most patients had recently undergone colonoscopy (67%). Only five patients (7.4%) had records of hospital admission due to the disease, while 12 (18%) underwent a surgical procedure during follow-up. Sixty patients (89.5%) were using aminosalicylates, while less than one fifth were using immunosuppressants or immunobiological drugs: 19.4% and 14.9%, respectively.

CONCLUSION: The profile of inflammatory bowel disease patients in this region of Brazil is similar in some characteristics to other published Brazilian data, although it differs in others such as higher frequency of pancolitis. A prospective study on these patients is planned in this region, in order to improve the data quality.

INTRODUCTION

Inflammatory bowel diseases comprise two major disorders: ulcerative colitis and Crohn's disease. These two pathological conditions have distinct and, at the same time, overlapping clinical characteristics, which might occasionally lead to indeterminate classification.

Globally, the regions with the highest prevalence of these conditions include North America and Northwest Europe. Even with a significant increase in incidence in the last couple of decades, Brazil is still considered to be a low-prevalence country. Nevertheless, there is a lack of clinical-epidemiological studies about inflammatory bowel disease in South America.[1,2] The factors that have been responsible for the remarkable increases in incidence of these diseases, especially in industrialized countries, are still unknown. These increases may have been related to changes in hygiene habits or diet, transition of the population to urban areas or improvements in diagnostic methods.[3] It is also possible that diagnosing of inflammatory bowel disease might suffer from underreporting; hence, it is not a disease with compulsory notification in Brazil.[1]

Despite the low mortality rates associated with inflammatory bowel disease, it has a high burden on the private and public health systems, given that it mostly affects young people, especially those of working age. In addition, its chronic profile, with remissions and exacerbations, has a high impact on patients' quality of life relating to psychological, professional and social matters, which consequently increases healthcare system costs and work incapacity.[4]

Although the pathogenesis and etiology of ulcerative colitis and Crohn's disease remain unknown, it is believed that genetically predisposed individuals are exposed to environmental factors that trigger the disease. This causes a chronic auto-inflammatory process that usually presents with periods of remission and recurrence.[5]

The clinical manifestations of inflammatory bowel disease can vary greatly. The most common symptoms are diarrhea, abdominal pain and rectal bleeding. However, these symptoms can be manifested in other highly prevalent conditions in Brazil, such as bacterial, viral and parasitic intestinal infections. Moreover, inflammatory bowel disease also has extra-intestinal manifestations, generally in the liver, skin, entheses and eyes, which might sometimes precede the intestinal manifestations. Nutritional disorders such as protein-calorie malnutrition, vitamin deficiency and trace elements can also occur.[4-6]

There is no gold-standard method for diagnosing inflammatory bowel disease. The diagnosis is made from a combination of clinical, endoscopic, radiological, serological and histological findings. However, these methods may not be enough for the diagnosis. In such cases, it is necessary to monitor and observe the natural history of the disease.[4-6]

Currently, treatments aim to reduce not only the symptoms, but the inflammatory process as well, so as to prevent potential complications. The modality of treatment is based on an assessment that defines degrees of severity and region of involvement. The pharmacological therapy includes anti-inflammatory drugs (salicylate in doses ranging from 2.4 g to 4.8 g daily and corticosteroids, generally prednisone, at a starting dose of 0.5 mg/kg to 1 mg/kg daily) and immunosuppressants (azathioprine 2-2.5 mg/kg/day, 6-mercaptopurine 1.5-2 mg/kg/day and methotrexate 25 mg intramuscularly per week). Recently, use of antitumor necrosis factor alpha (infliximab 5 mg/kg/dose or adalimumab 40 mg) or anti-integrin (vedolizumab 300 mg) has also started. Surgical approaches are reserved for selected patients, such as those who do not respond well to clinical therapy or who present complications (such as hemorrhage, obstruction, intestinal perforation and toxic megacolon).

OBJECTIVE

The aim of this study was to evaluate and characterize the clinical and epidemiological profile of patients with inflammatory bowel disease in the city of Caxias do Sul (RS), Brazil.

METHODS

This was a cross-sectional study investigating the profile of patients with inflammatory bowel disease, based on a review of medical records. Data were collected during 2016, through reviewing the medical records at a healthcare center in Caxias do Sul and at the gastroenterology and proctology outpatient clinic of a private university in Caxias do Sul. Both of these centers are referral locations for treatment of inflammatory bowel disease within the Brazilian National Health System (Sistema Único de Saúde, SUS). These centers cover an area of 49 municipalities that have an estimated population of 1,079,601 inhabitants, according to the 2010 population census.

This study was approved in October 2016 by a local ethics committee, under protocol number 57569816.1.0000.5341. Since this study only involved reviewing medical charts, the ethics committee exempted the researchers from the necessity for a consent form.

An active search for patients presenting conditions compatible with the International Classification of Diseases (ICD-10) codes for inflammatory bowel disease (K50 and K51) was conducted. The search was conducted in the municipality's special medications pharmacy and the patients included were living in Caxias do Sul and were using any of the following drugs (all of them supplied through SUS): mesalamine 2 g to 4 g daily, sulfasalazine 2 g to 4 g daily, azathioprine 2-2.5 mg/kg/day, adalimumab 40 mg and infliximab 5 mg/kg/dose. The patients included needed to be under active follow-up in a clinic, have a confirmed diagnosis and have a record of recent prescription refill. Patients younger than 16 years old and those whose medical records could not be accessed, were incomplete or did not exist were excluded from the study.

Physical medical records were analyzed manually and data were gathered in relation to each patient. Type and presentation of inflammatory bowel disease were defined not through the ICD code, but through review of the medical records. Data regarding patient symptoms, treatment, risk factors, extra-intestinal manifestations, examinations and procedures were gathered as described in their respective charts.

It had been planned to analyze Harvey-Bradshaw scores for the severity of Crohn's disease and Mayo Clinic scores for ulcerative colitis. Unfortunately, because of a lack of clinical data in the charts for completing the data for these scores, it was not possible to do this analysis. Data regarding the phenotype of Crohn's disease was not found to be reliable and therefore was not collected.

The statistical analysis on the data consisted of presentation of percentages for qualitative variables, and simple frequencies, averages and standard deviations for quantitative variables. These analyses were done using the IBM SPSS statistical software, version 15.0 (SPSS Inc., Chicago, United States).

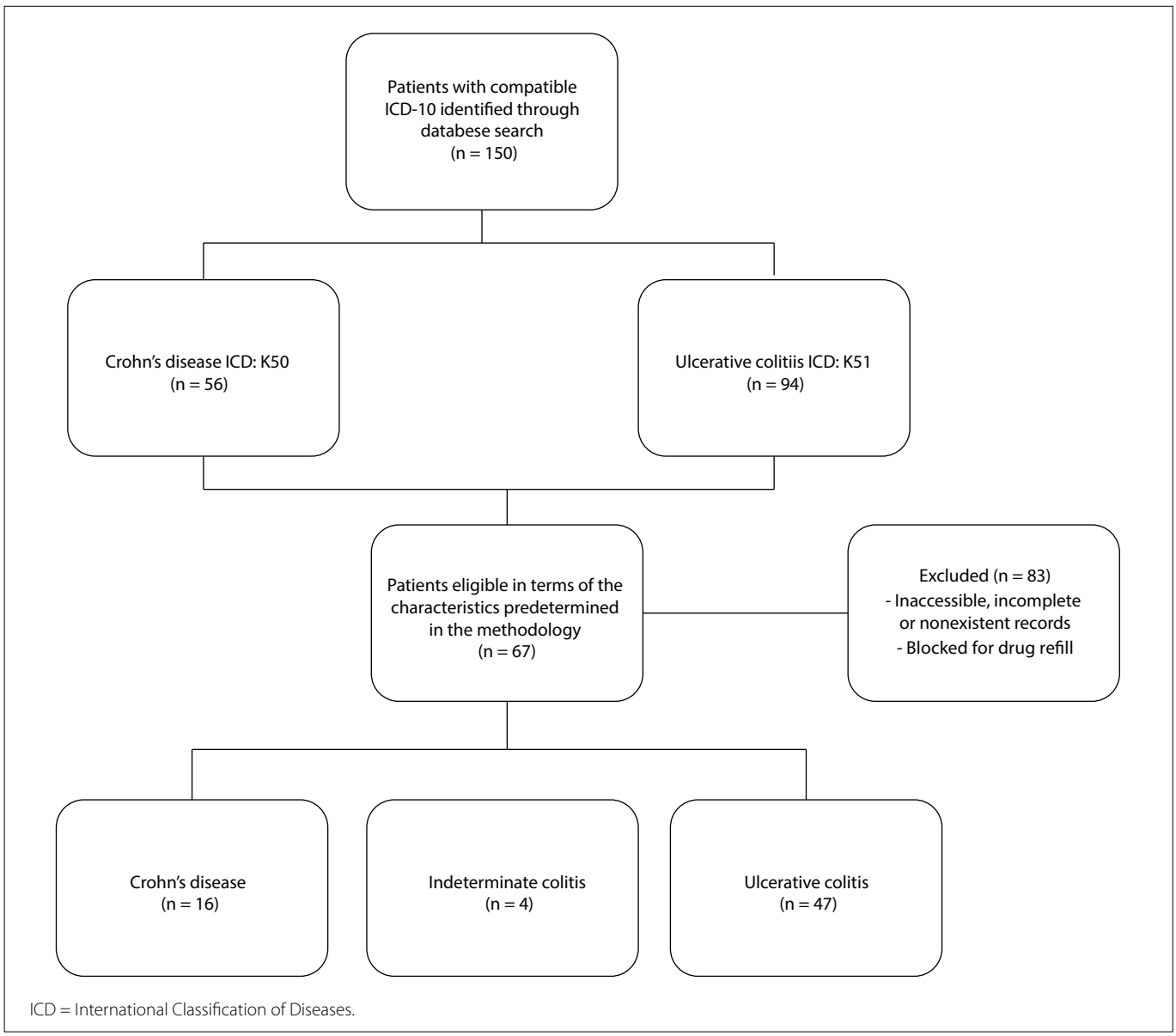
RESULTS

In the initial analysis (**Figure 1**), 150 patients with current follow-up presenting diseases compatible with ICD-10 codes K50 and K51 were found: 94 with ulcerative colitis and 56 with Crohn's disease. Among these, 85 (56%) were under follow-up at the outpatient clinic of the private university in Caxias do Sul, while the remaining 65 (44%) were attended at the specialized healthcare center. Considering the whole sample, 22 patients (14.6%) were undergoing treatment supervised by a gastroenterologist, while 128 (85.4%) were under the care of a proctologist. Eighty-three

patients were excluded from the study due to non-accessible records and/or blocked registrations for medication refill at the specialty center and no further data were available for collection. Therefore, the final number of patients included in the study whose data were gathered from their medical records was 67.

The main clinical characteristics of the population are described in **Table 1**. The mean age was 46.5 ± 16.2 years, with a predominance of females (71.6%). Ulcerative colitis was the most common disease, presented by 47 patients (70.2%), while 16 (23.8%) had Crohn's disease and four cases (6%) were undetermined. The mean number of years with the disease was 7.48 ± 6 years. The mean age at diagnosis was 39.1 ± 15.5 years, and the peak incidence was in the age range of 20-40 years (46.2%) (**Figure 2**).

The most common presentation was pancolitis in 18 patients (26.8%), followed by proctosigmoiditis in 11 (16.4%), proctitis in 10 (15%), left hemicolitis in 9 (13.4%), segmental colitis with ileitis in 4 (6%), pancolitis with ileitis terminal in 3 (4.5%) and terminal ileitis alone in 2 (3%). For 10 patients (15%), there was no record of the site of involvement. The majority of the sample (45 patients; 67%) had undergone colonoscopy within the last two years (2015 and 2016) and only seven patients (around 10%) had not undergone colonoscopy in the last five years. Five patients (7.4%) had histories of hospital admission due to some complication of the disease: two patients with one hospitalization, one with two, one with three and one with four. At some time during the evolution of the disease, 12 patients (18%) needed some type of surgical



ICD = International Classification of Diseases.

Figure 1. Flowchart for patient selection.

Table 1. Characteristics of the study population according to type of disease

Patients' characteristics	All patients (n = 67)	Crohn's disease (n = 16)	Ulcerative colitis (n = 47)	Indeterminate colitis (n = 4)
Gender				
Male	19 (28.4%)	6 (37.5%)	11 (23.4%)	2 (50%)
Female	48 (71.6%)	10 (62.5%)	36 (76.6%)	2 (50%)
Age (years)	46.5 ± 16.2	41.1 ± 16.7	47.8 ± 15.1	41.3 ± 10.9
Period of evolution (years)	7.4 ± 6	9.4 ± 7.1	6.9 ± 5.5	5 ± 3.3
Age at diagnosis (years)	39.1 ± 15.5	31.7 ± 15.1	40.9 ± 13.6	36.3 ± 9.8
Presentation				
Pancolitis	18 (26.8%)	3 (18.8%)	13 (27.7%)	2 (50%)
Proctosigmoiditis	11 (16.4%)	1 (6.3%)	9 (19.1%)	1 (25%)
Proctitis	10 (15%)	1 (6.3%)	9 (19.1%)	0
Left hemicolitis	9 (13.4%)	3 (18.8%)	6 (12.8%)	0
Segmental colitis with ileitis	4 (6%)	3 (18.8%)	1 (2.1%)	0
Pancolitis with terminal ileitis	3 (4.5%)	2 (12.5%)	1 (2.1%)	0
Terminal ileitis	2 (3%)	2 (12.5%)	0	0
Not available	10 (15%)	1 (6.3%)	8 (17%)	1 (25%)
Last colonoscopy				
2016	21 (31.3%)	7 (43.8%)	12 (25.5%)	2 (50%)
2015	25 (37.3%)	6 (37.5%)	19 (40.4%)	0
2014	9 (13.4%)	1 (6.3%)	8 (17%)	0
2013	3 (4.5%)	0	2 (4.3%)	1 (25%)
2012	3 (4.5%)	0	3 (6.4%)	0
Before 2011	6 (9%)	2 (12.5%)	3 (6.4%)	1 (25%)
Previous hospitalizations due to disease complications				
1	2 (3%)	0	2 (4.3%)	0
2	1 (1.5%)	0	0	1 (25%)
3	1 (1.5%)	1 (6.3%)	0	0
4	1 (1.5%)	1 (6.3%)	0	0
None	62 (92.5%)	14 (77.4%)	45 (95.7%)	3 (75%)
Surgical procedures performed to manage the disease				
Total colectomy	4 (6%)	1 (6.3%)	3 (6.4%)	0
Hemicolectomy	3 (4.5%)	3 (18.8%)	0	0
Anal surgery	3 (4.5%)	3 (18.8%)	0	0
Proctosigmoidectomy	1 (1.5%)	1 (6.3%)	0	0
Enterectomy	1 (1.5%)	1 (6.3%)	0	0
No procedure	55 (82%)	7 (43.8%)	44 (92.6%)	4 (100%)
Bowel evacuations per day				
1 to 3	39 (58%)	7 (43.8%)	30 (63.8%)	2 (50%)
4 to 6	9 (13.4%)	5 (31.3%)	4 (8.5%)	0
More than 7	5 (7.4%)	2 (12.5%)	3 (6.4%)	0
Not available	14 (20.8%)	2 (12.5%)	10 (21.3%)	2 (50%)
Smoking				
Yes	5 (7.5%)	0	5 (10.6%)	0
No or not available	62 (92.5%)	16 (100%)	42 (89.4%)	4 (100%)
Extraintestinal manifestations				
Hematological	6 (9%)	1 (6.3%)	5 (10.6%)	0
Osteomuscular/articular	3 (4.5%)	1 (6.3%)	1 (2.1%)	1 (25%)
Dermatological	1 (1.5%)	0	1 (2.1%)	0
None or not available	57 (85%)	14 (87.5%)	40 (85.1%)	3 (75%)
Medications in use for treatment				
Salicylates	60 (88%)	10 (62.5%)	42 (89.4%)	3 (75%)
Mesalamine	54 (80.5%)	10 (62.5%)	39 (83%)	3 (75%)
Sulfasalazine	6 (7.5%)	0	3 (6.4%)	0
Prednisone	8 (12%)	1 (6.3%)	6 (12.8%)	1 (25%)
Azathioprine	13 (19.4%)	6 (37.5%)	7 (14.9%)	0
Immunobiological drugs	16 (23.4%)	8 (50%)	8 (17%)	0
Infliximab	8 (11.7%)	4 (25%)	4 (8.5%)	0
Adalimumab	8 (11.7%)	4 (25%)	4 (8.5%)	0
Metronidazole	1 (1.5%)	0	1 (2.1%)	0

procedure: four of them underwent total colectomy (6%), three had hemicolectomy (4.5%), three had anal surgery (4.5%), one (1.5%) had rectosigmoidectomy and one (1.5%) had enterectomy.

At the time of the last medical appointment, more than half of the patients (39; 58%) were experiencing one to three bowel movements per day, while nine (13.4%) had four to six bowel movements per day and five (7.4%) had more than seven bowel movements per day. There was no record of the number of bowel movements in the cases of 14 patients (20.8%).

The great majority of the patients (62; 92.5%) were nonsmokers and only five (7.5%) were active smokers. In addition, a large proportion of the patients did not have any extraintestinal manifestations (57; 85%), while six (9%) had manifestations of hematological origin (anemia of chronic disease), three (4.5%) had manifestations of osteomuscular/articular etiology and a single patient (1.5%) had dermatological manifestations.

Regarding management, 60 patients (89.5%) were using aminosalicylates, and the most common of these was mesalamine (80%). Only eight (12%) were using oral corticosteroids, which in all cases were exclusively prednisone/prednisolone. Part of the sample was using immunosuppressants. Thirteen patients (19.4%) were using azathioprine. Only one patient (1.5%) was continuously using an antimicrobial, which was metronidazole. Among the Crohn's disease patients, eight (50%) were using immunobiological drugs: adalimumab in four cases and infliximab in the other four cases. Among the ulcerative colitis patients, eight (17%) were using immunobiological drugs: adalimumab in four cases and infliximab in the other four cases.

In the combined analysis, 49 (73.1%) were seen to be undergoing monotherapy and the most common drug was aminosalicylate (75.5%). Fourteen patients (19.4%) were using two drugs and the most common combination was salicylate in association with corticoid, immunosuppressive or biological. Only four patients (6%) were using three drugs and in all of these cases, this comprised salicylate in association with immunosuppressives and immunobiological drugs.

DISCUSSION

Epidemiological studies on inflammatory bowel diseases in Brazil are few in number and limited in extent. This is due to the significant problems with data record systems that exist in this country. As a result, information on the incidence and prevalence of these diseases are unavailable, although small local studies have identified that their incidence is increasing, particularly with regard to Crohn's disease, in comparison with ulcerative colitis.[7-9]

In the present study, data from the two referral services for follow-up and treatment of inflammatory bowel disease in the region were gathered. Despite the difficulties encountered in collecting the data and the lack of information in the medical records, this study provides important information on the regional profile, which, until now, has been largely unknown. We found higher prevalence of these diseases among females, a finding similar to what has been

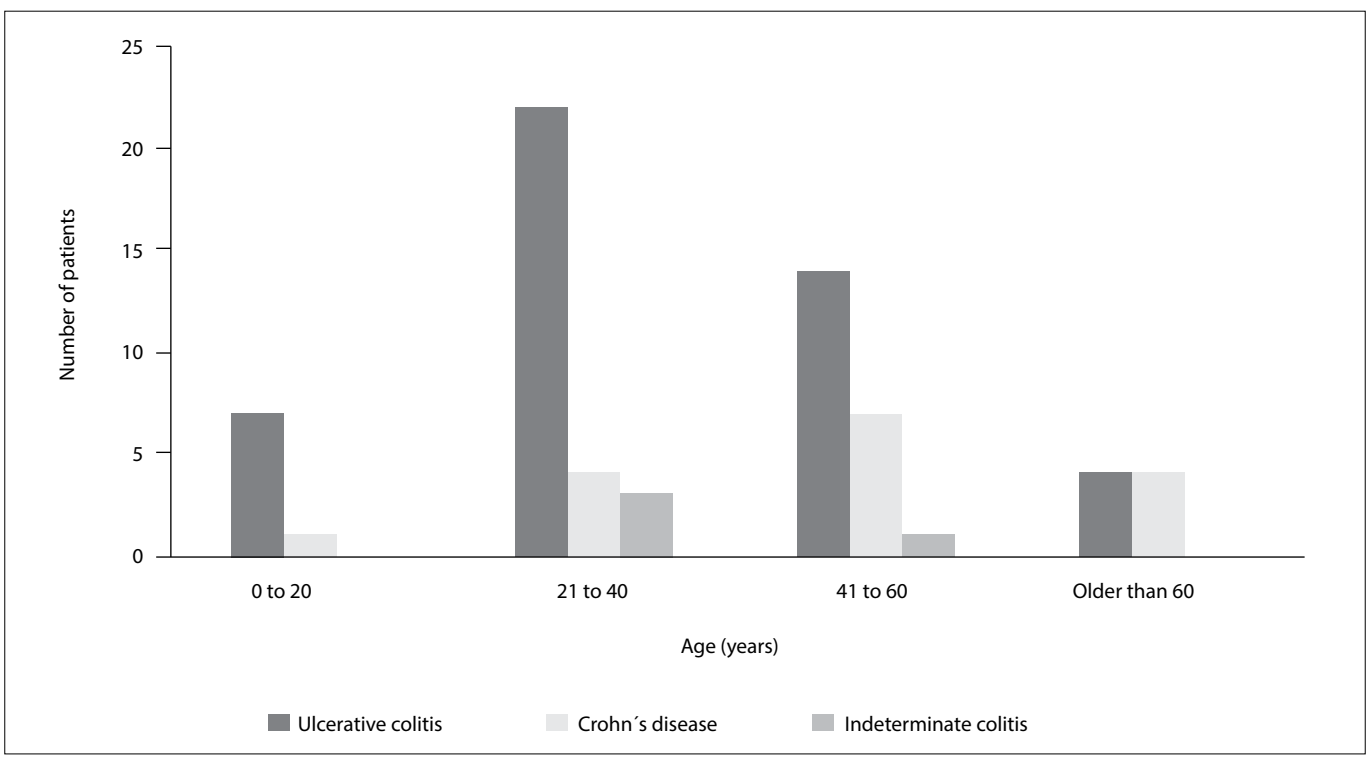


Figure 2. Age at the time of diagnosis.

reported in other Brazilian studies.[8-10] On the other hand, it has been observed in studies conducted in other countries that ulcerative colitis is predominantly found in males and Crohn's disease is predominantly found in females.[11,12]

The peak age at diagnosis in the present study was within the 20 to 40-year age group, which was already well established in the literature. However, we did not observe any second peak, as previously described in other studies, which usually occurs over the age of 50 years.[13] These findings are compatible with the data from a recently published systematic review, which found that the prevalence of inflammatory bowel disease has been increasing in Latin America and Carribbean.[14]

Ulcerative colitis was more prevalent than Crohn's disease, which is consistent with previous data from other countries, but discordant with previous Brazilian studies.[1,7] Unlike in some older Brazilian case series, which showed predominance of proctosigmoiditis and left hemicolitis,[7] pancolitis predominated in the present study. This finding was similar to the epidemiological profile observed in a study carried out in a municipality in the state of Santa Catarina in 2011.[9] One fifth of the sample of the present study had more than three evacuations per day, thus possibly indicating greater severity of disease activity. This subgroup of the sample, in its entirety, was already under treatment with azathioprine and/or immunobiological drugs.

The most common treatment was monotherapy. This was probably because of the mild-to-moderate condition of the disease, better adherence to treatment and reduced adverse effects. The preference for mesalamine was likely due to its availability and the fewer side effects associated with this treatment. The use of immunobiological drugs was three times higher among patients with Crohn's disease, probably due to the many possible complications associated with this disease and the patients' better response to this therapy. Surgical treatment was necessary for 18% of the patients, which is generally expected for inflammatory bowel disease. Although medical treatment has advanced, a large proportion of patients will still require surgery.[15,16]

One of the strengths of the present paper is that it reports on a locality where the realities for such patients were unknown. One limitation to this study is its retrospective nature, given that it analyzed medical records. Therefore, it is likely that incompleteness of the data and loss to follow-up interfered with adequate data collection. A prospective study on patients within the private and public systems in this region is planned, in order to improve the quality of the data.

CONCLUSION

The characteristics of the patients with inflammatory bowel disease in this study were similar to those encountered in the published literature from Brazil in terms of gender, type of disease and age at diagnosis. On the other hand, higher prevalence of pancolitis than previously described was found. An extension of this project, of prospective nature, may be beneficial with regard to establishing a database with which data from future studies can be correlated and compared.

REFERENCES

1. Barros PAC, Silva AMR, Neto MADFL. The epidemiological profile of inflammatory bowel disease patients on biologic therapy at a public hospital in Alagoas. J Coloproctol. 2014;34(3):131-5. doi: 10.1016/j.jcol.2014.05.004.
2. Loftus EV Jr. Clinical epidemiology of inflammatory bowel disease: Incidence, prevalence, and environmental influences. Gastroenterology. 2004;126(6):1504-17. PMID: 15168363; doi: 10.1053/j.gastro.2004.01.063.
3. Molodecky NA, Soon IS, Rabi DM, et al. Increasing incidence and prevalence of the inflammatory bowel diseases with time, based on systematic review. Gastroenterology. 2012;142(1):46-54. PMID: 22001864; doi: 10.1053/j.gastro.2011.10.001.
4. Zaltman C. Doença inflamatória intestinal: qual a relevância da doença no Brasil? Cad Saude Publica. 2007;23(5):992-3. doi: 10.1590/S0102-311X2007000500001.
5. Lennard-Jones JE. Classification of inflammatory bowel disease. Scand J Gastroenterol Suppl. 1989;170:2-19. PMID: 2617184; doi: 10.3109/00365528909091339.
6. Schirbel A, Fiocchi C. Inflammatory bowel disease: Established and evolving considerations on its etiopathogenesis and therapy. J Dig Dis. 2010:11(5):266-76. PMID: 20883422; doi: 10.1111/j.1751-2980.2010.00449.x.
7. Souza MH, Troncon LE, Rodrigues CM, et al. Evolução da ocorrência (1980-1999) da doença de Crohn e da retocolite ulcerativa idiopática e análise das suas características clínicas em um hospital universitário do sudeste do Brasil [Trends in the occurrence (1980-1999) and clinical features of Crohn's disease and ulcerative colitis in a university hospital in southeastern Brazil]. Arq Gastroenterol. 2002;39(2):98-105. PMID: 12612713; doi: 10.1590/s0004-28032002000200006.
8. Souza MM, Belasco AGS, Aguilar-Nascimento JE. Perfil epidemiológico dos pacientes portadores de doença inflamatória intestinal do estado de Mato Grosso [The epidemiological profile of patients with inflammatory Bowel disease in the State of Mato Grosso]. Rev Bras Colo-Proctol. 2008;28(3):324-8. doi: 10.1590/S0101-98802008000300009.
9. Kleinubing-Júnior H, Pinho MSL, Ferreira LC, Bachtold GA, Merki A. Perfil dos pacientes ambulatoriais com doenças inflamatórias intestinais [Outpatients profile with inflammatory bowel disease]. ABCD Arq Bras Cir Dig. 2011;24(3):200-3. doi: 10.1590/S0102-67202011000300004.
10. Thukkani N, Williams JL, Sonnenberg A. Epidemiologic characteristics of patients with inflammatory bowel disease undergoing colonoscopy. Inflamm Bowel Dis. 2011;17(6):1333-7. PMID: 21560196; doi: 10.1002/ibd.21513.

11. Munkholm P, Langholz E, Nielsen OH, Kreiner S, Binder V. Incidence and prevalence of Crohn's disease in the county of Copenhagen, 1962-87: a sixfold increase in incidence. Scand J Gastroenterol. 1992;27(7):609-14. PMID: 1641589; doi: 10.3109/00365529209000127.
12. Loftus EV Jr, Silverstein M, Sandborn WJ, et al. Ulcerative colitis in Olmsted County, Minnesota, 1940-1993: incidence, prevalence, and survival. Gut. 2000;46(3):336-43. PMID: 10673294; doi: 10.1136/gut.46.3.336.
13. Ekbom A, Helmick C, Zack M, Adami HO. The epidemiology of inflammatory bowel disease: a large, population-based study in Sweden. Gastroenterology. 1991;100(2):350-8. PMID: 1985033; doi: 10.1016/0016-5085(91)90202-v.
14. Kotze PG, Underwood FE, Damião AOMC, et al. Progression of Inflammatory Bowel Diseases Throughout Latin America and the Caribbean: A Systematic Review. Clin Gastroenterol Hepatol. 2020;18(2):304-12. PMID: 31252191; doi: 10.1016/j.cgh.2019.06.030.
15. Terres AZ, Furlan RG, Soldera J, Balbinot SS, Balbinot RA. Clinical and surgical therapy for fistulizing Crohn's disease: case report. GED Gastroenterol Endosc Dig. 2019:38(1):27-32
16. Shinagawa T, Hata K, Ikeuchi H, et al. Rate of Reoperation Decreased Significantly After Year 2002 in Patients With Crohn's Disease. Clin Gastroenterol Hepatol. 2020;18(4):898-907. PMID: 31336198; doi: 10.1016/j.cgh.2019.07.025.

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Validity of the short physical performance battery for screening for frailty syndrome among older people in the Brazilian Amazon region. A cross-sectional study

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Amazon.

ABSTRACT

BACKGROUND: Environmental and population characteristics seem to influence the variation in cut-off points of the Short Physical Performance Battery (SPPB) for diagnosing frailty syndrome among older adults.

OBJECTIVE: To verify the validity of the SPPB for screening for frailty syndrome among older adults in the Amazonian context.

DESIGN AND SETTING: Cross-sectional population-based study on older adults in the urban area of Coari (AM), Brazil.

METHODS: In total, 264 older adults (60 years of age or over) were included. Frailty syndrome was defined using the Fried phenotype criteria. The SPPB cutoff points were compared in relation to frailty and validity measurements were calculated for the test.

RESULTS: A strong association between poor physical performance and frailty was identified ($P < 0.001$). The cutoff point of 6 demonstrated the best validity measurements for frailty in the sample studied (sensitivity: 0.28; specificity: 0.94; accuracy: 0.88; area under the receiver operating characteristic curve, AUC-ROC: 0.61; likelihood ratio, LR+: 4.44; LR-: 0.77; prevalence: 8.3%; post-test probability, PTP+: 0.32; PTP-: 0.07), with emphasis on high specificity and the positive likelihood ratio value.

CONCLUSION: The SPPB was shown to be useful for screening frail older adults in the Amazon region. The score of 6 demonstrated the best cutoff point for this population. This could be used in healthcare services for diagnostic screening for frailty among older people within the Amazonian context.

INTRODUCTION

Among the conditions attributed to aging, frailty syndrome (FS) is among the main ones and is associated with functional decline, hospitalization and early death. FS is defined as a clinical syndrome of spiraling energy decline, of multifactorial nature, based on a trio of alterations: sarcopenia, neuroendocrine dysregulation and immune dysfunction. It has repercussions on individuals' ability to achieve homeostatic adaptation, thus leading to a state of increased physiological vulnerability in the presence of stressors.[1]

Identification of FS among older adults is essential, for appropriate prevention and treatment strategies to be developed. Over recent years, several measurements have been described for screening frail older adults, or those in the process of becoming frail; however, none has yet been established as a gold standard. The phenotype developed by Fried, in the United States, has been highlighted as one of the most commonly used instruments in this regard.[2-4]

In searching for low-cost instruments with good applicability in clinical practice, some studies have investigated the validity of the Short Physical Performance Battery (SPPB) for screening for frailty among older adults, given the relationship between frailty and disability that has already been established.[1,5] The SPPB is an objective, standardized, multidimensional instrument that is capable of assessing the physical performance of older adults,[6] in addition to being useful in screening for future disabilities,[7] frailty[8-10] and other outcomes such as hospitalization and death.[11] This instrument was translated and adapted for the Brazilian population by Nakano,[12] and was found to present good reliability. However, there is a need for validation of the test using different samples of the population. The results of a study carried out among older people from different socioeconomic contexts (Brazil and Canada) revealed differences in the validity measurements for use of

the SPPB between the samples, and suggested that this type of analysis is influenced by the characteristics inherent to the study population.[8] This influence is clear in the literature, as shown through the use of different cutoff points for screening frailty among older adults from different contexts.[8-10]

When considering frailty in the Amazonian context, it is necessary to take into account the peculiarities of the region, which presents a distinct demographic transition process,[13] large areas of demographic voids, unfavorable socioeconomic conditions and difficulty in accessing large cities, where the majority of the healthcare network is concentrated.[14] Thus, use of easy-to-apply and low-cost measurements to screen for frailty in this context is especially relevant, and could favor implementation of strategies for prevention and treatment of this condition, thereby minimizing the occurrences of associated negative outcomes. Through using an appropriate cutoff point, it is possible that these measurements could be useful in the initial screening of older adults, for later confirmation of the diagnosis of frailty.

OBJECTIVE

The objective of this study was to verify the validity of the SPPB as a screening tool for FS among older adults in a municipality in the interior of the state of Amazonas, Brazil.

METHODS

This was a cross-sectional, descriptive-analytical, population-based study that used data from the "Study of Health and Frailty of the Older Adults in the Brazilian Amazon" (Estudo da Saúde e Fragilidade do Idoso da Amazônia Brasileira, ESFRIA), carried out in the municipality of Coari (AM). This project was approved by the Research Ethics Committee of the Federal University of Amazonas (CEP-UFAM) under the number 15327413.0.0000.5020, on April 18, 2013.

The study included a representative sample of older adults aged 60 years or over who were living in the urban area of the municipality of Coari. These individuals agreed to participate in the research through signing a free and informed consent statement. Individuals with any of the following conditions: cognitive impairment, identified through the Mini-Mental State Examination (MMSE), based on scores of under 13 points for illiterate older adults, 18 points for individuals with 1–7 years of education and 26 points for those with 8 or more years of education;[15] a clinical condition that limited transference and movement; and limitations relating to physical effort. After these exclusions, the resultant sample comprised 274 older people. The characteristics of the municipality and sampling process, along with other additional information about the methodology used, were described in a previous study, by Freire Junior et al.[16]

Data collection took place between October 2013 and February 2015, in two stages. Initially, the older adults attended a structured interview at which they were asked questions relating to socioeconomic, demographic and health matters. In the second stage, they were taken to the laboratory of the Institute of Health and Biotechnology (ISB-Coari) at UFAM, where they underwent specific tests and were classified with regard to frailty using Fried's phenotype criteria, as follows:[1]

1. Unintentional weight loss: self-reported weight loss ≥ 4.5 kg or ≥ 5% of body weight in the previous year.
2. Exhaustion: self-reported via two questions from the Center for Epidemiologic Studies depression scale (CES-D): "How often in the last week did you feel that everything you did required a lot of effort?" and "How often in the last week did you feel that you could not do anything due to tiredness?". This criterion for frailty was considered to be present in participants who answered "always" or "most of the time".
3. Low level of physical activity: evaluated using version 8 (long) of the international physical activity questionnaire (IPAQ). The results were adjusted according to sex and the 20th percentile was established as the cutoff point, namely 171.3 kcal/week for men and 87 kcal/week for women.
4. Decreased handgrip strength: evaluated by means of dynamometry (Saehan hydraulic hand dynamometer, SH5001; Masan, South Korea). This criterion was considered to be present in individuals who scored below the established cutoff points (adjusted for sex and body mass index, BMI), based on the 20th percentile (worst performances for the sample).
5. Decreased gait speed: evaluated through the SPPB gait speed test. The criterion was considered to be present in individuals who performed the test in a length of time greater than the stipulated cutoff points (adjusted for sex and height).

The older adults who presented three or more of the criteria described above were considered frail; those who presented one or two criteria, pre-frail; and those who did not present any of these criteria, non-frail.[1]

To evaluate physical performance, the Brazilian version of the SPPB was used, composed of three subtests, as follows:

1. Balance test: This evaluated static balance in three standing positions: feet together; one foot partially in front of the other (*semi-tandem*); and one foot totally in front of the other (*tandem*). The older adults were required to remain in each position, looking ahead, for 10 seconds. Those who maintained balance for the necessary time in the first two positions received one point for each position. Those who were able to remain in the third position for 10 seconds received two points; those who maintained this position for 3 to 9.99 seconds received one point; and those maintained this for less than 3 seconds or who refused to try were awarded no points. The total score for the balance test was calculated by summing the points gained in each of the three positions.

2. Gait speed test: This required the participants to walk, with their usual gait, for a distance of three meters. Two attempts were timed and the shortest time obtained was used to assign the score, in accordance with the cutoff points proposed in the Brazilian version of the test.[12]
3. Chair stand test: This evaluated participants' lower-limb strength. They were asked to get up from and sit down again on a chair with a backrest, five times in a row, as quickly as possible, with the upper limbs crossed over the chest. Those who were unable to perform the test safely or who refused to take the test, along with those who failed to complete the test or completed it in more than 60 seconds, did not receive a score. The other participants received scores in accordance with the cutoff points recommended by Nakano.[12]

The total SPPB score was obtained through summing the scores obtained from each component. The total score possible ranged from 0 to 12 and was categorized as follows: 0-3 points = disability/very poor performance; 4-6 points = poor performance; 7-9 points = moderate performance; and 10-12 points = good performance.

Categorical variables were described using absolute and relative frequencies, and numerical variables using the mean and standard deviation (for age) or the median and interquartile range (for BMI and total SPPB score), according to whether the variable had normal distribution. The relationship between the total SPPB score and the frailty categories was analyzed using the Kruskal-Wallis test, and SPPB cutoff points were compared with frailty categories using the chi-square test.

The following validity measurement were used: sensitivity (proportion of individuals who truly do have frailty and present a positive test result); specificity (proportion of individuals who truly do not have frailty and present a correct negative test result); positive and negative predictive values (proportions of positive and negative results from the SPPB test that are true positive and true negative results, respectively); accuracy (proportion of individuals correctly classified as presenting frailty, among all the results); positive and negative likelihood ratios (probabilities of a positive result and of a negative result among individuals presenting frailty divided by the probabilities of a positive result and of a negative result among individuals who do not present frailty, respectively); and area under the receiver operating characteristic (ROC) curve (graphical representation of true positives plotted against false negatives).

The validity measurements were calculated for the main cutoff points of the SPPB, and served as a basis for calculating the prevalence of frailty and the post-test probability. The data were described and analyzed using the Statistical Package for the Social Sciences (SPSS) software, version 22.0 (Chicago, USA). The level of significance used in the analyses was 5% ($\alpha = 0.05$) with a 95% confidence interval.

RESULTS

Among the 274 individuals initially evaluated, a total of 10 losses were recorded due to absence of data referring to the SPPB (n = 1) or frailty (n = 9). Therefore, the current study analyzed a sample of 264 older people, with a mean age of 71.7 years (standard deviation, SD: 8), consisting mainly of women (62.5%) above ideal weight (52.6%), and who had lived for 20 years or more in riverside communities (52.7%). The illiteracy rate among the participants was 47.3%; 62.5% performed some type of subsistence activity (such as agriculture, fishing or latex extraction); and 83.7% had a family income of one or more monthly minimum wages (MW). In relation to health, more than half of these older adults (54.2%) classified their general health status as fair and 40.2% said they had three or more comorbidities (**Table 1**).

Table 1. Sociodemographic and health characteristics of the study sample (n = 264)

Variables	n (%)
Age range (years)	71.0 (12.0)*
60-69	114 (43.2)
70-79	106 (40.2)
80 or over	44 (16.7)
Sex	
Male	99 (37.5)
Female	165 (62.5)
Schooling	
Illiterate	125 (47.3)
Literate or more	139 (52.7)
Family income	
< 1 minimum wage	42 (15.9)
≥ 1 minimum wage	221 (83.7)
Time in riverside community	
0-19 years	122 (46.2)
20 or more years	139 (52.7)
Body mass index	27.3 (6.9)*
Malnourished	43 (16.3)
Normal weight	82 (31.1)
Overweight/obesity	139 (52.7)
Number of comorbidities	
0-2 diseases	158 (59.8)
3 or more diseases	106 (40.2)
Number of drugs	
None	102 (38.6)
1-2 drugs	101 (38.3)
3 or more drugs	61 (23.1)
Self-perceived health	
Very good/good	77 (29.2)
Fair	143 (54.2)
Poor/very poor	44 (16.7)
Frailty classification	
Non-frail	82 (31.0)
Pre-frail	157 (59.5)
Frail	25 (9.5)

*Median (interquartile range).

The prevalence of frailty was 9.5% and the prevalence of pre-frail individuals was 59.5%, which was the highest percentage of these older adults. The median total SPPB score was 10 (IQR: 2). According to the SPPB instrument, this showed that a significant proportion of the individuals had good (63.3%) to moderate (28.4%) ability. Additional information on the distribution of the sample regarding frailty can be found in a previous published paper.[17]

Table 2 presents the results regarding the distribution of the total SPPB score for classification of frailty and each of its components. Lower median SPPB scores were observed in the pre-frail group (10.0) and frail group (8.0), in relation to the non-frail group (11.0). Among the Fried criteria, slow gait and muscle weakness showed the worst results in relation to the SPPB scores.

The sensitivity, specificity and predictive values, along with other validity measurements for each cutoff point of the total SPPB score for identifying frail older adults, are described in **Table 3**, in comparison with the values for non-frail and pre-frail individuals. The results from this study showed that the sensitivity values were fairly low, especially for the cutoff points of 6 (0.28) and 7 (0.44). In contrast, the specificity showed higher values as the cutoff point decreased. The highest specificity (0.94) was obtained at the cut-off point of 6, which also presented the best accuracy value (0.88), positive predictive value (0.32) and positive likelihood ratio (LR +) (4.44), in comparison with the other scores. Figure 1 graphically

Table 2. Characterization of the total SPPB score for the classification of frailty and for each of its components.

Total SPPB score		
Frailty classification*	Median (IQR)	Min-Max
Non-frail	11.0 (2)	7-12
Pre-frail	10.0 (3)	3-12
Frail	8.0 (4)	4-12
Frailty variables	Median (IQR)	Min-Max
Fatigue	10.0 (2)	4-12
Weight loss	10.0 (3)	4-12
Slow gait	7.0 (2)	3-10
Muscle weakness	9.0 (3)	3-12
Low level of physical activity	10.0 (2)	5-12

*P < 0.001, Kruskal-Wallis test.

SPPB = Short Physical Performance Battery; IQR = Interquartile range; Min-Max = minimum-maximum.

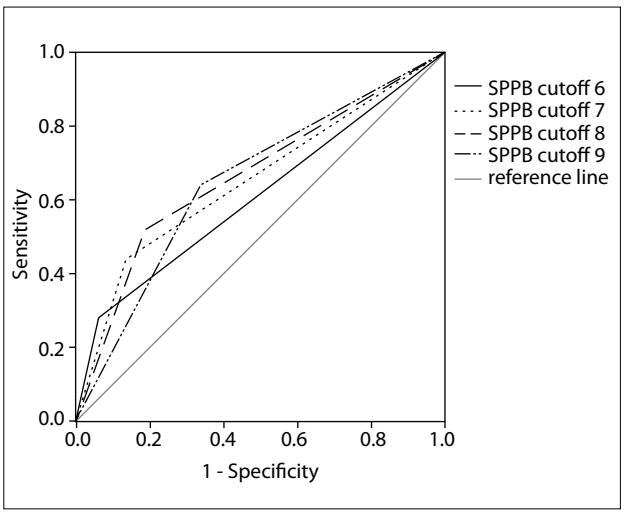


Figure 1. Receiver operating characteristic (ROC) curves for the Short Physical Performance Battery (SPPB) cutoff points of 6 to 9, for screening for frailty in the sample of older adults in the "Study of Health and Frailty of the Older Adults in the Brazilian Amazon" (Estudo da Saúde e Fragilidade do Idoso da Amazônia Brasileira, ESFRIA).

Table 3. Validity measurements for each Short Physical Performance Battery cutoff point for identifying frail older people, compared with the pre-frail and non-frail groups of the sample

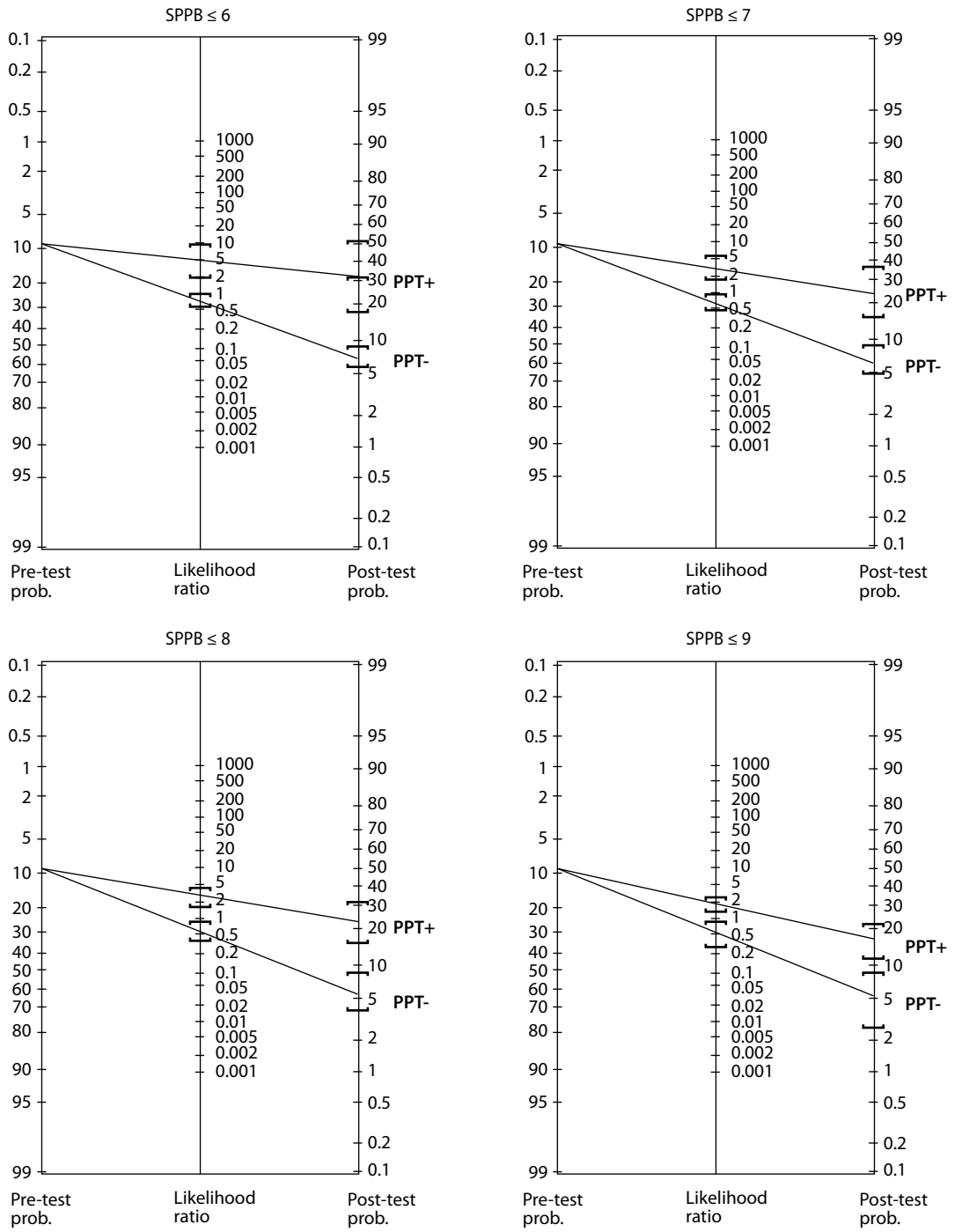
Measurements	**SPPB cutoff points**			
	≤ 6 points (CI)	**≤ 7 points (CI)**	**≤ 8 points (CI)**	**≤ 9 points (CI)**
Sensitivity	0.28 (0.14-0.48)	0.44 (0.27-0.62)	0.52 (0.34-0.70)	0.64 (0.44-0.80)
Specificity	0.94 (0.90-0.96)	0.86 (0.81-0.90)	0.81 (0.75-0.85)	0.66 (0.60-0.71)
PPV	0.32 (0.16-0.53)	0.25 (0.15-0.39)	0.22 (0.14-0.35)	0.17 (0.10-0.25)
NPV	0.93 (0.89-0.95)	0.94 (0.90-0.96)	0.94 (0.90-0.35)	0.95 (0.90-0.97)
Accuracy	0.88 (0.83-0.91)	0.82 (0.77-0.86)	0.78 (0.73-0.83)	0.66 (0.60-0.71)
AUC-ROC	0.61 (0.48-0.74)	0.65 (0.53-0.78)	0.67 (0.54-0.79)	0.65 (0.54-0.77)
LR+	4.44 (2.00-9.87)	3.19 (1.85-5.50)	2.77 (1.75-4.38)	1.89 (1.34-2.66)
PTP+	0.32 (0.17-0.51)	0.25 (0.16-0.37)	0.23 (0.16-0.31)	0.17 (0.12-0.22)
LR-	0.77 (0.60-0.98)	0.65 (0.46-0.92)	0.59 (0.39-0.89)	0.54 (0.32-0.92)
PTP-	0.07 (0.06-0.09)	0.06 (0.05-0.09)	0.06 (0.04-0.09)	0.05 (0.03-0.09)
Prevalence (%)	8.3 (5.6-12.3)	16.7 (12.7-21.6)	22.0 (17.4-27.4)	36.7 (31.2-42.7)
P-value	0.002*	0.001*	0.000	0.003

*Fisher's exact test.

CI = confidence interval (95%); PPV = positive predictive value; NPV = negative predictive value; AUC-ROC = area under the receiver operating characteristic curve; LR+ = positive likelihood ratio; LR- = negative likelihood ratio; PTP+ = positive post-test probability; PTP- = negative post-test probability.

presents the relationship between sensitivity and specificity, using the receiver operating characteristic (ROC) curve for each cutoff point analyzed.

In Figure 2, the post-test probabilities are represented by a Fagan nomogram, based on the reference prevalence (pre-test probability) and the LR + and LR- values. From the cutoff points



Note: The pre-test probability (prevalence) was taken to be 9.5%.
SPPB = Short Physical Performance Battery; prob. = probability.

Figure 2. Fagan nomogram: graphical representation of the positive post-test probability (PTP+) for cutoff points of 6 to 9, for the sample of the "Study of Health and Frailty of the Older Adults in the Brazilian Amazon" (Estudo da Saúde e Fragilidade do Idoso da Amazônia Brasileira, ESFRIA).

included in the analysis, the following prevalences were calculated: 8.3% (≤ 6 points), 16.7% (≤ 7 points), 22.0% (≤ 8 points) and 36.7% (≤ 9 points).

DISCUSSION

The current study analyzed the possible use of the SPPB as a screening tool for frailty among older adults in the municipality of Coari (AM). A strong association between low physical performance and frailty was identified in the sample studied. Among the cutoff points analyzed, the one with the best validity measurements for frailty was ≤ 6, especially regarding specificity values and positive likelihood ratios.

The condition of frailty may be present even in the absence of functional limitations.[18] However, some studies have already demonstrated that an association exists between frailty and worse physical performance.[19,20] The decreasing relationship between the total SPPB score and the frailty classification observed in the Coari sample is in accordance with previous studies, in which it was observed that older people with worse burden of frailty (frail and pre-frail) had worse performances in the total SPPB score than did non-frail older adults.[8,10,21] According to Mello,[10] from an analysis on the SPPB in relation to the frailty phenotype, the worst scores observed were in relation to the criteria of slow gait and muscle weakness. Those results were similar to what was observed in the current study. Andrade[22] emphasized this finding through stating that frail older people can develop muscle weakness and gait changes at proportions of 3.7 and 1.7 times greater, respectively, than the risk of developing weight loss, for example.

In our analysis, the cutoff point ≤ 6 stood out as the best score for screening for frailty since, despite having low sensitivity (0.28), it demonstrated high specificity (0.94). Similar results were shown in the study by Verghese and Xue,[21] among older Americans (70 years of age or over) living in the community, with no alteration in gait speed. Overall, they observed that lower SPPB scores demonstrated better specificity, but less sensitivity for identifying frailty. They highlighted the cutoff point ≤ 8 for the SPPB, as the most suitable for screening for frail older people in their sample, with sensitivity of 0.52 and specificity of 0.70.

Another study, carried out in Spain, in which the relationship between frailty and some functional assessment instruments was analyzed, showed that the SPPB was one of the best-performing tests for identifying frail older people. It was found that the best cutoff point was ≤ 6, with an area under the curve (AUC) of 0.956 and sensitivity and specificity of 0.88.[9]

Another study of this nature with findings similar to ours was carried out by the FIBRA Network. The results from that study showed that there was low sensitivity (0.27) and high specificity (0.85) for the cutoff point of 7. However, ≤ 8 was highlighted as the most-indicated cutoff point for positive identification of frail older adults, given that this score presented higher sensitivity (sensitivity = 0.79; specificity = 0.73).[10]

Câmara et al.[8] suggested that the test cutoff point should be 9, since this showed moderate ability to identify frail older people in two different socioeconomic contexts: Saint Bruno, Canada, and Santa Cruz, Brazil, with better results for the Canadian sample (AUC = 0.81; sensitivity = 0.92 and specificity = 0.80).

It is known that high values for specificity in relation to sensitivity are common and desirable in screening tests or diagnostic screening, because this is useful in excluding false positives.[23] In addition, it is common practice within clinical care to use serial tests, such that additional tests can be performed to confirm previously obtained results. Thus, the high specificity value found for the cutoff point of 6 in the Coari sample shows that the SPPB has good ability to identify individuals who are in fact not frail. Thus, this shows that it can be used as an initial screening test for the condition of frailty in that context.

In the current study, the cutoff point of 6 also presented the best accuracy value (0.88), compared with the other scores. The same cutoff point for screening for frailty was highlighted by Abizanda et al.,[9] although with a higher accuracy value (0.96). Despite the relevance of this measurement, other statistics are needed to complement a test approach, such as predictive validity and relative risk.[24] In our analysis on the cutoff point of 6, a high NPV (0.93) was observed, which is expected for conditions with low prevalence.[25] This measurement indicates that the probability that the individual is not frail is 93%, after obtaining a score higher than 6 for the total SPPB score, thus indicating a highly reliable negative result. This characteristic is also common and is expected in screening tests, in order to minimize occurrences of erroneous results.[23,25]

The likelihood ratios make it possible to transform the prevalence of a condition (pre-test probability) into post-test probability.[23] The LR+ value (4.44) and LR- value (0.77) for the cutoff point of 6 in the SPPB were the best values observed in this analysis. Mello (2015)[10] found similar results for the SPPB cutoff point of 7 (LR+: 4.2; and LR-: 0.4). These values show that there was a small but still important change in LR+ and minimal alteration in LR-, in the post-test probability.

The calculation of the prevalence of frailty based on the cutoff point of 6 for our sample showed that the value found (8.3%) was very close to the value of the reference prevalence, obtained by means of Fried's phenotype (8.5%). The prevalence of frailty varies considerably between populations, partly due to the particularities of the study sample and partly due to the procedures used to classify older adults regarding the syndrome. Previous studies recorded higher prevalences than those found in the current study: 19.6% in Latin American countries[26] and 13.5% in the ELSI-Brazil study.[18] A meta-analysis that brought together studies carried out in low and middle income countries found that the

prevalence of frailty ranged from 3.9% (China) to 51.4% (Cuba). In the studies that used Fried's five criteria (including measurements for weakness and slow gait), the mean rates were 12.7% for frailty and 55.2% for pre-frailty.[27]

Although an association between unfavorable socioeconomic conditions and frailty has already been demonstrated,[8,27] there is still little research of this nature in low-income populations such as that of Coari. A national study carried out among older people in seven Brazilian municipalities with different human development indexes (HDIs) found prevalences of frailty that ranged from 7.7% to 10.8%. A rate similar to ours (9.7%) was found in the municipality of Parnaíba (PI), which was the municipality with the lowest HDI among those investigated (0.674).[28]

Despite the characteristics inherent to the Amazonian population, the findings from our study point towards some similarities between the older adults in Coari and those in other regions of Brazil and around the world, with regard to the variables analyzed here, which indicates a certain consistency of the findings. Another strength of our study is that the sampling process used enabled representative and random selection of older adults in the municipality, thus minimizing selection biases that might have influence the results. One limitation of the study was the impossibility of carrying out stratified analyses according to age group, due to the small number of individuals aged 75 years or over in the sample. Therefore, one factor that should be considered in making comparisons with other populations is that the sample of our study was composed mainly of young older people who did not have any major functional limitations and were living in the community.

CONCLUSION

The current study demonstrated the importance and validity of the SPPB for screening for frailty syndrome among older people in an Amazonian context, especially considering its easy use within clinical care for older adults. It also confirmed that a strong association exists between frailty and low functional performance, as measured using the SPPB. A score of 6 was indicated as the best cutoff point for the population studied, with emphasis on better values of specificity, accuracy, PPV and LR+ than seen using other cutoff scores. Therefore, it is suggested that this instrument can be used in healthcare services to diagnose frailty among older people living in the Amazonian context.

REFERENCES

1. Fried LP, Tangen CM, Walston J, et al. Frailty in older adults: evidence for a phenotype. J Gerontol A Biol Sci Med Sci. 2001;56(3):M146-M156. PMID: 11253156; doi: 10.1093/gerona/56.3.m146.
2. Bouillon K, Kivimaki M, Hamer M, et al. Measures of frailty in population-based studies: an overview. BMC Geriatr. 2013;13:64. PMID: 23786540; doi: 10.1186/1471-2318-13-64.
3. Pritchard JM, Kennedy CC, Karampatos S, et al. Measuring frailty in clinical practice: A comparison of physical frailty assessment methods in a geriatric out-patient clinic. BMC Geriatr. 2017;17(1):264. PMID: 29132301; doi: 10.1186/s12877-017-0623-0.
4. Lourenço RA, Moreira VG, Mello RGB de, et al. Consenso brasileiro de fragilidade em idosos: conceitos, epidemiologia e instrumentos de avaliação [Brazilian consensus on frailty in older people: concepts, epidemiology and evaluation instruments]. Geriatr Gerontol Aging. 2018;12(2):121-35. doi: 10.5327/Z2447-211520181800023.
5. Fried LP, Ferrucci L, Darer J, Williamson JD, Anderson G. Untangling the Concepts of Disability, Frailty, and Comorbidity: Implications for Improved Targeting and Care. Journals Gerontol Ser A Biol Sci Med Sci. 2004;59(3):255-63. PMID: 15031310; doi: 10.1093/gerona/59.3.m255.
6. Cesari M, Onder G, Russo A, et al. Comorbidity and physical function: Results from the aging and longevity study in the Sirente geographic area (iISIRENTE Study). Gerontology. 2006;52(1):24-32. PMID: 16439821; doi: 10.1159/000089822.
7. Guralnik JM, Ferrucci L, Simonsick EM, Salive ME, Wallace RB. Lower-extremity function in persons over the age of 70 years as a predictor of subsequent disability. N Engl J Med. 1995;332(9):556-61. PMID: 7838189; doi: 10.1056/NEJM199503023320902.
8. da Câmara SMA, Alvarado BE, Guralnik JM, Guerra RO, Maciel AC. Using the Short Physical Performance Battery to screen for frailty in young-old adults with distinct socioeconomic conditions. Geriatr Gerontol Int. 2013;13(2):421-8. PMID: 22882512; doi: 10.1111/j.1447-0594.2012.00920.x.
9. Abizanda P, Romero L, Sánchez-Jurado PM, et al. Association between Functional Assessment Instruments and Frailty in Older Adults: The FRADEA Study. J Frailty Aging. 2012;162-8. PMID: 27093316; doi: 10.14283/jfa.2012.25.
10. Mello MJC. Análise da bateria de testes "Short Physical Performance Battery" de acordo com a classificação de fragilidade em idosos da comunidade - Estudo FIBRA [thesis]. Campinas: Universidade Estadual de Campinas (UNICAMP); 2015. Available from: http://repositorio.unicamp.br/jspui/handle/REPOSIP/312940. Accessed in 2020 (Sep 15).
11. Ferrucci L, Penninx BW, Leveille SG, et al. Characteristics of nondisabled older persons who perform poorly in objective tests of lower extremity function. J Am Geriatr Soc. 2000;48(9):1102-10. PMID: 10983911; doi: 10.1111/j.1532-5415.2000.tb04787.x.
12. Nakano MM. Versão brasileira da Short Physical Performance Battery - SPPB: adaptação cultural e estudo da confiabilidade [thesis]. Campinas: Universidade Estadual de Campinas (UNICAMP); 2007. Available from: http://www.repositorio.unicamp.br/handle/REPOSIP/252485. Accessed in 2020 (Sep 15).
13. Ministério do Planejamento, Orçamento e Gestão Instituto Brasileiro de Geografia e Estatística - IBGE. Censo demográfico 2010: Aglomerados subnormais - informações territoriais. Rio Janeiro: IBGE; 2010. Available from: https://biblioteca.ibge.gov.br/visualizacao/periodicos/552/cd_2010_agsn_if.pdf. Accessed in 2020 (Sep 15).

14. Gama ASM, Fernandes TG, Parente RCP, Secoli SR. Inquérito de saúde em comunidades ribeirinhas do Amazonas, Brasil [A health survey in riverine communities in Amazonas State, Brazil]. Cad Saude Publica. 2018;34(2):e00002817. PMID: 29489939; doi: 10.1590/0102-311X00002817.
15. Bertolucci PH, Brucki SM, Campacci SR, Juliano Y. O Mini-Exame do Estado Mental em uma população geral: impacto da escolaridade [The Mini-Mental State Examination in a general population: impact of educational status]. Arq Neuropsiquiatr. 1994;52(1):1-7. PMID: 8002795.
16. Freire Junior RC, Fernandes TG, Borges GF, Guerra RO, de Abreu DCC. Factors associated with low levels of physical activity among elderly residents in a small urban area in the interior of the Brazilian Amazon. Arch Gerontol Geriatr. 2018;75:37-43. PMID: 29180130; doi: 10.1016/j.archger.2017.11.007.
17. Fernandes TG, Silva KR, Guerra RO, et al. Influence of the Amazonian context on the frailty of older adults: A population-based study [published online ahead of print, 2020 Jun 23]. Arch Gerontol Geriatr. 2020;104162. PMID: 32624196; doi: 10.1016/j.archger.2020.104162.
18. Andrade JM, Duarte YAO, Alves LC, et al. Perfil da fragilidade em adultos mais velhos brasileiros: ELSI-Brasil [Frailty profile in Brazilian older adults: ELSI-Brazil]. Rev Saude Publica. 2018;52Suppl 2(Suppl 2):17s. PMID: 30379282; doi: 10.11606/S1518-8787.2018052000616.
19. Mello A de C, Engstrom EM, Alves LC. Fatores sociodemográficos e de saúde associados à fragilidade em idosos: uma revisão sistemática de literatura [Health-related and socio-demographic factors associated with frailty in the elderly: a systematic literature review]. Cad Saude Publica. 2014;30(6):1143-68. PMID: 25099040; doi: 10.1590/0102-311X00148213.
20. Fhon JRS, Rodrigues RAP, Santos JLF, et al. Fatores associados à fragilidade em idosos: estudo longitudinal [Factors associated with frailty in older adults: a longitudinal study]. Rev Saude Publica. 2018;52:74. PMID: 30066813; doi: 10.11606/S1518-8787.2018052000497.
21. Verghese J, Xue X. Identifying frailty in high functioning older adults with normal mobility. Age Ageing. 2010;39(3):382-5. PMID: 20051607; doi: 10.1093/ageing/afp226.
22. Andrade AN, Fernandes MGM, da Nóbrega MML, Garcia TR, Costa KNFM. Análise do conceito fragilidade em idosos. Texto Context - Enferm. 2012;21(4):748–56. doi: 10.1590/S0104-07072012000400004.
23. Bensenor IM, Lotufo PA. Epidemiologia Abordagem Prática. 2ª ed. São Paulo: Sarvier Editora de Livros Medicos Ltda; 2011.
24. Rockwood K, Theou O, Mitnitski A. What are frailty instruments for? Age Ageing. 2015;44(4):545-7. PMID: 25824236; doi: 10.1093/ageing/afv043.
25. Patino CM, Ferreira JC. Entendendo os testes diagnósticos: Parte 2 [Understanding diagnostic tests. Part 2]. J Bras Pneumol. 2017;43(6):408. PMID: 29340487; doi: 10.1590/S1806-37562017000000424.
26. Da Mata FA, Pereira PP, De Andrade KR, et al. Prevalence of frailty in Latin America and the Caribbean: A systematic review and meta-analysis. PLoS ONE. 2016;11(8):e0160019. PMID: 27500953; doi: 10.1371/journal.pone.0160019.
27. Siriwardhana DD, Hardoon S, Rait G, Weerasinghe MC, Walters KR. Prevalence of frailty and prefrailty among community-dwelling older adults in low-income and middle-income countries: A systematic review and meta-analysis. BMJ Open. 2018;8(3):e018195. PMID: 29496895; doi: 10.1136/bmjopen-2017-018195.
28. Neri AL, Yassuda MS, Araújo LF, et al. Metodologia e perfil sociodemográfico, cognitivo e de fragilidade de idosos comunitários de sete cidades brasileiras: Estudo FIBRA [Methodology and social, demographic, cognitive, and frailty profiles of community-dwelling elderly from seven Brazilian cities: the FIBRA Study]. Cad Saude Publica. 2013;29(4):778-92. PMID: 23568307; doi: 10.1590/S0102-311X2013000400015.

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Association between chronic diseases, multimorbidity and insufficient physical activity among older adults in southern Brazil: a cross-sectional study

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ABSTRACT

BACKGROUND: Being active has been shown to have beneficial effects for the health of individuals with chronic diseases. However, data on the association between multimorbidity and physical activity are limited.

OBJECTIVE: To investigate the association between chronic diseases, multimorbidity and insufficient physical activity among older adults in southern Brazil, according to sex.

DESIGN AND SETTING: Cross-sectional population-based and household-based study derived from the second wave (2013-2014) of the EpiFloripa Aging Cohort Study.

METHODS: Insufficiency of physical activity (outcome) was ascertained using the long version of the International Physical Activity Questionnaire (≤ 150 minutes/week). Eleven self-reported chronic diseases were identified. Multimorbidity was defined from the number of chronic diseases (none; 2 or 3; or 4 or more). The adjustment variables were age, schooling, marital status, income, smoking, alcohol consumption and cognition. Additionally, each chronic disease was adjusted for the others. Associations were tested using logistic regression (crude and adjusted).

RESULTS: Among the 1197 participants (≥ 63 years), women (54.0%) were more likely than men (39.6%) to be insufficiently active. In the adjusted analysis, women and men with depressive symptoms, and men with diabetes, were more likely to be insufficiently active than those without symptoms. Multimorbid women were more likely to be insufficiently active, and the magnitude of the effect was strongest for 4 or more diseases.

CONCLUSION: This study indicates that the associations were sex-specific. Depressive symptoms and multimorbidity were associated with insufficient physical activity among women, while diabetes was associated with insufficient physical activity among men.

INTRODUCTION

Population aging is a worldwide phenomenon that has led to increased prevalence of noncommunicable chronic diseases (NCDs). Among chronic diseases, cardiovascular diseases, cancers, respiratory diseases and diabetes are responsible for more than 80% of deaths worldwide.[1] In 2016, these diseases accounted for 73.8% of deaths in Brazil.[2] In addition to these diseases, musculoskeletal disorders and neurological and mental disorders are also prevalent.[3]

With the increasing prevalence of NCDs, another challenge for the healthcare of the older adult population is the coexistence of two or more chronic conditions in the same individual, called multimorbidity.[4] Multimorbidity is an important condition among older adults, and is often associated with disability and a higher chance of mortality. Also, multimorbidity has a higher cost, with greater utilization of healthcare services than would be expected from the individual effects of chronic diseases.[5] In Brazil, data from the 2013 National Health Survey showed that the prevalence of multimorbidity among men and women aged 60 or over was 43.4% and 57.1%, respectively.[6]

Regular practicing of physical activity stands out as a modifiable risk factor in relation to prevention and control of chronic diseases, and to improvement of the health and wellbeing of individuals or communities.[7] The World Health Organization (WHO)[8] recommends that individuals should accumulate at least 150 minutes per week of moderate to vigorous-intensity

physical activity or 75 minutes per week of vigorous physical activity. According to data from populational studies focusing on older adults (60 years and over), insufficient levels of physical activity are highly prevalent in Brazil, particularly among women and older age groups.[9,10]

Many studies have investigated the association between chronic disease and physical activity among older adults. However, these studies were based on a single-disease model,[11,12] without taking into account adjustments for other diseases, which is the model proposed in the present study.

Regarding the association between multimorbidity and physical activity among older adults, the data are limited and divergent, including in Brazil, thus suggesting that there is a need for further studies. While some studies have shown an association between multimorbidity and lower levels of physical activity among young adults, middle-aged adults and older adults,[13,14] others have found an association only for men (≥ 65 years)[15,16] or no association for adults.[17] Recently, Christofoletti et al.[18] investigated the association between multimorbidity and physical activity among Brazilian adults (≥ 18 years). However, their study involved different clusters of only four diseases and the analyses were not stratified according to gender and age group.

OBJECTIVE

Given the above, and considering the differences between men and women and the scarcity of data from the elderly population, the aim of the present study was to investigate the association between chronic diseases, multimorbidity and insufficient physical activity among older adults in southern Brazil, according to sex.

METHODS

Data source and study population

This cross-sectional epidemiological study consisted of an analysis on data from the second wave of the EpiFloripa Aging Cohort Study, conducted in 2013-2014. The baseline for this study was in 2009-2010. The EpiFloripa Aging Cohort Study is a prospective population-based and household-based cohort study carried out among older adults (≥ 60 years) living in the urban area of Florianopolis, state of Santa Catarina, in southern Brazil (http://www.epifloripa.ufsc.br/).

Information regarding the data collection, population and sampling process was published previously and is briefly presented here.[19,20] In the baseline study (2009-2010), a random sample of 1702 individuals (aged 60 years or over) was interviewed. The second wave of data was collected between November 2013 and November 2014, when the older adults of the baseline study had reached ages of 63 years or over. From this sample, eligibility for inclusion in the second wave took into account deaths and address changes. It was found that 217 deaths had occurred. There were 129 refusals to participate and 159 other losses, among which 111 were due to impossibility of localization. Thus, the sample for the present study was 1,197 interviewees.

This project was approved by the Human Research Ethics Committee of Universidade Federal de Santa Catarina (protocol number 329,650, issued on July 8, 2013; CAAE: 16731313.0.0000.0121). The participants signed an informed consent statement.

Physical activity

The subjects' practices of physical activity during leisure time and for transportation were investigated through face-to-face interviews using the long version of the International Physical Activity Questionnaire, as validated for Brazilian elderly people.[21] The physical activity level was determined based on a score expressed as minutes/week in each domain (leisure-time physical activity and transportation physical activity). These scores were calculated by summing the number of minutes spent in doing moderate activities plus the number of minutes spent in doing vigorous activities (which was multiplied by two), as recommended by the WHO.[8] These summed times spent on physical activity during leisure and for transport/traveling were categorized as either > 150 minutes/week, which was defined as sufficient level of physical activity or ≤ 150 minutes/week, which was defined as insufficient level of physical activity.[8]

Chronic diseases

The following chronic diseases were identified (yes or no) through the responses to a simple question ("Has a doctor or a health-care professional ever said that you have ...?): arthritis/rheumatism/arthrosis, cancer, diabetes mellitus, bronchitis or asthma, spinal disease, hypertension, coronary disease, chronic renal failure and/or cerebrovascular disease. These chronic diseases were recorded based on the questionnaire used in the National Household Sample Survey (Pesquisa Nacional por Amostra de Domicílios, PNAD).[22]

To evaluate depressive symptoms, the Geriatric Depression Scale (GDS - 15) was used. This provides validated measurements for identifying depressive symptoms among older adults, and it has been translated and validated for use in Brazil.[23] Interviewees were classified as presenting symptoms of depression using a cut-off point of ≤ 5. Thus, they were deemed not to present any symptoms of depression if a score of ≥ 6 was reached.

Multimorbidity

To analyze multimorbidity, the total number of diseases was categorized as follows: no multimorbidity (zero and one morbidity); two or three morbidities; or four or more morbidities.

Adjustment variables

In accordance with evidence from the literature,[13,24] the adjustment variables considered as possible confounding factors were the following: age (in years, as a continuous variable); marital status (married/with a partner; single; divorced/separated; or widowed); schooling level (without schooling; 1 to 4 years; 5 to 8 years; 9 to 11 years; or 12 years or more); monthly family income, categorized into quartiles (1st quartile: US$ 304.34; 2nd quartile: US$ 304.35 to US$ 524.45; 3rd quartile: US$ 524.46 to US$ 1,152.00; or 4th quartile: US$ 1,152.01; at the time of data collection, R$ 2.55 (Brazilian reais) was the equivalent of US$ 1.00 (United States dollars)); smoking (never smoked, current smoker or former smoker); and alcohol consumption (consumed or not consumed).[25] Cognitive status was measured using the Brazilian version of the Mini-Mental State Examination (MMSE),[26] and the results were presented as the total score.

Statistical analyses

The descriptive variables were presented as means, standard deviations, frequencies (absolute and relative) and confidence intervals (95% CI). Sex differences were tested using the chi-square test. Crude and adjusted logistic regression analyses were used to test possible associations between insufficient physical activity and each chronic disease.

In the adjusted analyses, three regression models were considered. In model 1, the analyses were adjusted for sociodemographic characteristics (age, schooling, marital status and income). Model 2 additionally included behavioral characteristics (smoking and alcohol consumption) and cognitive status. Lastly, model 3 additionally included all other chronic diseases, in order to eliminate the potential confounding effect of comorbidity. All variables were maintained in the analyses, regardless of statistical significance.

Logistic regression was also used to test the possible associations between multimorbidity (reference category: 0-1 morbidity) and insufficient physical activity. These analyses were adjusted for models 1 and 2.

All the analyses were stratified according to sex. The analyses were performed using the IBM SPSS Statistics for Windows software (version 22; IBM Corp., Armonk, NY, United States). The logistic regression analyses considered the sample plan (using the "complex sample" module). A significance level of 5% ($P < 0.05$) was adopted.

RESULTS

The sample of the present study consisted of 1,197 individuals (778 women). The average age of the women was 74.2 years (± 7.4); and of the men, 73.3 years (± 7.3) ($P = 0.037$). The mean MMSE score was higher among the men (25.1 ± 5.6) than among the women (24.3 ± 5.7) ($P = 0.008$). The mean body mass index (BMI) values were 28.5 kg/m^2 (± 5.4) for the women and 27.0 kg/m^2 (± 4.1) for the men ($P \leq 0.001$).

Table 1 presents the characteristics of the study sample. There were sex differences in all characteristics except for the presence of bronchitis or asthma, and cardiovascular disease. The women were more often insufficiently active (54.0%) than the men (39.6%). The prevalence of married status was higher among the men (83.0%) than among the women (39.8%). The women had lower education and lower household income than the men. The men had higher frequencies of alcohol intake and tobacco use than the women.

The most prevalent chronic diseases among the women were hypertension (69.9%), spinal disease (55.3%) and arthritis/rheumatism/arthrosis (41.1%). The prevalence of multimorbidity (2-3 and 4 or more diseases) was higher among the women than among the men (**Table 1**).

The associations between diseases and insufficient physical activity are presented in **Tables 2** and **3**, for women and men, respectively. For the women, the data from the crude analysis (**Table 2**) show that the diseases positively associated with insufficient physical activity were the presence of depressive symptoms, arthritis/rheumatism/arthrosis, diabetes, cardiovascular disease, cerebrovascular disease and hypertension. After adjusting for models 1 and 2, only the presence of depressive symptoms and cardiovascular disease maintained associations with insufficient physical activity, although the strength of association was reduced. After further adjustment for coexisting diseases (final model), only the presence of depressive symptoms remained positively associated with insufficient physical activity. Thus, the women with depressive symptoms were 2.8 times (95% CI: 1.6-4.7) more likely to have insufficient physical activity than were their peers.

For the men (**Table 3**), the results from the crude analysis showed that the presence of depressive symptoms was positively associated with insufficient physical activity (odds ratio, OR: 3.2; 95% CI: 1.4-7.1). After adjusting for model 1, the association remained significant. After adjusting for the characteristics in model 2, the association remained significant (OR: 2.5; 95% CI: 1.2-5.1) and diabetes (OR: 2.0; 95% CI: 1.0-3.8) became significant. After further adjustment for coexisting diseases (model 3), depressive symptoms (OR: 2.7; 95% CI: 1.2-5.7) and diabetes (OR: 2.2; 95% CI: 1.1-4.3) retained their positive association with insufficient physical activity.

Table 4 shows the results from the crude and adjusted logistic regression analyses for the association between multimorbidity and insufficient physical activity. For the women, the results from the crude analysis showed positive associations between multimorbidity and insufficient physical activity, both for two to three chronic diseases (OR: 2.1; 95% CI: 1.3-3.4) and for four or more diseases (OR: 3.9; 95% CI: 2.4-6.3). After adjusting for models 1 and 2, the associations were maintained, although to a lower magnitude,

Table 1. Distribution of older adults in Florianopolis (2013-2014), stratified by sex, according to the characteristics analyzed in the study.

Characteristics	Women (n = 778)			Men (n = 419)			P-value
	n	%	95% CI	n	%	95% CI	
Physical activity							
Sufficient	358	46.0	42.5-49.5	253	60.4	55.6-65.0	**< 0.001**
Insufficient	420	54.0	50.5-57.5	166	39.6	35.0-44.0	
Marital status							
Married	310	39.8	36.4-43.3	348	83.1	79.1-86.4	**< 0.001**
Single	62	8.0	6.3-10.1	14	3.3	2.0-5.6	
Divorced/separated	60	7.7	6.0-9.8	27	6.4	94.4-9.2	
Widowed	346	44.5	41.0-48.0	30	7.2	5.0-10.0	
Schooling (years)							
< 1	60	7.7	6.0-9.8	33	7.9	5.6-10.9	**< 0.001**
1 to 4	305	39.4	36.0-42.8	125	29.8	25.6-34.4	
5 to 8	135	17.4	14.9-20.2	64	15.2	12.1-19.1	
9 to 11	123	15.9	13.5-18.6	57	13.6	10.6-17.2	
≥ 12	152	19.6	17.0-22.6	140	33.5	29.0-38.1	
Income							
Quartile 4	171	22.0	19.2-25.1	127	30.4	26.1-35.0	**0.001**
Quartile 3	206	26.5	23.5-29.7	93	22.2	18.5-26.5	
Quartile 2	169	21.8	19.0-24.8	104	24.9	20.9-29.3	
Quartile 1	231	29.7	26.6-33.0	94	22.5	18.7-26.7	
Living arrangement							
With someone	582	74.8	71.6-77.7	374	89.3	85.9-92.0	**< 0.001**
Alone	196	25.2	22.3-28.4	45	10.7	8.1-14.1	
Smoking							
Never smoked	586	75.4	72.3-78.3	145	34.6	30.2-39.3	**< 0.001**
Smoked and stopped	149	19.2	16.5-22.1	233	55.6	50.8-60.3	
Current smoker	42	5.4	4.0-7.2	41	9.8	7.3-13.0	
Alcohol consumption							
No	570	73.3	70.0-76.3	180	42.9	38.2-47.8	**< 0.001**
Yes	208	26.7	23.7-30.0	239	57.1	52.2-61.7	
Functional disability							
None	196	25.2	22.3-28.4	171	41.1	36.4-45.9	**< 0.001**
1 - 3	305	39.3	35.9-42.7	149	35.8	31.3-40.6	
≥ 4	276	35.5	32.2-39.0	96	23.1	19.3-27.4	
Depressive symptoms							
No	571	78.0	74.8-80.9	336	84.4	80.5-97.7	**0.010**
Yes	161	22.0	19.1-25.1	62	15.6	12.3-19.5	
Spinal disease							
No	348	44.7	41.3-48.2	252	60.1	55.3-64.7	**< 0.001**
Yes	430	55.3	51.7-58.7	167	39.9	35.2-44.6	
Arthritis/rheumatism/arthrosis							
No	458	58.9	55.4-62.3	328	78.3	74.0-82.0	**< 0.001**
Yes	320	41.1	37.7-44.6	91	21.7	18.0-25.9	
Cancer							
No	708	91.0	88.8-92.8	351	83.8	79.9-87.0	**< 0.001**
Yes	70	9.0	7.2-11.2	68	16.2	13.0-20.0	
Diabetes							
No	563	72.4	69.1-75.4	333	79.5	75.3-83.1	**0.007**
Yes	215	27.6	24.6-30.9	86	20.5	16.9-24.7	
Bronchitis or asthma							
No	633	81.4	78.5-83.9	352	84.1	80.2-87.2	0.253
Yes	145	18.6	16.0-21.5	67	15.9	12.8-19.8	
Coronary disease							
No	530	68.1	64.8-71.4	276	65.9	61.2-70.3	0.428
Yes	248	31.9	28.6-35.2	143	34.1	29.7-38.8	
Chronic renal failure							
No	751	96.5	95.0-97.6	391	93.3	90.5-95.3	**0.011**
Yes	27	3.5	2.4-5.0	28	6.7	4.6-9.5	
Cerebrovascular disease							
No	701	90.1	87.8-92.0	361	86.2	82.5-89.2	**0.040**
Yes	77	9.9	8.0-12.2	58	13.8	10.8-17.5	
Osteoporosis							
No	520	66.8	63.4-70.1	392	93.6	90.7-95.5	**< 0.001**
Yes	258	33.2	29.9-36.6	27	6.4	4.4-9.2	
Hypertension							
No	234	30.1	26.9-33.4	182	43.4	38.7-48.2	**< 0.001**
Yes	544	69.9	66.6-73.0	237	56.6	51.7-61.2	
Multimorbidity							
0-1	134	18.3	15.5-21.1	125	31.4	26.8-36.0	**< 0.001**
2-3	302	41.3	37.7-44.8	177	44.5	39.6-49.4	
4+	296	40.4	36.9-44.0	96	24.1	19.9-28.3	

Note: P-value calculated using chi-square test; P ≤ 0.05 is in bold. CI = confidence interval.

for both categories. The results from the adjusted models suggest that multimorbid women were more likely to be physically inactive. This association was significant both for two to three chronic diseases (OR: 1.7; 95% CI: 1.0-2.8) and for four or more diseases (OR: 2.8; 95% CI: 1.6-4.8)

For the men, the results from the crude analysis showed a positive association between multimorbidity (four or more diseases) and insufficient physical activity (OR: 3.0; 95% CI: 1.4-6.6). However, after adjusting for the characteristics of models 1 and 2, the associations were not maintained.

DISCUSSION

This study investigated the association between chronic diseases, multimorbidity and insufficient level of physical activity among older adults in a city in southern Brazil. The results showed that depressive symptoms and multimorbidity (2-3 and ≥ 4 diseases) were positively associated with insufficient physical activity only for women. For men, depressive symptoms and diabetes were positively associated with insufficient physical activity.

According to the results, there was higher prevalence of insufficient levels of physical activity among women, which is consistent with the literature.[27,28] The factors contributing to this profile included the facts that this cohort of older women had had lower levels of schooling, were more involved in household/caring activities

Table 4. Simple and multiple logistic regression analyses on the association test between multimorbidity and insufficient physical activity.

Multimorbidity	Crude analysis OR (95% CI)	Model 1 OR (95% CI)	Model 2 OR (95% CI)
Women			
0-1	1	1	1
2-3	**2.1 (1.3-3.4)**	**1.9 (1.2, 3.0)**	1.7 (0.9-2.8)
≥ 4	**3.8 (2.3-6.3)**	**3.1 (1.8-5.2)**	**2.8 (1.6-4.8)**
Men			
0-1	1	1	1
2-3	1.4 (0.8, 2.5)	1.3 (0.7-2.3)	1.3 (0.7-2.3)
≥ 4	**3.0 (1.4-6.6)**	2.5 (1.1-5.4)	2.3 (1.0-5.3)

OR = odds ratio; CI = confidence interval. Model 1: Adjusted for age, schooling, marital status, living arrangement and income. Model 2: Adjusted for model 1 + smoking, alcohol consumption, cognition, body mass index and functional disability.

Table 2. Crude and adjusted logistic regression analyses on the association between each chronic disease and insufficient physical activity among women.

Diseases	Crude analysis OR (95% CI)	Model 1 OR (95% CI)	Model 2 OR (95% CI)	Model 3 OR (95% CI)
Depressive symptoms	**3.5 (2.1-5.7)**	**3.3 (2.0-5.5)**	**3.0 (1.8-5.0)**	**2.8 (1.6-4.7)**
Spinal disease	1.2 (0.8-1.6)	1.2 (0.8-1.7)	1.1 (0.7-1.7)	1.0 (0.6-1.6)
Arthritis/rheumatisms/arthrosis	**1.5 (1.0-2.1)**	1.3 (0.9-2.0)	1.5 (1.0-2.2)	1.4 (0.9-2.1)
Cancer	1.0 (0.6-2.0)	1.2 (0.6-2.5)	1.4 (0.7-2.8)	1.2 (0.6-2.6)
Diabetes	**1.4 (1.0-2.1)**	1.4 (0.9-2.0)	1.3 (0.9-2.0)	1.0 (0.7-1.7)
Bronchitis	1.4 (0.9-2.3)	1.4 (0.9-2.1)	1.2 (0.8-1.9)	1.1 (0.7-1.7)
Cardiovascular disease	**2.0 (1.4-2.9)**	**1.6 (1.1-2.5)**	**1.6 (1.1-2.5)**	1.5 (0.9-2.4)
Chronic kidney failure	0.8 (0.4-1.8)	0.8 (0.4-1.6)	0.6 (0.3-1.4)	0.5 (0.2-1.1)
Cerebrovascular disease	**2.1 (1.1-3.8)**	1.5 (0.7-3.1)	1.3 (0.6-2.7)	0.9 (0.4-2.2)
Osteoporosis	1.3 (0.9-1.9)	1.2 (0.8-1.8)	1.2 (0.8-1.8)	1.0 (0.7-1.7)
Hypertension	**1.6 (1.1-2.3)**	1.3 (0.9-1.8)	1.3 (0.9-1.9)	1.1 (0.7-1.6)

OR = odds ratio; CI = confidence interval. Model 1: Adjusted for age, schooling, marital status, living arrangement and income. Model 2: Adjusted for model 1 + smoking, alcohol consumption, cognition, body mass index and functional disability. Model 3: Adjusted for previous models and other chronic diseases.

Table 3. Crude and adjusted logistic regression analyses on the association between each chronic disease and insufficient physical activity among men.

Diseases	Crude analysis OR (95% CI)	Model 1 OR (95% CI)	Model 2 OR (95% CI)	Model 3 OR (95% CI)
Depressive symptoms	**3.2 (1.4-7.1)**	**3.0 (1.5-5.8)**	**2.5 (1.2-5.1)**	**2.7 (1.2-5.7)**
Spinal disease	0.9 (0.5-1.6)	0.8 (0.5-1.4)	0.8 (0.5-1.4)	0.8 (0.5-1.3)
Arthritis/rheumatisms/arthrosis	1.5 (0.9-2.7)	1.4 (0.8-2.5)	1.4 (0.8-2.6)	1.5 (0.9-2.8)
Cancer	1.1 (0.5-2.4)	1.0 (0.5-2.2)	1.1 (0.5-2.4)	1.1 (0.5-1.9)
Diabetes	1.5 (0.8-2.7)	1.7 (0.8-3.3)	**2.0 (1.0-3.8)**	**2.2 (1.1-4.3)**
Bronchitis	1.5 (0.7-3.0)	1.4 (0.7-2.8)	1.4 (0.7-2.7)	1.0 (0.5-2.0)
Cardiovascular disease	1.2 (0.7-2.0)	1.2 (0.7-1.9)	1.1 (0.6-1.9)	1.1 (0.6-2.1)
Chronic kidney failure	1.7 (0.6-5.2)	1.6 (0.5-5.0)	1.9 (0.6-6.2)	1.6 (0.4-5.8)
Cerebrovascular disease	1.8 (0.9-3.6)	1.3 (0.6-2.8)	1.0 (0.5-2.3)	0.7 (0.3-1.7)
Osteoporosis	1.3 (0.5-3.2)	1.0 (0.3-2.6)	1.0 (0.3-2.8)	0.9 (0.3-3.0)
Hypertension	1.2 (0.7-1.9)	1.0 (0.6-1.8)	1.2 (0.6-2.3)	1.0 (0.5-2.0)

OR = odds ratio; CI = confidence interval. Model 1: Adjusted for age, schooling, marital status, living arrangement and income. Model 2: Adjusted for model 1 + smoking, alcohol consumption, cognition, body mass index and functional disability. Model 3: Adjusted for previous models and other chronic diseases.

and did not have any paid employment.[29] Thus, the women's lower income levels, compared with men, along with their sociocultural role and family responsibilities, can hinder their possibilities for engaging in physical activity, in terms of both the time and the expense involved in accessing these activities.[30] Other factors that can contribute towards women's lower involvement in physical activity include higher prevalence of physical limitations, lack of confidence and lower levels of self-efficacy beliefs.[31] In the present study, the women had lower schooling and income levels, had higher prevalence of functional limitations and more often lived alone, without company. These results help to explain the higher prevalence of insufficient physical activity among women.

The association between depressive symptoms and insufficient levels of physical activity that was found in the present study is consistent with previous studies showing an inverse relationship between depressive symptoms and physical activity.[11,32] It is known that the association between depressive symptoms and physical activity may be bidirectional. Hence, physical activity is considered to be a healthcare strategy for reducing the risk of developing depression. However, depression is a risk factor for reduction of physical activity levels and sedentary behavior.[11] It is believed that the characteristics of depressive symptoms, such as apathy, dysphoria, cognitive impairment and feelings of discomfort make it difficult to practice physical activity,[33] regardless of other comorbidities. Therefore, these are considered to be barriers against practicing physical activity, among individuals with depressive symptoms.[34]

Our results partially agree with those from other studies.[11,32] Achttien et al.[11] showed that there was an association between symptoms of depression and lower levels of physical activity, without any difference between men and women (n = 1250; mean age 73.9 ± 6.9 years). In a study without stratification according to sex, Ludwig et al.[32] found a positive association between depressive symptoms and insufficient physical activity, regardless of sociodemographic and behavioral factors, or BMI. Depression is more prevalent among individuals with chronic diseases.[35] In the present study, most of the diseases were more prevalent among women, as was insufficient physical activity.

The association between diabetes and insufficient physical activity found in the present study is consistent with the findings of Hult et al.,[12] who showed that individuals with known diabetes were less active than were those without diabetes. It is known that regular physical activity is important for blood glucose management and overall health among individuals with diabetes.[7] However, diabetes-related complications such as peripheral neuropathy, muscle and joint pain, poor eyesight and fatigue can limit involvement in regular physical activity.[36]

The results showed that multimorbidity (2-3 and ≥ 4 diseases) was positively associated with insufficient levels of physical activity only among women, thus suggesting that there was a gender difference in this result. Few studies have explored associations between multimorbidity and physical activity among older adults and the results have been incongruent.[13-16] The data from the present study are partly in line with those from other studies that showed an association between multimorbidity (≥ 2 diseases) and lower levels of physical activity.[13,14] In a study on 228,024 adults (aged 18 years or over), without stratification according to sex, the results showed that those with multimorbidity were significantly less physically active.[14] Keats et al.[13] found associations both for men and for women in a study involving 18,709 participants (aged 35 to 79 years). Unlike in the present study, other authors[15,16] identified an association between lower levels of physical activity and multimorbidity among men aged 65 or over.

Some factors make it difficult to compare these studies. The observational nature, outcome and inclusion of older adults in the samples were similar characteristics between the present study and others.[13-16] The characteristics of the sample (stratification according to sex and age groups), the number and type of chronic diseases included for the categorization of multimorbidity, the instruments used to verify physical activity and the characteristics used in the fit analysis differed between the studies.

The categorization of multimorbidity may have an impact on the results, given that its prevalence estimate is affected by the number of chronic conditions included in the study, as well as the minimum number of diseases used in the categorization.[37] In studies evaluating the association between multimorbidity and physical activity, the lists of chronic conditions has ranged from nine[14] to twenty-three,[17] while in the present study eleven diseases were considered.

Most studies have categorized multimorbidity as the presence of two or more diseases.[13,14,17] Like in the present study, Hudon et al.[17] defined multimorbidity as the presence of two or more diseases in individuals; however, they also used other cutoff points for analyses (two, three, four and five or more diseases). Cimarras-Otal et al.[16] took the definition of multimorbidity to be the presence of three or more diseases in the individual, with the justification that the threshold of three or more diseases might provide greater specificity than just two or more. In the present study, four or more diseases was found to have the highest prevalence. This was also the category with the greatest strength of association with insufficient physical activity among women, which highlights the importance of considering other cutoff points for studies on multimorbidity. It is also important to note that the relationship between physical activity and multimorbidity can be bidirectional.[28] Thus, people with multimorbidity may be less physically active due to worse health conditions. On the other hand, worse health conditions resulting from multimorbidity may lead to insufficient physical activity.

The present study had several limitations. These included the self-reporting of chronic diseases, which may have given rise to

memory bias, and the fact that the severity and type of disease were not taken into consideration. Because our definition of multimorbidity was limited to self-reported diseases, these counted equally and their severity was not identified. Moreover, although we made adjustments for some important potential confounders, there may still have been some residual confounding. On the other hand, even though our use of the instrument for investigating physical activity (IPAQ) can be seen as a limitation due to the self-reported nature of the data, this instrument has been validated and is widely used in epidemiological studies.[13,14,16]

The strengths of this study include its representative sample and the methodological rigor of the EpiFloripa Aging Cohort Study, including the procedures used in the data collection, training of interviewers, standardized measurements and validated questionnaires. Stratification according to sex is another strong point of the present study, given that there are differences between men and women, especially regarding health conditions and physical activity.[9,38] Moreover, our study analyzed older adults' data and, prior to this, only limited data on the association between chronic diseases, multimorbidity and insufficient levels of physical activity among older adults had been available.

CONCLUSION

This study showed that the prevalence of insufficient levels of physical activity differs between the sexes, such that this prevalence is higher among females. It also indicated that sex-specific associations exist. Depressive symptoms and multimorbidity were associated with insufficient physical activity among women, while diabetes was associated with insufficient physical activity among men.

From the results obtained and the known benefits of physical activity, the need for longitudinal studies and interventions to better investigate the relationship between chronic diseases, multimorbidity and insufficient physical activity can be emphasized. These should include investigation of the severity of diseases and use of direct measurements of physical activity. Promotion of policies to encourage regular physical activity for individuals with chronic diseases, along with intervention programs, should be differentiated for men and women, and should take into account disease characteristics and individuals' limitations.

REFERENCES

1. World Health Organization [WHO]. Non communicable diseases. 2019. Available from: https://www.who.int/news-room/fact-sheets/detail/noncommunicable-diseases. Accessed in 2020 (Feb 12).
2. Pan American Health Organization [PAHO]. Noncommunicable diseases in the region of the Americas. Facts and Figures. 2019; Available from: http://iris.paho.org/xmlui/bitstream/handle/123456789/51483/PAHONMH19016_eng.pdf?sequence=1&isAllowed=y. Accessed in 2020 (Feb 15).
3. Prince MJ, Wu F, Guo Y, et al. The burden of disease in older people and implications for health policy and practice. Lancet. 2015; 385(9967):549-62. PMID: 25468153; https://doi.org/10.1016/S0140-6736(14)61347-7.
4. Tugwell P, Knottnerus, JA. Multimorbidity and comorbidity are now separate MESH headings. J Clin Epidemiol. 2019;105:vi-viii. PMID: 30522770; https://doi.org/10.1016/j.jclinepi.2018.11.019.
5. Marengoni A, Angleman S, Melis R, et al. Aging with multimorbidity: A systematic review of the literature. Ageing Rev. 2011;10(4):430-9. PMID: 21402176; https://doi.org/10.1016/j.arr.2011.03.003.
6. Carvalho JN, Roncalli ÂG, Cancela M, Souza DLB. Prevalence of multimorbidity in the Brazilian adult population according to socioeconomic and demographic characteristics. PLoS One. 2017;12(4): e0174322. PMID: 28384178; https://doi.org/10.1371/journal.pone.0174322.
7. Pedersen BK, Saltin B. Exercise as medicine – evidence for prescribing exercise as therapy in 26 different chronic diseases. Scand J Med Sci Sports. 2015;25(Suppl 3):1-72. PMID: 26606383; doi: 10.1111/sms.12581.
8. World Health Organization [WHO]. Global recommendations on physical activity for health. 2010 Available from: https://apps.who.int/iris/bitstream/handle/10665/44399/9789241599979_eng.pdf. Accessed in 2020 (Feb 4).
9. Sousa NFS, Lima MG, Cesar CLG, Barros MBA. Active aging: prevalence and gender and age differences in a population-based study. Cad Saude Publica. 2018;34(11):e00173317. PMID: 30484561; https://doi.org/10.1590/0102-311x00173317.
10. Souza AMR, Fillenbaum GG, Blay SL. Prevalence and correlates of physical inactivity among older adults in Rio Grande do Sul, Brazil. Plos One. 2015;10(2):e0117060. PMID: 25700161; https://doi.org/10.1371/journal.pone.0117060.
11. Achttien R, van Lieshout J, Wensing M, van der Sanden MN, Staal JB. Symptoms of depression are associated with physical inactivity but not modified by gender or the presence of a cardiovascular disease; a cross-sectional study. BMC Cardiovasc Disord. 2019;19(1):95. PMID: 31023228; https://doi.org/10.1186/s12872-019-1065-8.
12. Hult A, Johansson J, Nordström P, Nordström A. Objectively measured physical activity in older adults with and without diabetes. Clin Diabetes. 2019;37(2):142-9. PMID: 31057220; https://doi.org/10.2337/cd18-0041.
13. Keats MR, Cui Y, DeClercq V, et al. Multimorbidity in Atlantic Canada and association with low levels of physical activity. Prev Med. 2017;105:326-31. PMID: 28987335; https://doi.org/10.1016/j.ypmed.2017.10.013.
14. Vancampfort D, Koyanagi A, Ward PB, et al. Chronic physical conditions, multimorbidity and physical activity across 46 low-and middle-income countries. Int J Behav Nutr Phys Act. 2017;14(1):6. PMID: 28100238; https://doi.org/10.1186/s12966-017-0463-5.
15. Autenriet CS, Kirchberger I, Heier M, et al. Physical activity is inversely associated with multimorbidity in elderly men: Results from the KORA-Age Augsburg Study. Prev Med. 2013;57(1):17-9. PMID: 23485795; https://doi.org/10.1016/j.ypmed.2013.02.014.

16. Cimarras-Otal C, Calderón-Larrañaga A, Poblador-Plou B, et al. Association between physical activity, multimorbidity, self-rated health and functional limitation in the Spanish population. BMC Public Health. 2014;14:1170. PMID: 25404039; https://doi.org/10.1186/1471-2458-14-1170.
17. Hudon C, Soubhi H, Fortin M. Relationship between multimorbidity and physical activity: Secondary analysis from the Quebec health survey. BMC Public Health. 2008;8:304. PMID: 18775074; https://doi.org/10.1186/1471-2458-8-304.
18. Christofoletti M, Duca GF, Umpierre D, Malta, DC. Chronic noncommunicable diseases multimorbidity and its association with physical activity and television time in a representative Brazilian population**.** Cad Saude Publica. 2019;35(11):e00016319. PMID: 31691775; https://doi.org/10.1590/0102-311x00016319.
19. Confortin SC, Schneider IJC, Antes DL, et al. Condições de vida e saúde de idosos: resultados do estudo de coorte EpiFloripa Idoso [Life and health conditions among elderly: results of the EpiFloripa Idoso cohort study]. Epidemiol Serv Saúde. 2017;26(2):305-17. PMID: 28492772; https://doi.org/10.5123/s1679-49742017000200008.
20. Schneider IJC, Conforti SC, Bernardo CO, et al. EpiFloripa Aging cohort study: Methods, operational aspects, and follow-up strategies. Rev Saude Publica. 2017;51:104. PMID: 29166443; https://doi.org/10.11606/s1518-8787.2017051006776.
21. Benedetti TRB, Antunes PC, Rodriguez-Añez Cr, Mazo GZ, Petroski EL. Reproducibility and validity of the International Physical Activity Questionnaire (IPAQ) in elderly men. Rev Bras Med Esporte. 2007;13(1):11-6. https://doi.org/10.1590/S1517-86922007000100004.
22. Instituto Brasileiro de Geografia e Estatística [IBGE], 2018. Pesquisa Nacional por Amostra de Domicílios - PNAD 2008. Questionário da pesquisa. Rio de Janeiro: IBGE. Available from: https://biblioteca.ibge.gov.br/biblioteca-catalogo.html?id=52462&view=detalhes. Accessed in 2020 (Feb 14).
23. Almeida OP, Almeida SA. Confiabilidade da versão brasileira da escala de depressão em geriatria (GDS) versão reduzida [Reliability of the Brazilian version of the ++abbreviated form of Geriatric Depression Scale (GDS) short form]. Arq Neuro-Psiquiatr, 1999;57(2B):421-6. PMID: 10450349; https://doi.org/10.1590/S0004-282X1999000300013.
24. Dhalwani NN, Zaccardi F, O'Donovan G, et al. Association between lifestyle factors and the incidence of multimorbidity in an older English population. J Gerontol A Biol Sci Med Sci. 2017;72(4):528-34. PMID: 27470302; https://doi.org/10.1093/gerona/glw146.
25. Lima CT, Freire AC, Silva APB, et al. Concurrent and construct validity of the audit in an urban Brazilian sample. Alcohol Alcohol. 2005;40(6):584-9. PMID: 16143704; https://doi.org/10.1093/alcalc/agh202.
26. Almeida OP. Mini exame do estado mental e o diagnóstico de demência no Brasil [Mini mental state examination and the diagnosis of dementia in Brazil]. Arq. Neuropsiquiatr. 1998;56(3B):605-12. PMID: 9850757; https://doi.org/10.1590/S0004-282X1998000400014.
27. Li W, Procter-Gray E, Churchill L, et al. Gender and age differences in levels, types and locations of physical activity among older adults living in car-dependent neighborhoods. J Frailty Aging. 2017;6(3):129-35. PMID: 28721428; https://doi.org/10.14283/jfa.2017.15.
28. Salman A, Sellami M. Do older adults with multimorbidity meet the recommended levels of physical activity? An analysis of Scottish Health Survey. Int J Environ Res Public Health. 2019;16(19):3748. PMID: 31590293; https://doi.org/10.3390/ijerph16193748.
29. Castro CMS, Costa MFL, Cesar CC, Neves JAB, Sampaio RS. Influence of education and health conditions on paid work of elderly Brazilians. Cienc Saude Coletiva. 2019;24(11):4153-62. PMID: 31664388; https://doi.org/10.1590/1413-812320182411.05762018.
30. Justine M, Azizan A, Hassan V, Salleh Z, Manaf H. Barriers to participation in physical activity and exercise among middle-aged and elderly individuals. Singapore Med J. 2013;54(10):581-6. PMID: 24154584; https://doi.org/10.11622/smedj.2013203.
31. Edwards ES, Sackett SC. Psychosocial variables related to why women are less active than men and related health implications. Clin Med Insights Womens Health. 2016;9(Suppl 1):47-56. PMID: 27398045; https://doi.org/10.4137/CMWH.S34668.
32. Ludwig VM, Bayley A, Cook DG, et al. Association between depressive symptoms and objectively measured daily step count in individuals at high risk of cardiovascular disease in South London, UK: A cross-sectional study. BMJ Open. 2018;8(4): e020942. PMID: 29654044; https://doi.org/10.1136/bmjopen-2017-020942.
33. Watts AS, Mortby ME, Burns JM. Depressive symptoms as a barrier to engagement in physical activity in older adults with and without Alzheimer's disease. Plos One. 2018; 13(12):e0208581. PMID: 30532212; https://doi.org/10.1371/journal.pone.0208581.
34. Vancampfort D, Stubbs B, Sienaert P, et al. What are the factors that influence physical activity participation in individuals with depression? A review of physical activity correlates from 59 studies. Psychiatr Danub. 2015;27(3):210-24. PMID: 26400128.
35. Benton T, Staab J, Evans DL. Medical co-morbidity in depressive disorders. Ann Clin Psychiatry. 2007;19(4):289-303. PMID: 18058286; https://doi.org/10.1080/10401230701653542.
36. McCarthy MM, Davey J, Wackers FT, Chyun DA. Predictors of physical inactivity in men and women with type 2 diabetes from the detection of ischemia in asymptomatic diabetics (DIAD) study. Diabetes Educ. 2014;40(5):678-87. PMID: 24942531; https://doi.org/10.1177/0145721714540055.
37. Harrison C, Britt H, Miller G, Henderson J. Examining different measures of multimorbidity, using a large prospective cross-sectional study in Australian general practice. BMJ Open. 2014;4(7):e004694. PMID: 25015470; https://doi.org/10.1136/bmjopen-2013-004694.
38. Forechi L, Mill JG, Griep RH, Santos I, Pitanga F, Molina, MCB. Adherence to physical activity in adults with chronic diseases: ELSA-Brasil. Rev Saude Publica. 2018;52:31. PMID: 29641656; doi: https://doi.org/10.11606/S1518-8787.2018052000215.

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Incidence and spatial distribution of cases of dengue, from 2010 to 2019: an ecological study

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ABSTRACT

BACKGROUND: Dengue is an arbovirus that has caused serious problem in Brazil, putting the public health system under severe stress. Understanding its incidence and spatial distribution is essential for disease control and prevention.

OBJECTIVE: To perform an analysis on dengue incidence and spatial distribution in a medium-sized, cool-climate and high-altitude city.

DESIGN AND SETTING: Ecological study carried out in a public institution in the city of Garanhuns, Pernambuco, Brazil.

METHODS: Secondary data provided by specific agencies in each area were used for spatial analysis and elaboration of kernel maps, incidence calculations, correlations and percentages of dengue occurrence. The Geocentric Reference System for the Americas (Sistema de Referência Geocêntrico para as Américas, SIRGAS), 2000, was the software of choice.

RESULTS: The incidence rates were calculated per 100,000 inhabitants. Between 2010 and 2019, there were 6,504 cases and the incidence was 474.92. From 2010 to 2014, the incidence was 161.46 for a total of 1,069 cases. The highest incidence occurred in the period from 2015 to 2019: out of a total of 5,435 cases, the incidence was 748.65, representing an increase of 485.97%. Population density and the interaction between two climatic factors, i.e. atypical temperature above 31 °C and relative humidity above 31.4%, contributed to the peak incidence of dengue, although these variables were not statistically significant ($P > 0.05$).

CONCLUSION: The dengue incidence levels and spatial distribution reflected virus and vector adjustment to the local climate. However, there was no correlation between climatic factors and occurrences of dengue in this city.

INTRODUCTION

In the second half of the twentieth century, dengue fever spread throughout the tropics, threatening one-third of the world's population. It caused feverish illness in around 50 to 100 million people, with records of 500,000 cases of severe illness.[1] Dengue is caused by an arbovirus that is transmitted by the mosquitos *Aedes aegypti* and *Aedes albopictus*. Its symptoms range from an acute fever to a hemorrhagic condition, and can be caused by four different virus serotypes.[2] Once an *Aedes* female has become infected, it can transmit the virus to humans through blood transfers for the rest of its life, which leads to greater potential for spreading the disease.[3] *Aedes aegypti* also transmits other high-impact arboviruses such as chikungunya.[4]

Circulation of different virus serotypes has increased the number of infected patients, especially with the severe form of the disease.[5] There is no specific therapy for dengue infections and supportive treatment can save lives.[6]

The first cases of dengue in Brazil were recorded in the state of Roraima, in the northwestern area of the Amazon region, in 1981.[7]

Dengue has become a serious public health problem in the city of Garanhuns, state of Pernambuco, northeastern Brazil. Over the last five years, the incidence of dengue has increased by 485.97%. Epidemiological studies have confirmed that the dengue virus, which first appeared in this region in 1986, presents high intensity of transmission. This research has therefore characterized a situation of lack of knowledge about the behavior of the virus and its vector.[8]

In Pernambuco, the dengue virus serotype three (DENV-3) was associated with the most severe symptoms of the epidemic, from 1995 to 2006.[9] A total of 9,135 dengue cases were recorded in Pernambuco in 2018, corresponding to an incidence rate of 96.2 cases per 100,000 inhabitants.

There were 31,056 dengue cases in 2019, with an incidence rate of 327.0 cases per 100,000 inhabitants, which was a percentage increase of 240.0%.

In the adjacent states of Alagoas and Paraiba, totals of 17,486 and 13,959 cases respectively were recorded in 2019, corresponding to incidence rates of 526.2 and 349.3 cases per 100,000 inhabitants.[10] Throughout Brazil, a total of 1,439,471 probable dengue cases were recorded in the same year.[10]

Also in the same year, 2,384,029 cases of dengue were recorded throughout the Americas, corresponding to an incidence rate of 244.1 cases per 100,000 inhabitants, and 949 deaths were registered.[11]

OBJECTIVE

To describe the incidence and spatial distribution of dengue cases in a medium-sized city with a seasonal climate and high altitude, located in Brazil's northeastern region. Over the period studied (2010-2019), outbreaks and epidemics were observed, with an increased in the incidence rate of 485.97% over the last five years of that period.

METHODS

Study location

This descriptive ecological study was conducted in the city of Garanhuns, state of Pernambuco, northeastern Brazil, covering the years 2010 to 2019. Garanhuns is located 230 kilometers (km) west of the state capital, at an altitude of 896 meters (m) above sea level. It has an area of 472.5 square kilometers (km^2) and an estimated population density in 2019 of 295.84 inhabitants per km^2. The minimum temperature ranges from 15 to 16 degrees centigrade (°C) and the maximum, from 28 to 31.5 °C. The average rainfall over the study period was 68.90 mm per annum and the average relative humidity was 40.1%.[12,13] The climate of Garanhuns is influenced by meteorological systems that cause rainfall mostly in March, June and July.[12] The 2010 census registered a population of 129,408 inhabitants in this municipality, and a total of 139,788 inhabitants was estimated for 2019.[14]

Data collection

Information about dengue cases was obtained from the following secondary data sources: the Brazilian Ministry of Health's Notifiable Disease Information System (Sistema de Informação de Agravos de Notificação, Ministério da Saúde, SINAN/MS);[15] the Pernambuco State Health Department; and the City of Garanhuns Health Department. Socioeconomic and demographic information was obtained from the 2010 census data held by the Brazilian Institute for Geography and Statistics (Instituto Brasileiro de Geografia e Estatística, IBGE).[14] Climate data was collected from the Water and Climate Agency of the State of Pernambuco (Agência Pernambucana de Águas e Clima, APAC).[12]

Data processing

The information contained in the SINAN database was used for georeferencing of dengue cases in the city. This was then incorporated into the Geographic Information System (GIS), within the Quantum GIS (QGIS) software (Open Source Geospatial Foundation, Chicago, USA), version 2.18.11, through which data from multiple sources were integrated. TerraView 4.4.2, from the Image Processing Division, National Space Research Institute (Instituto Nacional de Pesquisas Espaciais, INPE; São José dos Campos, SP, Brazil), was the software used to perform the spatial statistics calculations regarding the distribution of dengue cases. The calculations made use of the Geocentric Reference System for the Americas, 2000 edition (Sistema de Referência para as Américas, SIRGAS), from the German Geodetic Research Institute (Deutsches Geodätisches Forschungsinstitut, DGFI; Munich, Germany).

QGIS was used to determine the spatial distribution of dengue cases. This enabled construction of heat maps showing the intensities of events in the region and the evidence of occurrences, in real time.

Spearman's test was used for correlation calculations. This is a nonparametric test that is recommended for use when it is undesirable to make any assumption of normal distribution or presence of any other variable distribution. This coefficient is based on observation points within each variable and on differences between the points observed, expressed as variables X and Y, for the same object of study.

Approximately 6,504 cases were georeferenced, out of the 7,524 cases reported, covering 86.44% of the total number of cases registered. The other 1,020 cases of dengue were not included either because of incompatibility of address with the cartographic references of the municipality or because the inclusion criteria were not met. The arithmetic "rule of three" was applied to determine the percentage increase in dengue over the last five years.

The incidence rate (IR) calculation was made by taking the number of cases notified to SINAN (NCN) divided by the number of years in the period surveyed (NYP) and the mean population over the period (MPP), and applying these in the formula: IR = (NCN/NYP/MPP) x 100,000. Three survey periods were chosen: 2010 to 2019; 2010 to 2014; and 2015 to 2019.

Ethics

This study was submitted to and approved by the Ethics Committee of the School of Medical Sciences of Universidade de Pernambuco (UFPE) on February 21, 2018, under opinion report number 2.503.713 (CAAE: 62649816.1.0000.5192).

RESULTS

The incidence rate for the entire period researched (2010 to 2019) was 480.27 cases per 100,000 inhabitants. A total of 6,504 dengue

cases were notified and the average population over this period was 135,422 people. Between 2010 and 2014, a total of 1,069 dengue cases were recorded, among an average population over this period of 132,415, with an incidence rate of 161.46 cases per 100,000 inhabitants. In the second half of the survey, from 2015 to 2019, there was a total of 5,435 cases among an average population of 138,532, with an incidence rate of 784.65 cases per 100,000 inhabitants. This latter rate represented a 485.97% increase in dengue cases.

In the first half of the period surveyed, i.e. between 2010 and 2014, 2012 was the year in which the highest incidence occurred, with 271.4 cases per 100,000 inhabitants. In that year, a total of 356 cases were notified and the average population was 131,169. **Figure 1** shows the spatial distribution of dengue cases in the year 2012, in the neighborhoods of São José, Santo Antônio, Heliópolis, Severiano Morais, Aluisio Pinto, Boa Vista and Francisco Simão.

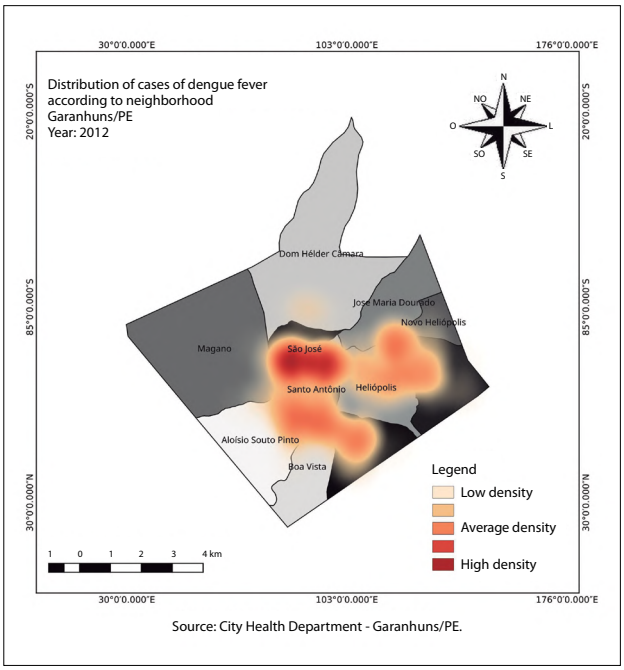
The highest occurrence of dengue cases in the period between 2015 and 2019 was in 2016. In that year, a total of 3031 cases of dengue was recorded among a population of 137,810 inhabitants. The incidence for this particular year was 2,199 cases per 100,000 inhabitants. 2016 was considered to be an epidemic year in the municipality, with greatest spatial distribution in the neighborhoods of São José, Santo Antônio, Heliópolis, Severiano Morais, and Boa Vista. The population densities in these neighborhoods were 4,797, 4,269, 3,710, 3,567 and 2,306 inhabitants per km^2, respectively (**Figure 2**).

The year 2016 represented the peak of dengue momentum in the municipality, with an incidence rate of 2,199 dengue cases per 100,000 inhabitants. The rainfall was not significantly higher than normal; the average temperature was 31.4 °C and the average humidity was 31.4%. These acted as ideal conditions for proliferation of transmitting agents and influenced the rate of occurrence of dengue, can be seen in **Table 1**.

The influence of demographic density on the incidence of dengue can be seen in **Table 2**. This depicts the relationship between the number of dengue cases and the density of inhabitants according to neighborhood. Annual data on average temperature, accumulated precipitation and average relative humidity were individually compared with the number of dengue cases. These correlations were not statistically significant (P > 0.0) (**Table 3**).

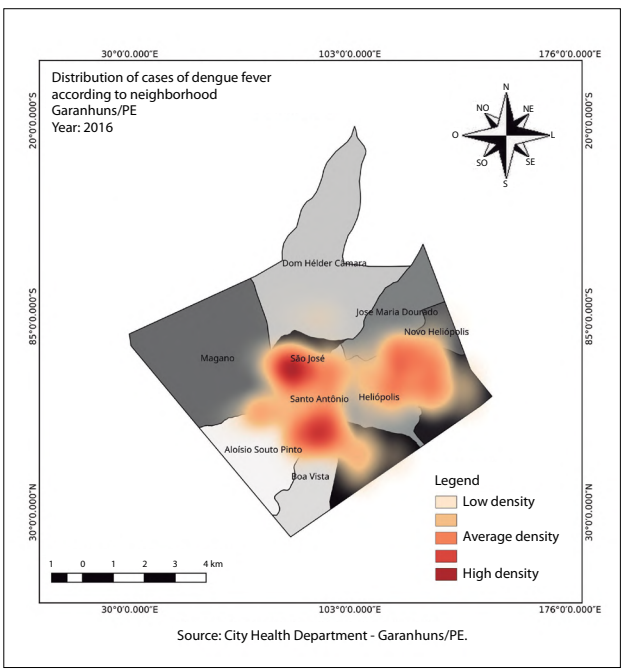
DISCUSSION

The incidence recorded over the 10 years of the survey, between 2010 and 2019, was 474.92 cases per 100,000 inhabitants, with a total of 6,504 cases. When we divided the survey into two periods, i.e. 2010-2014 and 2015-2019, we found the following levels of incidence per 100,000 inhabitants: In the first half of the survey, with a total of 1069 cases, the incidence was 161.46. In comparison, in the second half of the survey,



Source: City Health Department - Garanhuns/PE.

Figure 1. Spatial distribution of dengue cases in the municipality of Garanhuns, state of Pernambuco, in 2012, highlighting the neighborhoods of São José, Santo Antônio, Aluísio Pinto, Heliópolis, Severiano Morais and Francisco Simão, The year 2012 was the year with the highest incidence over the five-year period from 2010 to 2014.



Source: City Health Department - Garanhuns/PE.

Figure 2. Spatial distribution of dengue cases in the municipality of Garanhuns, state of Pernambuco, in 2016, highlighting the neighborhoods of São José, Santo Antônio, Aluísio Pinto, Heliópolis, Severiano Morais and Boa Vista, The year 2016 was the year with the highest incidence over the five-year period from 2015 to 2019.

a total of 5,435 cases were registered and the incidence was 784.65, thus representing an increase of 485.97% in the number of dengue cases.

Figure 1 represents 2012, the year with the highest incidence in the first period of the survey, between 2010 and 2014. There was a total of 356 cases in this year, representing an incidence rate of 271.4 cases per 100,000 inhabitants. In the second period of the survey, between 2015 and 2019, the highest incidence were observed in 2016, and this is represented in **Figure 2**. The incidence rate was 2,199 cases per 100,000 inhabitants, from a total of 3,031 cases recorded.

High spatial distribution in certain neighborhoods was also observed. **Table 2** shows that some neighborhoods with high population densities usually had more cases of dengue than did low-density neighborhoods.

Temperature, relative humidity and precipitation did not show any associations with occurrences of dengue in the municipality. These climatic correlations were not statistically significant (P > 0.05). Some studies carried out in northeastern, southeastern and northern Brazil and abroad[16,18,19,20] have shown correlations contrary to those of the present study, given that they reported associations between climatic factors and the incidence of dengue. On the other hand, some other studies[28,29] have confirmed the lack of correlation of climatic factors with the incidence of dengue.

In the city of Mossoró, state of Rio Grande do Norte, a study covering the years from 2001 to 2007 found that the incidence of dengue was 47.01 cases per 10,000 inhabitants, with greater intensities between the months of February and May. The average temperature for the entire period was 27 °C and the average precipitation was 69 mm.[16] A study on three municipalities in the state of Paraíba, northeastern Brazil, covering the years 2012 and 2013, found that *Aedes aegypti* was capable of completing its life cycle in temperatures that ranged from 22 °C to 36 °C.[17]

Table 3. Results from Spearman's correlation test on variables in relation to the number of dengue cases per year in Garanhuns, over the years from 2010 to 2019

Variable	Correlation	P-value
Average annual temperature (°C)	0.4061	0.2474
Average annual rainfall (mm)	-0.3091	0.3871
Average annual relative humidity (%)	-0.3091	0.3871

Table 1. Incidence of dengue per 100,000 inhabitants in the municipality of Garanhuns, in relation to environmental factors, over the period from 2010 to 2019

Year	Population	Average rainfall (mm)	Average temperature (°C)	Humidity %	Number of cases	Incidence (per 100,000)
2010	129,408	93.84	26.2	48.1	285	220.23
2011	130,303	79.25	25.7	50.0	354	271.67
2012	131,169	30.08	28.8	49.1	356	271.40
2013	135,138	60.34	29.6	35.6	42	31.07
2014	136,057	90.55	29.4	37.3	32	23.51
2015	136,949	49.15	30.3	34.5	1,375	1,004.00
2016	137,810	45.10	31.4	31.4	3,031	2,199.00
2017	138,642	107.29	29.2	38.8	464	334.67
2018	138,983	64.29	30.2	37.4	195	140.30
2019	139,788	69.18	30.6	38.8	370	264.68

Table 2. Population density in relation to the number of dengue cases, according to neighborhood. The significance of associations was higher for the neighborhoods of Heliopolis, São José and Boa Vista (population densities of these neighborhoods are therefore indicated in bold]

Neighborhood	Average population	Area (km²)	Density of inhabitants per km²	Average number of cases
Severiano Morais	20,833	5.84	3,567.00	28.2
Heliópolis	20,246	5.47	**3,710.14**	178.3
Magano	12,672	15.40	822.88	89.7
Aluísio Pinto	12,406	6.88	1.803.00	65.1
São José	12,138	2.53	**4,797.00**	71.6
Francisco Simão	11,756	4.30	2,734.00	39.6
Dom Helder	4,359	15.40	283.08	21.5
Boa Vista	11,184	4.85	**2,306.00**	156.3
Santo Antônio	6,232	1.46	4,269.00	24.4
José M. Dourado	2,323	5.12	453.73	29.1
Novo Heliópolis	2,295	1.73	1,326.00	22.7
Dom Thiago	423	0.31	1,591.00	0.2

A study carried out in Fortaleza covering the years 2001 to 2013 found that the climatic dynamics of the disease showed a significant variation of precipitation and humidity, with temperatures ranging between 25 °C and 28.8 °C.[18] In São Luis, state of Maranhão, a study covering 2002 to 2012 that included meteorological variables showed that the incidence of dengue fluctuated according to climatic periods, such that greater numbers of dengue cases occurred during the rainy season and at times of higher temperatures.[19] Another study carried out in northeastern Brazil in Maceió, state of Alagoas, covering 2010 to 2016, evaluated the correlation of meteorological parameters with the incidence of dengue. It showed that precipitation and humidity influenced the epidemiology of dengue.[20]

A study carried out in Pakistan showed that the incidence of the disease was influenced by climatic factors, such that the transmission rates among mosquitoes were higher within a favorable temperature range from 28 °C to 32 °C.[21] Laboratory data on larval development of Aedes aegypti have confirmed that these temperatures favor multiplication of these larvae, consequently enabling greater production of vectors and producing increased incidence of dengue.[22]

In an urban area of the city of São Paulo, Brazil, a study showed that the oviposition rates of *Aedes aegypti* and *Aedes albopictus* were influenced by the maximum and minimum temperatures.[23]

Temperature influences mosquitos' life cycles and plays a crucial role in the incidence of dengue. Analyzing the effects of temperature variations in cities can lead to preventive identification of thermal comfort zones favorable to the survival of mosquito populations.[24] Knowing how environmental conditions influence the dynamics of dengue epidemics is important for responding to its epidemics and for predicting the geographical and seasonal spread of the disease.[25]

Although there is no statistical association between temperature and dengue cases, it appears that dengue peaks coincide with temperature spikes.[26] This hypothesis was reinforced through a wintertime study carried out in Taiwan, which is a in subtropical region, where a low temperature of 13.8 °C resulted in the near disappearance of *Aedes aegypti*.[27] A study on the impact of dengue in the state of Tocantins, Brazil, revealed that climatic conditions did not influence proliferation of dengue but, rather, the conditions that would be ideal for reproduction of the vector.[28] An ecological study carried out in Araguaína, Tocantins, also did not find any correlation with climatic variables and concluded that these variables contributed to vector proliferation, but did not influence the spread of dengue.[29]

Data from 13 weather stations in Delhi, India, over the period from 2006 to 2015, indicated that there was a strong association between the incidence of dengue and the temperature, humidity, wind speed, summertime, settlement density and vegetation.[30] In China, results from sensitivity analyses indicated that temperature can be an effective or facilitating barrier for vector-borne diseases and can result in complex disease control.[31] Variations in daytime temperature, precipitation and relative humidity have had statistically significant results in multiple linear regressions for the number of dengue cases.[32] The association between climatic factors and dengue incidence suggests that application of any prospective dengue early warning system should be done on a local or regional basis rather than on a national scale.[33]

The years of 2015 and 2016 were years of drought for the city of Garanhuns, and this may have favored an increase in the number of mosquito breeding sites and thus may have caused the dengue epidemic of 2016. On the other hand, in some cases of dengue. its incidence may have been related to the Zika virus, as reported in a cross-sectional study carried out in the state of Pernambuco, which pointed out differential diagnoses of arboviruses, carried out between January and April 2015, based on clinical and epidemiological criteria. Among these diagnoses, 1,046 suspected cases were recorded, of which 895 (86%) were classified as probable cases of the Zika virus and 151 (14%) as cases of dengue.[34] However, of 8,429,735 cases of arboviruses reported in Brazil in 2015 and 2016, only 5% were suspected of being caused by the Zika virus.[35]

The limitations of this study comprised its inclusion criteria, i.e. the subjects needed to have an address in the municipality of Garanhuns, their cases needed to have been notified to SINAN and a diagnosis of dengue needed to have been made. Patients who did not meet these inclusion criteria and those whose addresses could not be georeferenced due to lack of information were excluded: these exclusions corresponded to 13.78% of the total number of notified cases.

CONCLUSION

The climate and local geography of the study area, characterized by wide variations in temperature and precipitation, with prolonged periods of drought and densely populated neighborhoods, may have contributed to greater reproduction and dissemination of the transmitting vector. This may have led to differences in dengue incidence rates over the last five years, thereby increasing the number of outbreaks and even epidemics.

These results should serve as the basis for the creation of new control and continued prevention strategies. They also demonstrate that there is a need for greater in-depth study of the spatial distribution of dengue, using regression analysis.

REFERENCES

1. Stephenson JR. Understanding dengue pathogenesis: implications for vaccine design. Bull World Health Organ. 2005;83(4):308-14. PMID: 15868023.
2. Harris E, Videa E, Pérez L, et al. Clinical, epidemiologic, and virologic features of dengue in the 1998 epidemic in Nicaragua. Am J Trop Med Hyg. 2000;63(1-2):5-11. PMID: 11357995; https://doi.org/0.4269/ajtmh.20010.63.5.

3. Donalisio MR, Glasser CM. Entomological surveillance and dengue vector control. Rev Bras Epidemiol. 2002;5(3):259-79. https://doi.org/10.1590/S1415-790X2002000300005.
4. Souza JL. Dengue, zika e chikungunya, Diagnóstico, tratamento e prevenção. Rio de Janeiro: Rubio; 2017.
5. Araújo VEM, Bezerra JMT, Amâncio FF, Passos VMA, Carneiro M. Increase in the burden of dengue in Brazil and federated units, 2000 and 2015: analysis of the Global Burden of Disease Study. Rev Bras Epidemiol. 2017;20(Suppl 01):205-16. PMID: 28658384; https://doi.org/10.1590/1980-5497201700050017.
6. Singhi S, Kissoon N, Bansal A. Dengue and hemorrhagic dengue: aspects of management in the intensive care unit. J. Pediatr. 2007;83(2). https://doi.org/10.1590/S0021-75572007000300004.
7. Osanai CH, Travassos da Rosa AP, Tang AT, et al. Dengue outbreak in Boa Vista, Roraima. Preliminary report. Rev Inst Med Trop São Paulo. 1983;25(1):53-4. PMID: 6879054.
8. Castanha PM, Cordeiro MT, Martelli CM, et al. Force of infection of dengue serotypes in a population-based study in the northeast of Brazil. Epidemiol Infect. 2013;141(5):1080-8. PMID: 22800513; https://doi.org/10.1017/S0950268812001367.
9. Cordeiro MT, Schatmayr HG, Nogueira RM, et al. Dengue and dengue hemorrhagic fever in the state of Pernambuco, 1995-2006. Rev Soc Bras Med Trop. 2007;40(6):605-11. PMID: 18200409; https://doi.org/10.1590/s0037-86822007000600001.
10. Ministério da Saúde, Secretaria de Vigilância em Saúde. Boletim epidemiológico. 2019;50(22). Available from: https://www.saude.gov.br/images/pdf/2019/setembro/11/BE-arbovirose-22.pdf. Accessed in 2020 (Apr 29).
11. Pan-American Health Organization/ World Health Organization. Epidemiological Update: Dengue. Washington, D.C.: PAHO/WHO; 2019. Available from: https://www.paho.org/hq/index.php?option=com_docman&view=download&category_slug=dengue-2217&alias=50321-13-september-2019-dengue-epidemiological-update&Itemid=270&lang=en. Accessed in 2020 (Apr 29).
12. Agência Pernambucana de Águas e Clima (APAC). Available from: www.apac.pe.gov.br. Accessed in 2020 (Apr 29).
13. Instituto Nacional de Meteorologia (INMET). Available from: www.inmet.gov.br. Accessed in 2020 (Apr 29).
14. Instituto Brasileiro de Geografia e Estatística (IBGE). Available from: http://www.ibge.gov.br/home/. Accessed in 2020 (Apr 29).
15. Sinan Dengue/Chikungunya. Available from: www.portalsinan.saude.gov.br/sinan-dengue-chikungunya. Accessed in 2020 (Apr 29).
16. Bessa Júnior FN, Nunes RF, de Souza MA, et al. Spatial distribution of dengue disease in municipality of Mossoró, Rio Grande do Norte, using the Geographic Information System. Rev Bras Epidemiol. 2013;16(3):603-10. PMID: 24896274; https://doi.org/10.1590/s1415-790x2013000300005.
17. Marinho RA, Beserra EB, Bezerra-Gusmão MA, et al. Effects of temperature on the life cycle, expansion, and dispersion of Aedes aegypti (Diptera: Culicidae) in three cities in Paraíba, Brazil. J Vector Ecol. 2016; 41(1):1-10. PMID: 27232118; https://doi.org/10.1111/jvec.12187.
18. Magalhães GB, Zanella ME. The variability climate and frequency of dengue in Fortaleza, CE, Brazil. Rev Eletrônica do Prodema [Internet]. 2015;9(1):35-50. Available from: www.revistarede.ufc.br/rede/article/view/296/71. Accessed in 2020 (Apr 29).
19. Pinho de Carvalho AC, Couto Portela F, Azevedo Feitosa Ferro T, Quaresma Bomfim MR. Epidemiology of dengue virus from 2002 to 2012 in São Luís, Maranhão State, Brazil. Revista De Patologia Tropical/Journal of Tropical Pathology. 2016;45(3):243-55. https://doi.org/10.5216/rpt.v45i3.43503.
20. Júnior CJS, Silva JP. Epidemiologia, fatores climáticos e distribuição espacial da dengue em uma capital do nordeste do Brasil. Revista Brasileira de Climatologia. 2019;15(25):755-68. https://doi.org/10.5380/abclima.v25i0.69421.
21. Malik A, Yasar A, Tabinda AB, et al. Assessing spatio-temporal trend of vector breeding and dengue fever incidence in association with meteorological conditions. Environ Monit Assess. 2017;189(4):189. PMID: 28353206; https://doi.org/10.1007/s10661-017-5902-x.
22. Araujo RV, Albertini MR, Costa-da-Silva AL, et al. São Paulo urban heat islands have a higher incidence of dengue than other urban areas. Braz J Infect Dis. 2015;19(2):146-55. PMID: 25523076; https://doi.org/10.1016/j.bjid.2014.10.004.
23. Heinisch MRS, Diaz-Quijano FA, Chiaravalloti-Neto F, et al. Seasonal and spatial distribution of Aedes aegypti and Aedes albopictus in a municipal urban park in São Paulo, SP, Brazil. Acta Trop. 2019;189:104-13. PMID: 30282003; https://doi.org/10.1016/j.actatropica.2018.09.011.
24. Misslin R, Vaguet Y, Vaguet A, Daudé É. Estimating air temperature using MODIS surface temperature images for assessing Aedes aegypti thermal niche in Bangkok, Thailand. Environ Monit Assess. 2018;190(9):537. PMID: 30132225; https://doi.org/10.1007/s10661-018-6875-0.
25. Huber JH, Childs ML, Caldwell JM, Mordecai EA. Seasonal temperature variation influences climate suitability for dengue, chikungunya, and zika transmission. PLoS Negl Trop Dis. 2018;12(5):0006451. PMID: 29746468; https://doi.org/10.1371/journal.pntd.0006451.
26. Carneiro MAF, Alves BDCA, Gehrke FS, et al. Environmental factors can influence dengue reported cases. Rev Assoc Med Bras (1992). 2017;63(11):957-61. PMID: 29451659; https://doi.org/10.1590/1806-9282.63.11.957.
27. Tsai PJ, Lin TH, Teng HJ, Yeh HC. Critical low temperature for the survival of Aedes aegypti in Taiwan. Parasit Vectors. 2018;11(1):22. PMID: 29310716; https://doi.org/10.1186/s13071-017-2606-6.
28. Valadares AF, Rodrigues C. Filho J, Peluzio JM. Impacto da dengue em duas principais cidades do Estado do Tocantins: infestação e fator ambiental (2000 a 2010) [Impact of dengue in two major cities of the state of Tocantins: infestation and environmental factors (2000-2010)]. Epidemiol Serv Saude. 2013;22(1):59-66. https://doi.org/10.5123/S1679-49742013000100006.
29. Oliveira AFM, Sousa ALL, Silva RC, Carmo Filho JR. Estudo Ecológico da Dengue em Araguaína-TO entre 2001 e 2010. Estudos Goiânia. 2016;42(4):517-26. Available from: http://seer.pucgoias.edu.br/index.php/estudos/article/download/4370/2505. Accessed in 2020 (Sep 24).

30. Mala S, Jat MK. Implications of meteorological and physiographical parameters on dengue fever occurrences in Delhi. Sci Total Environ. 2019;650(Pt 2):2267-83. PMID: 30292120; https://doi.org/10.1016/j.scitotenv.2018.09.357.
31. Jing Y, Wang X, Tang S, Wu J. Data informed analysis of 2014 dengue fever outbreak in Guangzhou: Impact of multiple environmental factors and vector control. J Theor Biol. 2017;416:161-79. PMID: 28039013; https://doi.org/10.1016/j.jtbi.2016.12.014.
32. Pakhare A, Sabde Y, Joshi A, et al. A study of spatial and meteorological determinants of dengue outbreak in Bhopal City in 2014. J Vector Borne Dis. 2016;53(3):225-33. PMID: 27681545.
33. Choi Y, Tang CS, McIver L, et al. Effects of weather factors on dengue fever incidence and implications for interventions in Cambodia. BMC Public Health. 2016;16:241. PMID: 26955944; https://doi.org/10.1186/s12889-016-2923-2.
34. Brito CA, Brito CC, Oliveira AC, et al. Zika in Pernambuco: rewriting the first outbreak. Rev Soc Bras Med Trop. 2016;49(5):553-8. PMID: 27812648; https://doi.org/10.1590/0037-8682-0245-2016.
35. de Oliveira WK, de França GVA, Carmo EH, et al. Infection-related microcephaly after 2015 and 2016 Zika virus outbreaks in Brazil: a surveillance-based analysis. Lancet. 20173;90(10097):861-70. PMID: 28647172; https://doi.org/10.1016/S0140-6736(17)31368-5.

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False positivity of Rose Bengal test in patients with COVID-19: case series, uncontrolled longitudinal study

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Dear Editor

At the end of 2019, a novel coronavirus was identified as the cause of a cluster of pneumonia cases in Wuhan, China, and it spread quickly to other countries. This has led to a pandemic that has spread throughout most countries of the world in 2020. A wide variety of symptoms and signs can be seen in coronavirus disease 2019 (COVID-19) infection, such as fever, coughing, shortness of breath, arthralgia, muscle pain and diarrhea.

COVID-19 infection may show clinical or laboratory features that are similar to those of a variety of diseases. For example, it is difficult to distinguish dengue and COVID-19 because they have shared clinical and laboratory features.[1,2] In a case report from Singapore, two patients with false-positive results from rapid serological testing for dengue, who were later confirmed to have severe acute respiratory syndrome COVID-19 infection, were reported.[3]

Brucellosis is the most common zoonosis worldwide and is a significant public health problem in many developing countries such as our country, Turkey.[4] Brucellosis typically presents with fever, malaise and arthralgia.[5] Common symptoms of COVID-19, such as fever, myalgia or arthralgia, can also be seen in brucellosis. The laboratory findings of these infections may be similar. Thrombocytopenia and leukopenia are common in COVID-19 and can also be seen in brucellosis. When there is a suspicion of brucellosis, the Rose Bengal test is recommended as the first test. This is a plaque agglutination test with high sensitivity that is easy to apply, has low cost and provides qualitative results. Therefore, it is frequently used as a screening test in human brucellosis cases. For this reason, we performed the Rose Bengal test on patients with COVID-19 presenting fever and arthralgia, because our country is within the endemic region for brucellosis.

In our tertiary-level medical facility, the patients received their diagnoses either through a positive polymerase chain reaction (PCR) for SARS-CoV-2 or through fulfilling three clinical criteria, including having fever and/or respiratory symptoms, compatible chest imaging findings and decreased lymphocyte count.[6] We questioned the patients in our case series to ascertain any history of brucellosis, but found that none of them had any history relating to brucellosis or other zoonotic diseases. In eight of these patients, Rose Bengal tests were positive. These results are provided in **Table 1**. The median age of these eight patients was 58.5 years, and five of them were female. Arthralgia and fatigue were present in all eight patients; fever and cough were present in seven (87.5%). No patient had anosmia, ageusia, abdominal pain or diarrhea. Fourteen days after treatment for COVID-19, we performed the Rose Bengal test on all patients again, and its positivity became negative.

The Rose Bengal test may sometimes give a false-positive result. Various antigens obtained from *Brucella melitensis* and *Brucella abortus* are generally used in serological tests. Among these, the most widely used antigen is smooth lipopolysaccharide (S-LPS). The Rose Bengal test detects S-LPS-specific immunoglobulin M (IgM), immunoglobulin G (IgG) and immunoglobulin A (IgA) antibodies. However, this test lacks specificity to discriminate the false-positive serological reactions caused by bacteria (especially Gram-negative bacteria) sharing S-LPS epitopes with *Brucella*.[7,8]

It has been shown that the Rose Bengal test might have cross-reactivity with certain bacteria, including are *Francisella tularensis*, *Afipia*, *Escherichia hermannii*, *Stenotrophomonas maltophilia*, *Yersinia enterocolitica*, *Escherichia coli*, *Salmonella urbana*, *Vibrio cholerae* and others.[9-11] Other

Table 1. Demographic and clinical characteristics and laboratory findings among eight patients with COVID-19

Characteristic or finding	Value in patients (n = 8)
Age – median (IQR) [years]	58.5 (47)
Female sex – n (%)	5 (62.5)
COVID-19 – n (%)	8 (100)
Duration of hospitalization – median (IQR) [days]	8.5 (5.25)
Fatigue – n (%)	8 (100)
Arthralgia - n (%)	8 (100)
Fever – n (%)	7 (87.5)
Cough – n (%)	7 (87.5)
Myalgia – n (%)	4 (50)
Dyspnea – n (%)	3 (37.5)
Headache – n (%)	2 (25)
Back pain – n (%)	1 (12.5)
Total lymphocytes – median (IQR) [per mm^3]	1195 (677.5)
Lactate dehydrogenase – median (IQR) [U/liter]	219.5 (90.25)
C-reactive protein – median (IQR) [mg/liter]	24.5 (89.5)
Serum ferritin – median (IQR) [µg/liter]	80 (155.75)
Fibrinogen – median (IQR) [g/liter]	3.49 (2)
D-dimer – median (IQR) [mg/liter]	0.4 (1)
Positive Rose Bengal test – n (%)	8 (100)

IQR = interquartile range.

false-positive reactions in the Rose Bengal test may be attributable to residual antibody activity from vaccinations, or to laboratory error.[12]

Our study is noteworthy in that it was the first case series to show cross-reactivity between the Rose Bengal test and the COVID-19 PCR test. Further studies are needed to explain the relationship between COVID-19 and the Rose Bengal test.

Ethics approval for this study was obtained from the Ethics Committee of a local hospital (number: E1-20-895; date: June 10, 2020).

REFERENCES

1. Chen N, Zhou M, Dong X, et al. Epidemiological and clinical characteristics of 99 cases of 2019 novel coronavirus pneumonia in Wuhan, China: a descriptive study. Lancet. 2020;395(10223):507-13. PMID: 32007143; doi: 10.1016/S0140-6736(20)30211-7.
2. Yan G, Pang L, Cook AR, et al. Distinguishing Zika and dengue viruses through simple clinical assessment, Singapore. Emerg Infect Dis. 2018;24(8):1565-8. PMID: 30016242; doi: 10.3201/eid2408.171883.
3. Yan G, Lee CK, Lam LTM, et al. COVID-19 and false-positive dengue serology in Singapore. Lancet Infect Dis. 2020;20(5):536. PMID: 32145189; doi: 10.1016/S1473-3099(20)30158-4.
4. Pappas G, Akritidis N, Bosilkovski M, Tsianos E. Brucellosis. N Engl J Med. 2005;352(22):2325-36. PMID: 15930423; doi: 10.1056/NEJMra050570.
5. Bosilkovski M, Krteva L, Dimzova M, et al. Human brucellosis in Macedonia – 10 years of clinical experience in endemic region. Croat Med J. 2010;51(4):327-36. PMID: 20718086; doi: 10.3325/cmj.2010.51.327.
6. Shen KL, Yang YH, Jiang RM, et al. Updated diagnosis, treatment and prevention of COVID-19 in children: experts' consensus statement (condensed version of the second edition). World J Pediatr. 2020;16(3):232-9. PMID: 32333248; doi: 10.1007/s12519-020-00362-4.
7. Muñoz PM, Blasco JM, Engel B, et al. Assessment of performance of selected serological tests for diagnosing brucellosis in pigs. Vet Immunol Immunopathol. 2012;146(2):150-8. PMID: 22445082; doi: 10.1016/j.vetimm.2012.02.012.
8. Corbel MJ. Brucellosis in humans and animals. Geneva: World Health Organization; 2006. Available from: https://www.who.int/csr/resources/publications/Brucellosis.pdf?ua=1. Accessed in 2020 (Aug 25).
9. Young EJ. Human brucellosis. Rev Infect Dis. 1983;5(5):821-42. PMID: 6356268; doi: 10.1093/clinids/5.5.821.
10. Díaz R, Casanova A, Ariza J, Moriyón I. The Rose Bengal Test in Human Brucellosis: A Neglected Test for the Diagnosis of a Neglected Disease. PLoS Negl Trop Dis. 2011;5(4):e950. PMID: 21526218; doi: 10.1371/journal.pntd.0000950.
11. Mert A, Ozaras R, Tabak F, et al. The sensitivity and specificity of Brucella agglutination tests. Diagn Microbiol Infect Dis. 2003;46(4):241-3. PMID: 12944013; doi: 10.1016/s0732-8893(03)00081-6.
12. Chothe SK, Saxena HM. Innovative modifications to Rose Bengal plate test enhance its specificity, sensitivity and predictive value in the diagnosis of brucellosis. J Microbiol Methods. 2014;97:25-8. PMID: 24345764; doi: 10.1016/j.mimet.2013.12.005.

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Comment on: Classification of plastic surgery malpractice complaints brought before the São Paulo Medical Board that were treated as professional-misconduct cases: a cross-sectional study

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Dear Editor,

In response to the article titled "Classification of plastic surgery malpractice complaints brought before the São Paulo Medical Board that were treated as professional-misconduct cases: a cross-sectional study" published in your esteemed journal, which is a well-thought-out and well-written paper, I would like to raise a few points regarding this study.

The article reported that the number of complaints lodged decreased over the last two years reviewed, although complaints regarding malpractice and poor doctor-patient relationships increased by 10% over the same period.[1]

The specialties with the greatest number of lawsuits in the United States are gynecology/obstetrics, general surgery and internal medicine.[2] The factors that may explain the increasing numbers of lawsuits include the population's greater knowledge about their rights and the influence of the media. Deterioration in the quality of the doctor-patient relationship has contributed to this situation.[3] Medical schools are focusing on training technical professionals, which thus reduces the teaching time available for bioethics.[4] Teaching of ethics has a dual function. The first is to improve students' capacity for bioethical reflection and the second is to shape them into citizens who are aware of the importance of their profession within society.

To avoid medical malpractice, improvement of the doctor-patient relationship and communication between the doctor and the family must be emphasized, in addition to encouraging proper filling out of medical records. Currently, technology occupies a large space within medical care and has replaced important moments for anamnesis and physical examination, which are essential factors that form part of Hippocratic medical practice. The medical curriculum needs to be complemented with lectures, online courses and direct exchanges of experiences between professionals, thereby providing greater exposure to ethical content and improving learning.

Thus, it is important to invest in prevention of bad practices, so as to train medical professionals who have greater commitment to good medical practice.

REFERENCES

1. Mariani PC, Constantino CF, Nunes R. Classification of plastic surgery malpractice complaints brought before the São Paulo Medical Board that were treated as professional-misconduct cases: a cross-sectional study [published online ahead of print, 2020 Mar 9]. Sao Paulo Med J. 2020; 138(2):140-5. PMID: 32159603; doi: 10.1590/1516-3180.2019.0363.09122019.
2. Studdert DM, Mello MM, Gawande AA, et al. Claims, errors, and compensation payments in medical malpractice litigation. N Engl J Med. 2006;354(19):2024-33. PMID: PMID: 16687715; doi: 10.1056/NEJMsa054479.
3. Floyd TK. Medical malpractice: trends in litigation. Gastroenterology. 2008;134(7):1822-1825.e1. PMID: 18482584; doi: 10.1053/j.gastro.2008.05.001.

4. Neves Jr WA, Araújo LZS, Rego S. Ensino de bioética nas faculdades de medicina no Brasil. Rev Bioét. 2016;24(1):98-107. doi: 10.1590/1983-80422016241111.

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Mental health survival kit

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The book "Mental health survival kit", written by the illustrious Danish physician Peter Gøtzsche, ought to be obligatory reading material for all who wish to specialize in psychiatry or, indeed, all who already are psychiatrists. The evidence that it provides unquestionably shows the degree of decadence into which this specialty has now fallen.[1] This book not only warns about the problem but also provides recommendations.

Starting in the second half of the 1980s, psychiatry came to be completely eaten up by the pharmaceutical industry. Through well-designed marketing, the industry implanted a pandemic of medications into the mentality of psychiatry, especially with regard to antidepressants.

Peter Gøtzsche draws attention to some extraordinarily important facts that have emerged through serious meta-analyses that involved several countries. For example, he points out that use of antidepressants significantly increases the number of suicides. Moreover, he shows that great difficulty exists in publishing articles critical of psychotropic drugs, given that this would go against the interests of multibillion-dollar pharmaceutical companies that, by the way, form part of all the main stock markets around the world.

Another significant fact that merits reflection among all psychiatrists is that, beyond the issue of prescription of antidepressants, especially when used for long periods, withdrawal from their use is difficult. Antidepressants cause physical dependence, and withdrawal leads to abstinence syndrome and severe effects on users' mental and physical health. This is not just the author's opinion based on his authority as an internationally respected physician, but is based on scientific evidence that is available for anyone who wishes to see it. It comes from statistical studies that bring together the results from several independent trials conducted in different countries, with systematic reviews of the literature, which obviously minimizes the chances of error.

It should be recalled that Gøtzsche was one of the founders of the Cochrane Collaboration, in Oxford, together with several other eminent physicians of international renown. Among these was the Brazilian Álvaro Nagib Atallah, who introduced evidence-based medicine here in Brazil. This teaches a way of seeing and practicing medicine that, incidentally, forms the necessary safe path that we doctors should follow.

The book proposes solutions that are far from easy. It shows that the current generation of psychiatrists is lost, a view that I fully agree with. At this point, the situation can no longer be reversed, such is the magnitude of the contamination of the minds of today's psychiatrists, who think that the human being is only or almost only a pile of neurons and neurotransmitters that needs drugs that they prescribe.

No, it is not at all like this. On the contrary, these medications are no more than a chemical straitjacket that acts on a biopsychosocial being, to tie it up inside itself. Moreover, these medications give rise to important side effects. This lost generation of psychiatrists can be seen to be negligent, imprudent and lacking in expertise regarding this extremely serious problem. To give a faint idea of the low level of these professionals, there are many who accept calling antidepressants "happy pills". Well, they cause impotence: "How can men be happy if they become impotent and women, if they become frigid?", asks Peter Gøtzsche.

The way forward is to invest in young people who will become psychiatrists. They will, I am sure, put an end to this matter of professionals who today, instead of caring for their psychiatric patients, turn them into victims. It will be hard work, but it needs to be done.

In this book, Peter Gøtzsche proposes ways to become free from these two present-day plagues of psychiatrists and psychotropic drugs. The following are some of these ways:

- Psychiatrists need to be reeducated so that they can function as psychologists.
- The focus should be on taking patients off psychiatric medications, given that they are harmful over the long term.
- A national network of 24-hour assistance and an associated website should be established to provide advice to people who have been harmed through dependence and have been taken off their prescribed drugs.
- "Say sorry". It is very important that victims of psychotropic drug abuse should receive apologies. People in government need to demand that psychiatric associations should apologize for the harm that has been caused to patients and for the systematic lies that have been told regarding protection through these drugs, against suicide or brain damage.
- Psychiatric diagnostic systems such as DSM-5 and CID-11 should be completely discarded. (My note: this is perhaps the most important step of all, given that these two catalogues not only are extremely poorly produced and worthless, but also have become "bibles" and the only "scientific" source for decadent psychiatry.)
- The psychiatric medications available should only be taken under strictly controlled circumstances.
- Nobody who works with psychiatric patients should have financial conflicts of interest with the pharmaceutical companies.
- All of us should do what we can to change the deceitful narrative of psychiatry.

I am sure that everyone who reads the book "Mental health survival kit"[1] will see both the size of the problem and some solutions that are feasible.

REFERENCE

1. Gøtzsche PC. Mental health survival kit and withdrawal from psychiatric drugs. Copenhagen: Institute for Scientific Freedom; 2020. Available from: https://www.deadlymedicines.dk/books/. Accessed in 2020 (Oct 20).

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Acknowledgements and funding

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

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The editorial team will then provide page proofs for the authors to review and approve. No article is published without this final author approval. All authors should review the proof, although the Journal asks the corresponding author to give final approval.

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The manuscript should be divided into two files. The first of these, the main document ("blinded"), should contain the article title, article type, keywords and abstract, article text, references and tables, but must omit all information about the authors. The second of these, the "title page", should contain all the information about the authors.

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The following are considered to be full-text original articles: clinical trials; cohort, case-control, prevalence, incidence, accuracy and cost-effectiveness studies; case series (i.e. case reports on more than three patients analyzed together); and systematic reviews with or without meta-analysis. These types of article should be written with a maximum of 3,500 words (from the introduction to the end of the conclusion).

Typical main headings in the text include Introduction, Methods, Results, Discussion and Conclusion. The authors can and should use short subheadings too, especially those concerning the reporting guideline items.

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All studies published in SPMJ must present a description of how the sample size was arrived at. If it was a convenience or purposive sample, the authors must declare so and explain the characteristics of this sample and recruitment method. For clinical trials, for instance, it is mandatory to inform each of the three main values used to calculate sample size:

- power (usually 80% or more);
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All drugs, including anesthetics, should be followed by the dosage and posology used.

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Short communications

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

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

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

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

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

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

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

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

FORMAT: FOR ALL TYPES OF ARTICLES

Title page

The title page must contain the following items:

1. Type of paper (original article, review or updating article, short communication or letter to the editor);
2. Title of the paper in English, which should be brief but informative, and should mention the study design.[14] Clinical trial, cohort, cross-sectional or case-control study, and systematic review are the most common study designs. Note: the study design declared in the title should be the same in the methods and in the abstract;
3. Full name of each author. The editorial policy of the *São Paulo Medical Journal* is that abbreviations of authors' names must not be used; therefore, we ask that names be stated in full, without using abbreviations;
4. Each author should present his/her ORCID identification number (as obtained from www.orcid.org);
5. Each author should indicate the way his/her name should be used in indexing. For example: for "João Costa Andrade", the indexed name could be "Costa-Andrade J." or "Andrade JC", as preferred;
6. Each author should indicate a valid, up-to-date email address for contact;
7. The author's professional background (Physician, Pharmacist, Nurse, Dietitian or another professional description, or Undergraduate Student); and his/her position currently held (for example, Master's or Doctoral Student, Assistant Professor, Associate Professor or Professor), in the department and institution where he/she works, and the city and country (affiliations);
8. Place or institution where the work was developed, city and country.
9. Date and venue of the event at which the paper was presented, if applicable, such as congresses, seminars or dissertation or thesis presentations.
10. Sources of financial support for the study, bursaries or funding for purchasing or donation of equipment or drugs. The protocol number for the funding must be presented with the name of the issuing institution. For Brazilian authors, all grants that can be considered to be related to production of the study must be declared, such as fellowships for undergraduate, master's and doctoral students; along with possible support for postgraduate programs (such as CAPES) and for the authors individually, such as awards for established investigators (productivity; CNPq), accompanied by the respective grant numbers.
11. Description of any conflicts of interest held by the authors (see above).
12. Complete postal address, e-mail address and telephone number of the author to be contacted about the publication process in the Journal (the "corresponding author"). This author should also indicate a postal address, e-mail address and telephone number that can be published together with the article. *São Paulo Medical Journal* recommends that an office address (rather than a residential address) should be informed for publication.

Second page: abstract and keywords

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

The following headings must be used in the structured abstract:

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

References

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

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

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

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

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

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

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

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

Figures and tables

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

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

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

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

All the figures and tables should be cited in the text. All figures and tables must contain legends or titles that precisely describe their content and the context or sample from which the information was obtained (i.e. what the results presented are and what the kind of

sample or setting was). The reader should be able to understand the content of the figures and tables simply by reading the titles (without the need to consult the text), i.e. titles should be complete. Acronyms or abbreviations in figure and table titles are not acceptable. If it is necessary to use acronyms or abbreviations inside a table or figure (for better formatting), they must be spelled out in a legend below the table or figure.

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

DOCUMENTS CITED

1. Internal Committee of Medical Journal Editors. Recommendations for the Conduct, Reporting, Editing, and Publication of Scholarly Work in Medical Journals. Available from: http://www.icmje.org/recommendations/. Accessed in 2019 (March 11).
2. The CONSORT Statement. Available from: http://www.consort-statement.org/. Accessed in 2018 (May 3).
3. Moher D, Cook DJ, Eastwood S, et al. Improving the quality of reports of meta-analyses of randomised controlled trials: the QUOROM statement. Br J Surg 2002. Available at: https://onlinelibrary.wiley.com/doi/abs/10.1046/j.1365-2168.2000.01610.x. Accessed in 2019 (April 4).
4. PRISMA. Transparent Reporting of Systematic Reviews and Meta-Analyses. Available from: www.prisma-statement.org. Accessed in 2019 (April 4).
5. STROBE Statement. Strengthening the reporting of observational studies in epidemiology. What is strobe? Available from: http://www.strobe-statement.org/. Accessed in 2018 (May 3).
6. von Elm E, Altman DG, Egger M, et al. The Strengthening the Reporting of Observational Studies in Epidemiology (STROBE) statement: guidelines for reporting observational studies. J Clin Epidemiol. 2008;61(4):344-9. PMID: 18313558. doi: 10.1016/j.jclinepi.2007.11.008.
7. The CARE Guidelines: Consensus-based Clinical Case Reporting Guideline Development. Enhancing the QUAlity and Transparency Of health Research. Available from: https://www.equator-network.org/reporting-guidelines/care/. Accessed in 2018 (May 3).
8. STARD Statement. STAndards for the Reporting of Diagnostic accuracy studies. Available from: http://www.equator-network.org/reporting-guidelines/stard/. Accessed in 2018 (May 3).
9. Rennie D. Improving reports of studies of diagnostic tests: the STARD initiative. JAMA. 2003;289(1):89-90. doi:10.1001/jama.289.1.89.
10. International Committee of Medical Journal Editors (ICMJE). Defining the Role of Authors and Contributors. Available from: http://www.icmje.org/recommendations/browse/roles-and-responsibilities/defining-the-role-of-authors-and-contributors.html. Accessed in 2019 (March 11).
11. International Committee of Medical Journal Editors. Overlapping Publications. Available from: http://www.icmje.org/recommendations/browse/publishing-and-editorial-issues/overlapping-publications.html. Accessed in 2018 (Feb 18).
12. Phillips B, Ball C, Sackett D, et al. Oxford Centre for Evidence-based Medicine Levels of Evidence (March 2009). Available from: https://www.cebm.net/2009/06/oxford-centre-evidence-based-medicine-levels-evidence-march-2009/. Accessed in 2018 (May 3).
13. Hoffmann TC, Glasziou PP, Boutron I, et al. Better reporting of interventions: template for intervention description and replication (TIDieR) checklist and guide. BMJ. 2014;348:g1687. PMID: 24609605; doi: 10.1136/bmj.g1687.
14. Non-randomised controlled study (NRS) designs. Available from: http://childhoodcancer.cochrane.org/non-randomised-controlled-study-nrs-designs. Accessed in 2018 (May 3).

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