JMRR

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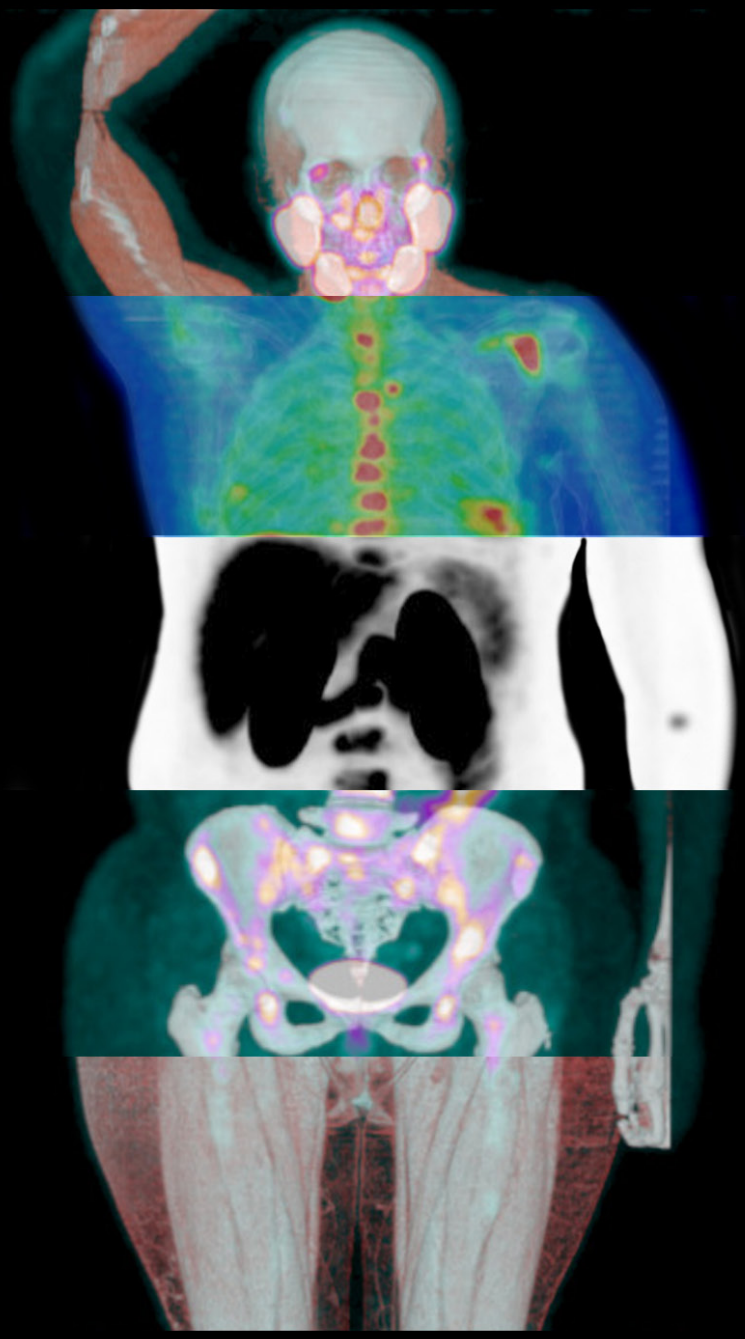

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CREMESP
CONSELHO REGIONAL DE MEDICINA DO ESTADO DE SÃO PAULO

JMRR

JOURNAL OF MEDICAL RESIDENT RESEARCH

The *Journal of Medical Resident Research* (JMRR), the first scientific journal of the State of São Paulo Medical Board (Cremesp), provides young physician-scientists with the opportunity to publish their research internationally, and to have technical and didactic support during the process of publishing their manuscripts. Submit your work!

NEW EDITION

CREMESP
CONSELHO REGIONAL DE MEDICINA DO ESTADO DE SÃO PAULO

JMRR

JOURNAL OF MEDICAL RESIDENT RESEARCH

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JOURNAL OF MEDICAL RESIDENT RESEARCH

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JMRR
JOURNAL OF MEDICAL RESIDENT RESEARCH

GUIDE FOR AUTHORS

The **Journal of Medical Resident Research** (JMRR), previously called *Revista do Médico Residente* (RMR), is an official scientific journal of the Regional Council of Medicine of the State of São Paulo (Cremesp), focused on the publication of medical articles by physician-scientists, who are at the begining of their careers. Its main objective is to disseminate medical-scientific knowledge, especially among doctors in training and residency programs.

In order to achieve this objective, contributions of this target audience in technical, ethical, bioethical and deontological articles are encouraged.

Each manuscript, in English and/or Portuguese, must clearly describe an objective or hypothesis; the design and methods, including the characteristics of the institution where the research took place, the criteria for the selection and exclusion of participants, and data sources; the essential points of the interventions and analyses; the main results of the study and its limitations. It must also include a "discussion" section that interacts with the scientific literature and conclusions.

Except when explicitly indicated, JMRR complies with rules and similar standards in the area, such as the Brazilian Federal Law No 6,932, of July 7, 1981, which provides for the activities of medical residents; those of the National Medical Residency Committee; and Resolution No 466/12 of the Brazilian National Health Council (CNS), from December 12th, 2012, which establishes guidelines for research involving human beings.

For the preparation/submission of articles, authors are suggested to follow the standards of the EQUATOR Reporting Guidelines (Enhancing the Quality and Transparency of Health Research), an organization that brings together researchers, editors of medical journals, reviewers, developers of guidelines on scientific texts, among others.

Other recommendations also include those of the International Committee of Medical Journal Editors (ICMJE), a group of editors of medical journals and related organizations that work together; the Committee on Publication Ethics (COPE); the Council of Science Editors (CSE); and the World Association of Medical Editors (WAME).

These standards aim to improve the quality of research, journals and medical science in general;

In addition to EQUATOR, the following are mentioned in this guide:

CONSORT – *Consolidated Standards of Reporting Trials*
MOOSE – *Meta-analyses Of Observational Studies in Epidemiology*
PRISMA – *Preferred Reporting Items for Systematic Reviews and Meta-Analyses*
STARD – *Standards for Reporting of Diagnostic Accuracy Studies*
ARRIVE – *Animal Research: Reporting of In Vivo Experiments*

After all the stages of preparation, realization and concretization of the final version have been completed, the manuscripts must be submitted to **jmrr@cremesp.org.br**.

BRIEF INDEX OF TERMS

For better understanding and standardization, some terms mentioned in this **Guide for Authors** are presented below:

Case-control studies – Study design in which participants are selected from those who have a certain disease (cases) and those who do not (controls) to compare the odds of exposure to a particular variable between groups.

Cohort studies – Observational surveys in which individuals are classified or selected according to exposure status, and the incidence of a disease or condition is compared.

Experimental study (intervention) – A study in which the researcher, in an intentional and controlled way, manipulates the exposure factor (intervention) to investigate its effects. This type of study investigates hypotheses previously formulated, or look for factors that contribute to the onset of a certain disease.

Clinical trial – Experimental study performed on human volunteers to evaluate the safety and efficacy of treatments or interventions against diseases and health conditions of any nature and to determine the pharmacological, pharmacokinetic, and pharmacodynamic effects of new therapies.

Randomized clinical trial – In general, it is a clinical trial that compares two or more interventions, which are control-

led by the researchers and applied randomly to a group of participants.

Quasi-experimental study – A study that does not contemplate all the characteristics of a "true" experiment, since a complete experimental control is not always possible, especially regarding the randomization and application of the intervention.

Observational study – Conducted without the action of the investigator, who simply observes and measures what is being studied (patients, the characteristics of the disease, etc.), without intervening or modifying any variable.

Prevalence or cross-sectional study – Measures the risk factors and the selected outcome concomitantly, not allowing any assumption about what came first (exposure or outcome).

Keywords – Section of the scientific article composed of three or four words, used for indexing it in databases. (Bireme Health Descriptors are suggested).

Qualitative research – Type of research that is not limited to numerical variables: in this approach, researchers seek to explain the reason for things, working with the universe of meanings, motives, aspirations, beliefs, values and attitudes.

Quantitative research – Its results can be quantified. When the samples are large and considered "representative", the statistically significant results can be extrapolated to the entire target population.

Abstract – Its main purpose is to provide an overview of the research. To this end, the objective, method, results and conclusions must be highlighted. Abstracts are classified in structured – formed by "strata", i.e., items or sections –, each preceded by a subtitle, and unstructured – which presents information in running text, usually in a single paragraph. (See more about the topic in Requirements for the Preparation and Submission of Articles > Structure).

Case report and series – Corresponds to the detailed description of clinical cases, containing important characteristics about the signs, symptoms, and other characteristics of the patient, the therapeutic procedures used, as well as the outcome. *Case reports* usually comprise no more than three cases, while case series comprise three to ten cases.

Systematic review with meta-analysis – It is an analysis of previous studies on a particular research object. Meta-analysis is understood as a statistical technique that is especially suitable for combining results from different independent studies, identifying and comparing, for example, the risks involved in two different treatments.

ARTICLE CATEGORIES

1. ORIGINAL RESEARCH

1.1 Original Articles

Usually include experimental, quasi-experimental or observational studies, program evaluations, randomized clinical trials, interventional studies, cohort studies, case-control studies, epidemiological studies, other observational studies, cost-effectiveness analyses, decision-making analyses, screening studies, and diagnostic tests. See specific guidelines for each type of study on the EQUATOR website.

Each article should contain its objectives and hypotheses, designs and methods, results, discussion and conclusions, which should be as timely and current as possible. A clear explanation of the methods and results is essential to make it easier to review the articles and to ensure the replicability of the results.

Original articles also involve theoretical essays (critiques and formulation of relevant theoretical knowledge), focused on the presentation and discussion of methodological aspects and techniques used in medical research.

Requirements:

- Maximum of 3,000 words
- Maximum of five tables and/or figures
- Structured abstract with no more than 350 words
- Up to 60 references
- Keywords

1.1.1. Clinical trials or studies

Any research project with participation of human beings inserted in groups for intervention and comparison, aiming to study the cause-effect relationship and the health outcome. Interventions include (but are not limited to) experiments with drugs, surgical procedures, equipment, behavioral treatments, educational programs, dietary interventions, quality of life improvements, and changes in the care processes.

Articles that present partial or integral results of clinical trials must be accompanied by the number and the agency of registration, as recommended by the Latin American and Caribbean Center on Health Sciences Information (BIREME); the Pan American Health Organization (PAHO); the World Health Organization (on the Register of Clinical Trials to be published based on WHO guidelines); and the International Committee of Medical Journal Editors (ICMJE).

Requirements:

- Maximum of 3,000 words
- Maximum of five tables and/or figures, including a CONSORT flowchart
- Structured abstract with no more than 350 words
- Keywords
- Registration number of the Clinical Trials in a database (e.g., clinicaltrials.gov)
- CONSORT checklist
- In accordance with EQUATOR guidelines
- Up to 60 references

1.2 Special Articles

1.2.1. Methodological Articles

These articles feature new, improved, or noteworthy comments on techniques or methods deemed as relevant to basic, clinical, or treatment studies.

Requirements:

- Maximum of 2,000 words
- Maximum of two tables and/or figures
- Structured abstract with no more than 350 words
- Up to 30 references

1.2.2. Short communications

Short reports of findings of interest, which do not include a more comprehensive analysis and discussion.

Requirements:

- Maximum of 1,200 words
- Maximum of three tables and/or figures
- Structured abstract with no more than 250 words
- Keywords
- Up to 15 references
- In accordance with EQUATOR guidelines

2. EDUCATION AND LITERATURE REVIEW

2.1 Systematic Reviews (without meta-analyses)

It aims to answer a specific question

by synthesizing results from original quantitative or qualitative studies, according to PRISMA guidelines, with evaluation of the scientific literature and data sources on a clinical topic, emphasizing factors such as cause, diagnosis, prognosis, therapy or prevention, and describing in detail the process of searching for original studies; the inclusion criteria; and how the results of these studies were synthesized.

Requirements:

• Maximum of 3,500 words

• Maximum of five tables and/or figures, including a PRISMA diagram

• Structured abstract with no more than 350 words

• Up to 100 references

• Keywords

• In accordance with PRISMA guidelines and submitted to the PRISMA Checklist

2.2 Narrative review

Up-to-date review on a topic of interest from the perspective of renowned experts, which addresses an issue that is relevant to clinical practice.

It may include (but does not require) a systematic review of the literature.

Conclusions can be based on recent evidence and guidelines, with an emphasis on factors such as cause, diagnosis, prognosis, therapy or prevention.

Requirements:

• Between 2,000-3,500 words

• Maximum of five tables and/or figures

• Structured abstract

• Up to 100 references

• Keywords

2.3 Meta-analyses

Systematic and critical evaluations of the literature and data sources, referring to clinical topics, with emphasis on factors such as cause, diagnosis, prognosis, therapy or prevention.

In research with meta-analysis, a statistical technique is adopted to quantitatively combine the results of more than one study into a single total estimate.

For each specific type of article or data source, the methodology, population, intervention, exposure and tests must be described.

They must be submitted to the PRISMA checklist, and present the PRISMA flowchart used for the selection of articles. Authors of meta-analyses of observational studies should submit them to the MOOSE checklist and follow EQUATOR guidelines.

Requirements:

• Maximum of 3,500 words

• Maximum of five tables and/or figures, including a PRISMA diagram

• Structured abstract with no more than 350 words

• Keywords

• In accordance with EQUATOR guidelines, especially PRISMA and MOOSE

• Up to 100 references

3. OPINIONS

3.1 Editorial

Article presenting JMRR's opinion on a given subject, reflecting the point of view of the majority of the editorial board and the journal's administrative body – therefore, it is not signed by a particular editor. In essence, it is an opinionated and objective report on a specific article – or a review of some relevant articles or topics - published in the current or past issues of the journal.

Doctors who are not involved in the journal's editorial board and administrative staff may be invited by the editors to write it, depending on the subject at hand.

3.2 Letter to the Editor

Consists of comments regarding the methods used to obtain or interpret the data presented in an article published in the latest issues of JMRR. It may perform a new analysis of the data based on other scientific articles and/or methods and/or journals. It can also include a case report that is capable of illustrating new information. When justified, a response from the author(s) of the study in question is requested.

Requirements (Letter to the Editor) :

• Maximum of 400 words

• Maximum of three authors

• Up to five references (one of which must be the article that is the object of the comments)

Requirements (Response from the author(s):

• Maximum of 500 words

• Up to six references

3.3 Point of view

External manuscript that is well-focused, academic and clearly presented, generally not linked to a specific article. It can address any important topic in Medicine, Medical Residency, Research, New Discoveries, Public Health, Prevention, Ethics and Bioethics, and Health Policies or Standards.

Requirements:

• Maximum of 1,200 words (or 1,000 if accompanied by a small table or figure)

• Maximum of three authors, with no more than two affiliations per author

• Up to seven references

REQUIREMENTS FOR THE PREPARATION AND SUBMISSION OF ARTICLES

1. PREPARATION

1.1 Structure

The structure of an original article or a review consists of pre-textual, textual and post-textual elements.

The **mandatory structural elements** are the *Title, Abstract and Submission and Approval Dates.* Title and Abstract in other language(s) are optional.

The **textual elements** are mandatory, and correspond to the elements usually standardized in scientific articles, as follows: *Title, Name of authors, Keywords, Abstract, Introduction, Materials and Methods, Results, Discussion, and Conclusions..*

As for the **post-textual elements**, the References are mandatory, whereas the *Glossary, Appendix, Annex, and Acknowledgments* are optional.

The Abstract should highlight the objective, method, results and conclusions of the study; be written in the active voice, third person singular; be composed of a sequence of concise, affirmative sentences, in a single paragraph. The first sentence should be significant, explaining the main theme, followed by information about the research category (case study, analysis of the situation, etc.).

The *Introduction* should provide a brief narrative, indicating the objectives/hypotheses of the current study. It should not include the results. As for the *Materials and Methods* section, it must include enough details to allow other researchers to disseminate and/or replicate the study.

Attention: The maximum word limits

of articles submitted to JMRR exclude Abstracts, Tables and Figures.

1.2 Formatting

The *Title* of the article and the subtitle (if any) must appear on the title page, in Portuguese or English, and be typographically differentiated or separated by a colon. Including the title in another language just below the original title is optional; additionally, centering it at the top of the title page and writing it in bold is recommended.

The name of the *Authors* must be inserted directly: first name (abbreviated or not) and last name, and they should be written in full, each separated by a comma, in the same way as the names of the *Institutions.*

If there is more than one author, the names can be written on the same line, separated by commas, or on different lines. A succinct resume of each author must be included, with corporate association and contact address.

The *Keywords* must appear just below the abstract, preceded by the term "Keywords". Each of them must be separated and finalized by a period.

The use of Health Descriptors from Bireme is recommended, which correspond to a translation of the Medical Subject Headings (MeSH) of the U.S National Library of Medicine, used by databases such as Scielo, Lilacs, VHL, MEDLINE and PubMed PubMed.

These descriptors contain terms in English, Portuguese and Spanish.

JMRR recommends the articles to be arranged in a *Single Column*, in an *A4 Sheet, Portrait Format.* Font: Times New Roman, with the title in 14 pt; the subtitles and body text in 12 pt; the abstract in 11 pt; and citations with more than three lines in 10 pt, with four cm indentation from the left margin.

Additionally, 1.5 spacing and justified alignment should be used for paragraphs in the text, marked with a 1.5 indentation. There must be no blank line between paragraphs.

Page numbers need to be inserted in the upper right margin, with the exception of the first. Margins: left and top: three cm / right and bottom: two cm (do not include frames).

It is also recommended to start all sections on separate pages and divide the sections and subsections by assigning them Arabic numerals, aligning the section code with the left margin, preceding the title and separated from it by a space. Numbering should be progressive up to the quinary section, e.g.:

Primary section "1"
Secondary section "1.1"
Tertiary section "1.1.1"
Quaternary section "1.1.1.1"
Quinary section "1.1.1.1.1".

1. 3 References and citations

References are a standardized set of essential elements that allow identifying or locating a document or part of it, published in different platforms or formats.

They must be presented in a standardized manner, according to the guidelines of specific organizations. Complementary elements can be added, whenever necessary, to facilitate the identification of the document.

The extraction of text citations from other studies can be done directly (literal transcription) and indirectly (paraphrase), duly documented with the name of the author of the original source.

JMRR adopts the standards established by the ICMJE, which adopts **Vancouver**. These standards govern all citations in the body text.

For example, in articles written by between **one and six authors**, the references will obey the following form:

Author AA, Author BB, Author CC, Author DD. Title of the article. Short name of the journal. Publication date YYYY; volume number(issue number): page numbers.

> Silva GR, do Carmo JC, Souza LC. Como resistir a um assédio moral durante a fase de internato. Rev Bioet. 2018; 54(1):111-114.

Articles with more than six authors are referenced as follows:

Author AA, Author BB, Author CC, Author DD, Author EE, Author FF, *et al.* Title of the article. Short name of the journal. Publication date YYYY; volume number (issue number): page numbers.

> Silva GR, do Carmo JC, Souza LC, Ribeiro KK, Tavares OPG, Santos BO *et al.* Relação do preceptor com os residentes e seus conflitos éticos.Saúde Soc. 2017; 200(6): 869-875.

* Learn more about the Vancouver standard at Samples of Formatted References for Authors of Journal Articles, NIH U.S. National Library of Medicine

1.4 Figures and tables

Overall, figures and tables are the fastest way to communicate large amounts of information, which would be complicated to explain in text.

Figures are ideal for displaying images, data graphs and layouts.

Images can help achieve the precision needed for a scientific manuscript: when choosing, the author must make sure to include scale bars, highlight important items, and identify the meaning of the different colors and symbols used.

Data graphs demonstrate the functional or statistical relationship between two or more items. In them, the axes must be highlighted, as well as the units for quantities, the curves, and the data sets, with legible font and size.

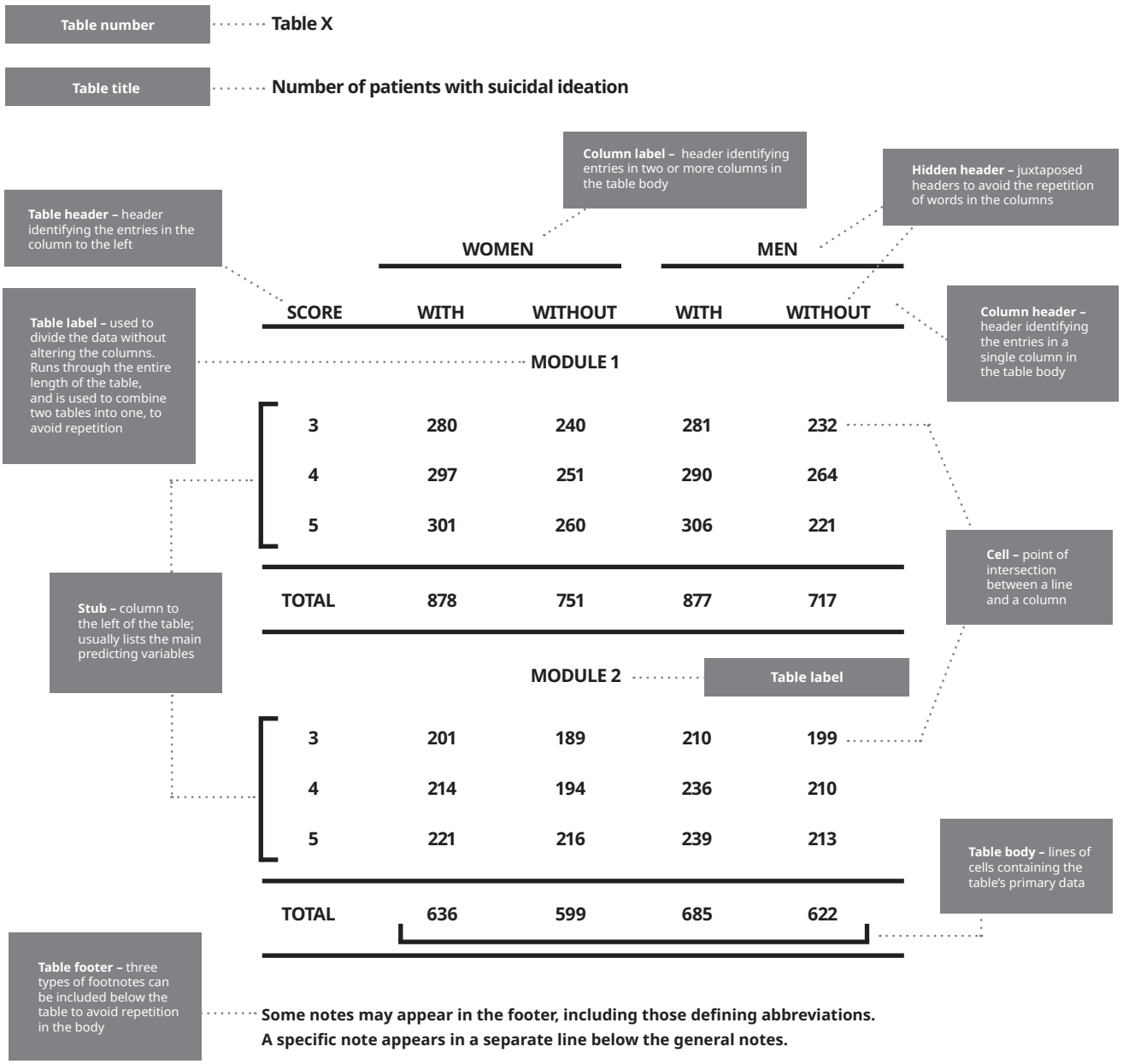
As for **schemes**, they correspond to the visual representation of abstract or immaterial concepts that relate to each other, forming a symbolic figure. Scientific and/or material schemes are used for investigative and theoretical purposes, and respond to a demonstrative or hypothetical objective to theorize about some aspect of science or logic.

Tables represent an objective way of presenting large amounts of data and communicating the results of studies. Thus, among other requirements, they must have clear and concise legends; data divided into categories; sufficient spacing between columns and rows; specification of units; and legible font and size.

Additionally, they must be cited in the text and numbered consecutively (i.e., 1, 2, 3) in the order in which they are mentioned, and must be provided in an editable format (Word or Excel). They can be included at the end of the manuscript's file or sent individually, but not both.

When the researcher plans to include tables in the manuscript, s/he must determine: 1) the details necessary for readers to understand the discussion; 2) a sufficient set of statistics that is capable of supporting the inferential methods used; 3) how to define it so that it can be understood in isolation.

For the preparation of tables, try to limit their content to essential materials: those with excess information become less effective. Although supplementary tables may be longer and more detailed than text tables, their role is to be di-



rectly and clearly related to the content and to be an integral part of the text.

The basic components of the table prototype are shown above, including the technical terms, the location of the items, and the definition of each element.

The layout must be logical and easily understandable to the reader. Table entries with data comparisons must be close to each other. Following this principle, in general, different indices (e.g., means, standard deviations, sample sizes) have to be segregated into different parts or lines.

Tables are designed to show something specific. For example, those with the purpose of communicating quantitative information will be effective only when they seem obvious to the reader at a glance. The same data can be organized in different ways, in order to emphasize the different characteristics of each datum.

An informational table complements the text, rather than duplicating it, guiding readers to what to look for: if it is necessary to search for each item in the text, then the table will be unnecessary. Likewise, if additional tables are included in supplementary online files, they must be mentioned briefly in the article's printed version. Additionally, tables designated as "supplementary materials" must be accompanied by enough information to be understood by themselves.

Expressions such as "the table above", "below", or "the table on p. 45" should be avoided, because the tables' placement is not defined until the layout has been designed.

Following the logic of objectivity, authors may consider combining tables with repeated data. In general, identical

columns and rows do not appear in two or more tables in the same article. The presentation of all tables in the manuscript should be consistent to facilitate comparisons, using similar formats and titles and the same terminology (e.g., response time or reaction time – not both).

Examples of figures and tables can be obtained in the manual of the Public Health School of the University of São Paulo (FSP-USP). Another suggestion is the Manual of the American Psychological Association (APA).

2. SUBMISSION

Before submitting an article, all authors must have approved the final version to be submitted. The full manuscript or data must not have been previously published (except in summary or pre-printed form) or be currently under evaluation for publication elsewhere.

All manuscripts must be sent to jmrr@cremesp.org.br, indicating a valid email address of all authors.

To ensure transparency, the authors are expected to declare other articles that have used the same dataset or sample, in addition to identifying tables, figures and/or data that have been published in another journal. The authors are responsible for obtaining permission from the copyright owner(s) if they decide to reproduce and/or modify any previously published material.

At the end of the submission, the individual designated in the system as the "corresponding author" (responsible for the intermediation with the editorial team of JMRR) will receive an email notification stating that the text was received by the Editorial Office. If this does not happen, it means that there was a problem during the submission process, which should be informed to JMRR. Any manuscripts that do not comply with these guidelines will be returned to the author for correction.

Once processed, the submission will receive a number. Throughout the process, the status of the article will be available to the corresponding author by email, who is allowed to upload the entire submission (except the cover letter) in a single file when sending it, with numbered pages, in Word or PDF.

Tables and figures can be placed in the body of the manuscript or presented separately at the end. The authors must ensure that all elements are clearly legible to editors and reviewers.

EDITORIAL POLICIES

Authorship

To qualify as an "author", the individual must have participated sufficiently in the study, assuming public responsibility for all or part of the content after it has been submitted, approved and published. "Participating" here means making substantial intellectual contributions to the study, in the form of: 1) conception and design and/or acquisition of data and/or data analysis; and 2) writing the article (or parts of it) and/or critically reviewing it contributing with important intellectual content.

All individuals who meet the criteria for authorship must be nominated as "authors". If the authorship is being assigned to a group, all of its members must meet the criteria described above.

Additionally, being an author also means agreeing to answer questions pertaining to the completeness of the article so that issues related to the accuracy or integrity of any part of it may be properly investigated and resolved.

Any changes in authorship after the initial submission, such as additions, exclusions, and reordering, must be approved in writing by the group, which may indicate the contribution of each author at the end of the article if they so wish.

When approving and finalizing the submission of a manuscript, JMRR assumes its recognition and acceptance, committing itself to reviewing and correcting the articles and ensuring that all individuals who meet the criteria for authorship are included on the title page, as well as that the submitted version is the one approved by all.

Disclosure of Financial Interests and Potential Conflicts of Interest

JMRR requires the authors of any type of articles to fully disclose possible conflicts of interest, including financial ones, in addition to specifying their nature. This is the responsibility of the entire group, under penalty of the article being returned, delaying the evaluation process.

Disclosure includes direct or indirect financial or personal relationships, as well as interests and affiliations that are relevant to the subject of the manuscript established in the last two years, or even those expected in the foreseeable future. It also covers (but is not limited to) grants or funding, affiliations, intellectual property/patents (in preparation, filed or granted), inventions, remuneration, consultancy and royalties.

Financial: financing and other payments, goods and services received or expected by the authors related to the subject of the study, or granted by an organization with an interest in the results.

Affiliations: being an employee, on the advisory board or a member of an organization with an interest in the results.

Intellectual property: patents or trademarks owned by someone or his/her organization.

Personal: friends, family, relationships and other close personal connections.

Ideological: beliefs or activism, for example, political or religious, that are relevant to the study.

Academic: competitors or someone whose study is criticized.

If an author has "nothing to declare", this should be made explicit.

The sources of financing, such as research grants from private and public institutions (development agencies), must be indicated at the end of the article.

Ethical Considerations

The authors should consider all ethical issues that are relevant to their research.

For example, in the Materials and Methods section, the institutional and/or licensing committee that approved the experiment(s) should be identified, confirming that the study was carried out in accordance with the relevant guidelines and regulations.

Studies involving human subjects must include detailed information about the informed consent process, including the method(s) used to assess the participants' ability to consent, the protection criteria included in the study, and relevant follow-up data, when available.

Among the ethical guidelines, JMRR follows those established by the Ministry of Health of Brazil, through the CEP/Conep system (CNS Resolution Nº 466/2012), and the ICMJE, although it reserves the right to take alternative actions if necessary, including contacting the authors' institution, funding agency, or other appropriate research authority.

Studies involving human beings must be submitted to the Research Ethics Committees (CEPs) of the institution where they will be carried out, and if necessary, to the National Research Ethics Commission (Conep), through the "Plataforma Brasil", an electronic system created by the Federal Government of Brazil to systematize the receipt of research projects by CEPs across the country. When analyzing and deciding, the CEP/Conep system becomes co-responsible for ensuring the protection of the participants.

When reporting experiments on animals, the authors should indicate that the institutional and national guidelines for the care and use of laboratory animals, such as ARRIVE, have been followed.

JMRR takes its responsibility for scientific integrity seriously, and will verify any allegations of misconduct, such as plagiarism, duplicate submission or publication, fabrication or falsification of data, unethical treatment of research subjects, authorship disputes, and undisclosed conflicts of interest.

Any corrections to the literature will be treated on a case-by-case basis, through errata or retractions.

Peer review

All submissions, with the exception of editorials, comments and correspondence, will be subject to peer review or refereeing, a process used in the publication of scientific articles that consists in passing them on to the evaluation of one or more more specialists with an advanced degree and expert level of knowledge on the subject addressed by the author.

These evaluators are supposed to make comments and suggest revisions, with the aim of contributing to the quality of the publication. JMRR excludes reviewers who work at the same institution or with any other conflicts of interest. The identity of the individual reviewers remains confidential to all parties except JMRR's scientific and technical editors.

Submission processing

After the article has been submitted, it is firstly analyzed by the editors of JMRR. If approved, it is passed on to external reviewers, after which the editorial decision and the reviewers' suggestions/corrections will be sent by email to the corresponding author.

In case the opinion of the reviewers differs, the editors reserve the right to invite an additional reviewer. Opinions may decide for accepting or rejecting the study, and suggest small or major changes. Rejected studies may be resubmitted if the authors believe that an important reformulation has been carried out or new findings have been included, in which case they must resubmit the article, including a letter to the Editor-in-Chief, justifying the resubmission. It will be up to the editorial board to accept it or not.

In the final phase, the article will be submitted to proofreading, the author being responsible for making final changes as requested and approving the final version.

JMRR will guide authors who submit their articles in Portuguese on English translation services.

After final acceptance, the article will be published online, becoming citable through the number assigned to the digital object identifier (DOI). The final written version will be published according to the journal's periodicity, in an issue selected by the Editorial Board, which will also define its circulation.

The authors are responsible for carefully reviewing the entire article in relation to precision. Once a corrected article is published online, additional corrections cannot be made without an errata.

Registration of Clinical Trials

As a condition for publication, in accordance with ICMJE, JMRR requires prospective registration of all clinical trials. Therefore, the name of the study, the name of the repository and the registration number must be included at the end of the abstract.

Observational-only studies will not require registration.

Return of articles and printing policies

If the editors of JMRR consider that the study did not reach the degree of interest or quality expected and/or is not in accordance with the journal's editorial and/or scientific standards, the manuscripts may be returned without undergoing an external revision. The editorial rejection has the purpose of speeding up the editorial process and allowing the articles to be reviewed and submitted to another scientific journal.

Returns at the discretion of the authors, in general, will not occur – exceptional cases will be assessed individually.

JMRR's cover art is chosen according to the relevance of one of the articles included in the current issue or images from the History of Medicine.

JMRR
JOURNAL OF MEDICAL RESIDENT RESEARCH

SUMMARY

IN THIS ISSUE

Number 2, 2022

This is a brief summary of the articles published in this volume of the *Journal of Medical Resident Research*

68Ga-PSMA PET/CT in Triple Negative Metastatic Breast Cancer

68Ga-PSMA is a radiopharmaceutical originally developed as a marker for prostate cancer, as it binds to a protein known as prostate-specific membrane antigen (PSMA). Although this radiopharmaceutical has become increasingly used in prostate cancer, researchers have innovated by using it as a marker for other tumors. In this article, researchers used 68Ga-PSMA in patients with triple-negative breast cancer, who lack diagnostic and therapeutic options. This line of research may eventually pave the way for new targeted therapies for this disease, according to the principle of theradiagnosis.

Hepatitis C virus infection in patients with diabetes mellitus type 2: a seroprevalence study

The association between hepatitis C virus infection and type 2 diabetes mellitus is explored in this seroprevalence study in diabetic outpatients. This is an important public health issue, as both diseases seem to interfere with the course of each other. Because they are chronic conditions, their clinical course is most of the time silent, resulting in serious complications if adequate treatment is not instituted early. For this reason, it is essential to study this topic so that public policies can be planned to minimize the risk of unfavorable outcomes.

Pleural solitary fibrous tumor: a case report

Pleural solitary fibrous tumors are rare soft tissue neoplasms associated with great diagnostic difficulty. Due to its insidious course, it is usually oligosymptomatic, which makes its detection difficult. In addition, the lack of knowledge about this disease, due to its rarity, represents another barrier to diagnosis. In addition, the lack of standardized treatments also results in clinical challenges when managing these patients. This article reports a case of solitary fibrous pleural tumor and describes the proposed treatment. The authors also discuss the topic based on the available literature. With this, the authors seek to disseminate knowledge about this pathology, aiming to positively impact patient care.

Neuroscientific Update on the Mechanisms of Action of Acupuncture in Chronic Pain

Acupuncture emerged thousands of years ago in China and has established itself as one of the main practices of traditional chinese medicine. In recent decades, it has become popular in the West, and is now a widely used treatment for chronic pain. However, the mechanisms of action of acupuncture, from the perspective of Western science, are still unclear. The authors of this narrative review, who are experts and pioneers of acupuncture in Brazil, guided a medical student to discuss this topic. Recent studies on the mechanisms of the analgesic effect of acupuncture on chronic pain were discussed, including molecular aspects and targets in the nervous system.

Identification of key elements for improving primary care for cancer patients using the ACIC questionnaire

Primary Health Care (PHC) has consolidated itself as an important component of the Brazilian Health System (SUS), having a fundamental role in the management of chronic diseases, especially thanks to its longitudinal nature and proximity to the system user. Cancer, in turn, is now considered a chronic disease, thanks to advances in early diagnosis and treatment, which have increased cancer patients survival. In this context, PHC started to play an essential role in the follow-up of these patients. In this study, the authors assessed the quality of PHC offered to cancer patients in the city of Votuporanga, Brazil, by using a tool originally developed to assess the quality of primary care for patients with chronic disease, the Assessment of Chronic Illness Care (ACIC) tool. Their aim was to carry out a diagnosis of the quality of PHC offered to oncologic patients, identifying strengths and aspects that need improvement.

JMRR
JOURNAL OF MEDICAL RESIDENT RESEARCH

EDITORIAL

Consolidating a project to awaken the scientific spirit at the beginning of physicians' journeys

The second issue of the Journal of Medical Resident Research (JMRR) consolidates an ambitious project that began in 2019 at the Regional Council of Medicine of State of São Paulo (Cremesp), the medical board of the State of São Paulo, Brazil, inheriting the legacy of the Revista do Médico Residente, launched by the Medical Board of the State of Paraná in 1999. By honoring this legacy, Cremesp values the gold-standard method of training specialist physicians: the medical residency. More than that, it underscores the notion that medical residency is a moment of professional immersion in medical knowledge, according to the tripod of teaching, clinical practice and research. The latter often ends up being overshadowed during training, largely due to the barriers that exist to publish scientific work.

Indeed, for many physicians at the beginning of their careers, getting their manuscript accepted by a journal can seem otherworldly. Furthermore, the process itself is intimidating as the researcher must submit their work to the judgment of demanding reviewers and editors. Many manuscripts must be revised numerous times, which requires resilience. With JMRR, it is no different, as the reviewers and the editorial board value scientific rigor. However, this journal has an additional purpose compared to conventional scientific journals. JMRR offers a didactic environment that supports authors in the long process of reviewing their manuscripts, until the reviewers' requirements are met. The journal also offers translation resources to open the doors of the world to these authors. The goal, above all, is to learn. The final result is to produce an excellent manuscript.

Consolidating this project makes Cremesp very proud and demonstrates to society that the board considers science to be a pillar of its activities. Thus, more than just being consumers of new evidences, physicians must cultivate a critical spirit and scientific curiosity, in order to also be knowledge producers. We invite everyone to read JMRR hoping to awaken this interest in those who are still in the contemplative phase and need a stimulus to do research at the beginning of their careers. In addition, reading this journal is also an opportunity to critically review its articles, contributing with new conclusions, comments and/or hypotheses. By doing so, a virtuous cycle of knowledge exchange that results from scientific endeavor is created.

It is with these words of encouragement that we publish the second issue of JMRR. Doing science is not easy, especially in the context of medical residency, with so many duty hours, so much tiredness and so many sacrifices the resident must make. However, the feeling of reward for contributing to the advancement of science is immeasurable. Count on JMRR and on Cremesp to overcome these obstacles and to continue on this journey. Enjoy reading this issue!

Douglas Kamei, Edoardo Filippo de Queiroz Vattimo
Editors of the Journal of Medical Resident Research

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JMRR
JOURNAL OF MEDICAL RESIDENT RESEARCH

EDITORIAL

Affectivity and Science

"But, in this context, affectivity must be seen as a refinement of training that, at some point, will make a difference in the life of the medical professional, because between two equally trained people, the more affectionate one will always prevail. To deny this is to believe in professional bad luck."
(Prof. J.J. Camargo)

The defense of science and ethics is one of the missions of Cremesp, the medical board of the State of São Paulo. And it is with renewed joy and pride that Cremesp releases the second issue of its scientific journal, the Journal of Medical Resident Research (JMRR), which will soon be available on the website: jmrr.cremesp.org.br

I feel rewarded and extremely proud for having left the former Revista do Médico Residente (RMR), which I founded in 1999, as a legacy now in the form of JMRR. This endeavor still lingers on thanks to the outstanding competence and industriousness of JMRR's editor-in-chief, Edoardo Filippo de Queiroz Vattimo, to the significant participation of Douglas Kamei, to the emotional and technical support from Mrs. Concília Ortona Reyes, from Cremesp's Communication Department and, by extension, to the entire Board, whose support now materializes as this relevant scientific publication made available to all of Brazil and the world.

JMRR aims to offer a seminal opportunity to medical residents and students in Brazil to participate in the universe of academic research and scientific publications, by having the possibility to have their articles reproduced in a bilingual scientific journal of extreme editorial rigor.

In this issue of JMRR, we will find up-to-date publications on relevant scientific topics with the effective participation of medical residents, students, nurses and medicine professors from different universities and teaching hospitals of excellence in the context of healthcare in Brazil.

Last but not least, I would like to wrap up with a message that I mentioned as the epigraph of this editorial, which I believe should always appear in scientific publications and during the training of medical residents and students: we must never neglect the ethics, humanism and affection of the doctor-patient-family relationship because the patient is the raison d'être of medicine.

Professor Dr. João Carlos Simões
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JMRR
JOURNAL OF MEDICAL RESIDENT RESEARCH

EDITORIAL

Science, always a priority for Cremesp

Cremesp, the Medical Board of the State of São Paulo, defends science.

We made it clear on various occasions and scenarios, such as during the height of an unprecedented pandemic, when we published the book *Manual de Melhores Práticas na Covid-19* (Best Clinical Practices Manual in Covid-19, unavailable in English). At that time, we held the stance of defending the best practices based on robust medical literature. Likewise, we provided doctors free access to 5-Minute Consult, an evidence-based platform for clinical decision-making. We also made available the MEDLINE Complete platform, which provides access to scientific articles published in the most renowned national and international peer-reviewed journals. By following this tradition, now we have the unique satisfaction of publishing the Journal of Medical Resident Research, a scientific publication now in its second issue.

JMRR is intended to consolidate the vocation of this Institution to defend science. It is impossible to see the young scientists, their work and the results presented in this and in the previous issue without being proud of the quality of the manuscripts, now published articles. These are researchers who, despite their still-increasing experience, are able to navigate with easiness in the universe of scientific methodology, under the careful guidance of their mentors. In addition, all articles underwent peer review, as required by major international scientific journals, such as Nature, JAMA, New England Journal of Medicine, and so many other publications known for their rigidity and reliability. It is important to emphasize that this was only possible by the silent, but selfless contribution of scientific reviewers, who dedicate themselves to this task having their academic satisfaction as their only motivation.

Just to have an idea of the rigor expected for the preparation of manuscripts, the JMRR's author's guide requires international quality standards to be followed, such as EQUATOR Reporting Guidelines (Enhancing the Quality and Transparency of Health Research), an organization that brings together researchers, medical journal editors, reviewers, developers of scientific guidelines, among others. For this issue of JMRR, we sought to select articles from different categories, including original research, case reports and literature reviews.

It is also noteworthy that medical education is an essencial aspect of medicine for Cremesp, as the board has chosen the didactic approach as a cornerstone of its first scientific journal, which is dedicated to physicians in training. Therefore, JMRR is not just a vehicle to publish scientific articles, rather, it is a didactic research project aimed at improving the scientific skills of early career doctors.

Finally, but far from being unimportant news, JMRR is now indexed on EBSCO's platforms, which is certainly an important step in the journal's trajectory. More than that, it is a recognition of the merits of this project and of the work of the selfless authors who contributed to this publication.

That's what we do.

Edoardo Filippo de Queiroz Vattimo
Editor-in-chief

Irene Abramovich
President of Cremesp

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68GA-PSMA PET-CT IN TRIPLE NEGATIVE METASTATIC BREAST CANCER

PET-CT com PSMA-Ga68 no Câncer de Mama Triplo Negativo Metastático

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ABSTRACT

Objectives: Triple negative breast cancer lacks specific markers and targeted treatments. In this context, the objective of this study is to evaluate, through case studies, the behavior of 68Ga-PSMA PET-CT to detect metastases in patients with triple negative breast cancer. **Methods:** Six patients with metastatic triple-negative breast cancer at initial diagnosis or who presented metastases due to disease progression were selected and evaluated. The participants underwent 68Ga-PSMA PET-CT, and the lesions were classified regarding their anatomical location and in grades ranging from 0 to 5 according to the intensity of tumor uptake. **Results:** As for the distribution of each type of lesion, one patient had local recurrence with grade 3 uptake; one patient had locoregional lymph nodes showing grade 4 uptake; two patients had distant lymph nodes, one with grade 2 uptake and the other with grade 3 uptake; four patients had bone metastases, two of them with grade 2 uptake and two with grade 3 uptake; three patients had lung metastases (one with grade 1 uptake, one with grade 2 uptake and one with grade 3 uptake); one patient had liver metastases with grade 3 uptake. One patient did not have any detectable radiopharmaceutical uptake (grade 0). **Conclusion:** This study demonstrated that 68Ga-PSMA, although originally described as a prostatic marker, is taken up by neoplastic lesions associated with triple negative breast cancer.

Keywords: PSMA, 68Ga-PSMA, triple-negative breast cancer, PET-CT, metastatic cancer.

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INTRODUCTION

Breast cancer is one of the most common malignant neoplasms affecting women all over the world. In Brazil, 74,000 new cases of this neoplasm are estimated for each year of the three-year period comprising 2023-2025[1]. The main challenge for the treatment of the disease is tumor heterogeneity, since even tumors with similar histological types, stages and degrees of differentiation may have different outcomes[2]. Breast neoplasms are divided according to the presence or absence of estrogen, progesterone and HER2

protein receptors. For tumors with positive hormone receptors, hormone therapy is already well established. Likewise, targeted therapies directed against HER2 receptors are used to treat HER2 positive tumors[4-6]. However, one of the most important clinical challenges lies in patients whose tumors do not have hormone or HER2 receptors, the so-called triple negative breast cancer[3]. In these cases, the diagnostic and therapeutic difficulty is due to the lack of cell surface markers that can be used as targets for the diagnosis and treatment of the disease.

Positron Emission Tomography-Computed Tomography (PET-CT) is a hybrid exam that aids diagnosis and treatment in oncology. It consists of a combination of metabolic images (PET), obtained by administering intravenous radiopharmaceuticals with affinity to tumor tissue, with tomographic images (CT), acquired by an X-ray-emitting tomograph. The clinical use of PET-CT has become more widespread with the use of fluorodeoxyglucose F18 (FDG), a glucose analogue radiopharmaceutical that accumulates in sites with high metabolic activity, such as some tumors[7]. Subsequently, the technique evolved by using newer radiopharmaceuticals directed at specific molecular targets for certain types of tumors.

As of 2013, the first studies on 68Ga-PSMA PET-CT were published[8]. 68Ga-PSMA is a radiopharmaceutical marked with the radioisotope gallium 68 that binds to a protein known as prostate-specific membrane antigen (PSMA). This radiopharmaceutical has been increasingly used in prostate cancer[9]. However, despite being known as a prostate-specific antigen, PSMA is not exclusive to the prostate, as it is overexpressed in the neovasculature of several other tumors, including neoplasms of the breast, central nervous system (glioblastomas), mouth (squamous cell carcinoma), salivary glands (cystic adenoid carcinoma), bladder, stomach, large intestine, pancreas and kidneys[10-15].

As for breast tumors, in a study with 315 patients with invasive mammary carcinoma of no special type or invasive lobular carcinoma, 60% of the lesions showed PSMA-positive endothelium, with higher expression in hormone receptor-negative tumors[16]. This finding is interesting, as the growth and progression of breast tumors are accompanied by an increase in neovascularization, a phenomenon that is even more evident and intense in triple-negative tumors[17]. As they do not have surface molecules to act as targets for diagnostic and therapeutic techniques, angiogenesis could be used as a diagnostic and prognostic marker and potentially, as a therapeutic target for these tumors[18]. In this context, 68Ga-PSMA PET-CT could be a useful tool to make this approach feasible, given the avidity of PSMA for the neovasculature of these neoplasms.

Once this clinical use of PSMA is established, possibilities may arise for targeted therapy with another radioisotope, lutetium-177, which, when used as the radiopharmaceutical 177Lu-PSMA, can specifically target tumor cells, destroying them through the emission of beta radiation[18-20]. This strategy follows the so-called teragnostic concept, in which radiopharmaceuticals directed to specific tumor targets are used in image acquisition (e.g. 68Ga-PSMA) to select patients who could benefit from therapies directed towards these same targets (e.g. 177Lu-PSMA)[21]. This technique would therefore be of great value for patients with triple-negative breast cancer, since these tumors lack therapeutic options[18]. Furthermore, it could help in prognostic estimation and minimize treatment side effects[21].

Considering this rationale, this study aims to evaluate the use of 68Ga-PSMA PET-CT in patients with metastatic triple negative breast cancer.

METHODS

This is a descriptive cross-sectional study, which included female patients over 18 years of age with triple-negative breast cancer and metastatic disease, confirmed by conventional radiological imaging (distant lymph nodes affected and/or distant metastases). Six patients undergoing follow-up at Conjunto Hospitalar de Sorocaba or at Santa Casa de Misericórdia de Sorocaba were recruited between 2019 and 2021. They underwent 68Ga-PSMA PET-CT scans at a nuclear medicine center in Sorocaba, Brazil.

In all stages of this study, ethical principles for human studies were respected, according to Resolution 466/2012 of the Brazilian National Health Council (Conselho Nacional de Saúde). The institution Research Ethics Committee approved the study under number 30165820.6.0000.5373.

Image acquisition

A Siemens Biograph™ TruePoint™ PET-CT scanner was used to obtain images from the skull to the root of the thighs one hour after the administration of a mean dose of 3.33±0.2 mCi (123.58 Mbq) of 68Ga-PSMA. Acquisition time was three minutes per bed-position. The scan did not require any preparation.

Image analysis

The images were analyzed by an experienced nuclear medicine physician and a radiologist. Lesions were classified according to their location and intensity of tumor uptake in standardized uptake value (SUV) units.

Lesions were classified in four groups according to anatomical location: 1) local recurrence; 2) localized lymph node lesion (axillary, supraclavicular, internal mammary or more than one locoregional chain); 3) distant lymph node lesion (lymph nodes that do not fit the classification of localized lymph node lesion); 4) metastatic disease (bone metastases and non-bone visceral metastases).

As for intensity of tumor uptake, lesions were classified in five different grades: grade 0 – absent tumor uptake or up to 25% of the mean hepatic SUV; grade 1 – tumor uptake between 25% and 50% of the mean hepatic SUV; grade 2 – tumor uptake between 50% and 100% of the mean hepatic uptake; grade 3 – tumor uptake greater than the mean hepatic uptake but less than the mean splenic uptake; and grade 4 – tumor uptake greater than the mean splenic uptake.

RESULTS

Patients differed according to the extent of metastatic disease. Table 1 presents clinical and demographic data for each patient, as well as their lesions showing 68Ga-PSMA uptake. Thus, four had bone involvement among all patients, three had lung involvement and one had liver involvement. Figure 1 shows the images of lung, liver and bone lesions with 68Ga-PSMA uptake.

TABLE 1 - Clinical and demographic data of patients that underwent 68Ga-PSMA PET-CT, and sites of lesions showing radiopharmaceutical uptake

PATIENT	AGE	PREVIOUS SURGERY	PREVIOUS CHEMOTHERAPY*	PREVIOUS RADIATION THERAPY	LESIONS WITH 68GA-PSMA UPTAKE
1	60	Yes	Yes	No	Bone metastasis
2	47	No	Yes	No	Local recurrence, lung metastasis, locoregional and distant lymph nodes
3	48	Yes	Yes	Yes	Bone and lung metastases, distant lymph nodes
4	66	No	Yes	No	Bone metastasis
5	39	No	Yes	Yes	-
6	50	Yes	Yes	No	Bone, lung, liver and liver metastases

* Patient 1 used Paclitaxel (PCT)/Capecitabine (CB) with Pamidronate, Gemcitabine (GCT) with Pamidronate and CB; patient 2 used vinorelbine (NVB); patient 3 used PCT; patient 4 used PCT/CB; patient 5 used PCT/CB; patient 6 used Doxorubicin + Cyclophosphamide for four Cycles (4XAC) and PCT.

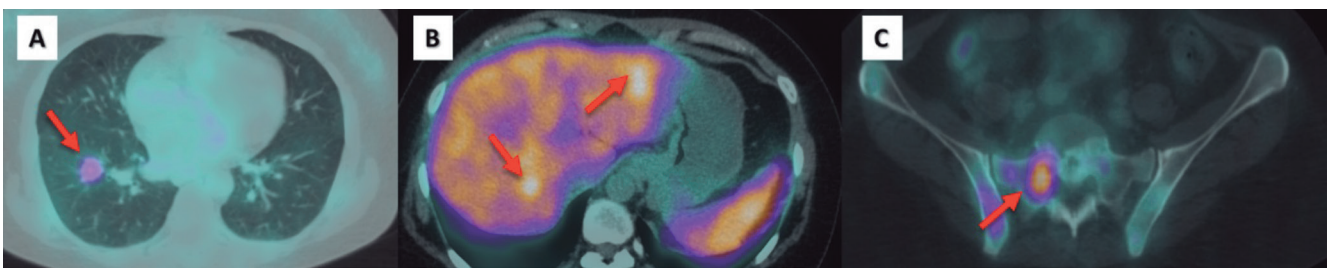

Figure 1. 68Ga-PSMA uptake in metastatic lesions, indicated by the red arrow: lung (Fig.1A), liver (Fig.1B) and bone (Fig.1C) metastases.

The mean SUV for all lesions, regardless of location, was 7.0, with the highest uptake intensity in locoregional lymph nodes (mean SUV = 13.9) and the lowest in bone and lung lesions (mean SUV = 3.0). Table 2 details the mean SUV observed in each type of lesion, as well as the corresponding number of cases.

The mean hepatic SUV used to classify the intensity of tumor uptake, as described in "Methods", was 5.9 (± 0.59), while the mean splenic SUV was 8.9 (±1.7). Only one patient did not have any lesion with 68Ga-PSMA uptake, so her case was classified only according to tumor uptake intensity (as grade 0) rather than regarding anatomical location. The number of cases with lesions in each anatomical location and their intensity of tumor uptake are listed on

TABLE 2 - Mean SUV observed in each type of lesion and corresponding number of cases

LESION TYPE		NUMBER OF CASES (% OF PATIENTS)	MEAN SUV (MINIMUM- MAXIMUM)
Local recurrence		1 (16.7%)	7.1 (7.1 - 7.1)
Locoregional lymph nodes		1 (16.7%)	13.9 (13.9 - 13.9)
Distant lymph nodes		2 (33.3%)	6.2 (3.8 - 8.5)
Distant metastases	Bone	4 (66.6%)	5.35 (3.0 – 7.6)
	Liver	1 (16.7%)	7.6 (7.6- 7.6)
	Lung	3 (50%)	6.36 (3.0 – 8.5)

Note: anatomopathological confirmation of lesions was not performed.

Table 3. Figures 2 and 3 illustrate the aspect of tumor uptake in different patients, compared to liver uptake.

DISCUSSION

Most patients had lesions with high 68Ga-PSMA uptake, including lymph node, lung, bone and liver metastases. Although it was originally described as a marker for prostate cancer, recent studies have reported the presence of the PSMA protein in the neovasculature of other solid tumors[10-15,18]. The avid 68Ga-PSMA uptake by metastatic triple negative breast cancer lesions in this study corroborates previous findings of PSMA overexpression in this type of breast cancer. As angiogenesis is essential in the pathophysiology of many types of metastases[22], especially in triple negative tumors[17], it is believed that the overexpression of PSMA may be a marker of metastatic disease[18].

This is the first study of its kind in Brazil. International literature on the subject is also still scarce. In a systematic review, Bertagna *et al.*[23] identified only 12 papers published on the subject, 11 of which were case reports, and, of these, only eight had breast cancer as a final diagnosis[16,24-30]. Interestingly, two of these cases were incidental findings of synchronous histologically confirmed malignant breast tumors in patients who underwent 68Ga-PSMA PET-CT during workup of prostate cancer[24,25]. The findings of this study, therefore, are in line with the hypothesis that metastatic triple negative breast cancer lesions indeed show positive 68Ga-PSMA uptake.

There are only two published studies that evaluated the performance of 68Ga-PSMA PET-CT in detecting lesions associated with breast cancer. Sathekge *et al.*[31] evaluated 19 women with breast cancer aged between 25 and 66 years, regardless of the type of disease, including cases of locoregional recurrence, metastatic disease, and progesterone receptor positive and negative tumors. The authors reported a detection rate of 84% of all lesions, with no statistically significant difference to the detection rate observed with FDG PET-CT. Another retrospective study by Medina-Ornelas *et al.*[32] compared the detection rates of 68Ga-PSMA PET-CT and FDG PET-CT, reporting a sensitivity of 84% and a specificity of 91.8% for 68Ga-PSMA PET-CT versus a sensitivity of

TABLE 3 - Number of patients presenting each type of lesion according to anatomical location and tumor uptake intensity (in SUV) compared to hepatic and splenic uptake.

	TUMOR UPTAKE INTENSITY IN SUV (LESION/HEPATIC OR SPLENIC)					
ANATOMICAL LOCATION	GRADE 0 (0 TO UP TO 1.4)	GRADE 1 (1.4 – 2.9)	GRADE 2 (2.9 – 5.9)	GRADE 3 (5.9 – 8.9)	GRADE 4 (> 8.9)	TOTAL
Local recurrence	1	-	-	1	-	1
Locoregional lymph nodes	1	-	-	-	1	1
Distant lymph nodes	1	-	1	1	-	2
Bone metastases	1	-	2	2	-	4
Lung metastases	1	1	1	1	-	3
Liver metastases	1	-	-	1	-	1

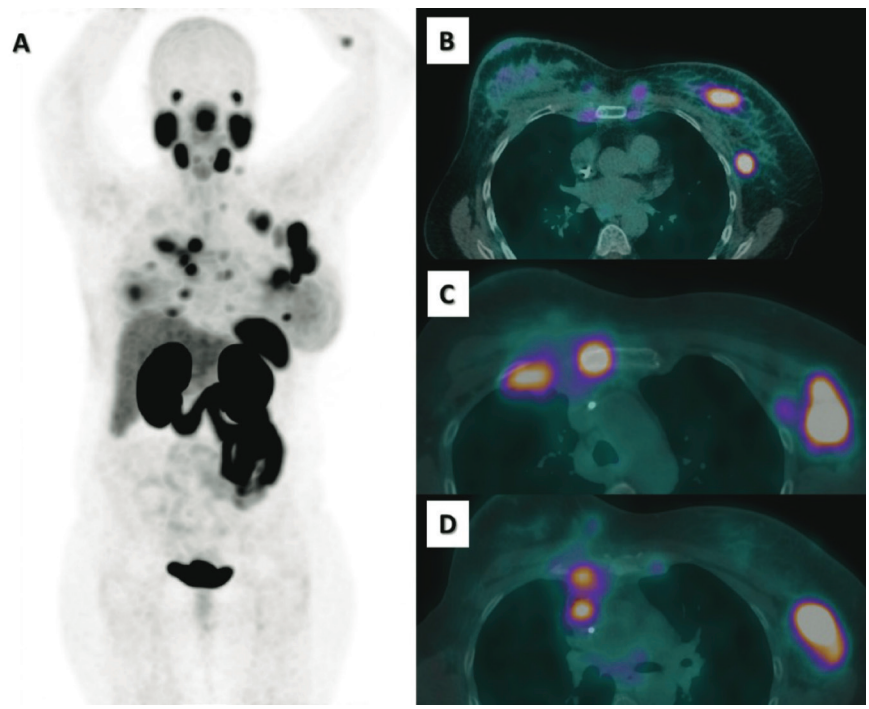

Figure 2. Maximum intensity projection (MIP) full-body images showing lesions with 68Ga-PSMA uptake at higher intensity compared to liver uptake (Fig. 2A). Tracer uptake can be observed in the breast and in axillary lymph nodes (Fig. 2B), in the sternum (Fig. 2C) and in anterior mediastinal lymph nodes (Fig. 2D).

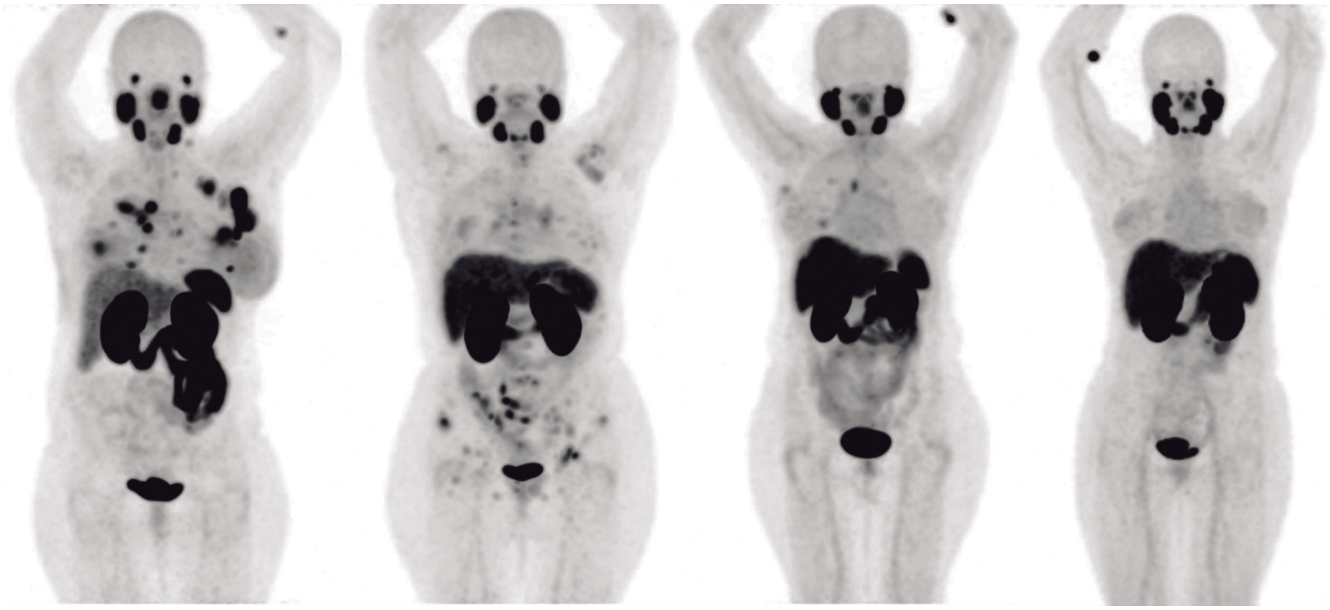

Figure 3. Aspect of 68Ga-PSMA uptake, compared to liver uptake, in MIP images of different patients

99.2% and a specificity of 93.6% for FDG PET-CT. Although that study included patients with different types of breast cancer, it divided them according to the molecular type of the tumor. Interestingly, a statistically significant lower detection rate with 68Ga-PSMA PET-CT compared to FDG PET-CT was observed in patients with luminal A and luminal B HER2 negative subtypes, with no difference for luminal B HER2 positive, HER2 overexpressing, and triple negative subgroups. In addition, all lesions identified by FDG PET-CT in patients with triple negative tumors were identified by 68Ga-PSMA PET-CT. These findings reinforce the importance of approaching breast cancer as a heterogeneous disease, not only from a clinical point of view, but also from a molecular standpoint. Considering such heterogeneity, triple negative breast cancer seems to have a unique profile of PSMA expression, which is up to 4.5 times greater in these tumors than other types of breast cancer[16], possibly due to a more intense angiogenesis.

Another issue that must be discussed is the possible difference in PSMA expression by metastases compared to primary and locoregional lesions. In the study by Sathekge *et al.*[31], the mean SUV found in metastases was significantly higher than the SUV found in primary lesions and in local and lymph node recurrences. This finding is consistent with an immunohistochemical study by Kasoha *et al.*[33], which reported higher PSMA expression in metastatic lesions compared to their respective primary lesions. However, this finding was observed only in the neovasculature of the lesions, but not in tumor cells. This reinforces the hypothesis that PSMA is more relevant for the pathophysiology of metastatic disease than for the primary tumor, possibly due to its role in tumor neoangiogenesis. It is important to consider, however, Medina-Ornelas *et al.*[32] did not observe this finding, possibly due to differences in the study design compared to the work of Sathekge *et al.*[31] Elucidating this issue is crucial for the development of 68Ga-PSMA PET-CT, since it is necessary to correctly identify the patients who could benefit the most from it.

It is also necessary to discuss the possible differences in 68Ga-PSMA uptake among lesions in different organs and tissues. The study by Medina-Ornelas *et al.*[32] did not find differences in the detection rates of bone metastases using 68Ga-PSMA PET-CT compared to FDG PET-CT, regardless of the tumor subtype. Hence, the differences observed in the detection rates of luminal A and luminal B HER2-negative subtypes were no longer found. This finding, however, may have occurred due to the low statistical power of the study, and due to the fact that this was not its main objective. The study by Sathekge *et al.*[31], in turn, did not assess differences in 68Ga-PSMA uptake according to lesion site. Immunohistochemical studies, however, suggest that PSMA expression varies across sites, as reported by Kasoha *et al.*[33], who found a higher expression of PSMA in the neovasculature (but not tumor cells) of brain metastases, compared to bone lesions. Furthermore, an immunohistochemistry study with 92 patients by Wernicke *et al.*[13] also found a PSMA positivity rate of 74% in the neovasculature of breast cancer, which rose to 100% when only brain metastases were evaluated. Our study found a higher uptake of 68Ga-PSMA in liver metastases compared to lungs and bones, which corroborates the previous findings of lower PSMA expression in bone metastases.

Notwithstanding, this study has important limitations. Initially, the sample size was small, although only two other studies in the world analyzed larger samples. Furthermore, no comparison was made between 68Ga-PSMA PET-CT and other imaging techniques, such as FDG PET-CT, which did not allow for sensitivity and specificity analyses. The lack of another confirmatory method also did not allow to control for false-positive results, which have already been described with 68Ga-PSMA PET-CT, including non-malignant breast conditions such as gynecomastia

and pseudoangiomatous stromal hyperplasia[34,35]. Moreover, studies have already reported 68Ga-PSMA uptake by benign lesions, such as granulomas associated with sarcoidosis, Paget's disease of the bone, fibrous dysplasia, healing fractures, senile amyloidosis, among others[36,37].

Despite the limitations, this study indicates that 68Ga-PSMA PET-CT is safe and well-tolerated, showing a good uptake by breast cancer metastatic lesions. This finding, reported for the first time in Brazil, reinforces the possible role of PSMA in the pathophysiology of metastatic breast cancer, especially in patients with triple negative tumors. This study paves the way for future research on the use of PSMA as a target for treatment with radiopharmaceuticals, which can be of great value for patients with triple negative breast cancer, given the limited therapeutic options currently available for these cases[18]. This will only be possible if patients are appropriately selected, given the heterogeneity of the disease, which includes different tumor biology across subtypes, and the role of angiogenesis in disease progression. Once these points are clarified, it will be possible to envisage, according to the concept of theragnostics, the eventual use of Ga68-PSMA PET-CT imaging to select patients eligible for new targeted therapies, such as 177Lu-PSMA, which already demonstrates promising results in the treatment of prostate cancer[20].

DISCLOSURES

The authors declare that they have no conflicts of interest to disclose.

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HEPATITIS C VIRUS INFECTION IN PATIENTS WITH DIABETES MELLITUS TYPE 2: A SEROPREVALENCE STUDY

Infecção pelo Vírus da Hepatite C em Pacientes com Diabetes Mellitus Tipo 2: um Estudo da Soroprevalência

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ABSTRACT

Objectives: To evaluate the seroprevalence of hepatitis C virus (HCV) infection in diabetic patients treated at the type 2 diabetes mellitus (T2DM) outpatient clinic of the University Hospital of the Federal University of Juiz de Fora, Brazil (HU-UFJF). **Methods:** This is a cross-sectional study, in which a convenience sample of 145 patients with T2DM was evaluated. Demographic, clinical and anthropometric data were collected and testing for anti-HCV antibodies was performed. **Results:** a seroprevalence of 2.76% was found in the sample, with a 95% confidence interval of [1,07%, 6,87%]. The only other variable that had a statistically significant difference between the HCV-positive and HCV-negative groups was the waist circumference, which was greater in the HCV--positive group. **Conclusion:** Considering the potential for worse outcomes of hepatitis C when associated with T2DM, as well as worse glycemic control in HCV-infected patients, we suggest that active screening for this viral infection should be performed in patients with T2DM, through routine serology, which is feasible within the scope of Primary Care.

Keywords: Diabetes mellitus. Hepatitis C. Insulin resistance.

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INTRODUCTION

Hepatitis C is one of the most common causes of chronic liver disease worldwide[1]. It is caused by the hepatitis C virus (HCV), a member of the Flaviviridae family, the same as the dengue and yellow fever viruses. The epidemiological bulletin on viral hepatitis, prepared by the Brazilian Ministry of Health (MS) in 2021, reported a detection rate of confirmed cases of hepatitis C of 4.4 per 100,000 inhabitants in Brazil[2]. Mathematical models, in turn, estimate that 0.7% of the Brazilian population between 15 and 69 years of age is seropositive for HCV[3], while the worldwide seroprevalence is estimated at 1.4%[4].

The clinical manifestations of hepatitis C show great individual heterogeneity, and may progress, in many cases, to cirrhosis and liver cancer. As the disease usually has a long asymptomatic period, the diagnosis is often only made in advanced stages of the disease. Due to this reason, it is estimated that 80% of all individuals infected with HCV worldwide are unaware of their serological status[5].

This rate depends on testing, because in countries with more resources, where more people are tested, this number drops to 54%. On the other hand, it reaches 92% in the poorest countries[6].

The advent of treatments that allow the cure of hepatitis C led the World Health Organization (WHO) to set the goal of eradicating the disease by 2030[7]. However, one of the obstacles to treatment is indeed the identification and diagnosis of asymptomatic cases, which reinforces the need for better screening programs[6]. In Brazil, the MS currently recommends that all people over 40 years of age be tested at least once in their lifetime. Some groups at higher risk for the disease should be tested regardless of age and more frequently. This is the case, for example, of homeless people, sex workers, health professionals, and men who have sex with men, among others[8].

Previous studies have shown that the risk of HCV infection in patients with type 2 diabetes mellitus (T2DM) is higher. A meta-analysis that included 78,051 individuals reported a statistically significant odds ratio of 3.5 for HCV infection in T2DM patients compared to non-diabetic patients[9]. Other studies have also demonstrated the opposite way of association. A meta-analysis that included 34 studies identified that patients with HCV infection have a statistically significant odds ratio of 1.68 to also have the diagnosis of T2DM, compared to patients without the virus infection. Prospective studies also follow the same line, indicating a 67% greater risk of patients with HCV developing T2DM[10]. Therefore, many authors consider the association between the two diseases bidirectional[11].

The pathophysiological mechanisms by which many patients with HCV develop T2DM are not fully established[12]. Hypotheses suggest that HCV can alter insulin cell signaling, leading to resistance to the hormone and preventing it from regulating glucose metabolism[13-15]. Other possible mechanisms would be lower insulin secretion and dysregulation of hepatic glucose production[12]. Although the mechanism is unknown, it is known that patients with HCV and insulin resistance (IR) tend to present with a quicker progression to liver cirrhosis and hepatocellular carcinoma (HCC) than those without IR[16]. Furthermore, in patients with advanced cirrhosis, T2DM increases the risk of liver cancer by four to five times, leading to worse outcomes[17].

Taking into account these findings, it is possible to conclude that patients with T2DM can be considered a group with specific clinical and epidemiological characteristics regarding HCV infection, both due to the higher risk of infection and to the worse outcomes more frequently observed in this group. Thus, testing and screening strategies should consider these issues, especially considering the high number of patients unaware of their status, but who risk an eventual late diagnosis leading to worse outcomes. The present study therefore seeks to study the seroprevalence of HCV infection in diabetic patients treated at the T2DM outpatient clinic of the University Hospital of the Universidade Federal de Juiz de Fora (HU-UFJF), in the city of Juiz de Fora, Brazil. Our objective is to carry out a cross-sectional epidemiological diagnosis to contribute to future public health policies aimed at improving the diagnosis of HCV, to identify undiagnosed cases and expand treatment availability.

METHODS

This is a cross-sectional study that evaluated a convenience sample of 145 patients with T2DM, after obtaining a favorable opinion from the Research Ethics Committee (CEP) of the HU-UFJF, under Certificate of Ethical Assessment Aproval (CAAE) No. 76969417.3.0000.5133.

All patients with T2DM seen from September 2017 to March 2018 at the Endocrinology outpatient clinic of the HU-UFJF Health Care Center (HU/CAS), in the city of Juiz de Fora, Brazil, were invited to undergo a rapid screening test for HCV after their clinic appointment.

The medical chart was reviewed to gather demographic (gender and age), clinical (time since diagnosis of T2DM, levels of glycosylated hemoglobin (HbA1c), total cholesterol, HDL, LDL, triglycerides, aspartate aminotransferase/AST and alanine aminotransferase/ALT) and anthropometric (weight, height, body mass index – BMI – and waist circumference) data. Waist circumference was measured at the midline between the costal margin and the upper edge of the iliac crest, at the time of the HCV testing.

Anti-HCV antibody testing was performed using the Alere HCV kit (produced by SD-65, Republic of Korea, and imported to Brazil by Alere SA), with a diagnostic sensitivity of 99.4% and specificity of 99.7%[18,19]. This is a qualitative, immunochromatographic, single-use, disposable test that provides visual results after 20 minutes for anti-HCV antibody detection.

Microsoft Excel 2016 was used to tabulate the data and obtain descriptive statistics and the seroprevalence rate of HCV infection in the sample. The two-sample, one-tailed Student's t test was then used to compare the patients with positive serology to those with negative serology regarding clinical, demographic and anthropometric variables, considering the hypothesis that seropositive patients have worse metabolic parameters.

The seroprevalence rate obtained in the sample was then used to calculate a 95% confidence interval (CI) for an estimated seroprevalence rate in a population with similar characteristics (patients with T2DM in an outpatient setting). The Wilson score method was used for this purpose, since this is the most appropriate test for samples in which the observed proportions are small[20].

RESULTS

A total of 145 patients who underwent the rapid test for anti-HCV antibodies were included. No patient refused to be tested or sign the informed consent form, and therefore, no patients were excluded from the study. The majority of the sample was female (66.2%), and the mean age was 61 years, ranging from 49 to 73 years. HCV seropositivity was identified in 2.76% of the patients studied, with a 95% CI [1.07%, 6.87%]. The mean time since T2DM diagnosis was 10.9 years $\pm$ 8.44.

The mean HbA1c level in the total sample was 7.6% $\pm$ 1.88%. As for the lipid profile, we found a mean total cholesterol level of 174.2 mg/dL; a mean HDL level of 45.2 mg/dL; and a mean LDL level of 95.9 mg/dL. The mean triglyceride level was 170.5 mg/dL. Regarding liver enzymes, we found a mean AST level of 26.5 mg/dL and a mean ALT level of 29.5 mg/dL. The mean BMI was 31.7 kg/m2 $\pm$ 7.00.

The only characteristic that significantly differed between anti-HCV seropositive patients compared to seronega-

tive ones was the waist circumference, which was higher in the seropositive group (mean = 116.5 cm, standard deviation = 2.12 cm) compared to the seronegative group (mean = 106.4 cm, standard deviation = 14.47 cm); t(143) = 2.405, p = 0.009. Table 1 summarizes the clinical-demographic findings of the entire sample, as well as those of each group.

DISCUSSION

In this study, we found a HCV seropositivity rate of 2.76% in outpatients with T2DM (95% CI: 1.07% 0 6.87%). This finding, from the endocrinology outpatient clinic at HU-UFJF, is almost numerically twice the prevalence estimated by the WHO in the world population, which is 1.4% (reported 95% CI: 1.2%-1.5%)[4]. However, it is not possible to conclude that the populational seropositivity rate in similar patients with T2DM is higher

TABLE 1 - Clinical and demographic characteristics of the total sample of patients with type 2 diabetes mellitus and of the hepatitis C seropositive and seronegative groups

CHARACTERISTIC	TOTAL (N=145)	HCV POSITIVE (N=3)	HCV NEGATIVE (N=142)
SEX (M:F)	49 (33.8%):96 (66.2%)	1 (33.3%):2 (66.7%)	48 (33.8%):94 (66.2%)

CHARACTERISTIC	TOTAL (N=145)		HCV POSITIVE (N=3)		HCV NEGATIVE (N=142)	
	Mean	Standard-deviation	Mean	Standard-deviation	Mean	Standard-deviation
Age (years)	61.4	12.07	74.7	22.03	61.1	11.75
Time since diagnosis of DM (years)	10.9	8.44	5.0	4.24	11.0	8.46
Glycosylated hemoglobin % (HbA1c)	7.6	1.88	8.6	1.91	7.6	1.88
BMI (kg/m²)	31.7	7.00	31.5	2.81	31.7	7.07
Waist circumference (cm)	106.6	14.39	**116.5***	2.12	**106.4***	14.47
Total cholesterol (mg/dL)	174.2	43.41	191.0	56.57	173.9	43.41
Triglycerides (mg/dL)	170.5	107.37	100.5	33.23	171.2	107.49
HDL (mg/dL)	45.2	13.22	74.0	22.63	44.7	12.63
LDL (mg/dL)	95.9	5.52	111.5	75.66	95.7	35.08
AST (mg/dL)	26.5	12.51	37.5	28.99	31.3	51.77
ALT (mg/dL)	29.5	15.55	27.0	2.83	34.6	53.77

DM: diabetes mellitus; BMI: body mass index; HDL: high density lipoprotein; LDL: low density lipoprotein; AST: aspartate aminotransferase; ALT: alanine aminotransferase.
* p = 0.009

than the global prevalence reported by the WHO, due to the overlapping IC of the two reported rates. Regarding the prevalence in the Brazilian population, the rate found in this study was almost four times higher than the rate found in a large sample of 484,300 patients who underwent rapid testing for HCV, which was 0.76%. The same study used a mathematical model to extrapolate the finding for the total Brazilian population, considering other variables. The study found an estimated prevalence of 0.7%[4], a value not contained in the CI of this sample. Although no CI was reported for the Brazilian population study, this finding suggests that the seropositivity in the general population in Brazil is lower than that observed in patients with T2DM undergoing outpatient treatment, considering the limitations of this study.

Another finding that should be highlighted in this sample was the high prevalence of clinical phenotypes associated with IR. In addition to having longstanding T2DM, most patients also had centripetal obesity and dyslipidemia, although, on average, their glycemic control was fair (mean HbA1c: 7.6%). However, these variables did not show a statistically significant difference between HCV seropositive and seronegative groups, except for waist circumference, which was significantly greater in the HCV-positive group. This particular finding is interesting, as it is in line with the results of a case-control study conducted in Taiwan, which also found a higher prevalence of increased waist circumference in HCV-seropositive patients compared to controls[21]. Another study that evaluated the rate of visceral adiposity in patients with hepatitis C – another way of estimating the amount of visceral fat – found an association of this measure with the degrees of steatosis and hepatic necroinflammation, as well as with a higher HCV viral load, regardless of IR. The authors suggested this finding reflects dysfunction of the adipose tissue in patients with hepatitis C, which could play a direct role in the pathophysiology of the infection. This could be mediated by the endocrine and immunological functions of the adipose tissue, on which HCV could act by favoring the production of pro-inflammatory cytokines[22]. In addition, findings that indicate greater adiposity – such as greater body fat mass and higher levels of hepatic steatosis – were also associated with the presence and faster progression of liver fibrosis in patients infected with HCV, as well as greater viral resistance to antiviral therapy with interferon. From these findings, it is believed that adipose tissue may favor the progression of HCV infection, possibly due to immunological mechanisms such as T cell dysfunction resulting from leptin resistance[23].

The high prevalence of IR and T2DM in HCV patients has already been widely studied, as was the opposite association[9,10]. Therefore, the association between HCV and T2DM is thought to be bidirectional, that is, the HCV may predispose to the onset of T2DM and aggravate it, but IR itself may worsen the evolution and prognosis of the infection[11]. This hypothesis is supported by studies that have shown that patients with T2DM and HCV have a higher incidence of complications resulting from T2DM, which reinforces the importance of HCV screening in this population[24]. Likewise, studies have reported a reduction in HbA1c levels in patients who achieved viral suppression after treatment with direct-acting antivirals against HCV[25].

The exact pathophysiological mechanism that mediates the association between IR and HCV infection is not completely established. One of the hypotheses postulates that HCV has a direct action on hepatocytes, causing a decrease in insulin receptor expression, an increase in its degradation, and phosphorylation of its serine residues, which would result in resistance to the hormone. In addition, another hypothesis suggests an indirect action of HCV, by inducing the expression of inflammatory cytokines such as Tumor Necrosis Factor Alpha (TNF-α) and Interleukin 6 (IL-6), which promote the activation of molecular cascades that lead to IR24-26. Furthermore, there is also evidence that HCV proteins, such as NS5A (HCV nonstructural protein 5A), induce the expression of the phosphoenolpyruvate carboxykinase and glucose 6-phosphatase genes, which are enzymes that make up the neoglucogenesis pathway, and therefore lead to an increase in blood glucose levels[27-29].

Another point that deserves attention is the influence of IR and T2DM on the clinical outcomes of patients with hepatitis C. Studies indicate diabetic patients with hepatitis C, with or without cirrhosis, have worse clinical outcomes compared to non-diabetics, such as increased risk of developing HCC[17,30]. In those with cirrhosis, however, there is an increased risk of developing ascites, renal failure and bacterial infections[17]. The use of metformin, in turn, was associated with a lower incidence of HCC, liver transplantation, and death due to liver complications in patients infected by HCV with T2DM and cirrhosis[31]. Furthermore, the presence of IR can negatively impact the treatment of HCV, as studies have shown a lower rate of sustained viral suppression in these patients following treatment with ribavirin and peginterferon alfa, which were the treatment of choice for HCV until recently[32]. The combination of metformin with this treatment scheme, however, not only improved the IR, but also increased the rate of sustained viral suppression[33].

More recently, new drugs with a direct antiviral action were approved for the treatment of HCV. They can eradicate the virus in most cases, apparently irrespective of the presence of IR before treatment[34]. However, even if these drugs may lead to a complete and sustained eradication of the virus, T2DM still seems to negatively influence clinical outcomes. This is suggested by a study with 33,000 patients infected with HCV, in which the presence of T2DM before treatment with direct-acting antivirals was associated with higher mortality and negative hepatic outcomes (cirrhosis and decompensations), even after sustained viral suppression. In those with cirrhosis before treatment, T2DM was associated with the development of HCC, despite viral suppression[35]. Thus, although studies have also shown that eradicating the virus reduces IR and also leads to better T2DM control[34], clinicians should remain vigilant regarding patients with this comorbidity, even after viral suppression[35]. Finally, the importance of diagnosing and treating T2DM in these patients is reinforced by findings that indicate that metformin may decrease the risk of HCC after successful antiviral treatment[36].

This study has limitations that must be discussed. First, the sample size is small,

considering the expected prevalence of HCV infection in this population, based on previous literature. This may have resulted in low statistical power, hampering the detection of a possible statistically significant difference between the prevalence of HCV in the sample and its estimated prevalence in the general population, according to WHO data. However, our findings, although not statistically significant, are compatible with a previous meta-analysis that reported an odds ratio of 3.5 for the diagnosis of hepatitis C in diabetic patients compared to controls[9]. This limitation also hampered the power to detect possible differences in other laboratory parameters, although an interesting finding involving visceral adiposity was observed in diabetic patients. The lack of other data in the sample also prevented the assessment of other parameters that could be addressed, such as the degree of liver fibrosis and viral load. Also, a rapid serological test was used for the diagnosis of the infection, which, despite its good specificity and sensitivity[18], was not confirmed by another method. Therefore, there was a risk of false positives and false negatives. Finally, the cross-sectional design of the study does not allow further conclusions about possible causal relationships between variables.

In summary, this study reinforces the importance of screening for hepatitis C in patients with T2DM, since, 2.76% of the participants in a random sample, whose serological status was previously unknown, tested positive for HCV. It is true that the primary objective of treating hepatitis C is to eradicate the virus from the organism and, therefore, to reduce the incidence of complications resulting from chronic liver disease, the transmissibility of the virus and its comorbidities. Currently, there are highly effective therapeutic alternatives with fewer side effects, which make it easier to achieve these goals and even allow envisioning to eradicate hepatitis C by 2030. However, it is necessary to aim not only for such outcomes, but also for longer survival with a better quality of life for the patient. For this, it is necessary to go beyond the eradication of HCV, because, as discussed, other systemic changes, especially T2DM, are associated with complications and lower survival, even after total viral suppression[34]. Thus, this study draws attention to the importance of routine screening for T2DM in patients with HCV, aiming at early diagnosis and treatment, which is feasible in primary care, including in individuals with normal liver function.

DISCLOSURES

The authors declare that they have no conflicts of interest to disclose.

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PLEURAL SOLITARY FIBROUS TUMOR: A CASE REPORT

Tumor fibroso solitário pleural: um relato de caso

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ABSTRACT

Objectives: To report a case of a pleural solitary fibrous tumor, a rare soft tissue neoplasm, demonstrating its clinical complexity and diagnostic difficulties, seeking to raise awareness about the disease. **Methods:** The patient underwent total tumor resection, and samples were obtained for anatomopathological and immunohistochemical studies. Additional information was obtained by analyzing the medical records made available by the Hospital Geral de Carapicuíba, after approval by the institution's ethics committee and literature review. **Results:** The patient had a good clinical outcome and is being followed up at the outpatient clinic to screen for possible recurrences. **Conclusion:** Knowledge about the clinical and anatomopathological features of solitary fibrous tumors is essential for the correct diagnosis and favorable outcomes, including lower risk of recurrence and higher survival rates.

Keywords: Solitary Fibrous Tumor, Pleural.

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INTRODUCTION

Solitary fibrous tumor (SFT) is a neoplasm of mesenchymal origin, which presents a low incidence and corresponds to less than 2% of all soft tissue tumors[1]. There is no risk factor associated with this pathology, such as environmental exposure to radiation, tobacco, asbestos or other toxic substances[2]. Due to its rarity, despite having been described in 1931, SFT is still a relatively little-known tumor, which represents a challenge for its diagnosis and treatment[1]. In addition, the diagnostic difficulty is compounded by the indolent clinical course and nonspecific symptoms of most STFs. As a result, most cases are diagnosed only after an incidental finding on radiological imaging[2-5].

Another feature that contributes to the clinical complexity of SFT is that it can affect almost all anatomic sites of the body, including the skin, meninges and gastrointestinal tract, among others. Originally described as a pleural tumor, it is currently known that only 30% of cases have a pleural origin[6]. On the other hand, different case series differ regarding the other most frequently affected sites, as some studies report the meninges in second place, with 27% of cases6, while others point to the peritoneal cavity (abdomen and pelvis)[7]. Within the thoracic cavity, in addition to the pleura, SFT has also been described in the lung parenchyma, mediastinum and pericardium8. Other less common sites include the extremities, oral cavity, orbits and paranasal sinuses1. The mean age of patients with pleural SFT is around 60 years[9], but the tumor has been reported in younger individuals, including children[4]. Extra-pleural SFT, on the other hand, tends to occur in younger patients, with a mean age of 50.3 years[10].

SFT also has histological characteristics in common with other soft tissue tumors, which led to several nomenclature changes in the past, such as the denomination hemangiopericytoma, widely used in the past[1]. With the advances in molecular, immunohistochemical and genetic techniques, the understanding of SFT is improving, and now it is possible to better characterize this neoplasm. This case report aims to raise awareness of this rare disease by discussing its clinical presentation and treatment, in light of its complexity and recent advances in its understanding.

CASE REPORT

The patient is a 47 year old non-smoker female patient with no relevant medical history, complaining of dry cough and pleuritic chest pain for nine months, without associated infectious symptoms. The patient had already been treated with antibiotic therapy on two occasions, without improvement. On physical examination, she was in good general condition, well-nourished, with absent breath sounds at the base of the right hemithorax on lung auscultation, dullness on percussion and increased vocal remits at the same location.

The initial chest X-ray (figure 1) shows a homogeneous opacity at the base of the right lung, which remained radiographically stable during follow up. Computed tomography (CT) of the chest was then performed (Figure 2), which showed a hypodense lesion measuring 11.8 x 8.3 cm occupying the right middle lung field, apparently with pleural origin, and without significant enhancement after intravenous contrast. The lesion was compressing the adjacent lung parenchyma, causing passive atelectasis. A basal posterior laminar pleural effusion on the right could also be seen.

The etiological investigation was performed with a video-assisted thoracoscopy biopsy, which was inconclusive. Then, a decision was made to perform thoracotomy with resection of the mass located in the chest wall. This time, the gross surgical pathology analysis of the piece revealed a mass weighing 710 grams and measuring 16 x 14 x 5 cm, with a smooth, brownish external surface. Upon cuts, a whitish and firm tissue was noticed. The microscopic examination, in turn, revealed a spindle cell neoplasm without atypia and with extensive collagenous areas in-between. The circumferential margin was positive.

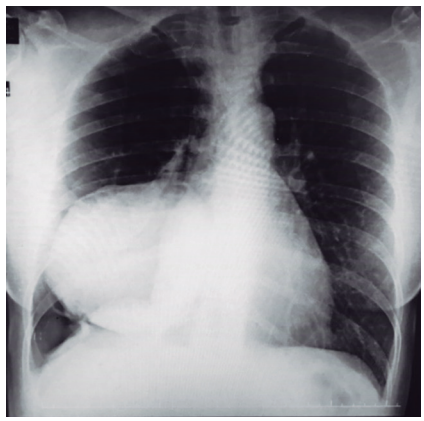

Figure 1. Chest x-ray performed before surgical resection of the tumor.

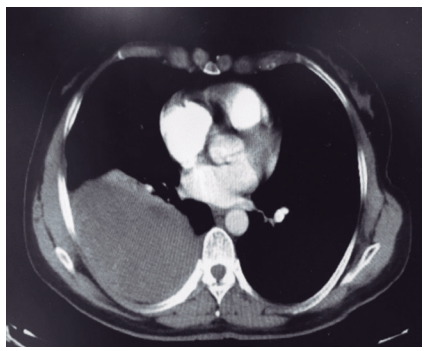

Figure 2. Chest CT with IV contrast performed before surgical resection of the tumor.

The immunohistochemical study was positive for actin (in vessels), BCL-2 and CD34 (strong and diffuse), with positive Ki-67 in 1% of neoplastic cells. The observed mitotic index was low. The diagnosis was consistent with a solitary fibrous tumor of the chest. Figure 3 illustrates the chest X-ray performed after tumor resection.

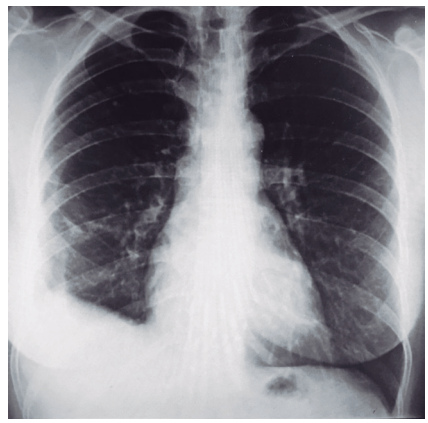

Figure 3. Chest x-ray performed after surgical resection of the tumor.

DISCUSSION

This report illustrates a case of SFT that manifested with nonspecific respiratory symptoms, although previously published case series have reported that only a minority of patients (about 23%) have any symptoms[7]. However, tumors that reach large volumes, in particular, can cause symptoms resulting from local compression, such as cough, chest pain, dyspnea and hemoptysis[2]. Cases of paraneoplastic syndromes associated with SFT have also been reported, especially Doege-Potter syndrome, characterized by hypoglycemia of unknown origin, resulting from the production of insulin-like growth factor 2 (IGF-2) by SFT cells[11]. Cases of secondary hypertrophic osteoarthropathy associated with SFT have also been described[2,12].

However, SFT is often asymptomatic and only incidentally diagnosed by imaging tests[5]. Thus, it is essential to know this pathology and the radiological findings associated with it as a first step towards the correct diagnosis. The initial investigation can be done with a simple chest X-ray, which typically shows a single nodule or mass with well-defined contours that originate from the pleura, with or without a pedicle[1]. The next step involves performing a chest CT with contrast, which also shows the nodule or mass with regular contours, but sometimes lobulated. The tumor is hypervascular and may have, especially if large, areas of necrosis. T2-weighted MRI scans may reveal foci of hyperintense signal associated with areas of necrosis, which give the lesion a non-homogeneous appearance[1].

Investigation with chest CT is useful for differentiating from other thoracic masses[2], since SFT accounts for less than 5% of pleural tumors[2]. Examples of differential diagnoses are malignant pleural mesothelioma, neurogenic mediastinal tumors, synovial tumor, fibrosarcoma, malignant fibrohistiocytoma and, in the case of anteriorly located masses, thymic pathologies and germ

cell tumors. The definitive diagnosis, however, is made through anatomic pathology, immunohistochemical and molecular analyses.

SFT histology shows areas of alternating cellularity, with areas rich in tumor cells and other that are hypocellular, but, rather, rich in stromal collagen. Tumor cells vary from ovoid to spindle-shaped1, with rounded to oval nuclei and small cytoplasm[1,5]. They are usually low-grade neoplasms, with minimal nuclear pleomorphism, and generally rare or absent mitoses[1]. Conventional immunohistochemical markers include CD34 expression in about 79% of cases, but this is a nonspecific marker, as neoplasms such as gastrointestinal stromal tumors (GIST) can also express it. Other markers that can be expressed by TDS include Bcl2, CD99, vimentin in the absence of actin, and epithelial markers, such as the epithelial membrane antigen[1,13].

A barrier to the immunohistochemical diagnosis of SFT, however, arises from other tumors with similar histology expressing these same markers[13]. Examples of differential diagnoses are monophasic synovial sarcoma, leiomyomas and desmoid tumors, which also express CD34[14]. The specificity of these markers is therefore relatively low[13], which, added to the histological complexity and possibility of SFT affecting several anatomic sites, contributes to the diagnostic challenge. SFT can also be mistaken for other tumors, such as other soft tissue neoplasms, such as schwannomas, spindle cell lipomas, dermatofibrosarcoma protuberans, liposarcomas, GIST, malignant peripheral nerve sheath tumors, and synovial sarcomas[13].

To minimize diagnostic challenges and better differentiate SFT, molecular techniques have emerged as a useful tool for this purpose[13]. One of the molecular markers that are known to be highly sensitive and specific for SFT is the NAB2 and STAT6 gene fusion, which is present in more than 90% of the samples, whereas it is absent even in histologically similar tumors. It is also possible to investigate the nuclear expression of STAT6 using immunohistochemical techniques. Studies have shown that a strong and diffusely positive result for STAT6 in the nucleus is highly specific for SFT, although weakly positive results can be observed in other tumors[1,13]. Thus, such tools contribute to the challenging diagnosis of SFT, which requires integrating clinical, anatomic pathology, immunohistochemical and molecular features[13].

The World Health Organization Classification of Tumors of Soft Tissue and Bone, fifth edition, classifies SFT as intermediate tumor (rarely produces metastases)[13], since most cases have a benign behavior, although it can be locally aggressive. Overall survival rates reflect this classification, ranging from 59-100% at one year and 40-89% at ten years, depending on the case series[1]. However, several cases present a malignant behavior, reportedly between 10% and 20%[15], which may recur and metastasize. At least three important studies have identified risk factors associated with malignant behavior and worse prognosis. They are: size > 10 cm (15 cm in one of the studies), age > 55 years, more than 4 mitoses/10 high-power fields, high nuclear pleomorphism, high cellularity, presence of necrosis, hemorrhage and/or a malignant component on the anatomic pathology analysis (e.g. stromal or vascular invasion)[16-18]. The presence of paraneoplastic syndromes, such as Doege-Potter's, is also associated with malignant tumors (up to 70%) and, consequently, with a worse prognosis[1,19]. Molecular markers were also observed more frequently in tumors with malignant behavior, such as the presence of mutations in the promoter region of telomerase reverse transcriptase[1]. The loss of CD34 expression was also associated with malignant tumors[13]. Table 1 summarizes the characteristics associated with malignant behavior of SFT.

The treatment of SFT is surgical and can be performed by open thoracotomy or videothoracoscopy (recommended for tumors smaller than 5 cm)[20]. Regardless of the technique, the objective of surgery should be the total resection of the tumor and obtaining free margins, which is associated with a lower rate of local recurrence and higher chance of survival[1,20]. The presence of a pedicle

TABLE 1 - Features associated with malignancy in Solitary Fibrous Tumors

Clinical and demographical features	• Age > 55 years; • Paraneoplastic syndromes, such as Doege-Potter's.
Anatomopathological features	• Size > 10 cm (15 cm in one of the studies); • > 4 mitoses/10 high-power fields; • High nuclear pleomorphism; • High tumor cellularity; • Necrosis and/or hemorrhage; • Malignant component on anatomopathological examination.
Molecular markers	• Telomerase reverse transcriptase promoter region mutations
Immunohistochemical markers	• Loss of CD34 expression.

Adapted from Davanzo *et al., Transl Gastroenterol Hepatol* 20181; Tariq *et al., Diagn Pathol* 2021[13]; Demicco *et al., Mod Pathol* 2012[16]; England *et al., Am J Surg Pathol* 1989[17]; Gold *et al., Cancer* 2002[18]; Herrmann *et al., Exp Clin Endocrinol Diabetes* 2000[19].

makes resection easier, but larger, invasive and sessile tumors can represent a surgical challenge. Some cases, such as large tumors attached to the lung or with parenchyma invasion, may require lobectomy to obtain free margins. The same applies to tumors that adhere to and/or invade the diaphragm, parietal pleura, and pericardium, which may require more extensive surgery[20].

SFT recurrence can occur during late follow-up, as far as 17 years after the initial resection, even when complete resection is achieved, with free margins, and even when the tumor is benign[1,21]. The recurrence rate reported in large case series varies from 10 to 18.2%[21,22], but may vary depending on the follow-up time and the characteristics of patients[1]. As for tumors with malignant characteristics, however, recurrence rates can be as high as 63%[1,22]. In a literature review, de Perrot *et al.* described a risk stratification system for SFT recurrence, based on histological and morphological characteristics of the tumor. According to the study, the tumors can be classified based on the presence of malignant in histological features (the same ones described above) and according to their gross morphology, which can be pedunculated or sessile. The risk of recurrence ranged from less than 2% in benign pedunculated tumors to 63% in sessile malignant tumors[22]. However, obtaining clear margins is the most important consideration after surgical resection to predict the risk of recurrence[2].

Adjuvant radiation therapy is indicated only in patients with sessile tumors with malignant features, whose risk of recurrence is high, as proposed by de Perrot *et al.*[22]. However, in other patients, when complete resection with negative margins is possible, radiation therapy in the treatment of SFT is not indicated, as it is a rare and indolent tumor, for which there are no controlled studies[1]. In cases of local recurrence, a new resection can be attempted[1,22,23]. The role of adjuvant radiation therapy in these cases, as well as when the margins are compromised, is not well established, due to the lack of controlled studies[1]. Only isolated case reports have shown a significant response of recurrent SFTs to radiation therapy[24].

SFT metastases are usually hematogenous and occur mainly in the liver, central nervous system, spleen, peritoneum, adrenal glands, gastrointestinal tract, kidneys and bones[22]. However, the ideal treatment for metastatic SFT, as well as for locally advanced and unresectable tumors, is not well established, as controlled studies are lacking, given the rarity of the tumor[1]. Most of the studies performed to date are retrospective, including the use of cytotoxic chemotherapy based on doxorubicin, which has shown low response rates[1]. Some studies also evaluated the effectiveness of targeted therapy in SFT, including drugs such as antiangiogenics (pazopanib, sorafenib, sunitinib, regorafenib and axitinib). Results were poor, and controlled studies are still needed to determine whether such drugs are effective or not[1].

After the surgery, the patient should be followed up periodically, focusing on the early identification of recurrences and metastatic disease. However, there are no well-defined guidelines on how such monitoring should be done, due to the lack of studies and the rarity of the disease. In general, the risk criteria described above (Table 1) are used to identify patients at higher risk of recurrence and metastatic disease[1,16-18]. De Perrot *et al.* proposed that high-risk patients (sessile tumors with malignant characteristics) should be followed up every six months for the first 24 months after resection, with CT and chest X-rays, as relapse occurs within this time interval in most of these patients[22]. Follow-up can be done annually thereafter. It is also possible to consider the guidelines for the follow-up of soft tissue sarcomas proposed by the National Comprehensive Cancer Network (NCCN), which recommend follow-up with imaging tests every six months for three years in low-risk patients, followed by annual follow-up until the fifth year. For intermediate and high risk patients, the interval is shorter, every three to four months for the first two years and then every six months until the fifth year[25]. However, it is prudent to continue monitoring these patients for several years, as recurrences have been described up to 17 years after resection of the primary tumor[1].

In summary, pleural SFT is a rare neoplasm with no known risk factors. The clinical course of most cases is indolent, and the diagnosis is generally made after incidental imaging findings. Diagnosis can be difficult due to the histological and immunohistochemical features shared by other soft tissue tumors, but advances in molecular techniques now allow better characterization of SFT. The patient of this case underwent total resection of the tumor, presented with good clinical outcomes, and has maintained outpatient follow-up to monitor for possible recurrences. These are the recommended treatments and the evolution of most cases, but up to 20% of patients may have tumors with malignant features, which indicate a worse prognosis and higher risks of recurrence. Due to the rarity of the disease, there are no controlled studies that validate the use of adjuvant radiation therapy or chemotherapy. Generally, adjuvant radiation therapy is reserved for cases with a high risk of recurrence. Also due to its rarity, clinical complexity and diagnostic difficulty, good knowledge about SFT is essential to obtain favorable results and good survival rates, as most tumors have benign features.

CONFLICTS OF INTERESTS

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NEUROSCIENTIFIC UPDATE ON THE MECHANISMS OF ACTION OF ACUPUNCTURE IN CHRONIC PAIN

Atualização Neurocientífica dos Mecanismos de Ação da Acupuntura em Dor Crônica

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ABSTRACT

Acupuncture is a treatment method that emerged in Ancient China according to specific philosophical concepts of Traditional Chinese Medicine, which has its own systems of diagnosis and treatment of diseases. Since the use of acupuncture spread throughout the West, theories and concepts have emerged to explain its effects, including the possible role of physiological mechanisms. For instance, one of these theories states that acupuncture promotes neuromodulation by applying stimuli to the so-called acupoints, which are transmitted throughout the peripheral and central nervous systems by vast neural networks. One of the clinical applications of acupuncture is the treatment of chronic pain, but its mechanisms of action are not completely understood. Recently, however, studies have contributed to deepening the knowledge about the topic, suggesting that central neural pathways and molecular and humoral mechanisms are involved in the perception of chronic pain and in its treatment using acupuncture. These studies suggest, among other mechanisms of action, possible neurochemical effects of acupuncture on central and peripheral nervous systems, as well as modulation of somatosensory, affective and cognitive areas of the brain, observed in neuroimaging studies. This review aims to provide an overview of the effects and mechanisms of action of acupuncture in chronic pain, based on recent neuroscientific evidence.

Keywords: acupuncture, chronic pain, analgesia.

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INTRODUCTION

Acupuncture is a complementary or integrative treatment method that emerged in Ancient China according to specific philosophical concepts of Traditional Chinese Medicine (TCM), which has its own systems of diagnosis and treatment of diseases[1]. As acupuncture spread throughout the world, theories and ideas emerged in the West to explain its effects, following the introduction of modern principles of anatomy and physiology, and advances in biochemistry and biophysics[1,2].

The practice involves the insertion of fine needles at specific points on the body (classical acupuncture) or by applying electrical stimuli conducted by the needles at variable frequencies (electroacupuncture)[2]. Both techniques have been increasingly used as a complementary therapy in the treatment of pain[3].

Acupuncture analgesia – which is the main purpose for which the technique has been widely studied – represents the effects of integrative processes at different levels of the nervous system,

including the peripheral, central, somatic and autonomic nervous systems[4]. Several studies have reported that acupuncture exerts reproducible neurobiological effects in animal models[5-8]. In recent years, electroneuromyography and neuroimaging techniques, such as functional magnetic resonance imaging (fMRI), have been used to study the neural mechanisms involved in the clinical outcomes of acupuncture[3,9]. In parallel, interest in clinical research has grown in recent decades, as well as the strength of evidence regarding the efficacy of acupuncture in pain management has increased as a result of randomized controlled trials (RCTs)[10].

This study presents an integrative review of the evidence on the various mechanisms of action of acupuncture analgesia, including neurophysiological and molecular effects. This review also provides a brief historical context of this technique and presents the clinical evidence of acupuncture in pain management. Finally, we present the main research gaps identified in the literature, aiming to guide further studies, and conclude with the authors' considerations on the subject. Due to the heterogeneous methods used in the reviewed studies, this study did not attempt to perform a meta-analysis. Instead, we intend to describe and discuss the evolution of the knowledge about the mechanisms suggested for the effects of acupuncture on pain modulation and analgesia, based on experimental studies.

BRIEF HISTORY OF ACUPUNCTURE

The development of acupuncture dates back to at least a few thousand years ago. The theory and practice of acupuncture originated in Ancient China, and gradually, the technique became one of the standard treatments in TCM, as well as massage, diet, herbs, and moxibustion[2,11,12]. It is believed that the specific points where the needles are inserted – the so-called acupoints – are distributed along the body and can be pierced by a needle or heated by burning the herb Artemisia vulgaris (better known as moxa, which is a type of mugwort, burned in a technique known as moxibustion). Cupping can also stimulate them, as well as pressure (acupressure), electrical stimulation (electroacupuncture) and, more recently, laser[1].

TCM understands human physiology and mental health through the concepts of Qi (vital energy), correlating it with physical and mental processes and also with emotional states. Diseases would appear due to interference in the circulation of Qi, which normally flows through energy channels known as meridians. They form a network-like system that connects different parts of the body and ensures the circulation of Qi[1]. Chinese medicine associates each meridian to a mental, physical or emotional function, and acupuncture is believed to restore the integrity of these elements. However, despite these beliefs having guided the practice of acupuncture for over thousands of years, there is currently no scientific evidence to support these concepts, and research has not yet been able to find any explanation according to current medical knowledge[13].

Nevertheless, acupuncture has become popular in recent decades, mainly for its effect on relieving acute or chronic pain of various origins, which is one of the reasons that have led to the interest in research on the mechanisms behind such analgesic effects[14]. In this regard, acupuncture research may be important not only to unravel the phenomena associated with its mechanisms of action, but also to explore new directions in human physiology that may not have been systematically studied yet.

EVOLUTION OF BASIC RESEARCH IN ACUPUNCTURE

Several questions about the mechanisms that mediate acupuncture analgesia have emerged in recent decades, especially regarding those involved in chronic pain. Initial studies, especially those using animal models, suggested the involvement of endogenous opioids in the nervous system, autonomic inhibition, axonal and medullary reflexes, and the release of non-opioid mediators and neurotransmitters, such as glutamate, serotonin and adenosine[4,15]. Other hormones, such as cholecystokinin (CCK), and immune mediators, such as inflammatory cytokines, appear to contribute to the mediation of acupuncture analgesia. In the latter case, they cause activation or inhibition of signal transduction pathways in target-cells, modulating mitogen-activated protein-kinase cascades (p38, ERK1/2, JNK). More recently, experiments regarding the anti-hyperalgesia effects of acupuncture have evaluated the control of inflammatory pain via inhibition of NMDA and AMPA receptors, neuroglial activation, and diffuse noxious inhibitory control (DNIC)[4,12,15].

In recent years, with the development of fMRI and positron emission computed tomography (PET/CT), the possible modulation of brain activity and pain pathways by acupuncture has attracted attention from the scientific community[9,12,16]. These new studies evaluated brain function during resting state, comparing it with the pattern of brain activity after performing acupuncture and electroacupuncture for painful stimuli. This technique allows the neuromodulatory effects of acupuncture on the brain to be identified, including the deactivation of the so-called default mode network and the modulation of regions linked to affective and pain processing and memory[17].

Therefore, this review divides the current knowledge gathered about the main mechanisms involved in acupuncture analgesia into two major types: neural (direct action on nervous tissue) and humoral/molecular.

REVIEW OF THE EVIDENCE ON THE MECHANISMS OF ANALGESIA ASSOCIATED WITH ACUPUNCTURE

Methods

An integrative literature review was carried out through bibliographic searches in the MEDLINE/PubMed, Latin American and Caribbean Health Sciences (LILACS) and EMBASE databases, including studies published from 2000 to 2021. The searches were performed in March and April 2021, and were limited to full-text articles published in English in peer-reviewed journals. Health descriptors and Medical Subject Headings (MeSH) were used to answer the question: "What are the possible mechanisms of acupuncture for the treatment of chronic pain?", using the keywords "analgesia", "pain", "mechanisms" and "acupuncture", with the addition of the Boolean operator AND. A descriptive analysis of the articles was then performed.

The analysis of the studies was descriptively carried out in order to answer the research question, taking into account ethical aspects, and respecting the authorship of the ideas, concepts and definitions present in the included articles. The titles and abstracts of the articles were initially evaluated to refine the sample, highlighting those that responded to the question of this review. Subsequently, each selected publication was thoroughly read, providing elements to discuss the neurophysiology and mechanisms of action of acupuncture, aiming to identify relevant aspects replicated or highlighted among studies. Articles were then organized to retrieve data to perform this integrative review.

Neural Mechanisms in Acupuncture

The direct effects that acupuncture stimulation causes on the nervous system seem to vary, and several neural mechanisms appear to mediate its analgesic properties. Studies suggest that acupuncture targets several areas distributed across the autonomic, peripheral and central nervous systems (CNS)[15,17]. In addition, it has also been suggested that the effects of acupuncture probably encompass extensive neural networks associated with affective, cognitive and somatosensory processing[9]. Furthermore, it has been demonstrated that the effects of acupuncture on the nervous system can continue even after the needle is removed, which suggests the procedure may have a long-term action[16].

The neural pathways related to acupuncture analgesia seem to be intertwined with the pathways involved in transmitting and detecting pain[4]. Moreover, it has already been observed that acupuncture not only acts on pathways responsible for somatic pain, but also on those involved in visceral, inflammatory, cancer and other types of pain[18,19]. Studies also suggest that acupuncture can attenuate central pain sensitization, which is often observed in states of hyperalgesia or allodynia[20,21]. A possible explanation for this diversity in neural mechanisms lies in the premise that the effects of acupuncture may vary according to stimulation parameters, such as its depth (dermatome, myotome, sclerotome, neurotome), intensity (weak, medium, strong, electrical), and anatomical location (motor, trigger, pain, skin or reflex points)[15].

Effects of classical acupuncture on sensory (afferent) pathways

Although initial studies indicate that acupuncture selectively stimulates primary afferent nerves, recent research has revealed that it can stimulate both myelinated and unmyelinated afferent fibers that innervate the skin and muscles[22,23]. In addition, acupuncture needle insertion has been shown to stimulate all four types of somatic afferent fibers: Group 1 (Aα type), Group 2 (Aβ type), Group 3 (Aδ type), and Group 4 (C type)24. However, analgesic the effects seem to be primarily mediated by fibers belonging to Groups 2, 3 and 4 (Aβ, Aδ, and C)[25].

Furthermore, studies suggest that acupuncture stimulation on somatic afferent pathways produces perceptible effects in three dimensions: 1) inhibition of nociceptive inputs resulting in analgesia, which could therefore justify the clinical use of acupuncture in pain syndromes; 2) regulation of visceral function via the reflex arc composed of somatic afferent pathways and autonomous visceral efferent pathways, also known as somatic-autonomic reflexes, which could justify the clinical use of acupuncture in non-painful visceral disorders; and 3) decreased skeletal muscle tone, determined by the somatic motor reflex, thus justifying the clinical use of acupuncture in conditions of sustained muscle tone[24].

Modulation of afferent signal processing in spinal cord pain induced by acupuncture

Studies suggest that spinal cord multireceptive neurons, especially those found in the dorsal horn (posterior column; laminae I-VI) and in the dorsal root ganglion, play an essential role in acupuncture analgesia[18,20,26-28]. Furthermore, modulation of several molecular pathways involved in pain processing in the spinal cord has been associated with acupuncture analgesia in pain models (Table 1). In particular, although the modulation of the opioid system remains the mechanism most widely associated with the action of acupuncture at the spinal level, the role of several other molecular mechanisms, including other neurotransmitters and protein kinases, has recently been reported[3,19,29]. Table 1 presents these molecular mechanisms, which will be further discussed below.

TABLE 1. Proposed mechanisms for the analgesic effects of acupuncture targeting the spinal cord

MECHANISM	PAIN TYPE
BDNF[19]	Inflammatory, neuropathic
C-FOS gene[3]	Visceral
CCK-8[4,15]	Inflammatory
Dopamine[3,4]	Inflammatory
EPHB3, EPHB6 and Ephrin-B genes[27]	Neuropathic
GABA[13,18]	Inflammatory, neuropathic
GDNF[15]	Neuropathic
Glial cells[15]	Inflammatory, neuropathic
NMDA glutamatergic receptors[3,15,44]	Visceral, inflammatory
Nociceptin / Orphanin FQ[4]	Inflammatory
Norepinephrine[4]	Inflammatory, neuropathic
p38 MAPK[3,15]	Visceral, inflammatory, neuropathic
Serotonin[3,4]	Visceral, Inflammatory, neuropathic
Substance P[3,15]	Inflammatory, neuropathic
μ, δ e κ opioid receptors[4]	Visceral, inflammatory, neuropathic, oncologic

BDNF: brain-derived neurotrophic factor; CCK-8: cholecystokinin octapeptide 8; EPHB: ephrin type-B receptor; GABA: gamma-aminobutyric acid; GDNF: glial cell line-derived neurotrophic factor; p38 MAPK: p38 mitogen-activated protein kinase

Acupuncture analgesia mechanisms related to the brainstem

Brainstem nuclei and their ascending pathways have been increasingly associated with chronic pain. For example, abnormalities in neuronal activity in the ventromedial rostral bulb and trigeminocervical complex have been implicated in migraine and may be attenuated by acupuncture, an effect that is attributed, as suggested by some studies, to calcitonin gene-related peptide (CGRP)[30]. Similarly, the dorsal column gracilis nucleus in the brainstem has been implicated in chronic pain states, and nitrous oxide has been suggested as the key molecular mechanism[28]. Furthermore, neurons in the dorsal periaqueductal gray matter (PAG) in the midbrain have been associated with acupuncture analgesia and seem to be modulated mainly by opioids and CCK-8[18,28]. Also, the reticular formation and other brainstem nuclei involved in pain pathways, which will be described below, play an important role in mediating acupuncture analgesia[31].

Acupuncture analgesia mechanisms related to the diencephalon

The targets of acupuncture analgesia in the diencephalon include the posterior and anterior hypothalamus, in addition to the centromedian nuclei of the thalamus, which connect to cortical regions involved in pain discrimination and perception, having an integrative role[4,28,32]. Furthermore, the suggested effect of acupuncture on thalamic nuclei, such as the parafascicular nucleus and lateral central nucleus, had already been described more than 50 years ago[32]. This effect on the thalamus was also found in a recent fMRI study, which suggests a role of thalamic nuclei in the habituation observed after repeated and prolonged acupuncture stimulation[33]. Another study using PET/CT suggested that the hypothalamus also mediates acupuncture analgesia[34].

Descending pain inhibitory pathways: central regulators of acupuncture analgesia

One of the methods used to explain the neural mechanisms of acupuncture classifies them as local, segmental (distal), and general or whole-body[35]. According to this model, descending pain inhibitory pathways, predominantly located in the medulla and midbrain, seem to be the main modulators of chronic pain, central hyperexcitability to pain, and acupuncture analgesia. A variety of neurotransmitters appear involved in these pathways, including acetylcholine, gamma-aminobutyric acid (GABA), serotonin, opioids, dopamine, and norepinephrine[20,35-40].

Since the 1970s, several nuclei related to pain pathways have been associated with acupuncture analgesia[20,38-40]. Those that make up the descending pain inhibitory pathways most strongly associated with acupuncture analgesia are listed in Table 2. More recently, the expression of the P2X3 receptor was found in the PAG, which is believed to undergo a modulatory effect by electroacupuncture, leading to analgesic effects in neuropathic pain[36]. Furthermore, studies have suggested that brain-derived neurotrophic factor (BDNF) is involved in the effect of acupuncture on the PAG and on the rostral ventromedial bulb, likely leading to increased central pain sensitization[20].

TABLE 2. Descending pain pathway nuclei implicated in acupuncture analgesia

Posterior arcuate nucleus[27,28]
Ventromedial hypothalamic nucleus[27,28]
Locus ceruleus[13]
Periaqueductal gray matter[3]
Nucleus raphe magnus[27,28,30]
Paragigantocellularis nucleus[27]
Gigantocellular reticular nucleus[27]
Rostral ventromedial medulla[3,27,28]
Nucleus tractus solitarii[3,28]
Anterior cingulate cortex[3,28]

Acupuncture mechanisms related to diffuse noxious inhibitory control

For many decades, it was believed that acupuncture itself was a noxious stimulus that produced pain, which, in turn, would activate a mechanism called DNIC through type Aδ and C afferent fibers4. Excitatory-inhibitory neurons in the raphe nuclei possibly regulate these mechanisms, and may be affected by descending pain pathways[4,40,41]. Extra-segmental acupuncture (which consists of inserting needles at sites distant from the original pain focus) could induce this type of diffuse inhibitory effect, causing distant analgesia[41]. In animal models, short-term DNIC can be observed through high-intensity electrical stimulation of acupoints[42,43]. However, a recent study, carried out with healthy volunteers, was not able to reproduce this effect using low-intensity stimulation. Even so, the authors noted that this does not exclude the possibility that acupuncture can exert this effect in a scenario of chronic pain or high-intensity stimulation[42]. Other authors have also suggested that an adequate intensity of stimulation for each individual may be necessary for this effect to completely manifest[43].

Neuroimaging studies and the brain mechanisms of acupuncture analgesia

Neuroimaging studies have revealed that pain processing and regulation are complex functions involving several areas of the brain. The sensation of pain seems to be mediated by several integrated and diffuse neural networks involving somatosensory (S1, S2 and thalamus), affective (hippocampus and amygdala) and cognitive (cingulate and insular cortex) areas[44,45]. Furthermore, abnormal plasticity has been observed in brain neural networks during pain states[45-47].

Regarding the brain mechanisms of acupuncture in chronic pain, interesting findings have been reported by neuroimaging studies[9,16,48,49]. A systematic review and meta-analysis of studies using fMRI revealed that acupuncture stimulated vast brain networks, including areas involved in somatosensory, affective and cognitive processing[9]. Another systematic review of several neuroimaging techniques reported that acupuncture can reverse the abnormal neural plasticity associated with chronic pain and restore normal plasticity, thus improving clinical symptoms[48]. Furthermore, acupuncture may induce several other neural responses, such as improvements in neural network efficiency and connectivity, activation of specific areas, as well as temporal changes, affecting the somatosensory, affective and cognitive areas of the brain. Also, changes in blood oxygenation levels in critical regions of the brain, including the limbic

system, brainstem, and various areas of the cerebellum, have also been observed after acupuncture stimulation[49].

HUMORAL AND MOLECULAR MECHANISMS OF ACUPUNCTURE ANALGESIA

Recently, studies have suggested that needle acupuncture may affect the body's neuroendocrine-immune regulatory network via molecular and humoral mechanisms shared between the two systems, including neuropeptides and neurotransmitters, as well as cytokines and hormones[4,50].

In addition to evidence suggesting that acupuncture can directly modulate the secretion of these mediators through stimulation of the nervous system, studies also suggest it can indirectly modulate the production of several cytokines and hormones through, respectively, the inflammation pathways related to the local injury at the acupoints and secretion of releasing hormones by the hypothalamus[50,51]. Consistently, studies have also proposed that the humoral mechanisms of acupuncture may be largely responsible for the therapeutic benefits in cases of inflammatory, visceral, and cancer pain, and that the use of acupuncture may also alleviate other associated symptoms, such as anxiety or depression[19, 52-54].

Many theories also discuss the effects of connective tissue manipulation by acupuncture needles, suggesting that this could be an important factor that induces humoral responses via mechanotransduction. This could be especially important considering that the acupoints are thought to be located in anatomical areas rich in loose connective tissue and intermuscular fascia[55]. To investigate this hypothesis, a study analyzed mast cell activation after mechanical stimulation of peripheral nerves, revealing that these cells release adenosine triphosphate (ATP) after the stimulation[56]. Likewise, the response of mechanically stimulated fibroblasts has also been studied, revealing that the cytoskeleton of these cells responds to the stimulation by the acupuncture needle[56,57].

Role of endogenous opioid peptide activity in acupuncture analgesia

Central and peripheral release of endogenous opioid peptides (β-endorphin, enkephalin, and endomorphin-1 via stimulation of δ- and -μ-opioid receptors, and dynorphin via stimulation of κ-opioid receptor) is the best-established molecular mechanism thought to mediate analgesia by acupuncture[4,58,59]. Since the 1970s, it has been demonstrated that the modulation of chronic pain induced by acupuncture is mediated by the action of opioid neurotransmitters in different points of several peripheral, spinal and supraspinal neural pathways, in models of inflammatory, oncologic, neuropathic and visceral pain[4,18,59].

Of all endogenous opioids, it is believed that β-endorphin is the predominant peptide in acupuncture analgesia, while enkephalins seem to be responsible for other effects, such as anti-anxiety and antidepressive[31,59]. Acupuncture stimulation may also induce short- and long-term increases in μ-opioid receptor binding potentials in brain regions that process pain, such as the cingulate cortex, caudate nucleus, and the thalamus[60].

The characteristics of opioid system stimulation, such as the profile of endogenous opioid peptide release and receptor activation, may depend on the intensity of the stimulus produced by acupuncture[4,61]. Recently, the growing awareness of the effects of acupuncture on endogenous opioids has resulted in studies regarding its possible effects on the consumption of exogenous opioids, including clinical scenarios such as analgesia and addiction to these substances. An interesting finding reported by one of these studies was a reduction of the need to use exogenous opioids in chronic pain syndrome after stimulation of endogenous opioids by acupuncture[62]. In addition, acupuncture has shown potential benefits in some cases of addiction to opioids[63].

Role of monoamines (serotonin, dopamine and noradrenaline) in acupuncture analgesia

Several studies indicate that monoamines seem involved in the analgesic effects of acupuncture[64,65]. For instance, evidence indicates that acupuncture regulates the activity of the serotonergic and dopaminergic neurotransmission systems in the central nervous system[4,59,66]. Several serotonin receptors, such as 5-HT1, 5-HT2, 5-HT3, 5-HT7, appear related to the analgesic effects of acupuncture, acting predominantly through pain inhibitory pathways located in the nucleus raphe magnus and in the dorsal horn of the spinal cord[67-70]. Likewise, acupuncture action on peripheral and cortical structures may also contribute to serotonin-mediated analgesic effects[4,58,67]. In addition to the effects on serotonergic transmission, it was observed that acupuncture also seems to cause an increase in dopaminergic activity via D1 and D2 receptors in the nucleus accumbens, associated with its analgesic effects[4,71,72].

Although the role of norepinephrine in acupuncture analgesia has been known for a long time, especially regarding the activity of locus coeruleus neurons and the stimulation of the descending pain inhibitory pathway[73], the exact mechanisms are not yet fully understood. Both the increase and decrease in noradrenergic activity after acupuncture have been reported[4,74]. Studies have also shown that the α2A adrenergic receptor can mediate the analgesic effect of acupuncture in cases of inflammatory pain[75], although its expression levels in the brain and spinal cord after electroacupuncture vary 76.

Acupuncture mechanisms related to inhibition of microglial activation

The maintenance of neuronal homeostasis is considered a fundamental mechanism of acupuncture[4]. Moreover, there is increasing evidence that acupuncture attenuates neuropathic pain caused by peripheral nerve injury. In the nervous system, glial cells – including microglia, astrocytes and oligodendrocytes (in the peripheral nervous system, Schwann cells only) – surround neurons and regulate and maintain their homeostasis and cellular function, in addition to participating in responses after acute and chronic injuries[25,27]. Because of this, great interest has arisen regarding the possible role of these cells in the analgesic effects of acupuncture.

Hence, studies have shown that microglia and astrocytes in the spinal dorsal horn are involved in the maintenance and onset of pathological pain by releasing pro-inflammatory cytokines and chemokines, in addition to other substances and factors that control pain signaling, such as glutamate and CGRP[3]. Microglia inhibition in rats is associated with a reduction in inflammation-induced mecha-

nical allodynia and with an enhancement of the analgesic effects of electroacupuncture in inflammation-induced pain[77].

Humoral and molecular mechanisms of electroacupuncture analgesia

Electroacupuncture has been the preferred modality in studies investigating the effects of acupuncture on chronic pain due to its known advantages, which include the possibility of standardizing and controlling the stimulus frequency, voltage, and waveform[78]. Many of these studies suggest that several neurotransmitters and their receptors, such as endogenous opioids (μ, δ, and κ), noradrenaline (α2), serotonin (5-HT1 and 5-HT3), acetylcholine (M1), glutamate (NMDA) and GABA (GABAA and GABAB), play a role as mediators of the analgesic effects of electroacupuncture. It is believed that these neurotransmitters act in structures such as the anterolateral tracts of the spinal cord and in the descending pain inhibitory pathways[79,80]. The release of cytokines by astrocytes in rats, as well as other molecules such as adenosine, has been suggested as another mechanism involved in electroacupuncture analgesia[81,82].

Furthermore, it has been observed that differences in the frequency of electrical stimulation affect the analgesic effects of electroacupuncture and its mechanisms, such as the activation profile of the opioid system. For example, it has been suggested that low-frequency electroacupuncture stimulates both μ- and -δ-opioid receptors and serotonergic pathways, while high-frequency acupuncture stimulates κ-opioid receptors[78].

Recent studies have also shown that electroacupuncture may play a role in modulating the signaling network of the endocannabinoid system, regulating numerous physiological and cognitive processes. One of the findings was the activation of cannabinoid receptors 1 (CB1) in the ventrolateral area of the PAG, which seems essential for the central antinociceptive effect of electroacupuncture. The activation of cannabinoid receptors 2 (CB2) in the periphery, on the other hand, seems related to its anti-inflammatory effects. Activation of both CB1 and CB2 would therefore alleviate behavioral responses to inflammatory and neuropathic pain[83]. Furthermore, other studies in rats have shown an increase in the levels of endocannabinoids AEA and 2-AG in the brain[84] after electroacupuncture.

RESEARCH GAPS

In recent years, large randomized clinical trials and systematic reviews have reported good qualitative and quantitative results of acupuncture[85]. On the other hand, some recent high-quality studies comparing acupuncture with sham acupuncture (sham) have found small differences in clinical outcomes[86,87].

Despite recent advances, there is still a significant gap in acupuncture research, especially regarding the translation of experimental evidence into clinical practice3. Likewise, there are several methodological challenges and major inconsistencies in clinical research on acupuncture for pain, starting with the clinical condition studied, which is broad and complex. Other methodological challenges include difficulties to ensure adequate blinding and to define the best clinical trial design. For instance, consensus regarding the best comparator for acupuncture still lacks, such as no treatment, waitlist assignment, pharmacological treatment, and sham acupuncture; the ideal follow-up time; and the most clinically relevant outcomes86. Added to this is the lack of standardization of treatment protocols, which differ both in randomized clinical trials and in clinical practice, given that the TCM diagnostic method is complex and individualized[88,89]. This can include variability in acupuncture point locations, as well as differences in point selection (fixed or variable point approach) and in the duration, frequency, and intensity of acupuncture or electroacupuncture. As a result, the technique varies among practitioners, making its replication more difficult and challenging[90].

Moreover, despite the possible analgesic mechanisms attributed to acupuncture, the main target of the procedure has not yet been clarified, including transmission, perception or modulation of pain. Multiple mechanisms are likely to occur, with many overlapping effects, resulting in a complexity that poses additional challenges to acupuncture research. Isolating different mechanisms is also challenging, especially considering that the use of simulated or minimal needling in clinical research is controversial, as even minimal superficial sensory inputs may be sufficient to stimulate some of the same neural pathways thought to mediate the analgesic effects of acupuncture. As a result, sham acupuncture could not be considered completely physiologically inert, as traditional placebo pills[91].

Furthermore, recent research has shown that acupuncture analgesia is likely due, in part, to integrative processes at different levels in the peripheral and central nervous systems. Thus, the concept of neuromodulation, which is also associated with a wide range of cellular and molecular inflammatory pathways, may play a central role in acupuncture analgesia and should therefore be further investigated. Finally, much of the current knowledge about possible mechanisms of acupuncture analgesia results from studies that used animal models, which are difficult to translate to the clinical setting. Nevertheless, despite these remaining gaps regarding the applicability of the results of preclinical experiments in humans, acupuncture analgesia is a promising strategy for several pain disorders. Therefore, the main goal of future prospective research should be to translate the findings of mechanistic studies into clinical applications.

CONCLUSION

Although acupuncture has been used in TCM for the treatment of pain for thousands of years and has gained significant popularity in medical practice around the world, there has been a strong impetus in recent decades towards studying the neurobiological mechanisms underlying the analgesic effects of the technique. Understanding these mechanisms is crucial for the general acceptance and consolidation of acupuncture in the treatment of chronic pain.

Despite the great advances in the methodology used in acupuncture research, the mechanisms of its analgesic effects are not yet fully understood. Based on the most recent findings reported in the literature, our review suggests two types of mechanisms possibly associated with these effects: neural and humoral/molecular. The first includes inhibition of pain sensory pathways (primarily targeting Aβ, Aδ, and C afferent fibers); modulation of pain signal processing in the spinal

cord (in posterior gray matter columns and anterolateral tracts); changes in pain processing in the brainstem, diencephalon (hypothalamic and thalamic nuclei) and cerebral cortex (cognitive, affective and somatosensory areas); and activation of descending pain inhibitory pathways and of the DNIC. Changes in connectivity and brain activity were observed in studies with neuroimaging, which allowed to identify possible effects of acupuncture on the brain. Humoral and molecular mechanisms, in turn, involve modulation of the endogenous opioid system and several other neurotransmitters and their receptors, including monoamines and neuropeptides involved in pain processing. At the cellular level, microglial activation seems also involved. These neurobiological mechanisms probably underlie the effects of acupuncture on different types of pain, such as somatic, visceral, oncologic and inflammatory, and are likely concurrent.

As with other pain models, most knowledge regarding acupuncture analgesia comes from experiments with animal models, in which the effects and mechanisms described may not be applicable to humans. Important research gaps, including differences in acupuncture techniques and study design, as well as other issues regarding research methodology in the area, which are not yet consensual, must be discussed and addressed. Future studies on the mechanisms of acupuncture should consider these issues, so that it will be possible to translate most of these basic and preclinical research findings to relevant clinical applications.

CONFLICTS OF INTERESTS

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JMRR

IDENTIFICATION OF KEY ELEMENTS FOR IMPROVING PRIMARY CARE FOR CANCER PATIENTS USING THE ACIC QUESTIONNAIRE

Identificação de Dimensões-Chave para a Melhoria do Cuidado ao Paciente com Câncer na Atenção Primária em Saúde pelo Questionário ACIC

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ABSTRACT

Objectives: To identify key elements for the improvement of cancer patient care in the primary care setting. **Methods:** This is an analytical, cross-sectional and quantitative study. Healthcare professionals from all primary care teams of the city of Votuporanga (Brazil) answered the Assessment of Chronic Illness Care (ACIC) questionnaire, used by the Pan-American Health Organization/World Health Organization for the assessment of the quality of chronic care. **Results:** The average score obtained in the seven evaluated elements was 5.4±2.0 on a scale from zero to 11. The integration of the elements of the care model, with an average of 3.9±2.3, and support for clinical decisions, with an average of 3.5±2.4, were the elements with the lowest scores. **Conclusion:** The average score obtained in the ACIC tool, according to the responses of primary care professionals in Votuporanga, indicates the city has a fair capacity to care for patients with cancer. On the other hand, the items integration components of the healthcare system, and clinical support for care, received the lowest scores, which indicates that these elements should be prioritized in the implementation of improvements.

Keywords: Continuity of Patient Care. Oncology. Primary health care.

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INTRODUCTION

Cancer is a prevalent disease with a high mortality rate. Its care has worrisome deficiencies, especially in developing countries. However, the number of patients living with it has increased due to greater survival, which was possible by the expansion of the care network and technological advances in oncology[1]. Advances such as genetic and molecular studies, the discovery of new drugs, and new procedures already incorporated into clinical protocols allow, in many cases, adequate control of the disease and lower mortality[2,3]. Due to these advancements, many patients now live with the disease for long periods, a fact that has led many authors to consider cancer a chronic disease[4].

The Brazilian public health system – Sistema Único de Saúde (SUS) – already recognizes cancer as a noncommunicable chronic disease (NCD). In 2013, the ordinance of the Brazilian Ministry of Health (Portaria no 874) established the National Policy for the Prevention and Control of Cancer (Política Nacional para a Prevenção e Controle do Câncer - PNPCC), recognizing cancer as a preventable chronic disease that requires comprehensive care[5]. The PNPCC also defined that the follow-up of patients diagnosed with cancer should be carried out in highly complex oncology care units and centers, which should offer timely and safe treatment as close as possible to the patient's home. However, for cancer care to be offered comprehensively, a referral and counter-referral system is necessary, in which primary health care (PHC) services also play a fundamental role, often accompanying cancer patients in parallel to more specialized services6. In this system, the PHC service refers the patient to a more specialized service to start their treatment, which must start within 60 days after the diagnosis[7]. The counter-referral process, which is the referral back to the PHC service of origin, guarantees the continuity of the necessary care, ensuring the principle of comprehensive care.

In this comprehensive care network for cancer patients, PHC is much more than just the system's "gate keeper". On the contrary, PHC has a strategic role in providing qualified health services, important for humanized care, which also includes primary prevention, early detection and palliative care. It acts therefore at all levels of the natural history of the disease. Because it is closer to the population, PHC also has a greater reach for health promotion actions, which reinforces its importance in cancer control[8]. However, a study carried out in the Brazilian Federal District indicated that 35.5% of patients diagnosed with breast cancer started their treatment only 60 days after the initial diagnosis, which reveals gaps and deficiencies in the integration of the system, a sharp contrast to what is ideally enshrined in the law[9]. Thus, it is essential that studies are carried out to assess the quality of care for patients with cancer in PHC services, to diagnose its main problems.

Following the concept that cancer has characteristics in common with other NCDs, studies have shown that some tools for assessing outcomes in chronic diseases may also be applicable to cancer, as is the case of the EQ-5D questionnaire[10]. Therefore, the same principle could be applied to assess the quality of care for cancer patients, by using instruments that assess the quality of care for NCDs, such as the Assessment of Chronic Illness Care (ACIC) questionnaire, used by the Pan American Health Organization (PAHO) for this purpose[11,12].

Based on this rationale, the present study employed the ACIC in the context of PHC services provided to cancer patients, aiming to make a situational diagnosis of the quality of care. Thus, the objective of this study is to identify the key elements of the Chronic Care Model (CCM) that need improvement in the context of PHC for cancer patients.

METHODS

This is a cross-sectional, quantitative and analytical study. It was carried out in Votuporanga, a city in the countryside of the State of São Paulo, Brazil, which had an estimated population of 96,106 inhabitants, in 2021[13]. At the time of the study, 19 healthcare teams from the Family Health Program (*Programa de Saúde da Família* – PSF), a national PHC program of SUS, participated. These teams were responsible for a catchment area covering 89.3% of the city, and were distributed across 12 Family Health Clinics (Unidades de Saúde da Família – USF), which are PHC clinics.

Descriptive data on the characteristics of each USF were obtained, namely: number of teams on site, of doctors and nurses, catchment population and number of cancer patients being cared for at the USF. To anonymize the final scores, each clinic was identified with a letter, and each team received a number when the USF had more than one.

For the evaluation of the PHC service regarding the care of cancer patients, the Brazilian version of the ACIC, which was adapted to Brazilian Portuguese in 2012[12,14] was used. The ACIC evaluates the elements of the CCM[15], measuring the capacity of the health institution to care for NCDs, and establishing a situational diagnosis of the operational environment in which the care is provided. The tool divides the assessment into seven essential elements: organization of the health care system, community resources, self-management support, delivery system design, clinical decision support, clinical information systems and integration of the elements. Each of these aspects receives a score of zero to 11. The highest value indicates the described action has been completely put into practice, and the lowest, that further action is still needed.

The tool was applied in one USF every two weeks. The researchers first presented the ACIC to the clinic's staff, detailing the objectives and methods of the study, and then trained each group to apply it. Between three and 11 members of each healthcare team were then selected and invited by their peers to answer the ACIC, according to the member's involvement in the care of cancer patients, in addition to their interest in participating in the study. The questionnaire was then answered at the USF, on a scheduled date, in a face-to-face meeting, in which the researchers, who acted as facilitators, also participated without influencing the answers. The ACIC was answered individually after an initial debate between the participants of each group.

The final score for each clinic was obtained by averaging the participants' responses, after evaluating the data for normal distribution and sphericity. For descriptive purposes, scores between 0 and 2 were considered "limited capacity"; between 3 and 5 were considered "basic"; between 6 and 8, "fair"; and between 9 and 11, "excellent". The ANOVA test was used to compare the differences between the final score of each team and clinic, with a 95% confidence interval. The seven elements of the CCM were also analyzed individually. The final score of each element was compared between the different clinics using the ANOVA test, but due to the multiple comparisons performed, the Bonferroni correction was used, establishing a p value for statistical significance of 0.007.

To control possible confounding variables influencing the final scores, the study also analyzed demographic data of each of the participants, such as gender, age, training and experience, such

as time worked in public health, time working at the same USF and their education. The following variables were also analyzed: number of cancer patients treated at the clinic, population catchment of the team, and number of staff members participating in the research. At this stage, the Pearson's chi-square test was used to investigate a possible relationship between the categorical variables (gender and professional training) and the final scores given by participants in the questionnaire. Pearson's linear correlation coefficient, in turn, assessed the association of continuous variables such as age, time working in public health, and time working at the same USF with the final scores given to each service.

RESULTS

The characteristics of the USF included in the study are described in Table 1. Of the 453 healthcare professionals working in the USF studied, 81 (17.9%) were invited to participate in the research, including seven of the 19 physicians (36.8%), with no refusals. The population catchment averaged 4,909±3,306 patients per team, ranging from 2,120 to 15,600. On average, each participating USF had 10.9±8.3 patients with cancer treated at the location. Of the 12 participating PHC clinics, six had 10 or more patients with cancer, comprising 107 patients in these services (81.68% of the total sample).

The 81 healthcare professionals participating in this study were mostly female (76%), with a mean age of 39.5±10 years, ranging from 20 to 68. The professionals worked at the USF in eight-hour shifts, have been in the public health area for an average of 7 years, and have worked at the same USF for an average of 4.5 years. Furthermore, 28.9% of the participating professionals declared having a postgraduate degree.

Table 2 demonstrates the characteristics of the members of each team. The separate analysis of the seven physicians who answered the ACIC showed a mean age of 31.5±5.9 years, ranging from 26 to 42, and only one was male. These physicians have worked at the same USF for 2.9 years, the same length of time they have worked in the public health system, in all cases.

TABLE 1 - Characteristics of the Family Health Clinics (USF) in Votuporanga

CLINIC	NUMBER OF TEAMS	CATCHMENT POPULATION	NUMBER OF PATIENTS WITH CANCER*	NUMBER OF PHYSICIANS	NUMBER OF REGISTERED NURSES
A	3	21,797	8	5	3
B	1	9,271	14	1	1
C	1	2,188	16	1	2
D	1	3,673	2	1	1
E	1	3,247	4	3	1
F	2	8,789	24	2	2
G	1	3,500	10	1	1
H	1	15,600	20	3	1
I	3	6,361	4	4	3
J	1	3,700	1	2	1
K	1	2,350	5	3	1
L	3	13,000	23	3	3

(*) Number of patients receiving cancer care at the USF in 2018.

TABLE 2 - Characteristics of the participating healthcare professionals of each team

TEAM*	MEAN AGE (YEAR)	MEAN TIME WORKING IN PRIMARY CARE (YEARS)	MEAN TIME WORKING AT THE SAME PRIMARY CARE CLINIC (YEARS)
A1	35.5	8.6	3.7
A2	37	6.5	6.5
A3	39.6	7.3	4.6
B	42.8	7.2	4.9
C	40.7	2.7	2.4
D	46.4	13.9	8.5
E	42.5	6.5	2.5
F1	43	6	6
F2	43.3	6.5	4.6
G	39.3	10.6	5.5
H	40	8.6	3
I1	33.6	4.3	3.3
I2	32.3	4.6	3.3
I3	37	5	3
J	33.8	7.6	4.7
K	36.7	7	6.8
L1	44.7	9	5.7
L2	36.3	5.3	4.6
L3	36.5	5.7	2.6

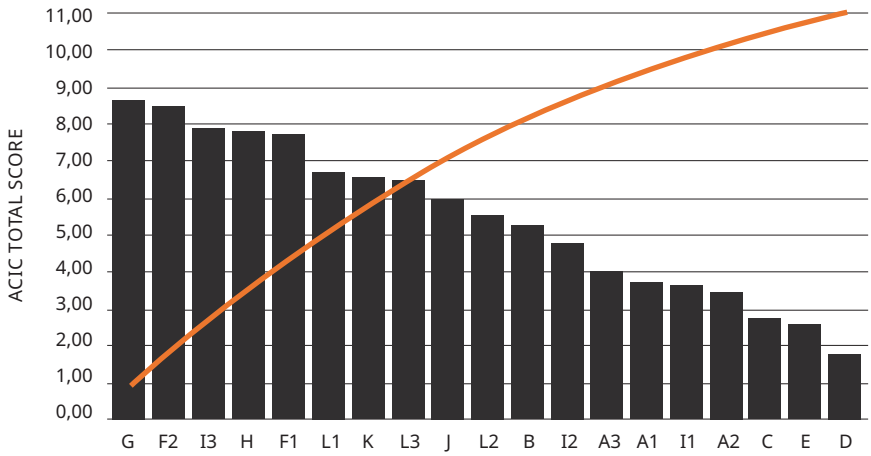
*Letter: Family Health Clinic (USF) and Number: Team;

The average final ACIC score obtained by the USFs in Votuporanga was 5.4±2.0 ("fair"), ranging from 1.8 to 8.6, on a scale of zero to 11. The ANOVA test that compared the mean total scores of each of the 12 USFs yielded a statistically significant difference across the clinics [F(11,69) = 4.25, p=0.03]. As for the evaluations of each team, according to the score classification criteria described in "methods", nine teams (47.3%) considered their USF had a fair institutional capacity for cancer care; seven teams (36.9%) considered the institutional capacity basic; and three teams (15.8%) considered it limited. Chart 1 orders the teams' final scores from highest to lowest.

Table 3 presents the results of the ANOVA test, which compared the different clinics regarding their mean score in each of the seven elements of the CCM. A significance level of 0.7% was considered, after Bonferroni correction for multiple comparisons. The average score obtained by the six USF that treated more than 10 cancer patients was 6.4±2.0, ranging from 2.71 to 8.65 (scale of zero to 11). For the other six clinics, the mean score was 4.32±1.8, ranging from 1.78 to 6.51. However, the number of users with cancer assisted in each clinic was not significantly associated with the ACIC score obtained by that clinic.

It is important to highlight that the answers to the ACIC are a result of the collective decision of the participating professionals, who belong to different areas in healthcare. In eight teams, the ACIC was only applied to community health agents (agentes comunitários de saúde - ACS), with an average score of 5.79±2.61. In the eleven remaining teams, at least one participating professional had a university degree (physician or nurse), yielding an average score of 5.19±2.03. In seven teams (36.8%), the USF physician was present among the professionals who answered the assessment instrument, yielding an average score of 5.02±2.43. There was no association between the training background of the participant professionals and their correspondent ACIC scores. No statistically significant associations were found between age, sex, time working in public healthcare and time working at the same USF. Nor was any association found between the clinic's final ACIC score and the population catchment of each clinic or the number of professionals participating in the study.

CHART 1 - Final ACIC scores for each team according to the Pareto chart



site: letter - clinic; number - team

TABELA 3 - ACIC scores in elements of the Chronic Care Model of each Family Health Clinic and total final score

ELEMENT*	CLINIC												MEAN SCORE	P VALUE**
	A	B	C	D	E	F	G	H	I	J	K	L		
1	1.3	8	5.1	0	2.1	8.9	10.5	9.5	4.1	5.5	5.8	6.6	5.6	0.043
2	4.9	5.5	2.7	1.7	2	7.5	7.5	7.7	5.8	6.7	6	5.4	5.3	**0.003**
3	3.9	7.5	4.5	1.7	1.5	10.3	9	8.2	5	6.2	8.5	8.5	6.2	0.12
4	2	0	0.7	1	1.5	5.6	8.2	5.5	3.8	4.2	4.7	5.4	3.5	0.073
5	4.4	9	4.5	1.3	2.5	10.8	10.5	10.8	8.5	7.1	7.5	8	7.1	**<0.001**
6	6.9	4	1.3	4.6	5.3	7.2	5.8	6	7.9	7.5	8.1	6.5	5.9	0.129
7	2.2	3.1	0	2	2.5	6	9	6.5	2.7	4.8	4.8	3.1	3.9	0.043
TOTAL MEAN SCORE	3.7 ± 1.9	5.3 ± 3.2	2.7 ± 2	1.8 ± 1.4	2.5 ± 1.3	8 ± 2	8.6 ± 1.6	7.7 ± 1.9	5.4 ± 2.1	6 ± 1.2	6.5 ± 1.5	6.2 ± 1.7	5.4 ± 2	**0.03 *****

*Elements assessed: 1: Organization of systems of cancer care; 2: Coordination with community resources for cancer care; 3: Support for cancer-related self-management; 4: Support for cancer-related clinical decisions; 5: Design of the cancer-related service delivery system; 6: Clinical information system of cancer-related data; 7: Integration of the elements of the cancer care model. Letters indicate each USF studied. **P values of the ANOVA test used to compare the scores of each clinic in the seven elements of the CCM, F(11,69). There was a significant difference for elements 2 and 5 (p<0.007 after correction for multiple comparisons). *** P value of the ANOVA test used to compare the total final ACIC scores of each clinic, F(11,69) p <0.05.

DISCUSSION

This study, using an instrument that evaluates the quality of care for patients with NCDs, applied to cancer care, found a "fair" score for this type of healthcare provided in the 12 USF in the city of Votuporanga, São Paulo, Brazil. The result is consistent with other studies that sought to assess the quality of PHC in regions of Brazil with similar socio-demographic characteristics. For example, Castro *et al.*[16] used the Primary Care Assessment Tool (PCATool), version for health professionals, to assess the services in the city of Porto Alegre, Rio Grande do Sul, Brazil. Although it used different methods compared to this study, including a focus on care as a whole and not just chronic diseases, the primary care clinics in Porto Alegre received an average score of 6.58, that is, on the limit between which is considered a low and high score (6.6). Thus, despite the limitations of this comparison, it is possible to infer that the perception of these professionals regarding the service can also be considered intermediate, compatible with the "fair" result found in the current sample.

It is also possible to infer that a "fair" score reflects a mixed perception of the quality of care provided. Therefore, part of the evaluation can be positive, thanks to aspects of the service that have improved since the implementation of the current PHC model based on the Brazilian public health policy known as "Family Health Strategy" (Estratégia de Saúde da Família - ESF). Previous studies pointed out that the elements of PHC that have been strengthened include: the size of the geographical area covered by the PSF, the population's access to health care, the structure of the services, the availability of physicians and the coverage of health initiatives. Public policies aimed at improving access and quality in PHC have also been implemented in recent years[16]. In this study, in turn, the element that showed the most positive results, according to the perception of the participating professionals, was the design of the cancer-related service delivery system, with a mean score of 7.1±3.1. Preventive campaigns, home care programs and availability of services to cancer patients throughout the network may be some of the measures implemented in recent years that contributed to a better perception of this element of the CCM. The design of the service delivery system was also reported as the best evaluated element by another Brazilian study that used the ACIC tool to assess the quality of PHC, although, in this case, the instrument was not restricted to care for a specific disease. This study, carried out in the city of Campo Grande, state of Mato Grosso do Sul, also yielded a "fair" score of the clinics in that city[17].

Contrasting with the strengths of PHC, several studies have pointed out elements of the system that still leave much to be desired, which often arises from problems that affect the completeness and comprehensiveness of care18. Difficulties in the referral and counter-referral system within the network have been identified as one of these problems. A study that evaluated the quality of PHC for patients with cervical cancer pointed out problems such as the limited number of spots for referred patients; deficient communication between the referring provider and the specialist about the case; and, many times, even the lack of the counter-referral[19]. In another study, which also used the ACIC tool in Votuporanga, but to evaluate the care for type 2 diabetes mellitus, the integration of the elements of care and clinical decision support obtained low scores[20]. The findings of this study go in the same direction, since the two elements that presented the lowest scores were the integration of the elements of care and clinical decision support. The first of these two elements considers that a quality health system is organized in a clear, synchronized and effective way. Clinical decision support, on the other hand, guarantees that medical decision-making is up to date and based on scientific grounds, which can be guaranteed by clinical protocols and well-defined care algorithms.

Another noteworthy finding is the difference observed in scores across clinics, which may indicate heterogeneity in the network. Castro *et al.*[16] also found differences between PHC clinics in the city of Porto Alegre, Brazil, which were associated with their structure and coordination with the rest of the system. In that study, the clinics that had physicians specialized in primary care and other health professionals, such as psychologists, social workers, dietitians, among others, scored better. Easier referral procedures to more complex levels of care were also one of the characteristics observed in clinics with higher scores. In this study, differences were also observed among the PHC clinics regarding the score of the element "integration of the components of the CCM", which may suggest heterogeneity regarding the ease of referring patients to specialized services. However, this finding did not survive Bonferroni correction for multiple comparisons.

Two other elements of the CCM (design of the service delivery system and coordination with community resources) showed significant differences among the USF, even after Bonferroni correction. This finding indicates that there are other sources of heterogeneity across the network, which need further studies to identify possible causes. Some factors may have contributed to the differences across the clinics, such as the variability in the number of individuals served, ranging from 2,120 to 15,600 people. According to the city administration, this number was determined by socio-economic criteria, which further increases the heterogeneity of the population served by the network. In addition, the number of participants in each clinic varied, which may have led to possible selection biases and low statistical power in some clinics, making it difficult for additional differences to be observed.

Another limitation of this study is the low number of physicians participating in the research, which may have possibly led to selection bias. Physicians may have different quality standards for health care than other members of the multidisciplinary team, due to the inherent characteristics of each one's role. In fact, the average score obtained in teams in which only ACS participated was higher (5.79) than in the seven teams with at least one participating physician (5.02). Although no statistically significant association was found between the training background of the participant and the final ACIC score, such differences in types of participating professionals among the USF may have led to selection bias in the final scores. It is also possible that differences resulting from the professional's training background were not detected due to the low statistical power of the sample. Thus, this factor may have been responsible for the difference in scores obtained by each clinic. Furthermore,

many participating physicians revealed in this study that they did not have much experience working in PHC, as this was their first job in the field. Although this variable was not associated with the final ACIC score of the clinic, it may have influenced the answers and, therefore, the final result. This is important, as in the aforementioned study by Castro *et al.*[16], the clinics with unexperienced physicians, in conjunction with other factors, had worse ACIC scores compared to those with experienced practitioners and specialists in primary care medicine. Finally, despite differences in training background among participants in each clinic, other variables such as sex, age and number of cancer patients treated at the clinic seem not to have influenced the final result.

This study reports findings that can collaborate with a diagnosis of the quality of care for cancer patients in the PHC setting. We identified aspects that could be improved by working with the teams and the rest of the healthcare system to improve the quality of care for cancer patients. In particular, the worst scores were observed in elements that comprise the integration of the elements of the care model and support for clinical decisions, which indicates that the focus of improvement should be placed on actions in these areas. The findings are compatible with other studies that evaluated the quality of PHC in Brazil and pointed out deficiencies in these same two elements.

CONFLICTS OF INTERESTS

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