ISSN 1516-3180

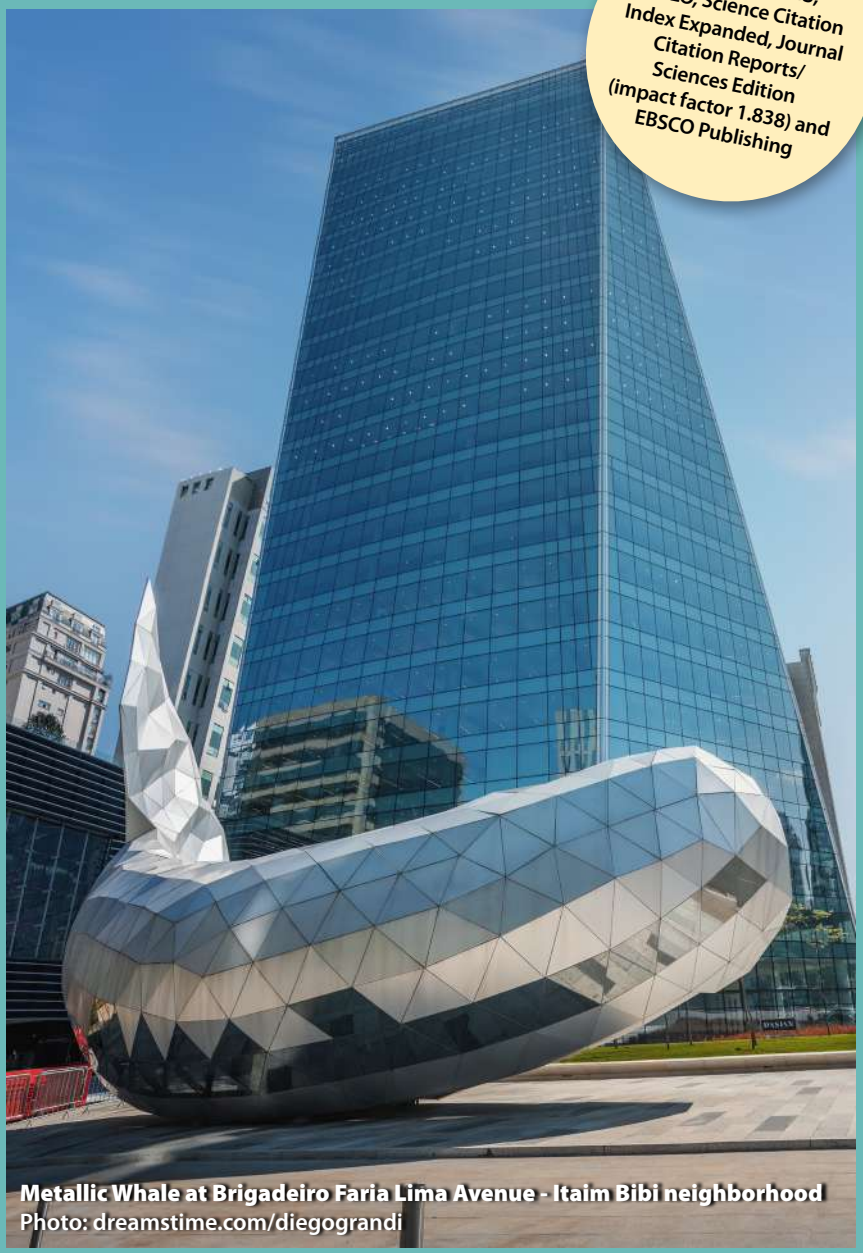
São Paulo Medical Journal/Evidence for Health Care, 2022 July 7; 140(4):515-623

São Paulo Medical Journal

EVIDENCE FOR HEALTH CARE

Medline, LILACS, SciELO, Science Citation Index Expanded, Journal Citation Reports/ Sciences Edition (impact factor 1.838) and EBSCO Publishing

July 7 - Volume 140 - Number 4



Metallic Whale at Brigadeiro Faria Lima Avenue - Itaim Bibi neighborhood
Photo: dreamstime.com/diegograndi

São Paulo Medical Journal does not charge authors for publication.

APM ASSOCIAÇÃO PAULISTA DE MEDICINA

Federada da AMB Associação Médica Brasileira

V Jornada de DOR na Mulher

3.SET

8h às 17h

Sede da APM: Av. Brigadeiro Luís Antônio, 278 - Bela Vista - São Paulo/SP

VAGAS PRESENCIAIS LIMITADAS

O evento abordará as principais queixas femininas, qualidade de vida das mulheres, atualizações, direito da mulher, diagnósticos e tratamentos. Confira!

Temas:

- Dor e climatério
- Enxaqueca e ciclo hormonal
- Demência e Climatério
- Hormônios e Dor
- Exercícios físicos na dor feminina
- Opioides e insônia
- Canabis e dor na mulher

MODERADORES

Dra. Camilla Zakka

Dra. Telma Zakka

Dr. Rogério Adas

PALESTRANTES

Dra. Andrea Toscanini

Dr. Malebranche Berardo

Dra. Telma Zakka

Prof. Dr. Rogério Adas

Dr. Gabriel Kubota

Dr. Hélio Plapler

Profa. Dra. Pérola Plapler

Dr. Diego Toledo

Dra. Carolina Kobayashi

Profa. Dra. Claudia Palmeira

Dr. Caio Simione

REALIZAÇÃO, ORGANIZAÇÃO, PROMOÇÃO E COMERCIALIZAÇÃO

APM ASSOCIAÇÃO PAULISTA DE MEDICINA

PATROCINADOR MASTER

SUPERA

INSCREVA-SE!

São Paulo Medical Journal
EVIDENCE FOR HEALTH CARE

INDEX

Editorial

Original article

APM ASSOCIAÇÃO PAULISTA DE MEDICINA

Correspondence to:

ASSOCIAÇÃO PAULISTA DE MEDICINA
Publicações Científicas
Av. Brig. Luís Antônio, 278 - 7º andar – São Paulo (SP) – Brasil – CEP 01318-901
Tel. (+55 11) 3188-4310/3188-4311 E-mail: revistas@apm.org.br

www.scielo.br/spmj

CNPq Conselho Nacional de Desenvolvimento Científico e Tecnológico
CAPES

Founded in 1932, a bimonthly publication of the Associação Paulista de Medicina
e-mail: revistas@apm.org.br

Editors: Paulo Manuel Pêgo Fernandes, Renato Azevedo Júnior and Álvaro Nagib Atallah.
Editorial assistant: Marina de Britto.
Associate editors: Adriana Seber, Aécio Flávio Teixeira de Góis, Airton Tetelbom Stein, Alexander Wagner Silva de Souza, Antonio José Gonçalves, Aytan Miranda Sipahi, Cristina Muccioli, Delcio Matos, Edina Mariko Koga da Silva, Fernando Antonio de Almeida, Flávio Faloppa, Heráclito Barbosa de Carvalho, José Antônio Rocha Gontijo, José Carlos Costa Baptista-Silva, José Maria Soares Júnior, José Roberto Lapa e Silva, Laércio Joel Franco, Maria do Patrocínio Tenório Nunes, Milton de Arruda Martins, Moacir Fernandes de Godoy, Olavo Pires de Camargo, Renato Corrêa Baena, Sergio Tufik, Vania dos Santos Nunes.
Proofreading: David Elliff.
Desktop publishing: Zeppelini Publishers (www.zeppelini.com.br).
Listed in: Medline, Lilacs, SciELO, Science Citation Index Expanded and Journal Citation Reports/Sciences Edition and EBSCO publishing.
International Board: Alexandre Wagner Silva de Souza (University Medical Center Groningen, Groningen, Netherlands), Charles J. Menkes (Cochin Hospital, Paris, France), José Fragata (CUF Infante Santo Hospital, Lisbon), Luiz Dratcu (Guy's Hospital, London, and Maudsley NHS Trust, York Clinic, London), Marcelo Cypel (University Health Network, Toronto, Canada), Karla Soares-Weiser (Enhance Reviews Ltd, Wantage, United Kingdom), Tirone Espiridião David (Toronto General Hospital, Toronto, Canada), Mário Viana de Queiroz (Hospital de Santa Maria, Lisbon), Wadih Arap (MD Anderson Cancer Center, University of Texas, Houston, United States), Wellington V. Cardoso (Boston University, Boston, United States).

Scientific Council

Diretoria Executiva da Associação Paulista de Medicina (Triênio 2020-2023)

Checklists as a central part of surgical safety culture

Omar Asdrúbal Vilca Mejia[I], *Paulo Manuel Pêgo Fernandes*[II]

Instituto do Coracao, Hospital das Clinicas HCFMUSP, Faculdade de Medicina, Universidade de Sao Paulo, Sao Paulo, SP, BR

[I]MD, PhD. Coordinator of the Surgical Quality and Safety Unit, Cardiac Surgery Division, Instituto do Coracao, Hospital das Clinicas HCFMUSP, Faculdade de Medicina, Universidade de Sao Paulo, Sao Paulo, SP, BR.
https://orcid.org/0000-0002-1635-4984

[II]MD, PhD. Titular Professor of the Thoracic Surgery Program, Instituto do Coracao, Hospital das Clinicas HCFMUSP, Faculdade de Medicina da Universidade de Sao Paulo, Sao Paulo, SP, BR; and Director of the Scientific Department, Associação Paulista de Medicina, São Paulo (SP), Brazil.
https://orcid.org/0000-0001-7243-5343

The number of surgical procedures performed is increasing worldwide. In 2004, the number of major operations performed reached 281 million, i.e. approximately one operation per year for every 25 individuals.[1] However, the numbers of complications among surgical patients has also been increasing and this has become the greatest cause of death and disability worldwide.[2] A systematic review has demonstrated that one in every 150 hospitalized patients dies as a consequence of complications related to an adverse event and that almost two thirds of these deaths are associated with surgical treatment.[3] Half of these adverse events are considered to be avoidable.[4]

In the 1970s, following a series of air accidents, analysis on these events demonstrated that a combination of stress, fatigue, lack of communication and avoidable errors caused up to 80% of them.[5] Through use of safety checklists and continuous training for crews, the incidence of air accidents has continually fallen since then, despite significant increases in the volume of air traffic. These checklists are now used routinely in aviation and other high-complexity industries.[6] Use of checklists offers a singular opportunity to correct any problems before proceeding and provides awareness of situations that are still to come.

Faced with such evidence regarding patient safety, in 2002 the World Health Organization (WHO) adopted resolution 5518 (WHA 55.18), which called on its member countries to strengthen the care taken regarding safety, and demanded standardization of norms in order to construct a culture of surgical safety. Soon afterwards, in May 2004, it launched the campaign "WHO Patient Safety", in which leaders of prominent healthcare institutions, political representatives and patient groups around the world came together with the aim of reducing the numbers of adverse events caused by lack of care for patients.

At the first meeting, in January 2007, difficulties in improving surgical safety were identified and reviewed. The concept of surgery was defined as: "Any procedure that takes place in an operating theater, involving incision, excision, manipulation or suturing of tissues, which would normally require regional anesthesia, general anesthesia or deep sedation in order to control pain". It was recognized that surgical safety is multifactorial and requires reliable implementation of a variety of measures that are needed for attending to patients, not only by the surgeon but also by the entire team of professionals who work together for patients' benefit.

It has been observed that reliability in various areas of medicine can be improved through identifying the care to be provided and standardizing the routines. This can be done through using tools such as safety checklists. The WHO checklist consists of a simple instrument that is divided into three parts or sections. The first part is applied before induction of anesthesia; the second, before the incision in the skin is made; and the third, before the patient leaves the operating theater. These checks make us feel that we are within a system, thus improving communication and preparing us for the unexpected.

The checklist is composed of items such as confirmation of the patient's identity, the location of the surgical site and the type of procedure to be performed; and items relating to checking ventilation and monitoring. The list includes data on the patient's allergies, airways and risk of bleeding, and for anticipating critical events. Within this process, there is a "time out" moment[7] immediately before the skin incision is made, at which all members of the team give verbal confirmation of the patient's identity, the location of the surgical site and the procedure to be performed.

This pause prepares us in the same way as if we were airplane pilots about to take off, with a focus on items that could cause danger.

The WHO checklist was tested in eight countries (Canada, India, Jordan, New Zealand, Philippines, Tanzania, England and United States), using the hypothesis that a simple checklist, consisting of only 19 items, could improve communication between the teams and the consistency of care in the surgical environment, thereby reducing the numbers of complications and deaths.[8] The results among 3,733 patients who had undergone operations before the checklist came into use were compared with those among 3,955 patients whose operations took place after its use had started. Use of the list was found to have reduced the risks of death, infection of the surgical site and reoperation.[9] Indeed: an instrument that took two minute to apply decreased the complication rate by 35% and the mortality rate by 47%.

Meta-analyses have confirmed the importance of sharing information for ensuring that the team's performance reaches effectiveness[10] and have shown that effective communication becomes the key to fundamental process such as coordination, cooperation, cognition and conflict resolution.[11] To facilitate adherence to the WHO checklist, it has been implemented in several counties and institutions around the world and has been adapted to different surgical specialties. There was a clear need to adapt it for use in relation to cardiac and thoracic surgery[12] in order to attend to critical points that are inherent to these specialties, such as prevention of blood loss, inclusion of extracorporeal circulation and details of patient monitoring and management during transportation to the intensive care unit.

The main cardiothoracic surgery associations in the United States (Society of Thoracic Surgeons, STS) and Europe (European Association for Cardio-Thoracic Surgery, EACTS) have made adaptations to the WHO checklist, while taking care not to remove any item. Rather, they have added specific details for this specialty, including small modifications for adult, congenital, thoracic and transplantation-related cardiac surgery.[13] Other features that have been implemented have included two terms used in aeronautics: *briefing*, i.e. important instructions that are passed on to the crew at the outset; and *debriefing*, i.e. a report on the mission after the tasks have been executed.[14] Thus, use of a checklist within cardiothoracic surgery is rated at recommendation level I with evidence level B.

In Brazil, the Ministry of Health has instituted the National Program for Patient Safety (ordinance no. 529/2013), with the aim of contributing to qualification of care in all healthcare services in this country.[15] Resolution no. 36 of the National Agency for Sanitary Surveillance (Agência Nacional de Vigilância Sanitária, ANVISA), of July 25, 2013, strengthens this program through instituting mandatory actions for promoting patient safety and improving the quality of care.[16] Among the actions that this legislation establishes, creation of a specific protocol for safe surgery can be cited.[17] This was drawn up by the Ministry of Health on the basis of the WHO manual "Safe surgery saves lives".

The Heart Institute (Instituto do Coração, InCor) of Hospital das Clínicas, University of São Paulo Medical School (Faculdade de Medicina da Universidade de São Paulo) implemented its checklist (InCor Checklist) in 2014. It sets forth five steps to be taken for safe surgery: *briefing*, *sign in*, *time out*, *sign out* and *debriefing*. The InCor Checklist started to be applied in 2015 and since 2018 has been used in 100% of cardiothoracic operations at this institution.[18] The project to implement this checklist included an educational program composed of standardized classes, teaching material, videos and simulations in scenarios that were set up in the surgical center. Surprisingly, an analysis conducted after five years of use of the InCor Checklist showed that this use was associated with a decrease of 58% in surgical mortality at this institution.[19]

One point that we must emphasize is that standardization of the surgical process should not be limited to the surgical center itself, given that several studies have demonstrated that the majority of errors or adverse events (53% to 70%) occur outside of the surgical room, either before or after the operation.[20] To address this matter, the Surgical Patient Safety System (SURPASS) collaborative group was created.[21] After implementation of this broader and more systemic checklist, the number of complications diminished from 27.3% to 16.7%, the number of reoperations from 2.7% to 1.1% and the hospital mortality rate from 1.5% to 0.8%.

Thus, we have seen that checklists have had an impact as a central part of surgical safety culture. They have taught us that we all work within a system. Checklists have made specialists better, even with the increasing complexity of their tasks, through the requirement for pauses for verification and checking. Although implementation of checklists is still not a rule within surgery, their use forces us to face up to the fact that we were not in a system. Their use also obliges us to embrace values such as humility, discipline and teamworking, which differ from those through which medicine was created, instead of the values of independence, self-sufficiency and autonomy.

It is time to rethink and understand that we must work within a system. This is the great task of the new generation of healthcare professionals. In every field of medicine, knowledge has been increasing and has been bringing complexity and specialization. No matter how individualistic we might wish to be, complexity requires checklists and teamworking because this is a central part of surgical safety culture.

REFERENCES

1. Weiser TG, Regenbogen SE, Thompson KD, et al. An estimation of the global volume of surgery: a modelling strategy based on available data. Lancet. 2008;372(9633):139-44. PMID: 18582931; https://doi.org/10.1016/S0140-6736(08)60878-8.

2. World Health Organization. WHO Guidelines for Safe Surgery 2009. Safe surgery save lives. WHO [Internet]. 2009;125. WHO/IER/PSP/ 2008.08-1E. Available at: http://whqlibdoc.who.int/publications/2009/9789241598552_eng.pdf. Accessed in 2022 (Mar 24).
3. de Vries EN, Ramrattan MA, Smorenburg SM, Gouma DJ, Boermeester MA. The incidence and nature of in-hospital adverse events: A systematic review. Qual Saf Health Care. 2008;17(3):216-33. PMID: 18519629; https://doi.org/10.1136/qshc.2007.023622.
4. Yii Mk, Ng KJ. Risk-adjusted surgical audit with POSSUM scoring system in a developing country. Physiological and Operative Severity Score for the enUmeration of Mortality and morbidity. Br J Surg. 2002;89(1):110-3. PMID: 11851674; https://doi.org/10.1046/j.0007-1323.2001.01979.x.
5. Ross P. Human Factors Issues of the Aircraft Checklist. Journal of Aviation/Aerospace Education & Research. 2004;13(2):4. Available from: https://commons.erau.edu/jaaer/vol13/iss2/4. Accessed in 2022 (Mar 24).
6. Clark SC, Dunning J, Alfieri OR, et al. EACTS guidelines for the use of patient safety checklists. Eur J Cardio-thoracic Surg. 2012;41(5):993-1004. PMID: 22411264; https://doi.org/10.1093/ejcts/ezs009.
7. The Joint Commission. The Universal Protocol. The Universal Protocol for Preventing Wrong Site, Wrong Procedure, Wrong Person Surgery is part of the National Patient Safety Goals chapter of the Joint Commission accreditation manual. Available from: http://www.jointcommission.org/patientSafety/Universalprotocol. Accessed in 2022 (Mar 24).
8. Haynes AB, Weiser TG, Berry WR, et al. A surgical safety checklist to reduce morbidity and mortality in a global population. N Engl J Med. 2009;360(5):491-9. PMID: 19144931; https://doi.org/10.1056/NEJMsa0810119.
9. Weiser TG, Haynes AB, Lashoher A, et al. Perspectives in quality: designing the WHO Surgical Safety Checklist. Int J Qual Health Care. 2010;22(5):365-70. PMID: 20702569; https://doi.org/10.1093/intqhc/mzq039.
10. Mesmer-Magnus JR, Dechurch LA. Information sharing and team performance: a meta-analysis. J Appl Psychol. 2009;94(2):535-46. PMID: 19271807; https://doi.org/10.1037/a0013773.
11. Holleman G, Poot E, Mintjes-de Groot J, van Achterberg T. The relevance of team characteristics and team directed strategies in the implementation of nursing innovations: a literature review. Int J Nurs Stud. 2009;46(9):1256-64. PMID: 19371873; https://doi.org/10.1016/j.ijnurstu.2009.01.005.
12. Clark S, Hamilton L. WHO surgical checklist. Needs to be customised by specialty. BMJ. 2010;340:c589. PMID: 20124374; https://doi.org/10.1136/bmj.c589.
13. Clark SC, Dunning J, Alfieri OR, et al. EACTS guidelines for the use of patient safety checklists. Eur J Cardiothorac Surg. 2012;41(5):993-1004. PMID: 22411264; https://doi.org/10.1093/ejcts/ezs009.
14. Hill MR, Roberts MJ, Alderson ML, Gale TC. Safety culture and the 5 steps to safer surgery: an intervention study. Br J Anaesth. 2015;114(6):958-62. PMID: 25783742; https://doi.org/10.1093/bja/aev063.
15. Ministério da Saúde (Brasil). Portaria nº 529, de 1 de abril de 2013. Institui o Programa Nacional de Segurança do Paciente [Internet]. Diário Oficial da União 2 abr 2013. Available from: http://bvsms.saude.gov.br/bvs/saudelegis/gm/2013/prt0529_01_04_2013.html. Accessed in 2022 (Mar 24).
16. Agência Nacional de Vigilância Sanitária (Brasil). Resolução da Diretoria Colegiada – RDC nº 36 de 25 de julho de 2013. Institui ações para a segurança do paciente em serviços de saúde e dá outras providências. Diário Oficial da União 2013. Available from: https://bvsms.saude.gov.br/bvs/saudelegis/anvisa/2013/rdc0036_25_07_2013.html. Accessed in 2022 (Mar 24).
17. Ministério da Saúde (Brasil). Portaria nº 1.377, de 9 de julho de 2013. Aprova os Protocolos de Segurança do Paciente. Diário Oficial da União, 10 jul 2013. Available from: https://bvsms.saude.gov.br/bvs/saudelegis/gm/2013/prt1377_09_07_2013.html. Accessed in 2022 (Mar 24).
18. Mejia OAV, Lisboa LAF, Caneo LF, et al. Analysis of >100,000 Cardiovascular Surgeries Performed at the Heart Institute and a New Era of Outcomes. Arq Bras Cardiol. 2020;114(4):603-12. PMID: 32074203; https://doi.org/10.36660/abc.20190736.
19. Mejia OAV, de Mendonça FCC, Sampaio LABN, et al. Adherence to the cardiac surgery checklist decreased mortality at a teaching hospital: A retrospective cohort study. Clinics (Sao Paulo). 2022;77:100048. PMID: 35594622; https://doi.org/10.1016/j.clinsp.2022.100048.
20. Griffen FD, Stephens LS, Alexander JB, et al. The American College of Surgeons' closed claims study: new insights for improving care. J Am Coll Surg. 2007;204(4):561-9. PMID: 17382214; https://doi.org/10.1016/j.jamcollsurg.2007.01.013.
21. de Vries EN, Hollmann MW, Smorenburg SM, Gouma DJ, Boermeester MA. Development and validation of the SURgical PAtient Safety System (SURPASS) Checklist. Qual Saf Heal Care. 2009;18(2):121-6. PMID: 19342526; https://doi.org/10.1136/qshc.2008.027524.

https://doi.org/10.1590/1516-3180.2021.0075.R1.14092021

Alcohol consumption is associated with excessive risk of multiple sclerosis: a meta-analysis observational study

Haoyou Xu[I], Lijun Qiao[II], Supeng Fang[III], Zhanneng Ren[IV], Guangliang Wu[V], Yu Zheng[VI], Biying Yang[VII], Yuanqi Zhao[VIII]

Guangdong Provincial Hospital of Chinese Medicine, Second Affiliated Hospital of Guangzhou University of Chinese Medicine, Guangzhou, China

[I]MD. Physician and Associate Professor, Department of Neurology, Guangdong Provincial Hospital of Chinese Medicine, Second Affiliated Hospital of Guangzhou University of Chinese Medicine, Guangzhou, China.
https://orcid.org/0000-0002-2161-7611

[II]PhD. Physician and Associate Professor, Department of Neurology, Guangdong Provincial Hospital of Chinese Medicine, Second Affiliated Hospital of Guangzhou University of Chinese Medicine, Guangzhou, China.
https://orcid.org/0000-0003-1834-3290

[III]BSc. Nurse, Department of Operating Theatre, Guangdong Provincial Hospital of Chinese Medicine, Second Affiliated Hospital of Guangzhou University of Chinese Medicine, Guangzhou, China.
https://orcid.org/0000-0002-7180-6859

[IV]MD. Physician and Assistant Professor, Department of Neurology, Guangdong Provincial Hospital of Chinese Medicine, Second Affiliated Hospital of Guangzhou University of Chinese Medicine, Guangzhou, China.
https://orcid.org/0000-0002-2772-7651

[V]PhD. Physician and Associate Professor, Department of Neurology, Guangdong Provincial Hospital of Chinese Medicine, Second Affiliated Hospital of Guangzhou University of Chinese Medicine, Guangzhou, China.
https://orcid.org/0000-0002-3296-9209

[VI]MD. Physician and Associate Professor, Department of Neurology, Guangdong Provincial Hospital of Chinese Medicine, Second Affiliated Hospital of Guangzhou University of Chinese Medicine, Guangzhou, China.
https://orcid.org/0000-0003-3694-0988

[VII]MD. Physician and Associate Professor, Department of Neurology, Guangdong Provincial Hospital of Chinese Medicine, Second Affiliated Hospital of Guangzhou University of Chinese Medicine, Guangzhou, China.
https://orcid.org/0000-0001-8890-954X

[VIII]PhD. Physician and Professor, Department of Neurology, Guangdong Provincial Hospital of Chinese Medicine, Second Affiliated Hospital of Guangzhou University of Chinese Medicine, Guangzhou, China.
https://orcid.org/0000-0003-1254-6732

KEY WORDS (MeSH terms):
Alcohol drinking.
Multiple sclerosis.
Meta-analysis [publication type].
Psychoneuroimmunology.
Demyelinating diseases.

AUTHORS' KEY WORDS:
Alcohol intake.
Psychoimmunology.
Demyelinating disorders.

ABSTRACT

BACKGROUND: There have been inconsistent results regarding the association between alcohol intake and susceptibility to multiple sclerosis.

OBJECTIVE: To assess the potential role of alcohol intake regarding the risk of multiple sclerosis by using a meta-analytic approach.

DESIGN AND SETTING: Observational meta-analysis study conducted in a hospital in China.

METHODS: The electronic databases of PubMed, EMBASE and the Cochrane library were systematically searched for eligible studies from their inception up to January 2020. The summary odds ratio (OR) with 95% confidence interval (CI) was applied to assess the association between alcohol intake and multiple sclerosis, using a random-effects model.

RESULTS: One prospective cohort study and eight case-control studies involving a total of 211,396 subjects and 10,407 cases of multiple sclerosis were selected for the final meta-analysis. From the pooled data, no significant association between alcohol intake and multiple sclerosis risk was found (OR: 0.94; 95% CI: 0.73-1.22; P = 0.668), and this conclusion was judged to be robust. Subgroup analysis found that intake of beer was associated with an increased risk of multiple sclerosis (OR: 1.58; 95% CI: 1.12-2.23; P = 0.010).

CONCLUSION: This study found that beer intake could cause an excess risk of multiple sclerosis. Further large-scale prospective studies should be conducted to verify this conclusion.

INTRODUCTION

Multiple sclerosis is an autoimmune disease of the central nervous system and is characterized by multifocal inflammatory demyelination and secondary axonal degeneration.[1] It is a common neurological disorder and affects more than 2.3 million people worldwide. The most susceptible portion of the population is young adults.[2,3] There is ample evidence to suggest that behaviorally and environmentally modifiable lifestyle factors could affect the progression, severity, symptoms and/or comorbidities of autoimmune diseases.[4,5] Moreover, progression of multiple sclerosis might be balanced through changes to lifestyle, given that its progression involves inflammatory, metabolic and neurodegenerative disease processes.[6-8]

Studies have found that a healthy lifestyle could slow the progression and severity of multiple sclerosis. This indicates that a secondary prevention strategy should be applied to avoid deterioration due to multiple sclerosis.[9,10] Smoking and alcohol intake have been identified as risk factors for autoimmune diseases. However, whether alcohol intake could affect the progression of multiple sclerosis remains a matter of debate.[11,12] A study conducted by Hedström et al. found that alcohol intake presented a dose-dependent inverse association with multiple sclerosis.[13] On the other hand, Massa et al. found that alcohol intake was not associated with the risk of multiple sclerosis.[14]

OBJECTIVE

Clarifying the role of alcohol intake regarding the risk of multiple sclerosis is particularly important in the general population. We therefore attempted to undertake a comprehensive examination of published articles, in order to assess the association of alcohol intake with the risk of multiple sclerosis. Moreover, stratified analyses were also performed to assess whether the association between alcohol intake and multiple sclerosis might differ on the basis of study design, sex, type of alcohol or study quality.

METHODS

Data sources, search strategy and selection criteria

The Preferred Reporting Items for Systematic Reviews and Meta-Analysis (PRISMA) statement published in 2009 was used to guide the conduct of this meta-analysis.[15] Eligible studies investigating the association between alcohol intake and multiple sclerosis risk were identified. The PubMed, EMBASE and Cochrane library databases were systematically searched to identify eligible studies up to January 2020, and the following core terms were applied: ("alcohol" or "beer" or "wine" or "hard liquor") AND "multiple sclerosis". The reference lists of relevant studies or reviews were also evaluated in order to select any new study that might meet the inclusion criteria.

The details of the inclusion criteria used in this study were as follows: 1) Study design: prospective cohort or case-control studies; 2) Exposure: alcohol intake, irrespective of the type of alcohol or alcohol dose; 3) Outcome: incidence of multiple sclerosis; and 4) the study needed to report on effect estimates, in order to make comparisons between high and low alcohol intake, regarding the risk of multiple sclerosis. The study selection process was conducted by two authors independently, and any conflicts were resolved through discussion with each other until a consensus was reached.

Data collection and quality assessment

The abstracted information included the first author's surname, publication year, country, study design, sample size, number of cases, age, percentage males, definition of alcohol intake, covariates in the full adjusted model and effect estimate with its 95% confidence interval (CI). Effect estimates that had been maximally adjusted for covariates were selected if the study reported several adjusted effect estimates. The quality of the studies included was assessed by using the Newcastle-Ottawa scale (NOS), which is based on selection (four items), comparability (one item) and outcome (three items), and the scoring system (expressed as a number of stars) ranged from 0 to 9 for each individual study.[16]

Statistical analysis

The association between alcohol intake and the risk of multiple sclerosis was examined based on the effect estimate with 95% confidence interval (CI) for each study. The pooled odds ratio (OR) with 95% CI was then assessed using a random-effects model.[17,18] Heterogeneity across the studies included was assessed using I^2 and Q statistics. $I^2 > 50.0\%$ or $P < 0.10$ for the Q statistic was regarded as representing significant heterogeneity.[19,20] The robustness of the pooled conclusion was assessed using sensitivity analysis, by means of sequentially excluding each study.[21] Subgroup analyses were conducted based on study design, sex, alcohol type and study quality, and differences between groups were assessed using an interaction test.[22] Publication bias was assessed by means of funnel plots, Egger tests and Begg tests.[23,24] The inspection level for all pooled results was two-sided, and $P < 0.05$ was regarded as denoting a significant association between alcohol intake and multiple sclerosis risk. All statistical analyses in this meta-analysis were conducted using the Stata software (version 10.0; Stata Corporation, College Station, Texas, United States).

RESULTS

Literature search

A total of 643 articles were identified from the initial electronic search, of which 240 were excluded because of duplicate titles. A further 361 studies were then excluded because of irrelevant titles. The remaining 42 studies were identified as meriting further full-text evaluations. Out of these, 33 studies were subsequently excluded, for the following reasons: other risk factors were addressed (n = 17); the patients already had multiple sclerosis (n = 12), whereas the aim of the present review was to assess the potential role of alcohol intake on the risk of multiple sclerosis and thus participants needed to be without this disease upon initial enrollment; or the study consisted of a review or meta-analysis (n = 4). No additional eligible study was found through reviewing the reference lists of the remaining studies that had been retrieved. In the end, nine studies that included a total of 211,396 subjects and 10,407 cases of multiple sclerosis were selected for the final meta-analysis.[13,14,25-31] The details of the study selection are presented in **Figure 1**.

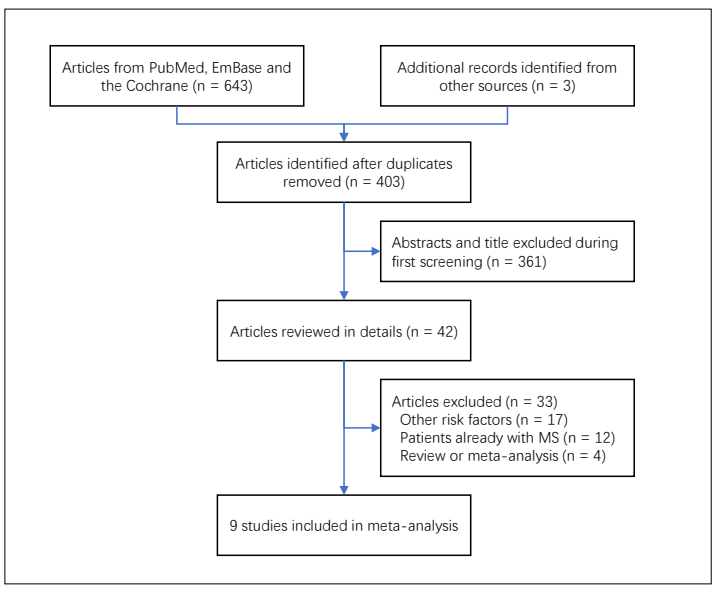


Figure 1. Flow diagram for the study selection process.

Study characteristics

The baseline characteristics of the studies included and participants are summarized in **Table 1**. There was one study with a prospective cohort design, and the remaining eight studies were of case-control design. The sample size of the studies included ranged from 153 to 187,326, while 94 to 6,619 cases of multiple sclerosis were included in each study. Five studies were conducted in Europe, three studies were conducted in the United States or Canada, and the one remaining study was conducted in Iran. Study quality was assessed using the NOS: six studies had seven stars, two studies had six stars and the one remaining study had five stars.

Meta-analysis

After pooling all the studies included, we noted that alcohol intake was not associated with the risk of multiple sclerosis (OR: 0.94; 95% CI: 0.73-1.22; P = 0.668; **Figure 2**). Moreover, significant heterogeneity was seen across these studies (I^2 = 88.1%; P < 0.001). The result from the sensitivity analysis suggested that it could be concluded that the data were robust and were not changed by sequentially excluding individual studies (**Figure 3**).

Subgroup analysis

Subgroup analysis on the association between alcohol intake and multiple sclerosis risk was conducted based on study design, sex, type of alcohol and study quality (**Table 2**). We noted that beer intake was associated with an increased risk of multiple sclerosis (OR: 1.58; 95% CI: 1.12-2.23; P = 0.010). Moreover, although no significant association between alcohol intake and multiple sclerosis risk was seen when males and females were analyzed together, there was a statistically significant difference between subgroups (P = 0.001). Similarly, although study quality could have affected the association between alcohol intake and multiple sclerosis risk, alcohol intake did not affect the risk of multiple sclerosis, irrespective of whether the pooled studies were of high quality or low quality (P = 0.022).

Publication bias

The publication bias regarding the association of alcohol intake with the risk of multiple sclerosis is displayed in **Figure 4**. No significant publication bias was detected by using the Egger test (P = 0.339) or Begg test (P = 0.721).

Table 1. Baseline characteristics of studies included in the meta-analysis

Study	Country	Study design	Sample size	Number of cases	Age (years)	Percentage males (%)	Definition of alcohol intake	Adjusted factors	Study quality
Brosseau et al.[25]	Canada	Case-control	216	108	38.5	N/A	Self-administered questionnaire	Sex, age and same post-diagnostic period	5
Ghadirian et al.[26]	Canada	Case-control	399	197	39.0	31.3	Self-administered questionnaire	Age, sex and phone number	7
Pekmezovic et al.[27]	Serbia	Case-control	420	210	33.8	26.7	Self-administered questionnaire	Sex, age and residence in Belgrade district	6
Kotzamani et al.[28]	Greece	Case-control	1,250	657	43.6	38.2	Self-administered questionnaire	Age, sex and current residence	7
Massa et al.[14]	USA	Prospective cohort	187,326	258	25.0-55.0	0.0	Self-administered questionnaire	Age, total intake of vitamin D, residence at age 15 years, pack years of smoking and ethnicity	7
Hawkes et al.[29]	UK	Case-control	153	94	22.0-55.0	N/A	Self-administered questionnaire	Age of first symptoms, sex and smoking	6
Hedström et al.[13]	Sweden	Case-control cohort 1	2,506	745	16.0-70.0	24.8	Self-administered questionnaire	Age, sex and residential area	7
		Case-control cohort 2	11,120	5,874		26.9			
Abdollahpour et al.[30]	Iran	Case-control	1,604	547	31.0	41.1	Self-administered questionnaire	Age, sex, drug abuse, passive smoking, water-pipe smoking, tobacco smoking, sun exposure and current SES	7
Andersen et al.[31]	Denmark	Case-control	6,402	1,717	15.0-19.0	48.1	Self-administered questionnaire	Age, smoking at ages 15-19, body mass index at age 20, education and heredity.	7

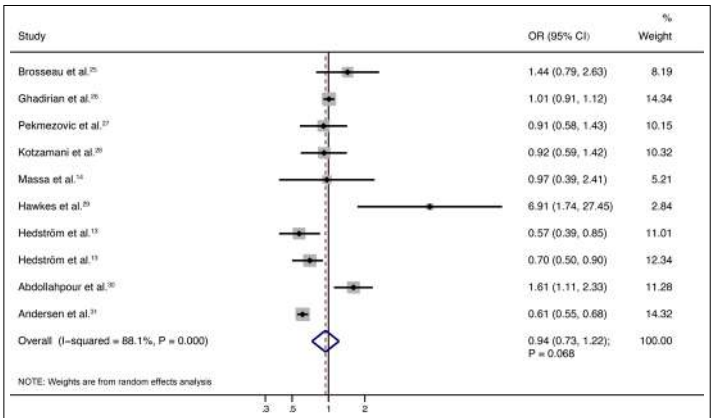
N/A = not available; USA = United States of America; UK = United Kingdom; SES = socioeconomic status.

DISCUSSION

The symptoms of multiple sclerosis are wide-ranging, including visual impairment, muscle weakness, sensory impairment and pain, which may be associated with increased risk of mood disorders and suicidal ideation. Whether drinking habits could affect the risk of multiple sclerosis has not been well studied, although the symptoms of multiple sclerosis are often correlated with alcohol disorders. Our meta-analysis was conducted on the basis of published articles and explored any potential role that alcohol intake might have in relation to subsequent multiple sclerosis risk. This study combined a total of 211,396 subjects and 10,407 cases of multiple sclerosis from one prospective cohort study and eight case-control studies across a wide range of characteristics among these individuals. We found that alcohol intake was not associated with the risk of multiple sclerosis, and this conclusion was relatively stable. Moreover, subgroup analysis found that beer intake was associated with an excess risk of multiple sclerosis.

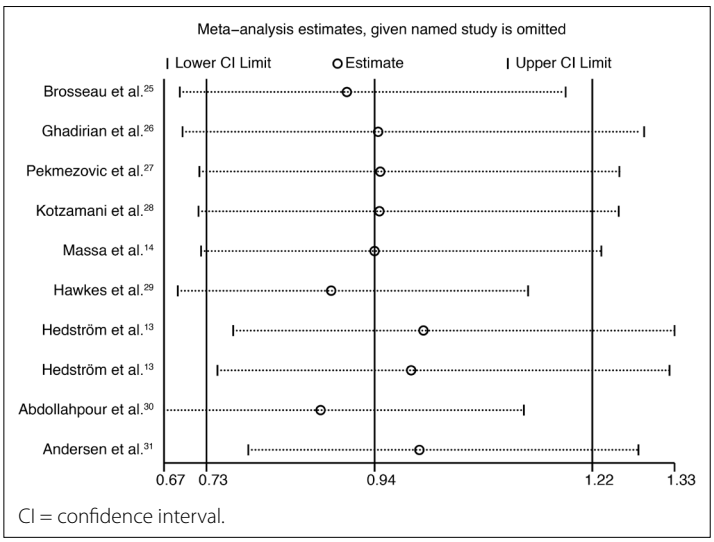
A previous meta-analysis on seven studies found that alcohol intake was not associated with the risk of multiple sclerosis, and that conclusion was not altered by using sensitivity and subgroup analysis.[32] Moreover, it was found that alcohol intake might protect against the risk of multiple sclerosis in the general population, while it caused a harmful effect on the risk of multiple sclerosis among people with other diseases. However, these effects were not associated with statistically significant differences.

Nevertheless, additional new published studies should be entered into the meta-analysis, and the conclusion regarding the association between alcohol intake and multiple sclerosis risk needs to be updated. Furthermore, there is a need to explore whether the type of alcohol intake yields different results in relation to the risk of multiple sclerosis. Hence, the current updated meta-analysis was conducted to systematically assess the role of alcohol intake and subsequent multiple sclerosis risk.



OR = odds ratio; CI = confidence interval.

Figure 2. Association between alcohol intake and the risk of multiple sclerosis.



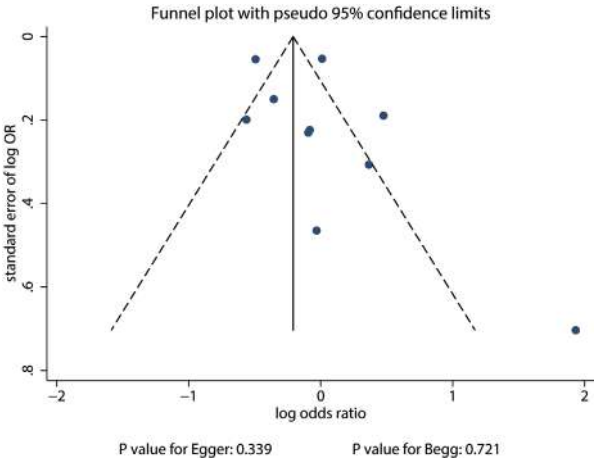
CI = confidence interval.

Figure 3. Sensitivity analysis on the association between alcohol intake and the risk of multiple sclerosis.

Table 2. Subgroup analysis on the association between alcohol intake and the risk of multiple sclerosis, based on study design, sex, type of alcohol and study quality

Factors	Subgroups	Number of studies	OR and 95% CI	P-value	Heterogeneity (I^2)	P-value for I^2	P-value between subgroups
Study design	Prospective cohort	1	0.97 (0.39-2.41)	0.948	-	-	0.700
	Case-control	8	0.94 (0.72-1.24)	0.679	89.4	< 0.001	
Sex	Male	3	1.21 (0.89-1.63)	0.223	80.2	< 0.001	0.001
	Female	4	0.94 (0.67-1.34)	0.742	90.5	< 0.001	
Type of alcohol	Liquor	2	1.33 (0.38-4.74)	0.656	89.0	0.003	0.758
	Beer	2	1.58 (1.12-2.23)	0.010	0.0	0.621	
	Wine	2	1.41 (0.77-2.57)	0.270	54.1	0.140	
Study quality	High	6	0.85 (0.64-1.12)	0.241	90.4	< 0.001	0.022
	Low	3	1.63 (0.72-3.69)	0.239	74.9	0.018	

OR = odds ratio; CI = confidence interval.



OR = odds ratio.

Figure 4. Publication bias for the association between alcohol intake and the risk of multiple sclerosis.

There was no significant association between alcohol intake and the risk of multiple sclerosis when all of the studies included were pooled. Although most of the studies included reported similar conclusions, it has been found in several other studies that alcohol intake may present beneficial or harmful effects regarding the risk of multiple sclerosis. Hawkes et al. found that alcohol intake was associated with an increased risk of multiple sclerosis after adjustments for the age at which the first symptoms appeared, sex and smoking.[29] However, that study had a smaller sample size and included cases of pre-existing multiple sclerosis, and the result was not robust. Hedström et al. found that alcohol intake displayed a dose-dependent inverse relationship regarding the risk of multiple sclerosis. Moreover, alcohol intake could balance the potential role of smoking in relation to the risk of multiple sclerosis.[13] In addition, Abdollahpour et al. suggested that alcohol intake was significantly associated with an increased risk of multiple sclerosis.[30] Lastly, Andersen et al. suggested that alcohol intake during adolescence plays a protective role regarding the risk of multiple sclerosis, irrespectively for males or females.[31] The potential reason for this could be that alcohol might have a dose-dependent immunomodulatory property.[33,34] Alcohol could cross the blood-brain barrier and affect the immune and nervous systems.

Through subgroup analysis, it was found that beer intake might have a harmful effect regarding the risk of multiple sclerosis. This result may be explained by the findings from the study conducted by Abdollahpour et al., in which it was found that alcohol intake was associated with an increased risk of multiple sclerosis, irrespective of the type of alcohol.[30] On the other hand, this result was calculated on the basis of only two studies and the pooled conclusion was variable. Furthermore, we noted that the potential role of alcohol intake regarding the risk of multiple sclerosis differed between males and females, although the protective or harmful effect trends were not associated with any statistically significant difference. In addition, the association between alcohol intake and the risk of multiple sclerosis could be affected by study quality. Potential differences in this regard might be correlated with immunomodulatory properties, dose of alcohol intake and the evidence level of published articles.

Several limitations of this meta-analysis need to be acknowledged: 1) the analysis contained both prospective and retrospective observational studies, and the results may have been affected by selection, recall and confounder biases; 2) the dose-response relationship for the role of alcohol intake in relation to multiple sclerosis risk was not investigated because the analysis needed restricted cubic splines with three knots at fixed percentiles of 10%, 50%, and 90% of the distribution, which was not available from the studies included; 3) the adjusted covariates across the studies included were different, which could have affected the association between alcohol intake and the risk of multiple sclerosis; and 4) there are inherent limitations to any meta-analysis based on published articles, including the fact that the analysis was not based on individual patient data and the inevitable publication bias.

CONCLUSION

This study found that alcohol intake was not associated with the risk of multiple sclerosis, whereas beer intake was associated with an increased risk of multiple sclerosis. Moreover, the role of alcohol intake on the risk of multiple sclerosis might differ between males and females, which needs further verification through a large-scale prospective cohort study.

REFERENCES

1. Koch MW, Metz LM, Agrawal SM, Yong VW. Environmental factors and their regulation of immunity in multiple sclerosis. J Neurol Sci. 2013;324(1-2):10-6. PMID: 23154080; https://doi.org/10.1016/j.jns.2012.10.021.
2. Murray TJ. Diagnosis and treatment of multiple sclerosis. BMJ. 2006;332(7540):525-7. PMID: 16513709; https://doi.org/10.1136/bmj.332.7540.525.
3. Multiple Sclerosis International Federation. Atlas of MS 2013: Mapping Multiple Sclerosis Around the World; 2013. Available from: http://www.msif.org/wp-content/uploads/2014/09/Atlas-of-MS.pdf. Accessed in 2021 (Sep 16).
4. Coetzee T, Thompson A. When are we going to take modifiable risk factors more seriously in multiple sclerosis? Mult Scler. 2017;23(4):494-5. PMID: 28287364; https://doi.org/10.1177/1352458517694433.
5. Hempel S, Graham GD, Fu N, et al. A systematic review of modifiable risk factors in the progression of multiple sclerosis. Mult Scler. 2017;23(4):525-33. PMID: 28151053; https://doi.org/10.1177/1352458517690270.

6. Trapp BD, Nave KA. Multiple sclerosis: an immune or neurodegenerative disorder? Annu Rev Neurosci. 2008;31:247-69. PMID: 18558855; https://doi.org/10.1146/annurev.neuro.30.051606.094313.
7. Mahad DH, Trapp BD, Lassmann H. Pathological mechanisms in progressive multiple sclerosis. Lancet Neurol. 2015;14(2):183-93. PMID: 25772897; https://doi.org/10.1016/s1474-4422(14)70256-x.
8. Heidker RM, Emerson MR, LeVine SM. Metabolic pathways as possible therapeutic targets for progressive multiple sclerosis. Neural Regen Res. 2017;12(8):1262-7. PMID: 28966637; https://doi.org/10.4103/1673-5374.213542.
9. Jelinek GA, De Livera AM, Marck CH, et al. Associations of Lifestyle, Medication, and Socio-Demographic Factors with Disability in People with Multiple Sclerosis: An International Cross-Sectional Study. PLoS One. 2016;11(8):e0161701. PMID: 27560626; https://doi.org/10.1371/journal.pone.0161701.
10. Paz-Ballesteros WC, Monterrubio-Flores EA, de Jesus Flores-Rivera J, Corona-Vazquez T, Hernandez-Giron C. Cigarette Smoking, Alcohol Consumption and Overweight in Multiple Sclerosis: Disability Progression. Arch Med Res. 2017;48(1):113-20. PMID: 28577864; https://doi.org/10.1016/j.arcmed.2017.03.002.
11. Degelman ML, Herman KM. Smoking and multiple sclerosis: A systematic review and meta-analysis using the Bradford Hill criteria for causation. Mult Scler Relat Disord. 2017;17:207-16. PMID: 29055459; https://doi.org/10.1016/j.msard.2017.07.020.
12. Costenbader KH, Gay S, Alarcon-Riquelme ME, Iaccarino L, Doria A. Genes, epigenetic regulation and environmental factors: which is the most relevant in developing autoimmune diseases? Autoimmun Rev. 2012;11(8):604-9. PMID: 22041580; https://doi.org/10.1016/j.autrev.2011.10.022.
13. Hedström AK, Hillert J, Olsson T, Alfredsson L. Alcohol as a modifiable lifestyle factor affecting multiple sclerosis risk. JAMA Neurol. 2014;71(3):300-5. PMID: 24395432; https://doi.org/10.1001/jamaneurol.2013.5858.
14. Massa J, O'Reilly EJ, Munger KL, Ascherio A. Caffeine and alcohol intakes have no association with risk of multiple sclerosis. Mult Scler. 2013;19(1):53-8. PMID: 22641303; https://doi.org/10.1177/1352458512448108.
15. Moher D, Liberati A, Tetzlaff J, Altman DG. Preferred reporting items for systematic reviews and meta-analyses: the PRISMA statement. PLoS Med. 2009;6(7):e1000097. PMID: 19621072; https://doi.org/10.1371/journal.pmed.1000097.
16. Wells G, Shea B, O'Connell D. The Newcastle-Ottawa Scale (NOS) for assessing the quality of nonrandomised studies in meta-analyses. Ottawa (ON): Ottawa Hospital Research Institute 2009. Available from: http://www.ohri.ca/programs/clinical_ epidemiology/oxford.htm. Accessed in 2022 (Mar 22).
17. DerSimonian R, Laird N. Meta-analysis in clinical trials. Control Clin Trials. 1986;7(3):177-88. PMID: 3802833; https://doi.org/10.1016/0197-2456(86)90046-2.
18. Ades AE, Lu G, Higgins JP. The interpretation of random-effects meta-analysis in decision models. Med Decis Making. 2005;25(6):646-54. PMID: 16282215; https://doi.org/10.1177/0272989x05282643.
19. Deeks JJ HJ, Altman DG. Analysing Data and Undertaking Meta-Analyses. In: Higgins J GS, editor. Cochrane Handbook for Systematic Reviews of Interventions. UK: Oxford; 2008. p. 243-96.
20. Higgins JP, Thompson SG, Deeks JJ, Altman DG. Measuring inconsistency in meta-analyses. BMJ. 2003;327(7414):557-60. PMID: 12958120; https://doi.org/10.1136/bmj.327.7414.557.
21. Tobias A. Assessing the influence of a single study in the meta-analysis estimate. Stata Technical Bulletin. 1999;8(47). Available from: https://ideas.repec.org/a/tsj/stbull/y1999v8i47sbe26.html. Accessed in 2021 (Sep 20).
22. Altman DG, Bland JM. Interaction revisited: the difference between two estimates. BMJ. 2003;326(7382):219. PMID: 12543843; https://doi.org/10.1136/bmj.326.7382.219.
23. Egger M, Davey Smith G, Schneider M, Minder C. Bias in meta-analysis detected by a simple, graphical test. BMJ. 1997;315(7109):629-34. PMID: 9310563; https://doi.org/10.1136/bmj.315.7109.629.
24. Begg CB, Mazumdar M. Operating characteristics of a rank correlation test for publication bias. Biometrics. 1994;50(4):1088-101. PMID: 7786990.
25. Brosseau L, Philippe P, Methot G, Duquette P, Haraoui B. Drug abuse as a risk factor of multiple sclerosis: case-control analysis and a study of heterogeneity. Neuroepidemiology. 1993;12(1):6-14. PMID: 8327025; https://doi.org/10.1159/000110294.
26. Ghadirian P, Jain M, Ducic S, Shatenstein B, Morisset R. Nutritional factors in the aetiology of multiple sclerosis: a case-control study in Montreal, Canada. Int J Epidemiol. 1998;27(5):845-52. PMID: 9839742; https://doi.org/10.1093/ije/27.5.845.
27. Pekmezovic T, Drulovic J, Milenkovic M, et al. Lifestyle factors and multiple sclerosis: A case-control study in Belgrade. Neuroepidemiology. 2006;27(4):212-6. PMID: 17095875; https://doi.org/10.1159/000096853.
28. Kotzamani D, Panou T, Mastorodemos V, et al. Rising incidence of multiple sclerosis in females associated with urbanization. Neurology. 2012;78(22):1728-35. PMID: 22592376; https://doi.org/10.1212/WNL.0b013e31825830a9.
29. Hawkes CH, Boniface D. Risk associated behavior in premorbid multiple sclerosis: A case-control study. Mult Scler Relat Disord. 2014;3(1):40-7. PMID: 25877972; https://doi.org/10.1016/j.msard.2013.05.002.
30. Abdollahpour I, Nedjat S, Mansournia MA, Sahraian MA, van der Mei I. Lifestyle factors and multiple sclerosis: A population-based incident case-control study. Mult Scler Relat Disord. 2018;22:128-33. PMID: 29677591; https://doi.org/10.1016/j.msard.2018.03.022.
31. Andersen C, Søndergaard HB, Bang Oturai D, et al. Alcohol consumption in adolescence is associated with a lower risk of multiple sclerosis in a Danish cohort. Mult Scler. 2019; 25(12):1572-9. PMID: 30124094; https://doi.org/10.1177/1352458518795418.
32. Zhu T, Ye X, Zhang T, et al. Association between alcohol consumption and multiple sclerosis: a meta-analysis of observational studies. Neurol Sci. 2015;36(9):1543-50. PMID: 26160450; https://doi.org/10.1007/s10072-015-2326-7.
33. Goral J, Karavitis J, Kovacs EJ. Exposure-dependent effects of ethanol on the innate immune system. Alcohol. 2008;42(4):237-47. PMID: 18411007; https://doi.org/10.1016/j.alcohol.2008.02.003.

34. Mandrekar P, Catalano D, White B, Szabo G. Moderate alcohol intake in humans attenuates monocyte inflammatory responses: inhibition of nuclear regulatory factor kappa B and induction of interleukin 10. Alcohol Clin Exp Res. 2006;30(1):135-9. PMID: 16433741; https://doi.org/10.1111/j.1530-0277.2006.00012.x.

Authors' contributions: All authors contributed to manuscript writing or revising, and read and approved the final manuscript. We all agree to be accountable for all aspects of the work and for ensuring that questions relating to the accuracy or integrity of any part of the work are appropriately investigated and resolved. Other substantial contributions in detail: Xu H: Study design, data acquisition, data analysis, data interpretation; Zhao Y: Study design, literature research; Qiao L: Study design, literature research; Wu G: Literature research, data interpretation; Zheng Y: acquisition, analysis and interpretation of data for the work (equal); Yang B: acquisition, analysis and interpretation of data for the work (equal); Fang S: acquisition, analysis and interpretation of data for the work (equal); Ren Z: acquisition, analysis and interpretation of data for the work (equal).

Sources of funding: This study was supported by Guangdong Provincial Key Laboratory of Research on Emergency in Traditional Chinese Medicine [grant number 2017B030314176]; special support for scientific and technological research in traditional Chinese medicine of Guangdong Provincial Hospital of Traditional Chinese Medicine [grant number YN2019MJ07]; and special fund for science and technology innovation strategy of Guangdong Province [grant number 2020A1515010595]
Conflicts of interest: None

Date of first submission: January 28, 2021
Last received: July 28, 2021
Accepted: September 14, 2021

Address for correspondence:
Haoyou Xu
Guangdong Provincial Hospital of Chinese Medicine, Second Affiliated Hospital of Guangzhou University of Chinese Medicine
No. 111, Dade Road, Yuexiu District, Guangzhou, Guangdong
Tel (+86) 020 8188 7233 — Fax (+86) 020 8186 7705
E-mail: xuhaoyou123@126.com

Awareness towards stroke among high school students in Brazil: a cross-sectional study

Mateus de Sousa Rodrigues[I], Leonardo Fernandes e Santana[II], Alanderson Passos Fernandes Castro[III], Karyne Krysley Almeida Coelho[IV], Manoel Pereira Guimarães[V], Orlando Vieira Gomes[VI], Paulo Adriano Schwingel[VII], Renato Bispo de Cerqueira Filho[VIII], Marcos Duarte Guimarães[IX], José Carlos de Moura[X]

Universidade Federal do Vale do São Francisco (UNIVASF), Petrolina (PE), Brazil

[I]Undergraduate Medical Student, Universidade Federal do Vale do São Francisco (UNIVASF), Petrolina (PE), Brazil
https://orcid.org/0000-0003-4664-2351

[II]Undergraduate Medical Student, Universidade Federal do Vale do São Francisco (UNIVASF), Petrolina (PE), Brazil
https://orcid.org/0000-0001-7729-8392

[III]Undergraduate Medical Student, Universidade Federal do Vale do São Francisco (UNIVASF), Petrolina (PE), Brazil
https://orcid.org/0000-0002-7745-0013

[IV]Undergraduate Medical Student, Universidade Federal do Vale do São Francisco (UNIVASF), Petrolina (PE), Brazil
https://orcid.org/0000-0001-7004-0348

[V]Undergraduate Medical Student, Universidade Federal do Vale do São Francisco (UNIVASF), Petrolina (PE), Brazil
https://orcid.org/0000-0001-7780-8946

[VI]MSc. Professor, School of Medicine, Universidade Federal do Vale do São Francisco (UNIVASF), Petrolina (PE), Brazil
https://orcid.org/0000-0001-6324-7594

[VII]PhD. Professor, Human Performance Research Laboratory, Universidade de Pernambuco (UPE), Pernambuco (PE), Brazil
https://orcid.org/0000-0002-2935-3403

[VIII]MD. Professor, School of Medicine, Universidade Federal do Vale do São Francisco (UNIVASF), Petrolina (PE), Brazil
https://orcid.org/0000-0001-6946-643X

[IX]PhD. Professor, School of Medicine, Universidade Federal do Vale do São Francisco (UNIVASF), Petrolina (PE), Brazil
https://orcid.org/0000-0002-9458-5649

[X]PhD. Professor, School of Medicine, Universidade Federal do Vale do São Francisco (UNIVASF), Petrolina (PE), Brazil
https://orcid.org/0000-0001-6943-1560

KEY WORDS (MeSH terms):
Stroke.
Risk factors.
Education.
Awareness.
Surveys and questionnaires.

AUTHORS' KEY WORDS:
Cerebrovascular accident.
Self-structured questionnaire survey.
Situation awareness.

ABSTRACT

BACKGROUND: Stroke is one of the main causes of death worldwide. Educational interventions on stroke are potentially effective in reducing the period between the onset of symptoms and the initial emergency medical assistance.

OBJECTIVE: To assess high school students' knowledge of stroke.

DESIGN AND SETTING: Cross-sectional study conducted in high schools in northeastern Brazil.

METHODS: A self-structured questionnaire survey regarding stroke awareness was applied among high school students in northeastern Brazil. Data were collected between 2018 and 2019. The chi-square test and other descriptive statistics were used. Univariate and multivariate analyses were performed using logistic regression.

RESULTS: A total of 1,788 students were analyzed. Eighty percent (n = 1430) of them did not have the minimum knowledge on how to act in a stroke situation. Only 10% (n = 179) presented the ideal knowledge on how to act. Males presented lower levels of knowledge on risk factors (odds ratio, OR: 0.62%; 95% confidence interval, CI: 0.49-0.79) and signs and symptoms of stroke (OR: 0.63%; 95% CI: 0.52-0.77). Students with ≥ 10 years of schooling (OR: 1.64%; 95% CI: 1.30-2.07) demonstrated greater knowledge of signs and symptoms of stroke. Students aged 18 years (OR: 1.70%; 95% CI: 1.14-2.52) demonstrated greater knowledge than other ages regarding the telephone number of the emergency medical services.

CONCLUSIONS: There was a knowledge deficit with regard to recognizing stroke and activating the emergency medical services. The findings apply to the sample investigated and suggest that there is a need for stroke educational interventions, starting in high school.

INTRODUCTION

Stroke is one of the main causes of morbidity and mortality worldwide.[1] In addition to affecting individuals, it also requires significant expenditure from healthcare budgets.

Developing countries, such as Brazil, are in epidemiological transition, characterized by a drop in the incidence of infectious diseases and, at the same time, an accumulation of modifiable and non-modifiable risk factors for chronic non-communicable diseases (CNCDs).[2] Analogously, CNCDs are risk factors for stroke and other vasculopathies, and it may therefore be foreseen that aging of the population will be accompanied by significantly increased incidence of stroke.[3]

Educational measures regarding stroke are potentially effective in reducing the critical period between the onset of symptoms and the initial emergency medical assistance.[4] Early recognition of stroke is of utmost importance because it can modify the natural course of the disease by enabling specific treatment strategies in its early stages. Based on this assumption, it is therefore imperative that the population should possess knowledge concerning stroke; be able to recognize the risk factors, signs and symptoms; and be aware of preventive measures for this condition, as well as the correct conduct when faced with a stroke.[5]

With this in mind, it can be understood that this knowledge is important for the young population, since many of these individuals, after leaving high school, will take up jobs in places with large gatherings of people, such as shopping malls, airports or parks. They should therefore be able to recognize the signs and symptoms of stroke, so that the emergency services can be called. This scenario should therefore be seen as an ideal substrate for dissemination of preventive and health promotion measures, in order to minimize the negative impact of this nosological entity.

OBJECTIVE

The aim of the present study was to assess the knowledge of high school students about stroke.

METHODS

This was a cross-sectional study conducted in five municipalities in northeastern Brazil (Petrolina, Afrânio, Dormentes, Salgueiro and Cedro) between August 2018 and July 2019. Volunteer high school students agreed to participate in the study and respond to the data collection instrument in the form of a questionnaire. The following inclusion criteria were adopted: (I) aged between 15 and 18 years and (II) attending a public high school. Those who did not complete the entire questionnaire were excluded.

The questionnaire was prepared specifically for this study and was based on a review of the literature encompassing other studies that had also assessed the level of knowledge regarding stroke in their respective target audiences. Each participant was required to answer the following questions: 1) Do you know what a stroke is? 2) Can you indicate at least three signs or symptoms of a stroke? 3) Can you indicate at least three risk factors for a stroke? 4) What would you do in a stroke situation? and 5) What is the telephone number of the emergency medical services (Serviço de Atendimento Móvel de Urgência, SAMU) in Brazil? Sociodemographic data such as age, sex and schooling were also collected.

In accordance with the definition used in the present study, knowledge of stroke was assessed based on the ability to make decisions when faced with a stroke situation. It was classified into three levels: a) ideal (able to recognize three symptoms and three risk factors, and knowing how to activate the emergency medical services); b) minimum required (able to recognize one symptom and one risk factor, and knowing how to activate the emergency medical services); and c) below the minimum (not meeting any of the abovementioned characteristics).

Thus, respecting the ethical principles of the Declaration of Helsinki (1964), ethical approval was obtained from the Universidade Federal do Vale do São Francisco (UNIVASF); under protocol No. 3.609.473; date: September 30, 2019. During the survey, no subject consent was required because no identifiable data were collected. The final survey instrument contained eight items (**Annex 1**).

RESULTS

A total of 1,870 questionnaires were obtained, of which 82 were excluded due to insufficient data. Thus, the final analysis included a spectrum of 1788 students, of whom 982 (54.9%) were female and 806 were male (45.1%), as presented in **Table 1**. The participants were aged between 15 and 18 years. There were 882 students (49.3%) with 10 years of schooling; 538 students (30.1%) with 11 years; and 368 students (20.6%) with 12 years (**Table 1**).

The Brazilian acronym for stroke ("AVC") was recognized by 77.8% (n = 1,368) of the participants (**Table 1**). However, 58.6% (n = 1,047) of the students did not know any signs and symptoms of stroke. Only 14.0% (n = 250) of the participants knew three or more signs and symptoms of stroke, and 79.0% (n = 1,413) were unaware of the risk factors for the disease. Only 10.9% (n = 194) knew three or more risk factors for stroke. A total of 70.6% (n = 1,262) of the students were unaware of the telephone number of the emergency medical services (192) (**Table 1**).

With regard to the ability to act in the event of a stroke, 80% of the students interviewed did not have the minimum knowledge on how to proceed when faced with this event, and only 10% demonstrated that they had the ideal knowledge on how to act, as presented in **Figure 1**.

Based on the odds ratio calculated for the association between basic characteristics and knowledge of stroke, males presented lower knowledge regarding risk factors (odds ratio, OR: 0.62%; 95% confidence interval, CI: 0.49-0.79) and signs and symptoms of stroke (OR: 0.63%; 95% CI: 0.52-0.77). Students with more than 10 years of schooling (OR: 1.64%; 95% CI: 1.30-2.07) presented greater knowledge of the signs and symptoms of stroke. Students aged 18 years (OR: 1.70%; 95% CI: 1.14-2.52) knew the emergency medical services telephone number more often than those of other ages (**Table 2**).

Table 1. Demographics and stroke knowledge mentioned by participants (n = 1,788)

Variables	n	%
Sex		
Male	806	45.1
Female	982	54.9
Years of schooling		
10	882	49.3
11	538	30.1
12	368	20.6
I know what stroke is		
Yes	1,368	76.5
No	420	23.5
I know some signs and symptoms for stroke		
None	1,047	58.6
1	237	13.3
2	254	14.2
≥ 3	250	14.0
I know some risk factors for stroke		
None	1,413	79.0
1	97	5.4
2	84	4.7
≥ 3	194	10.9
I know the emergency medical services telephone number		
Yes	1,262	70.6
No	526	29.4

DISCUSSION

This study established that only 10% of the population studied (high school students) were aware of how to act correctly in the event of a stroke. This demonstrates a worrying reality concerning deficiencies in the basic training of students in terms of the concept of first aid.

However, this observed deficiency is not exclusive to this study, since these data are in agreement with previous studies. Thus, it was observed that only 14% of adults in the state of Michigan would take the right attitude when faced with this situation.[6] Within the same perspective, the results presented in **Figure 1** demonstrate that 80% of high school students in Brazilian public schools did not present even the minimum conditions to be able to assist an individual in the event of a stroke situation, and 79.5% of these students were unaware of any risk factors regarding this condition (**Table 1**).

Other studies, in which it was shown that the prognosis for stroke victims who receive early care was better, have demonstrated that the costs resulting from treatment of stroke cases are lower when patients are attended early.[7,8] Early arrival of patients at medical services depends on prior knowledge of stroke symptoms. One strategy for increasing the population's awareness about stroke symptoms is to provide training on stroke recognition, starting from the time of high school education. Planning for this could be facilitated by means of investments in first aid education. Through this learning, students would be better prepared to activate the emergency services in a timely manner.[7,8] The present study evaluated the level of knowledge of high school students about stroke and can guide educational policies regarding the subject, and especially regarding the deficit in recognizing stroke and activating the emergency medical services.

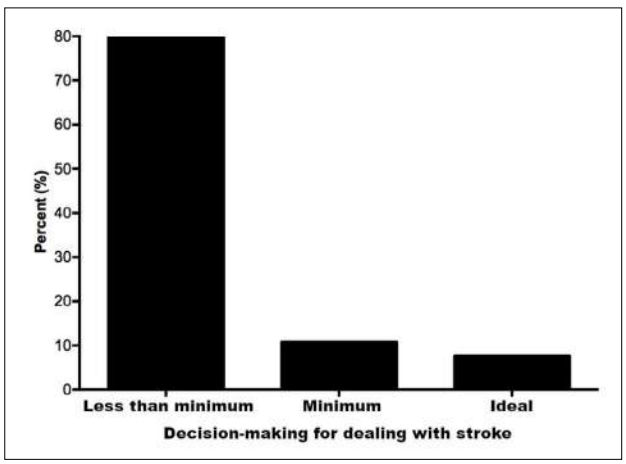


Figure 1. Decision-making capacity for dealing with stroke.

The students' lack of knowledge regarding first aid for stroke may reflect a lack of interest in the topic and an absence of infrastructure in educational institutions that focuses on theoretical and practical training relating to strokes. This lack of information results from the fact that this topic is rarely addressed in schools. Recent studies conducted outside of Brazil have indicated that there is a need for a broad educational program on stroke within the school context.[9] Moreover, Brazilian students are not trained for this because educators are unprepared in relation to basic first aid measures in emergency situations.[10]

Investment in education is a potential solution for mitigating the low preparedness of Brazilian students in the event of a stroke and for providing training for educators and students. Seminars and posters are among the teaching strategies that have been recommended by a number of authors.[11] Studies conducted in countries such as the United States, Portugal and South Korea have demonstrated that stroke intervention taught in schools is an effective alternative for making students aware of the risk factors, symptoms and management of stroke patients.[12,13] Additionally, this approach in educational institutions has also increased the knowledge of students' parents.[11] Dissemination of knowledge acquired within the school scenario tends to provide a long-term contribution to the knowledge of the population, since parents may also disseminate this knowledge. Furthermore, this knowledge may also be used in the job market, since upon leaving school, many young people choose to enter the job market working in places with large gatherings of people, such as shopping malls, parks and airports, where the chances of witnessing a stroke are greater.

Table 2. Odds ratios of the association between baseline characteristics and stroke knowledge

Variables	n (%)	Knowledge of at least one stroke symptom or risk factor		
		Stroke symptoms	Stroke risk factors	EMS telephone
		OR (95% CI)	OR (95% CI)	OR (95% CI)
Sex				
Female	982 (54.9)	1	1	1
Male	806 (45.1)	0.63 (0.52-0.77)	0.62 (0.49-0.79)	1.04 (0.85-1.28)
Schooling (years)				
10	882 (49.3)	1	1	1
> 10	906 (50.7)	1.64 (1.30-2.07)	1.27 (0.96-1.68)	1.19 (0.93-1.52)
Age (years)				
15	427 (23.9)	1	1	1
16	697 (39.0)	1.29 (0.83-2.00)	0.86 (0.63-1.18)	1.04 (0.66-1.65)
17	486 (27.2)	1.02 (0.68-1.51)	0.88(0.60-1.28)	1.21 (0.81-1.81)
18	178 (9.9)	0.98 (0.68-1.40)	1.19(0.74-1.91)	1.70 (1.14-2.52)

OR = odds ratio; CI confidence interval; EMS = emergency medical services.

The lack of knowledge of high school students in Brazilian schools regarding stroke, along with their inability to activate the emergency services, may cause complications for patients. The time that elapses until hospital admission, among individuals with acute stroke, is an important determinant of the prognosis. The ideal, for patients to receive care with the greatest chance of success, is that admission should not be more than 4.5 hours after the onset of the first symptoms of the most prevalent type of stroke, i.e. the ischemic subtype.[14] Delaying patient admission to a hospital will considerably reduce the chances of being able to treat complications, considering that studies have reported that if patients are not treated during an ischemic stroke, they may lose 1.9 million neurons every minute.[15]

In reality, few patients arrive at emergency units in a timely manner and, therefore, patients are not always able to receive the initial treatment.[16,17] The main reason why stroke patients experience delays in arriving at a hospital relates to the lack of knowledge on this subject.[17] Analysis on the situation of students in Brazilian high schools from the results presented here shows that most of the target population of this study constituted a group presenting characteristics that are likely to cause delay in the admission of patients with stroke, i.e. this was a group with little understanding of the subject.

Students with more than 10 years of schooling (OR: 1.64%; 95% CI: 1.30-2.07) had greater knowledge of the signs and symptoms of stroke (**Table 3**). This result is similar to what had been observed in other studies developed in the Brazilian population, in which individuals with higher levels of education had greater ability to recognize the signs and symptoms of stroke.[18,19] The group of 18-year-old students (OR: 1.70%; 95% CI: 1.14-2.52) knew the emergency medical services telephone number more often than did other age groups (**Table 2**). This pattern was probably due to the fact that the longer a person lives, the greater the chances will be that this person will witness a situation in which there is a need to call the emergency medical services, or will watch a newscast containing information on the emergency medical services telephone number or will study this information when taking part in a public job or educational entrance competition. In Brazil, young people aged 18 years intensify their studies with a view to entering college/university and/or the labor market. On the other hand, the difficulties in recognizing stroke were more evident among males.

Males demonstrated less knowledge with regard to risk factors (OR: 0.62%; 95% CI: 0.49-0.79) and signs and symptoms of stroke (OR: 0.63%; 95% CI: 0.52-0.77), as presented in **Table 2**. In general terms, there was a tendency for female adolescents to be more interested in a greater number of health-related topics than were male adolescents.[20] Population studies carried out in Brazil have also reported that there was greater lack of knowledge among men, in terms of both risk factors and the signs and symptoms of stroke.[18,19]

Development of the present study has reinforced the hypothesis that greater inability to recognize stroke is a trend that is perpetuated from adolescence onwards. Thus, it was observed in this study that, like in developed countries such as the United States,[11] Brazilian high school students also seem to share similar difficulties in recognizing stroke. This highlights the importance of consolidating knowledge on health-related topics even during high school. Previous studies have reported that knowledge of good practices in healthcare that is consolidated during adolescence tends to last throughout life.[18]

Nonetheless, although the present study provides a useful panorama to guide educational and public health policies, it is important to note that these findings reflect the reality of five municipalities in northeastern Brazil.

CONCLUSIONS

Although stroke is among the major causes of morbidity and mortality in the world, a considerable deficit of knowledge was observed with regard to recognizing the clinical features of stroke, particularly among males, and to activating the emergency services. The data presented here, from the sample investigated, are alarming, since such knowledge is essential for reducing the interval between the onset of symptoms and instituting the first therapeutic measures, which is a determining factor for the prognosis of stroke victims.

REFERENCES

1. GBD 2016 Stroke Collaborators. Global, regional, and national burden of stroke, 1990–2016: a systematic analysis for the Global Burden of Disease Study 2016. Lancet Neurol. 2019;18(5):439-58. PMID: 30871944; https://doi.org/10.1016/S1474-4422(19)30034-1.
2. Rodrigues MDS, Santana LF, Galvão IM. Fatores de risco modificáveis e não modificáveis do AVC isquêmico: uma abordagem descritiva. Revista de Medicina. 2017;96(3):187-92. https://doi.org/10.11606/issn.1679-9836.v96i3p187-192.
3. Rodrigues MDS, Santana LF, Leal DB, Gomes OV. Diferenças entre os sexos e faixas etárias na epidemiologia acidentes vasculares cerebrais isquêmicos em um hospital de Uberlândia entre 2011 e 2015. Revista de Medicina. 2018;97(2):135-40. https://doi.org/10.11606/issn.1679-9836.v97i2p135-140.
4. Hawkes MA, Ameriso SF, Willey JZ. Stroke knowledge in Spanish-speaking populations. Neuroepidemiology. 2015;44(3):121-9. PMID: 25871697; https://doi.org/10.1159/000381100.
5. Marques MT, Guachala MC, Schoeps VA, et al. Popular knowledge of stroke in São Paulo: a cross-sectional study within the World Stroke Campaign. Sao Paulo Med J. 2021;139(2):117-122. PMID: 33729417; https://doi.org/10.1590/1516-3180.2020.0116.R1.18112020.
6. Fussman C, Rafferty AP, Lyon-Callo S, Morgenstern LB, Reeves MJ. Lack of association between stroke symptom knowledge and intent to call 911: a population-based survey. Stroke. 2010;41(7):1501-7. PMID: 20466995; https://doi.org/10.1161/STROKEAHA.110.578195.
7. Yarnoff B, Khavjou O, Elmi J, et al. Estimating Costs of Implementing Stroke Systems of Care and Data-Driven Improvements in the Paul

Coverdell National Acute Stroke Program. Prev Chronic Dis. 2019;16:E134. PMID: 31580797; https://doi.org/10.5888/pcd16.190061.

8. van Dishoeck AM, Dippel DW, Dirks M, et al. Measuring Quality Improvement in Acute Ischemic Stroke Care: Interrupted Time Series Analysis of Door-to-Needle Time. Cerebrovasc Dis Extra. 2014;4(2):149-55. PMID: 25076959; https://doi.org/10.1159/000363535.
9. Thapa L, Sharma N, Poudel RS, et al. Knowledge, attitude, and practice of stroke among high school students in Nepal. J Neurosci Rural Pract. 2016;7(4):504-9. PMID: 27695228; https://doi.org/10.4103/0976-3147.188635.
10. Galindo Neto NM, Carvalho GCN, Castro RCMB, et al. Teachers' experiences about first aid at school. Rev Bras Enferm. 2018;71(suppl 4):1678-84. PMID: 30088640; https://doi.org/10.1590/0034-7167-2017-0715. Erratum in: Rev Bras Enferm. 2018;71(suppl 5):2348.
11. Umar AB, Koehler TJ, Zhang R, et al. Stroke knowledge among middle and high school students. J Int Med Res. 2019;47(9):4230-41. PMID: 31307252; https://doi.org/10.1177/0300060519858887.
12. Marto JP, Borbinha C, Filipe R, Calado S, Viana-Baptista M. Impact of stroke education on middle school students and their parents: A cluster randomized trial. Int J Stroke. 2017;12(4):401-11. PMID: 27799456; https://doi.org/10.1177/1747493016677980.
13. Park H, Jeong J, Lee H, Lee SH, Suk SH. Stroke awareness in Korean high school students. Acta Neurol Belg. 2017;117(2):455-9. PMID: 28154990; https://doi.org/10.1007/s13760-017-0754-2.
14. Powers WJ, Rabinstein AA, Ackerson T, et al. 2018 Guidelines for the Early Management of Patients With Acute Ischemic Stroke: A Guideline for Healthcare Professionals From the American Heart Association/American Stroke Association. Stroke. 2018;49(3):e46-e110. PMID: 29367334; https://doi.org/10.1161/STR.0000000000000158. Erratum in: Stroke. 2018;49(3):e138.
15. Saver JL. Time is brain-quantified. Stroke. 2006;37(1):263-6. PMID: 16339467; https://doi.org/10.1161/01.STR.0000196957.55928.ab.
16. Adeoye O, Hornung R, Khatri P, Kleindorfer D. Recombinant tissue-type plasminogen activator use for ischemic stroke in the United States: a doubling of treatment rates over the course of 5 years. Stroke. 2011;42(7):1952-5. PMID: 21636813; https://doi.org/10.1161/STROKEAHA.110.612358.
17. Fladt J, Meier N, Thilemann S, et al. Reasons for Prehospital Delay in Acute Ischemic Stroke. J Am Heart Assoc. 2019;8(20):e013101. PMID: 31576773; https://doi.org/10.1161/JAHA.119.013101.
18. Pontes-Neto OM, Silva GS, Feitosa MR, et al. Stroke awareness in Brazil: alarming results in a community-based study. Stroke. 2008;39(2):292-6. PMID: 18162624; https://doi.org/10.1161/STROKEAHA.107.493908.
19. Falavigna A, Teles AR, Vedana VM, et al. Awareness of stroke risk factors and warning signs in southern Brazil. Arq Neuropsiquiatr. 2009;67(4):1076-81. PMID: 20069223; https://doi.org/10.1590/s0004-282x2009000600022.
20. Park E, Kwon M. Health-Related Internet Use by Children and Adolescents: Systematic Review. J Med Internet Res. 2018;20(4):e120. PMID: 29615385; https://doi.org/10.2196/jmir.7731.

Authors' contributions: Rodrigues MS: conception and design, analysis and interpretation, data collection, writing the article, critical review of the article and final approval of the article; Santana LF: conception and design, analysis and interpretation, data collection, writing the article, critical review of the article and final approval of the article; Fernandes Castro AP: conception and design, data collection, writing the article and final approval of the article; Almeida Coelho KK: conception and design, data collection, writing the article and final approval of the article; Guimarães MP: conception and design, analysis and interpretation, data collection, writing the article, critical review of the article and final approval of the article; Gomes OV: conception and design, analysis and interpretation, data collection, writing the article, critical review of the article and final approval of the article; Schwingel PA: analysis and interpretation, writing the article, critical review of the article, final approval of the article and statistical analysis; Cerqueira Filho RB: analysis and interpretation, writing the article, critical review of the article and final approval of the article; Guimarães MD: analysis and interpretation, writing the article, critical review of the article and final approval of the article; Moura JC: conception and design, analysis and interpretation, writing the article, critical review of the article and final approval of the article. All authors actively contributed to discussion of the study results, and reviewed and approved the final version to be released.

Acknowledgements: To the Pró-Reitoria de Extensão (Proex) da Universidade Federal do Vale do São Francisco (PROEX-UNIVASF) and the Department of Education of Pernambuco

Sources of funding: None

Conflicts of interest: The authors declare that there was no conflict of interest regarding the publication of this paper

Date of first submission: July 30, 2021
Last received: September 24, 2021
Accepted: October 13, 2021

Address for correspondence:
Manoel Pereira Guimarães
Av. José de Sá Maniçoba, s/nº
Petrolina (PE) — Brasil
CEP 56.330-400
Tel. (+55 87) 2101- 6705
E-mail: manoel.guimaraes@cardiol.br

Annex 1. English version of the questionnaire.

Questions on stroke knowledge:
1. Age:
2. Sex: F_ M_
3. Years of schooling:
4. Do you know what a stroke is?
5. Can you indicate at least three signs or symptoms of a stroke?
6. Can you indicate at least three risk factors for a stroke?
7. What would you do in a stroke situation?
8. What is the telephone number of the emergency medical services in Brazil?

The effect of the shock index and scoring systems for predicting mortality among geriatric patients with upper gastrointestinal bleeding: a prospective cohort study

Umran Dogru[I], Melih Yuksel[II], Mehmet Oguzhan Ay[III], Halil Kaya[IV], Aksel Ozdemır[V], Yesim Isler[VI], Mehtap Bulut[VII]

Department of Emergency Medicine, University of Health Sciences, Bursa Yuksek Ihtisas Training and Research Hospital, Bursa, Turkey

[I]MD. Emergency Medicine Specialist, Department of Emergency Medicine, University of Health Sciences, Bursa Yuksek Ihtisas Training and Research Hospital, Bursa, Turkey.
https://orcid.org/0000-0002-9733-4538

[II]MD. Associate Professor of Emergency Medicine, Department of Emergency Medicine, University of Health Sciences, Bursa Yuksek Ihtisas Training and Research Hospital, Bursa, Turkey.
https://orcid.org/0000-0002-0793-3693

[III]MD. Associate Professor of Emergency Medicine, Department of Emergency Medicine, University of Health Sciences, Bursa Yuksek Ihtisas Training and Research Hospital, Bursa, Turkey.
https://orcid.org/0000-0003-1061-5327

[IV]MD. Professor of Emergency Medicine, Department of Emergency Medicine, University of Health Sciences, Bursa Yuksek Ihtisas Training and Research Hospital, Bursa, Turkey.
https://orcid.org/0000-0003-2005-6100

[V]MD. Emergency Medicine Specialist, Department of Emergency Medicine, University of Health Sciences, Bursa Yuksek Ihtisas Training and Research Hospital, Bursa, Turkey.
https://orcid.org/0000-0002-5344-0726

[VI]MD. Emergency Medicine Specialist, Department of Emergency Medicine, University of Health Sciences, Bursa Yuksek Ihtisas Training and Research Hospital, Bursa, Turkey.
https://orcid.org/0000-0002-6389-5361

[VII]MD. Professor of Emergency Medicine, Department of Emergency Medicine, University of Health Sciences, Bursa Yuksek Ihtisas Training and Research Hospital, Bursa, Turkey.
https://orcid.org/0000-0003-2131-9099

KEY WORDS (MeSH terms):
Emergencies.
Geriatrics.
Mortality.

AUTHORS' KEY WORDS:
Gastrointestinal bleeding.
Shock index.
Rockall score.
Glasgow-Blatchford score.
AIMS-65 score.

ABSTRACT

BACKGROUND: Gastrointestinal (GI) bleeding is an important cause of mortality and morbidity among geriatric patients.

OBJECTIVE: To investigate whether the shock index and other scoring systems are effective predictors of mortality and prognosis among geriatric patients presenting to the emergency department with complaints of upper GI bleeding.

DESIGN AND SETTING: Prospective cohort study in an emergency department in Bursa, Turkey.

METHODS: Patients over 65 years admitted to a single-center, tertiary emergency service between May 8, 2019, and April 30, 2020, and diagnosed with upper GI bleeding were analyzed. 30, 180 and 360-day mortality prediction performances of the shock index and the Rockall, Glasgow-Blatchford and AIMS-65 scores were evaluated.

RESULTS: A total of 111 patients who met the criteria were included in the study. The shock index ($P < 0.001$) and AIMS-65 score ($P < 0.05$) of the patients who died within the 30-day period were found to be significantly different, while the shock index ($P < 0.001$), Rockall score ($P < 0.001$) and AIMS-65 score ($P < 0.05$) of patients who died within the 180-day and 360-day periods were statistically different. In the receiver operating characteristic (ROC) analysis for predicting 360-day mortality, the area under the curve (AUC) value was found to be 0.988 (95% confidence interval, CI, 0.971-1.000; $P < 0.001$).

CONCLUSION: The shock index measured among geriatric patients with upper GI bleeding at admission seems to be a more effective predictor of prognosis than other scoring systems.

INTRODUCTION

Gastrointestinal (GI) bleeding is a serious and potentially life-threatening condition that causes approximately one million hospitalizations per year in the United States alone. GI bleeding covers bleeding originating from any part of the gastrointestinal tract and may extend from the mouth to the anus.[1] It is divided into two categories: upper and lower GI bleeding.

Upper GI bleeding is defined as bleeding in any area from the mouth to the ligament of Treitz.[2] Patients with upper GI bleeding usually present to emergency services with hematemesis or melena, while patients who are hemodynamically unstable and have a large amount of bleeding may also present with hematochezia.[3] Upper GI bleeding is estimated to occur in 80-150 out of every 100,000 people per year. The estimated mortality rates are between 2% and 15%.[4] The most common risk factors are a history of upper GI bleeding, use of anticoagulants, use of high doses of non-steroidal anti-inflammatory drugs (NSAIDs) and advanced age.[2,5]

GI bleeding is the most common cause of non-traumatic hemorrhagic shock. Shock is generally accompanied by hypotension. However, not every hypotensive patient is in shock. In order to clarify the diagnosis, the "shock index", which is higher in patients with left ventricular dysfunction and fluid loss, has been proposed. It is obtained by dividing the heart rate by the systolic blood pressure, and its normal range is considered to be 0.5-0.7. The shock index increases in cases of trauma and bleeding, in which the left ventricular stroke volume decreases.[6-8] It presents great potential for determining possible short-term negative outcomes among patients with upper GI bleeding. Additionally, it may be used in emergencies to ascertain changes to the clinical picture and is as effective as other risk-scoring systems that have been suggested in the literature.[9]

Various scoring systems are used to predict prognosis and mortality among patients with upper GI bleeding. The most frequently used scoring systems for this purpose are Rockall, Glasgow-Blatchford and AIMS-65. These use clinical information and results from laboratory tests and endoscopy.[10] The Rockall score, which has the aim of helping to discharge low-risk patients and reduce costs, was created based on criteria such as age, comorbidity, shock status, endoscopic diagnosis and findings of new bleeding, in order to predict rebleeding in patients with upper GI bleeding.[11] The aim of the Glasgow-Blatchford scoring system is to predict the need for intervention to control bleeding. Endoscopic findings are not included in the evaluation. Scoring is between 0 and 23, and as the score increases, the need for endoscopy also increases.[12] AIMS-65, which is an easy-to-remember and simple scoring system, provides a risk score for predicting in-hospital mortality, length of stay and cost, for patients with acute upper GI bleeding. It is based on the patient's age, systolic blood pressure, mental status and laboratory data.[13]

OBJECTIVE

The aim of this study was to investigate whether the shock index and other scoring systems measured at admission to the emergency department are effective predictors of mortality and prognosis among geriatric patients with upper GI bleeding.

METHODS

Patient selection and location

This study was carried out in the Department of Emergency Medicine, University of Health Sciences Turkey, Bursa Yuksek Ihtisas Training and Research Hospital, with approval from the clinical research ethics committee of the same hospital (protocol number: 2011-KAEK-25-2019/05-02; date: May 8, 2019).

In this study, patients over 65 years of age with a diagnosis of upper GI bleeding who presented to the Department of Emergency Medicine, University of Health Sciences Turkey, Bursa Yuksek Ihtisas Training and Research Hospital, between May 8, 2019, and April 30, 2020, were prospectively examined.

Exclusion criteria

- Patients aged under 65 years
- Patients with lower GI bleeding
- Upper GI bleeding due to traumatic causes
- Patients who did not undergo endoscopy
- Patients in whom upper GI bleeding was not detected, according to the results from endoscopy

Inclusion criteria

- Patients aged 65 and over
- Patients with upper GI bleeding, according to the results from endoscopy

Methods and measurements

A total of 128 patients were included in the study. Two of the patients were excluded because endoscopy could not be performed; five were excluded because no focus of bleeding could be detected through endoscopy; and ten patients were excluded because they could not be reached. Thus, a total of 111 patients over the age of 65 years who met the criteria and were diagnosed with upper GI bleeding through the tests and examinations were included in the study.

The patients' vital signs and laboratory findings, and especially their demographic information, pulse rate and systolic and diastolic blood pressures, were recorded at admission. The "shock index" was calculated by dividing the patients' pulse rate at the time of first admission by the systolic blood pressure. The patients' existing comorbidities, current medications and endoscopy results were followed up and recorded on the case report forms.

All patients underwent endoscopy at the University of Health Sciences Turkey, Bursa Yuksek Ihtisas Training and Research Hospital. Upper GI bleeding due to peptic ulcer was recorded according to the forest classification. The Rockall, Glasgow-Blatchford and AIMS-65 scores were calculated for all patients.

The study endpoints were defined as mortality within 30 days, within 180 days and within 360 days. Consent and contact information were obtained from the patients or their relatives. The patient and/or patient's relatives were called on days 30, 180 and 360 to get information about his or her latest status, following the outcome from the emergency department.

Statistical analysis

IBM SPSS Statistics for Windows, version 21.0, released 2012 (IBM Corp., Armonk, New York, United States), was used for statistical analysis. Descriptive statistics were expressed as the mean ± standard deviation or the median plus interquartile range (IQR) (25%-75%), while categorical variables were expressed as the number and percentage (%). The Kolmogorov-Smirnov test was used to test the normality of the distribution of the data. The assumption of homogeneity of variances was investigated using Levene's test.

The significance of differences between the groups, in terms of continuous numerical variables in which the statistical assumptions of parametric tests were met, was evaluated using Student's t test. The significance of differences, regarding continuous numerical variables in which the statistical assumptions of parametric tests were not met, was investigated using the Mann-Whitney U test. Spearman's correlation analysis was used to evaluate the relationship between variables with nonparametric distribution.

A receiver operating characteristic (ROC) curve was drawn to investigate the 30, 180 and 360-day mortality prediction performances of the shock index and Rockall, Glasgow-Blatchford and AIMS-65 scores. Logistic regression analysis was performed to determine the factors affecting mortality. The results were reported with the 95% confidence interval (CI), and $P < 0.05$ was considered statistically significant.

RESULTS

A total of 111 patients were included in the study. The patients' median age was 76 years (IQR 25-75: 69-82), and 72 (64.9%) of them were male. Among all the patients, 97 (87.4%) had a history of drug use. The most commonly used drug was acetylsalicylic acid (ASA), which was used by 33.3%. There were 100 patients (90.1%) with a history of comorbidities. The most common comorbidities were hypertension (HT) (42.3%) and coronary artery disease (CAD) (38.7%), respectively. Seventeen of the patients (15.3%) died within 30 days while the 360-day mortality rate was 38.7% (**Table 1**). The median heart rate of the patients was 97/min (IQR 25-75: 83-118), the median systolic blood pressure (SBP) value was 108 mmHg (IQR 25-75: 90-126), and the mean shock index was 0.996 ± 0.389 (**Table 2**).

The Mann-Whitney U test was performed to investigate whether there were any differences in the patients' median shock index or Rockall, Glasgow-Blatchford and AIMS-65 scores, with regard to 30, 180 and 360-day mortality. The results showed that the shock index and AIMS-65 score were significantly different among patients who died within 30 days ($P < 0.001$ and $P < 0.05$). Additionally, the shock index, Rockall score and AIMS-65 score were found to be significantly different in patients with 180-day mortality ($P < 0.001$, $P < 0.001$ and $P < 0.05$). Lastly, the shock index, Rockall score and AIMS-65 score were found to be significantly different among patients with 360-day mortality ($P < 0.001$, $P = 0.001$ and $P < 0.05$) (**Table 3**).

The diagnostic value of the patients' shock index and Rockall, Glasgow-Blatchford and AIMS-65 scores for 30, 180 and 360-day mortality were analyzed using ROC. For 30-day mortality, the area under the curve (AUC) for the shock index was 0.911 ($P < 0.001$) while the AUC for the AIMS-65 score was 0.662 ($P < 0.05$). For 180-day mortality, the AUC for the shock index was found to be 0.960 ($P < 0.001$), the AUC for the Rockall score was 0.714 ($P < 0.001$) and the AUC for the AIMS-65 score was 0.657 ($P < 0.05$). For 360-day mortality, the AUC for the shock index was 0.988 ($P < 0.001$), the AUC for the Rockall score was 0.690 ($P < 0.05$) and the AUC for the AIMS-65 score was 0.641 ($P < 0.05$) (**Figure 1**).

When the cutoff value of the shock index for 30-day mortality was 1.240, the sensitivity was found to be 82.4% and the specificity was 81.9%. When the cutoff value of the AIMS-65 score was 1.5, the sensitivity was found to be 76.5% and the specificity was 50.0%. When the cutoff value of the shock index for 180-day mortality was 1.205, the sensitivity was 91.2% and the specificity was 92.2%. When the cutoff value of the Rockall score was 5.5, the sensitivity was found to be 38.2% and specificity was 61.8%. When the cutoff value of the shock index for 360-day mortality was 1.06, the sensitivity was 95.3% and the specificity was 94.1%. Accordingly, it can be seen that the performance of the shock index was significantly better than that of the other scoring systems (**Table 4**).

Logistic regression analysis was performed using variables of gender, comorbidities and drug use history, which were thought to have an effect on 360-day mortality. The history of drug use was found to be an effective factor for diagnosing 360-day mortality (Exp beta = 6.489; 95% CI, 1.607-26.208; $P = 0.009$) (**Table 5**).

DISCUSSION

The history of drug use has an important place in the etiology of patients with upper GI bleeding. ASA and NSAIDs cause bleeding by inhibiting platelet aggregation and causing damage to the GI mucosa.

In a study by Loperfido et al., aspirin use was shown to be in first place among the causes, in patients presenting with upper GI bleeding.[14] In a study by Laursen et al., use of ASA took first place with a rate of 41%.[15] In our study, 87.4% of the patients had a history of drug use. The most commonly used drug was ASA, by 33.3% of the patients. Another important finding from our study was that the drugs used by the patients were an independent factor for 360-day mortality (odds ratio, OR = 6.489; 95% CI, 1.607-26.208; $P = 0.009$). Additionally, the most commonly used drug among the patients was ASA, which was consistent with the findings in the literature.

One of the most important factors that increase mortality and morbidity in cases of upper GI bleeding is the patients' existing comorbidities. In a prospective study conducted by Palmer, involving 14,000 people, the most common comorbidities were found to be HT and CAD.[16] In a prospective study by Köksal et al., in which patients with upper GI bleeding were examined, the most common comorbidity was found to be chronic liver disease, with a rate of 30%.[17] Stanley et al., on the other hand, showed that CAD was the most common comorbidity in patients with upper GI bleeding.[18] In our study, 90.1% of the patients had a history of comorbidities. The most common comorbidities were HT (42.3%) and CAD (38.7%), respectively. Examination of the literature shows that there are differences in terms of comorbidities. The reason for this may be the distribution of the frequency of the disease according to geographical region and the differences in the age groups of the patients.

The shock index is obtained by dividing the heart rate by the systolic blood pressure, and its normal value is between 0.5 and 0.7. When the shock index is greater than 0.9, presence of

Table 1. Clinical and demographic data

Variables		n	%
Gender	Female	39	35.1
	Male	72	64.9
Hematemesis	No	63	56.8
	Yes	48	43.2
Melena	No	14	12.6
	Yes	97	87.4
History of drug use	No	14	12.6
	Yes	97	87.4
LMWH	No	106	95.5
	Yes	5	4.5
Clopidogrel	No	96	86.5
	Yes	15	13.5
Factor Xa inhibitor	No	99	89.2
	Yes	12	10.8
Warfarin	No	96	86.5
	Yes	15	13.5
ASA	No	74	66.7
	Yes	37	33.3
NSAIDs	No	95	85.6
	Yes	16	14.4
PPI/H2-receptor antagonists	No	81	73
	Yes	30	27
Comorbidities	No	11	9.9
	Yes	100	90.1
DM	No	83	74.8
	Yes	28	25.2
HT	No	64	57.7
	Yes	47	42.3
AF	No	99	89.2
	Yes	12	10.8
CAD	No	68	61.3
	Yes	43	38.7
CHF	No	98	88.3
	Yes	13	11.7
CVDs	No	105	94.6
	Yes	6	5.4
COPD/Asthma	No	100	90.1
	Yes	11	9.9
Liver cirrhosis	No	105	94.6
	Yes	6	5.4
Malignancy	No	101	91
	Yes	10	9
Other disorders	No	74	66.7
	Yes	37	33.3
Outcome from emergency	Admission	96	86.5
	Discharge	11	9.9
	Referral	4	3.6
30-day mortality	No	94	84.7
	Yes	17	15.3
180-day mortality	No	77	69.4
	Yes	34	30.6
360-day mortality	No	68	61.3
	Yes	43	38.7
	Total	111	100

LMWH = low molecular weight heparin; ASA = acetyl salicylic acid; NSAIDs = nonsteroid anti-inflammatory drugs; PPI = proton pump inhibitor; DM = diabetes mellitus; HT = hypertension; AF = atrial fibrillation; CAD = coronary artery disease; CHF = congestive heart disease; CVDs = cerebrovascular diseases; COPD = chronic obstructive pulmonary disease.

conditions that cause a decrease in left ventricular stroke volume, such as sepsis, trauma or bleeding, needs to be considered.[6-8] In patients with upper GI bleeding, a decrease in left ventricular volume due to the amount of bleeding causes an increase in the shock index. In a study conducted by Jung et al. in 2019, the mean shock index was found to be 0.72 in patients with upper GI bleeding.[10] Rassameehiran et al. observed that mortality and the need for transfusion became greater among patients with upper GI bleeding when the shock index was above 0.78. They also claimed that the shock index would be a good predictor for determining the short-term negative outcomes of patients with upper GI bleeding.[9] In our study, the mean shock index was found to be 0.996 ± 0.389. We believe that the value that we found differed from what had been reported in the literature because the population examined was 65 years of age and over, comorbidities that cause mortality occurred more frequently in these patients and the drugs used by the patients may have had an effect.

Considering mortality, which was the most important endpoint of our study, we observed that the results in the literature differed between studies. The mean mortality among patients with upper GI bleeding was reported to be 2%-15% in the literature.[4] Robertson et al. found that the in-hospital mortality rate due to upper GI bleeding was 4.2%, while Budimir et al. indicated that the 30-day mortality rate due to peptic ulcer bleeding was 5.2%.[19,20] Additionally, Yaka et al. found that the in-hospital mortality rate due to upper GI bleeding was 7.1%.[21] Similarly, in a study by Stanley et al., the 30-day mortality rate was found to be 7%.[18] Most of the studies in the literature investigated in-hospital or 30-day mortality. In our study, in addition to 30-day mortality, we also examined 180 and 360-day mortality rates. We think that these results will contribute to the literature. In addition, the mortality rates in our study were generally higher, contrary to the data in the literature. We think that this was because the population that we examined consisted of elderly patients and because they had high numbers of comorbidities.

Table 2. Frequency table of variables

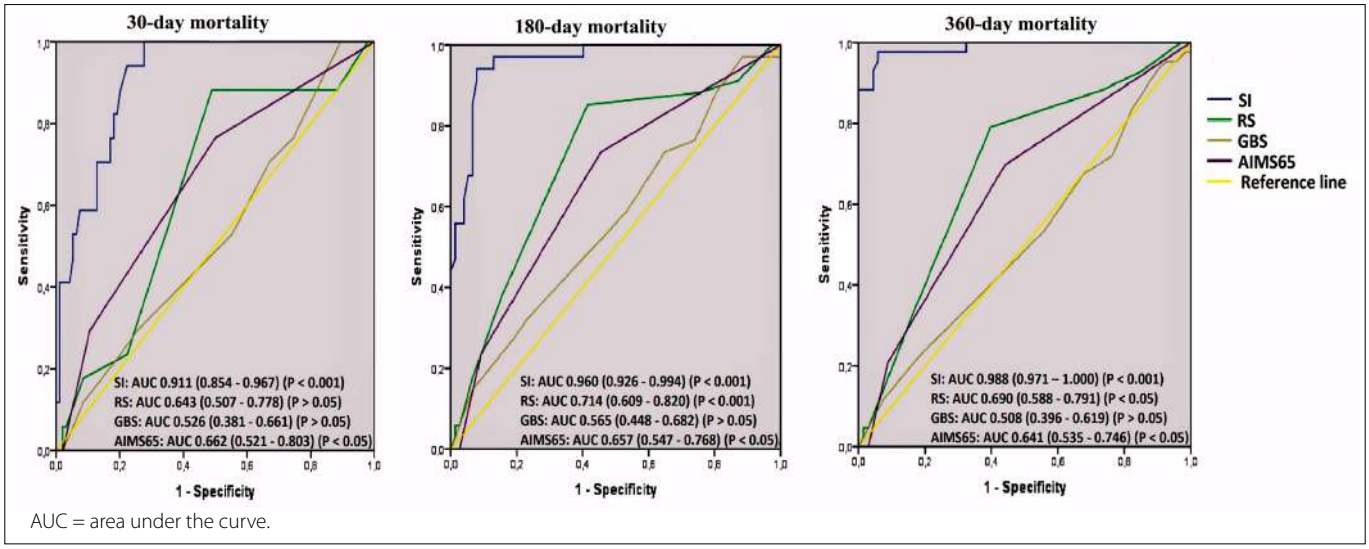
Variables	Value
GCS, median (IQR 25-75)	15 (15-15)
SBP, median (IQR 25-75)	108 (90-126)
DBP, median (IQR 25-75)	70 (60-78)
Fever, mean ± SD	36.53 ± 0.64
SpO_2, median (IQR 25-75)	96 (95-98)
Pulse, median (IQR 25-75)	97 (83-118)
Shock index, mean ± SD	0.996 ± 0.389
Rockall score, median (IQR 25-75)	5 (4-5)
Glasgow-Blatchford score, median (IQR 25-75)	11 (8-12)
AIMS-65 score, median (IQR 25-75)	2 (1-2)

GCS = Glasgow coma scale; SBP = systolic blood pressure; DBP = diastolic blood pressure; IQR = interquartile range; SD = standard deviation; SpO_2 = oxygen saturation.

Table 3. Mortality analysis on variables using Mann-Whitney U test

	30-day mortality	n	Median (IQR 25-75)	P value	180-day mortality	n	Median (IQR 25-75)	P value	360-day mortality	n	Median (IQR 25-75)	P-value
Shock index	No	94	0.76 (0.67-1.18)	< 0.001	No	77	0.73 (0.64-0.91)	< 0.001	No	68	0.70 (0.63-0.83)	< 0.001
	Yes	17	1.53 (1.26-1.76)		Yes	34	1.43 (1.24-1.60)		Yes	43	1.36 (1.22-1.56)	
	Total	111	0.86 (0.68-1.28)		Total	111	0.86 (0.68-1.28)		Total	111	0.86 (0.68-1.28)	
Rockall score	No	94	4.00 (4.00-5.00)	> 0.05	No	77	4.00 (3.50-5.00)	< 0.001	No	68	4.00 (3.00-5.00)	< 0.05
	Yes	17	5.00 (5.00-5.50)		Yes	34	5.00 (5.00-6.00)		Yes	43	5.00 (5.00-6.00)	
	Total	111	5.00 (4.00-5.00)		Total	111	5.00 (4.00-5.00)		Total	111	5.00 (4.00-5.00)	
Glasgow-Blatchford score	No	94	11.00 (8.00-12.00)	> 0.05	No	77	11.00 (8.00-11.00)	> 0.05	No	68	11.00 (8.00-11.75)	> 0.05
	Yes	17	11.00 (8.50-12.50)		Yes	34	11.00 (8.75-13.00)		Yes	43	11.00 (8.00-12.00)	
	Total	111	11.00 (8.00-12.00)		Total	111	11.00 (8.00-12.00)		Total	111	11.00 (8.00-12.00)	
AIMS-65 score	No	94	1.50 (1.00-2.00)	< 0.05	No	77	1.00 (1.00-2.00)	< 0.05	No	68	1.00 (1.00-2.00)	< 0.05
	Yes	17	2.00 (1.50-3.00)		Yes	34	2.00 (1.00-2.25)		Yes	43	2.00 (1.00-2.00)	
	Total	111	2.00 (1.00-2.00)		Total	111	2.00 (1.00-2.00)		Total	111	2.00 (1.00-2.00)	

IQR = interquartile range.



AUC = area under the curve.

Figure 1. Receiver-operating characteristic curves of the shock index (SI), Rockall score (RS), Glasgow-Blatchford score (GBS) and the AIMS-65 scores for predicting 30, 180 and 360-day mortality.

Table 4. Cutoff values for the shock index, Rockall score, Glasgow-Blatchford score and AIMS-65 score for predicting 30, 180 and 360-day mortality

Variables	AUC (95% CI)	P	Risk factor	Cutoff value	Sensitivity %	Specificity %
30-day mortality	0.911 (0.854-0.967)	< 0.001	Shock index	1.125	94.1	72.3
				1.240	82.4	81.9
				1.265	76.5	83.0
	0.643 (0.507-0.778)	> 0.05	Rockall score	3.5	88.2	22.3
				4.5	88.2	51.1
				5.5	23.5	77.7
	0.526 (0.381-0.671)	> 0.05	Glasgow-Blatchford score	8.5	76.5	25.5
				9.5	70.6	33.0
				10.5	52.9	44.7
	0.662 (0.521-0.803)	< 0.05	AIMS-65 score	1.5	76.5	50.0
				2.5	29.4	89.4
180-day mortality	0.960 (0.926-0.994)	< 0.001	Shock index	1.100	97.1	87.0
				1.170	82.4	81.9
				1.205	91.2	92.2
	0.714 (0.609-0.820)	< 0.001	Rockall score	3.5	88.2	11.8
				4.5	85.3	14.7
				5.5	38.2	61.8
	0.565 (0.448-0.682)	> 0.05	Glasgow-Blatchford score	8.5	76.5	23.5
				9.5	73.5	26.5
				10.5	58.8	41.2
	0.657 (0.547-0.768)	< 0.05	AIMS-65 score	1.5	73.5	26.5
				2.5	23.5	76.5
360-day mortality	0.988 (0.971-1.000)	< 0.001	Shock index	0.955	97.7	91.2
				1.060	95.3	94.1
				1.125	90.7	95.6
	0.690 (0.588-0.791)	< 0.05	Rockall score	3.5	88.4	26.5
				4.5	79.1	60.3
				5.5	32.6	83.8
	0.508 (0.396-0.619)	> 0.05	Glasgow-Blatchford score	8.5	72.1	23.5
				9.5	67.4	32.4
				10.5	53.5	44.1
	0.641 (0.535-0.746)	< 0.05	AIMS-65 score	1.5	69.8	55.9
				2.5	20.9	91.2

AUC = area under the curve; CI = confidence interval.

Table 5. Analysis of variables using logistic regression

Variables	B	S.E.	Wald	df	P	Exp(B)	95% CI	
							Lower	Upper
Gender	-278	438	402	1	526	757	321	1.789
Drug use	1.870	712	6.895	1	009	6.489	1.607	26.208
Comorbidities	-1.747	926	3.559	1	059	174	028	1.070
Constant	-458	274	2.796	1	094	632		

B = coefficient; S.E. = standard error; df = degrees of freedom; Exp(B) = exponentiation of the B coefficient; CI = confidence interval.

Various scoring systems are used to predict prognosis and mortality among patients with upper GI bleeding. The most commonly used ones are the Rockall, Glasgow-Blatchford and AIMS-65 scores. These are obtained using the clinical information, laboratory data and endoscopy results of the patients.[10,19] In the study by Robertson et al., the AIMS-65 score was found to be better than the Glasgow-Blatchford and Rockall scoring systems for predicting mortality and the need for intensive care.[19] In the study by Laursen et al., it was shown that the Glasgow-Blatchford and Rockall scoring systems were not useful for predicting 30-day mortality.[15] A study by Bryant et al. on 708 patients showed that the Glasgow-Blatchford score was better than the Rockall score for predicting re-bleeding, need for surgery, need for transfusion and mortality.[22] Wang et al. considered that all three scoring systems were inadequate.[23] In a study on 3,012 patients, Stanley et al. found that the Glasgow-Blatchford score was better than the Rockall and AIMS-65 scores for predicting intervention or mortality.[18] In the study by Jung et al. in 2019, comparing the shock index and the Rockall, Glasgow-Blatchford and AIMS-65 scores, they found that the Glasgow-Blatchford score and shock index were better for predicting possible adverse events.[10] In a study by Tang et al., the AIMS-65 and Glasgow-Blatchford scores were clinically more useful for predicting 30-day mortality than the pre-endoscopic Rockall and Baylor scores, among patients with acute upper GI bleeding presenting to emergency services.[24] In a review of 16 studies. Ramaekers et al. claimed that these scoring systems were not strong and that their use was not recommended in clinical practice.[25]

There is not enough data in the literature for the shock index, with regard to predicting mortality among geriatric patients with upper GI bleeding. In a retrospective study by Rassameehiran et al., the shock index was compared with other scoring systems and was found to be the best predictor of the need for endoscopic treatment among patients with acute upper GI bleeding.[9] In a study by Saffouri et al., the shock index was found to have weaker performance than other scoring systems for predicting 30-day mortality among patients with acute upper GI bleeding.[26]

In our study, we found that the shock index and AIMS-65 score had statistically better results than the Rockall and Glasgow-Blatchford scores for predicting 30-day mortality. Similarly, we found that the shock index and AIMS-65 and Rockall scores had statistically better results than the Glasgow-Blatchford score for predicting the 180-day and 360-day mortality rates. Both the shock index and the AIMS-65 score outperformed other scoring systems for predicting mortality within 30, 180 and 360 days.

However, we believe that the fact that the patients included in our study were older than 65 years may have affected the success of the AIMS-65 score. As seen in the literature, there is no consensus on the effectiveness of the shock index and other scoring systems for predicting mortality and other possible complications among patients with upper GI bleeding. Saffouri et al. found that the performance of the shock index was weak with regard to predicting the 30-day mortality rate in their study.[26] We think that the fact that the patients included in their study were younger and had less comorbidity may have caused that result. We also believe that the shock index could not be evaluated as a significant predictor of mortality in the study by Saffouri et al. due to the hemodynamical instability of their patients at the time of admission, relatively young age of the patients and presence of cardiovascular compensation.

In our study, we found that the shock index was much more effective for predicting 30, 180 and 360-day mortality, which were the endpoints of the study, than the other scoring systems. In particular, both the AUC and the cutoff values of the shock index were statistically more significant than other scoring systems. When the cutoff value for the shock index regarding 30-day mortality was 1.240, the sensitivity was found to be 82.4% and the specificity was 81.9%. When the 180-day mortality cutoff value was 1.205, the sensitivity was found to be 91.2% and the specificity was 92.2%. Lastly, when the 360-day mortality cutoff value was 1.06, the sensitivity was found to be 95.3% and the specificity was 94.1%. We believe that these cutoff values determined for the shock index will have a major role in the treatment and follow-up of geriatric patients with upper GI bleeding.

Limitations

The most important limitation of our study was that it was a single-center study. In addition, we think that the relatively small number of patients was another important limitation. In order to obtain results with greater accuracy and reliability, further multicenter studies with larger populations would be required.

CONCLUSION

The shock index, which is a simple, inexpensive and noninvasive parameter that can be obtained only from vital signs, is a more effective predictor for prognosis than other scoring systems, among geriatric patients with upper GI bleeding presenting to emergency departments.

REFERENCES

1. Nable JV, Graham AC. Gastrointestinal Bleeding. Emergency medicine clinics of North America. 2016;34(2):309-25. PMID: 27133246; https://doi.org/10.1016/j.emc.2015.12.001.
2. Tielleman T, Bujanda D, Cryer B. Epidemiology and Risk Factors for Upper Gastrointestinal Bleeding. Gastrointest Endosc Clin N Am. 2015;25(3):415-28. PMID: 26142028; https://doi.org/10.1016/j.giec.2015.02.010.
3. Kamboj AK, Hoversten P, Leggett CL. Upper Gastrointestinal Bleeding: Etiologies and Management. Mayo Clin Proc. 2019;94(4):697-703. PMID: 30947833; https://doi.org/10.1016/j.mayocp.2019.01.022.
4. Antunes C, Copelin IE. Upper Gastrointestinal Bleeding. StatPearls. Treasure Island (FL): StatPearls Publishing Copyright © 2021, StatPearls Publishing LLC.; 2021.
5. Wilkins T, Wheeler B, Carpenter M. Upper Gastrointestinal Bleeding in Adults: Evaluation and Management. Am Fam Physician. 2020;101(5):294-300. PMID: 32109037. Erratum in: Am Fam Physician. 2021;103(2):70.
6. Rady MY, Smithline HA, Blake H, Nowak R, Rivers E. A comparison of the shock index and conventional vital signs to identify acute, critical illness in the emergency department. Ann Emerg Med. 1994;24(4):685-90. PMID: 8092595; https://doi.org/10.1016/s0196-0644(94)70279-9. Erratum in: Ann Emerg Med 1994;24(6):1208.
7. Rady MY, Nightingale P, Little RA, Edwards JD. Shock index: a re-evaluation in acute circulatory failure. Resuscitation. 1992;23(3):227-34. PMID: 1321482; https://doi.org/10.1016/0300-9572(92)90006-x.
8. Allgöwer M, Burri C. "Schockindex" ["Shock index"]. Dtsch Med Wochenschr. 1967;92(43):1947-50. PMID: 5299769; https://doi.org/10.1055/s-0028-1106070.
9. Rassameehiran S, Teerakanok J, Suchartlikitwong S, Nugent K. Utility of the Shock Index for Risk Stratification in Patients with Acute Upper Gastrointestinal Bleeding. South Med J. 2017;110(11):738-43. PMID: 29100227; https://doi.org/10.14423/SMJ.0000000000000729.
10. Jung DH, Ko BS, Kim YJ, Kim WY. Comparison of risk scores and shock index in hemodynamically stable patients presenting to the emergency department with nonvariceal upper gastrointestinal bleeding. Eur J Gastroenterol Hepatol. 2019;31(7):781-5. PMID: 31008809; https://doi.org/10.1097/MEG.0000000000001422.
11. Rockall TA, Logan RF, Devlin HB, Northfield TC. Selection of patients for early discharge or outpatient care after acute upper gastrointestinal haemorrhage. National Audit of Acute Upper Gastrointestinal Haemorrhage. Lancet. 1996;347(9009):1138-40. PMID: 8609747; https://doi.org/10.1016/s0140-6736(96)90607-8.
12. Blatchford O, Murray WR, Blatchford M. A risk score to predict need for treatment for upper-gastrointestinal haemorrhage. Lancet. 2000;356(9238):1318-21. PMID: 11073021; https://doi.org/10.1016/S0140-6736(00)02816-6.
13. Saltzman JR, Tabak YP, Hyett BH, et al. A simple risk score accurately predicts in-hospital mortality, length of stay, and cost in acute upper GI bleeding. Gastrointest Endosc. 2011;74(6):1215-24. PMID: 21907980; https://doi.org/10.1016/j.gie.2011.06.024.
14. Loperfido S, Baldo V, Piovesana E, et al. Changing trends in acute upper-GI bleeding: a population-based study. Gastrointest Endosc. 2009;70(2):212-24. PMID: 19409558; https://doi.org/10.1016/j.gie.2008.10.051.
15. Laursen SB, Hansen JM, Schaffalitzky de Muckadell OB. The Glasgow Blatchford score is the most accurate assessment of patients with upper gastrointestinal hemorrhage. Clin Gastroenterol Hepatol. 2012;10(10):1130-1135.e1. PMID: 22801061; https://doi.org/10.1016/j.cgh.2012.06.022.
16. Palmer ED. The vigorous diagnostic approach to upper-gastrointestinal tract hemorrhage. A 23-year prospective study of 1,4000 patients. JAMA. 1969;207(8):1477-80. PMID: 5304356.
17. Köksal Ö, Özeren G, Özdemır F, et al. Prospective validation of the Glasgow Blatchford scoring system in patients with upper gastrointestinal bleeding in the emergency department. Turk J Gastroenterol. 2012;23(5):448-55. PMID: 23161321; https://doi.org/10.4318/tjg.2012.0385.
18. Stanley AJ, Laine L, Dalton HR, et al. Comparison of risk scoring systems for patients presenting with upper gastrointestinal bleeding: international multicentre prospective study. BMJ. 2017;356:i6432. PMID: 28053181; https://doi.org/10.1136/bmj.i6432.
19. Robertson M, Majumdar A, Boyapati R, et al. Risk stratification in acute upper GI bleeding: comparison of the AIMS65 score with the Glasgow-Blatchford and Rockall scoring systems. Gastrointest Endosc. 2016;83(6):1151-60. PMID: 26515955; https://doi.org/10.1016/j.gie.2015.10.021.
20. Budimir I, Stojsavljević S, Baršić N, et al. Scoring systems for peptic ulcer bleeding: Which one to use? World J Gastroenterol. 2017;23(41):7450-8. PMID: 29151699; https://doi.org/10.3748/wjg.v23.i41.7450.
21. Yaka E, Yılmaz S, Doğan NÖ, Pekdemir M. Comparison of the Glasgow-Blatchford and AIMS65 scoring systems for risk stratification in upper gastrointestinal bleeding in the emergency department. Acad Emerg Med. 2015;22(1):22-30. PMID: 25556538; https://doi.org/10.1111/acem.12554.
22. Bryant RV, Kuo P, Williamson K, et al. Performance of the Glasgow-Blatchford score in predicting clinical outcomes and intervention in hospitalized patients with upper GI bleeding. Gastrointest Endosc. 2013;78(4):576-83. PMID: 23790755; https://doi.org/10.1016/j.gie.2013.05.003.
23. Wang CH, Chen YW, Young YR, Yang CJ, Chen IC. A prospective comparison of 3 scoring systems in upper gastrointestinal bleeding.

Am J Emerg Med. 2013;31(5):775-8. PMID: 23465874; https://doi.org/10.1016/j.ajem.2013.01.007.

24. Tang Y, Shen J, Zhang F, et al. Scoring systems used to predict mortality in patients with acute upper gastrointestinal bleeding in the ED. Am J Emerg Med. 2018;36(1):27-32. PMID: 28673695; https://doi.org/10.1016/j.ajem.2017.06.053.
25. Ramaekers R, Mukarram M, Smith CA, Thiruganasambandamoorthy V. The Predictive Value of Preendoscopic Risk Scores to Predict Adverse Outcomes in Emergency Department Patients With Upper Gastrointestinal Bleeding: A Systematic Review. Acad Emerg Med. 2016;23(11):1218-27. PMID: 27640399; https://doi.org/10.1111/acem.13101.
26. Saffouri E, Blackwell C, Laursen SB, et al. The Shock Index is not accurate at predicting outcomes in patients with upper gastrointestinal bleeding. Aliment Pharmacol Ther. 2020;51(2):253-60. PMID: 31642558; https://doi.org/10.1111/apt.15541.

Authors' contributions: Dogru U: data curation (equal), formal analysis (equal), investigation (equal), resources (equal), software (equal), validation (equal), writing-original draft (equal) and writing-review and editing (equal); Yuksel M: conceptualization (equal), data curation (equal), formal analysis (equal), funding acquisition (equal), investigation (equal), methodology (equal), project administration (equal), resources (equal), software (equal), supervision lead), validation (equal), visualization (equal), writing-original draft (equal) and writing-review and editing (lead); Ay MO: conceptualization (equal), data curation (equal), formal analysis (equal), project administration (equal), resources (equal), software (equal), validation (equal), visualization (equal) and writing-original draft (equal); Kaya H: conceptualization (equal), data curation (equal), formal analysis (equal), funding acquisition (equal), methodology (equal), software (equal), supervision (equal), visualization (equal) and writing-original draft (equal); Ozdemir A: conceptualization (equal), data curation (equal), investigation (equal), methodology (equal), project administration (equal), resources (equal), software (equal) and visualization (equal); Isler Y: data curation (equal), investigation (equal), methodology (equal), project administration (equal), resources (equal), software (equal) and writing-original draft (equal); and Bulut M: formal analysis (equal), funding acquisition (equal), investigation (equal), methodology (equal), supervision (equal), validation (equal), visualization (equal) and writing-original draft (equal). All authors read and approved the final manuscript

This article was presented as an oral presentation at the 17th National Emergency Medicine Congress, October 14-17, 2021, in the Titanic Convention Center, Antalya, Turkey

Sources of funding: There was no financial or non-financial competing interest
Conflicts of interest: There was no conflict of interest among the authors

Date of first submission: August 30, 2021
Last received: August 30, 2021
Accepted: October 13, 2021

Address for correspondence:
Melih Yuksel
Department of Emergency Medicine, University of Health Sciences, Bursa Yuksek Ihtisas Training and Research Hospital, 16310, Yildirim, Bursa, Turkey
Tel. (+90) 5326013107
E-mail: melihdr@gmail.com

https://doi.org/10.1590/1516-3180.2021.0622.R1.29102021

Prematurity and functional gastrointestinal disorders in infancy: a cross-sectional study

Marcela Montenegro Braga Barroso Gondim[I], Ana Lucia Goulart[II], Mauro Batista de Morais[III]

Universidade Federal de São Paulo (UNIFESP), São Paulo (SP), Brazil

[I]MD. Physician, Division of Pediatric Gastroenterology, Escola Paulista de Medicina (EPM), Universidade Federal de São Paulo (UNIFESP), São Paulo (SP), Brazil.
https://orcid.org/0000-0003-3712-8035

[II]MD, PhD. Physician and Associate Professor, Division of Neonatal Pediatrics, Escola Paulista de Medicina (EPM), Universidade Federal de São Paulo (UNIFESP), São Paulo (SP), Brazil.
https://orcid.org/0000-0001-5894-5515

[III]MD, PhD. Physician and Full Professor, Division of Pediatric Gastroenterology, Escola Paulista de Medicina (EPM), Universidade Federal de São Paulo (UNIFESP), São Paulo (SP), Brazil.
https://orcid.org/0000-0003-4014-5549

KEY WORDS (MeSH terms):
Colic.
Constipation.
Gastroesophageal reflux.
Diarrhea, infantile.
Gastrointestinal diseases.

AUTHORS' KEY WORDS:
Preterm newborn.
Gastroenteropathies.
Childhood diarrhea.
Prematurity.
Functional gastrointestinal disorders.
Rome IV criteria.

ABSTRACT

BACKGROUND: Functional gastrointestinal disorders (FGIDs) are defined as a variable combination of chronic or recurrent gastrointestinal symptoms that are not explained by structural or biochemical abnormalities. Their relationship with prematurity has been increasingly studied.

OBJECTIVE: To compare the frequency of FGIDs in preterm and term infants and to evaluate whether invasive procedures during the neonatal period in preterm infants are associated with greater likelihood of FGIDs in the first two years of life.

DESIGN AND SETTING: Controlled nested cross-sectional study conducted in a Brazilian university hospital.

METHODS: This was a controlled nested cross-sectional study on a retrospective cohort of infants born preterm who were compared with infants born at term regarding the presence of FGIDs. Medical consultations were conducted by a single pediatric gastroenterologist to obtain information on the gestational and neonatal periods and on clinical manifestations of the digestive tract. The Rome IV criteria for the diagnosis of FGIDs were used.

RESULTS: A total of 197 infants (< 24 months), including 99 preterm and 98 term infants, were studied. Infant regurgitation was more prevalent in term infants (35.1% and 15.6%; $P < 0.001$). The frequencies of other FGIDs (infant colic, functional constipation, functional diarrhea and infant dyschezia) in preterm infants did not differ from those of term infants ($P > 0.05$). No relationship was found between invasive procedures during the neonatal period and development of FGIDs in preterm infants.

CONCLUSION: Infants born preterm did not have higher frequency of FGIDs in the first two years of life.

INTRODUCTION

Functional gastrointestinal disorders (FGIDs) are defined as a variable combination of chronic or recurrent gastrointestinal symptoms that are not explained by structural or biochemical abnormalities.[1] In addition to the discomfort caused by clinical manifestations, FGIDs cause stress and anxiety in families. They compromise these families' quality of life and cause them to incur increased healthcare expenditure.[2,3]

A review of the literature[4] published in 2015 showed that the prevalence of FGIDs in infants shows wide variability due to the heterogeneity of the diagnostic criteria used in different studies. The Rome IV criteria[5] are currently the most widely accepted method for diagnosing FGIDs.

The pathophysiology of FGIDs is still not fully established.[6] It has been proposed that interaction of multiple factors, such as genetic susceptibility, early life experiences, sociocultural issues and coping mechanisms, leads to development of different phenotypes and pain response behaviors, including FGIDs.

Prematurity is considered to be a risk factor for the development of some FGIDs, especially infant colic[7] and regurgitation.[8] A recent study[9] using the Rome III criteria showed that there was higher prevalence of FGIDs among infants born preterm than among infants born full term; however, both groups showed high prevalence of FGIDs. Recent studies conducted in Colombia and Europe have found no association between prematurity and functional gastrointestinal disorders, respectively, in the age ranges of 10 to 18 years and under 4 years.[10,11]

In general, preterm infants face greater complications during the neonatal period, such as longer hospital stays, greater need for invasive painful procedures and higher use of medications, which may lead to changes to the development and maturation of some organs, such as the brain and intestines; these changes might explain abnormalities in pain processing[12] and thus contribute to the onset of FGIDs.

OBJECTIVE

The main objective of this study was to compare the frequency of FGIDs in infants born preterm with that in infants born at term, using the Rome IV criteria. The secondary objective was to evaluate whether there was any association between sociodemographic variables and invasive procedures during the neonatal period and the development of FGIDs in preterm infants during their infancy.

METHODS

Study design

This was a controlled nested cross-sectional study in a retrospective cohort of premature infants who were compared with a group of full-term babies, with regard to the presence of FGIDs.

All infants in both groups underwent a consultation with a pediatric gastroenterologist. In the consultation, information on the infant's gestational and neonatal history and any occurrence of gastrointestinal symptoms was obtained, and a complete physical examination was performed. The Rome IV criteria were used to characterize FGIDs.

Infants were included after their guardians had agreed to participate in the study and had signed an informed consent statement. The project was approved by the Research Ethics Committee of the Universidade Federal de São Paulo (UNIFESP) under CAAE no. 66233517.0.0000.5505, on May 5, 2017.

Preterm and term groups

All preterm infants seen consecutively at the Preterm Outpatient Clinic of the Neonatal Pediatric Division of the Department of Pediatrics of Escola Paulista de Medicina (EPM), UNIFESP, during the study period (2017-2019), were recruited. The following inclusion criteria were adopted: gestational age less than 37 weeks and current corrected age at the time of the study of between 30 days and 24 months.

The group of full-term infants (aged 30 days to 24 months) was recruited from a primary care unit and an immunization center, both in the metropolitan region of São Paulo. Infants born at a gestational age greater than or equal to 37 weeks and a birth weight > 2500 g were included.

The following exclusion criteria were used for both groups: previous abdominal surgery, presence of past or current gastrointestinal tract disease, cerebral palsy, severe congenital malformations and presence of an alternative feeding route (such as gastrostomy or enteral probe) or tracheostomy.

Gestational and neonatal history and economic classification

Records containing information on the cohort of preterm infants since their birth are kept at the Preterm Outpatient Clinic of the Neonatal Pediatric Division of Escola Paulista de Medicina (EPM). Thus, data were collected regarding the gestational period (parity and age of the mother and complications during pregnancy) and neonatal period (gestational age, weight and length at birth, type of delivery, neonatal complications and type of feeding started in the maternity ward). The weight-for-gestational age was classified in accordance with the INTERGROWTH-21st curve.[14] Data on invasive procedures performed during the stay in the neonatal unit (orotracheal intubation, umbilical catheterization or use of orogastric tube), any use of red blood cell transfusion, parenteral nutrition, cardiopulmonary resuscitation in the delivery room or antibiotics in the neonatal period, the length of hospital stay and any occurrence of sepsis were recorded.

For the full-term infants, these data were obtained from the maternity discharge summary in the child's health record or, in the absence of these documents, from information provided by the mother or guardian.

Socioeconomic class was evaluated based on the points system of the Brazil Criterion version 2015 of the Brazilian Association of Survey Companies (Associação Brasileira de Empresas de Pesquisa, ABEP; São Paulo, Brazil).

Standardized consultation with pediatric gastroenterologist

Pediatric consultations for the infants in both groups were conducted by a single pediatric gastroenterologist. The frequency of regurgitation and its warning signs (retching, hematemesis, aspiration, apnea, failure to thrive, feeding or swallowing difficulties or abnormal posturing), daily duration of crying and irritability, presence and duration of efforts to evacuate, frequency of evacuation, stool consistency, presence of pain when evacuating and any history of fecal impaction were recorded. Considering these clinical characteristics, the diagnosis of FGIDs was established in accordance with the Rome IV criteria[5] for infant regurgitation, infant colic, functional diarrhea, infant dyschezia and functional constipation. To ensure greater accuracy of the results and avoid memory bias, only the clinical gastrointestinal tract manifestations that occurred at the time of the study were considered. FGIDs that had occurred in the past and had disappeared by the time of the study were not considered.

During the consultation with the pediatric gastroenterologist, the following information was also collected: history of previous infection (acute otitis media, bronchiolitis, pneumonia, urinary tract infection or acute gastroenteritis); family history of gastrointestinal disorders; current type of breastfeeding (breast milk, infant formula or cow's milk); and current use of medications (use of ranitidine, domperidone, anticonvulsants, antibiotics, prednisolone and inhaled corticosteroids was investigated).

Regarding the family history of gastrointestinal disorders, information was collected about any family history (among parents and

first-degree siblings) of chronic constipation, abdominal pain or gastroesophageal reflux.

A physical examination was performed, and the results, including weight and length, were recorded. Weight was measured using a Welmy digital pediatric scale (Welmy, Santa Bárbara d'Oeste, Brazil) among the term infants; and using a Filizola Baby digital pediatric scale (Filizola, São Paulo, Brazil) among the preterm infants. Length was measured using a child stadiometer (0-99 cm). Weight-for-age, height-for-age and body mass index-for-age Z scores were calculated using the Anthro software, version 3.2.2 (World Health Organization, Geneva, Switzerland).

Statistical analysis

The qualitative variables and occurrence of FGIDs in both groups (preterm and full-term infants) were compared using the chi-square test or Fisher's exact test. Regarding the quantitative variables, Student's t test was used to compare the mean ± standard deviation when the data were normally distributed; otherwise, the median and first and third quartiles were compared using the Mann-Whitney test. When necessary, a logistic regression model adjusted for age was used. The results from the logistic regression were presented as the odds ratio (OR) and respective 95% confidence interval (95% CI).

All analyses were performed using STATA/SE 15.1 for Windows (StataCorp, College Station, Texas, United States). P-values < 0.05 were considered statistically significant.

RESULTS

The study included 103 infants who were born preterm. Among these, four were excluded because they had a gastrointestinal tract disease (one had gastroesophageal reflux disease, one had cow's milk protein allergy and two had lactose intolerance, according to information provided by their mothers). The group of infants born full term consisted of 99 infants, and one was excluded due to gastroesophageal reflux disease. Thus, 99 infants born preterm and 98 born full term were studied. In the preterm group, the current corrected age was used.

Table 1 shows the characteristics of the infants and their gestational and neonatal histories. The corrected age of the preterm infants was significantly higher than that of the term infants. There was a higher proportion of male infants in the preterm infant group, but the difference was not significant. The mean gestational age was 31.4 weeks for the preterm infants and 39.2 weeks for the term infants. The preterm group had lower birth weight and length and higher proportions of cesarean delivery, need for resuscitation in the delivery room and small-for-gestational-age (SGA) infants,

Table 1. Characteristics and histories of the preterm and term infants

	Preterm (n = 99)	Term (n = 98)	P
Age (months)	7.2 (3.6; 13.2)	5.3 (3.1; 10.6)	0.010[a]
Sex (M/F)	58/41	48/50	0.176[b]
Gestational age (weeks)	31.4 ± 2.6	39.2 ± 1.0	< 0.001[c]
Weight at birth (g)	1,404.2 ± 379.8	3,321.9 ± 402.8[e]	< 0.001[c]
Length at birth (cm)	38.5 ± 3.4	48.9 ± 2.0[f]	< 0.001[c]
Cesarean delivery	76.8%	46.4%[g]	< 0.001[b]
Small for gestational age	33.3%	12.4%[h]	0.001[b]
Resuscitation in the delivery room	43.4%	2.2%[i]	< 0.001[b]
Antibiotic use in the neonatal period	96.9%[j]	0.0%	< 0.001[b]
Exclusive breastfeeding in the maternity ward	0.0%	84.4%[e]	< 0.001[d]
Mixed feeding in the maternity ward	89.9%	15.6%[e]	< 0.001[d]
Current weight-for-age Z score	-0.670	-0.185	< 0.001[a]
Current length-for-age Z score	-0.940	-0.510	0.002[a]
Current BMI-for-age Z score	-0.32	+0.33	< 0.001
Maternal disease during pregnancy	33.3%	14.4%[g]	0.002[b]
Socioeconomic classes C, D and E	86.8%	71.7%[l]	0.016
Current feeding type			
Breast milk	13.1%	79.4%[g]	< 0.001[b]
Infant formula	74.7%	37.1%[g]	< 0.001[b]
Cow's milk	25.3%	17.5%[g]	0.253
Personal history of infection	52.5%	28.9%[g]	0.003[b]
Current use of medications	40.4%	4.1%[g]	< 0.00[b]
Family history of gastrointestinal disorders	31.3%	24.5%[m]	0.566[b]

M = male; F = female. [a]Mann-Whitney test; [b]chi-square test; [c]Student's t test; [d]Fisher's exact test; [e-m]information available from the following numbers of infants: [e]n = 96; [f]n = 91; [g]n = 97; [h]n = 89; [i]n = 90; [j]n = 65; [l]n = 92; [m]n = 98.

and these differences were significant. A higher rate of exclusive breastfeeding in the maternity ward was observed for the infants who were born full term. There were also significant differences in the current weight-for-age, length-for-age and body mass index-for-age Z scores between the groups. Most of the infants in both groups belonged to social classes C, D or E. Preterm infants had higher rates of previous infections and were currently using more medications and consuming less breast milk than full-term infants.

Table 2 shows the frequency of FGIDs in both groups. The number of infants evaluated for each disorder varied according to the age established through the Rome IV criteria: infant colic, up to 5 months; regurgitation, up to 12 months; dyschezia, up to 9 months; constipation, up to 24 months; and functional diarrhea, between 6 and 24 months.

The frequency of infant regurgitation was higher in term infants than in preterm infants (**Table 2**). Among the infants in the age group for the evaluation of regurgitation, it was observed that the mean age of the term infants (4.7 ± 2.6 months) was lower (P = 0.01) than that of the preterm infants (6.0 ± 3.5 months). In turn, the proportion of infants who received breast milk was higher (P < 0.001) in the full-term group than in the preterm infant group. Considering the differences between the groups regarding age and proportion of breastfeeding, a multivariate analysis was performed (**Table 3**) with adjustment for these factors. Infant regurgitation remained associated with full-term birth and younger age.

For regurgitation, we also did a separate analysis according to semester for the two groups, with the following results. Regarding regurgitation among infants < 6 months, 7/34 (18.9%) of the premature infants and 25/55 (45.6%) of the term infants had regurgitation. When analyzed using the chi-square test, we found a statistical difference between the groups, with P = 0.032, i.e. those born at term continued to present a higher prevalence of regurgitation even when analyzed according to semester. Regarding regurgitation among infants > 6 months, this was present in 3/30 (10%) of the preterm infants and 1/19 (5.53%) of the term infants. As expected, the prevalence of regurgitation in the second age category was low in both groups.

Despite the higher frequencies of infant colic, functional constipation, functional diarrhea and infant dyschezia in the group of preterm infants, the differences were not significant. When the presence of at least one FGID was evaluated, no difference was observed between the groups (**Table 2**).

In the group of preterm infants, the association between sociodemographic variables and neonatal factors (including invasive procedures) and FGIDs was studied. The factors of sex, method of delivery, gestational age, birth weight, SGA, resuscitation in the delivery room, orotracheal intubation, arterial or venous umbilical catheterization, use of an orogastric tube, blood transfusion, use of parenteral nutrition, presence of sepsis, use of antibiotic in the neonatal period and length of hospital stay did not show any relationships (P > 0.05) with occurrences of infant regurgitation, infantile colic, functional diarrhea, dyschezia or constipation.

When necessary, the guardians of infants with an FGID were instructed by the researcher regarding specific therapeutic measures. Infants with more severe clinical manifestations were referred for evaluation and follow-up at the outpatient clinic of the Pediatric Gastroenterology Division of UNIFESP.

Table 2. Functional gastrointestinal disorders among preterm and term infants according to the Rome criteria, considering age ranges

Disorder (with age range)	Preterm % (n/N)	Term % (n/N)	P
Infant regurgitation (21 days to 12 months)	15.6% (10/64)	35.1% (26/74)	< 0.001[a]
Infant colic (birth to 5 months)	10.7% (3/28)	4.3% (2/46)	0.360[b]
Infant dyschezia (birth to 9 months)	9.3% (4/43)	7.5% (5/67)	0.735[b]
Constipation (birth to 24 months)	17.2% (17/99)	9.2% (9/98)	0.098[a]
Functional diarrhea (6 to 24 months)	4.6% (3/65)	0.0% (0/43)	0.274[b]
One or more FGIDs			
(1 to 8 months)	37.8% (17/45)	47.8% (32/67)	0.298[a]
(9 to 12 months)	36.8% (7/19)	14.3% (1/7)	0.375[b]
(13 to 24 months)	20% (7/35)	16.7% (4/24)	0.747[a]

[a]Chi-square test; [b]Fisher's exact test. FGIDs = functional gastrointestinal disorders.

DISCUSSION

In our study, higher frequency of FGIDs among preterm infants or those with a history of invasive neonatal procedures was not observed. A recent American study[13] using the Rome IV criteria and based on data collected online from 58 infants in the first

Table 3. Bivariate and multivariate analyses on the odds of infant regurgitation according to the Rome IV criteria, adjusted for breastfeeding and infant age

Factor	OR_{crude}	95% CI	P-value	$OR_{adjusted}$	95% CI	P-value
Group						
(term versus preterm)	2.93	1.28-6.68	0.011	3.85	1.26-11.78	0.018
Age, months	0.78	0.67-0.91	0.001	0.76	0.63-0.91	0.002
Breastfeeding	1.77	0.82-3.84	0.149	0.50	0.16-1.51	0.219

OR = odds ratio; CI = confidence interval.

year of life and 238 children between one and three years of age found prevalences of FGIDs that were similar to ours: 24.1% for infant regurgitation, 5.2% for infant colic and 12.0% for constipation. None of the infants had functional dyschezia or functional diarrhea. Our results provide evidence compatible with that of other studies in the literature,[13,15,16] but in addition, it is one of the few studies based on information obtained during face-to-face consultations performed specifically for this purpose by a pediatric gastroenterologist.

There are few studies in the literature comparing the prevalence of FGIDs among infants born preterm with that of infants born full term. A prospective study[9] on Italian infants born preterm or at term showed that during the first year of life, occurrence of at least one FGID according to the Rome III criteria was more prevalent among preterm infants (86%) than among term infants (73%). The high cumulative prevalence of at least one FGID in that study, compared with the findings in our study and in reviews of the literature is noteworthy.[4,15] Preterm infants had higher prevalence of regurgitation (45.7%) than term infants (37.3%; $P < 0.015$), in contrast with the results obtained in our study. In our study, regurgitation occurred in 35.1% of term infants and in 15.6% of preterm infants ($P < 0.001$). This difference could be explained by the type of feeding, since infants fed with maternal milk may present more regurgitation.[17]

However, the multivariate analysis (**Table 3**) showed that the greater frequency of breastfeeding in the group of term infants did not explain the higher frequency of regurgitation. In the Italian study,[9] no relationship was found between the type of feeding and infant regurgitation. The age difference between the two groups may be one of the factors explaining the higher prevalence of regurgitation among infants born at term. However, according to this multiple regression analysis, the greater chance of regurgitation among full-term infants was maintained even after adjusting for age (odds ratio, OR = 3.85; 95% confidence interval, CI: 1.26; 11.78; $P = 0.018$) (**Table 3**).

Although there was no significant difference in the frequency of infant colic in our study, it was higher among preterm infants. This was also observed in the Italian study.[9] However, the high cumulative rate of infant colic (more than 40% of the study population) in that study is noteworthy. This rate was higher than what was found in a Danish study[7] on a cohort of 62,761 infants that was based on the results from a computer-assisted telephone interview. In that study, prevalences of colic of 7.6% among term infants and 10.7% among preterm infants were found. These values were similar to those found in our study.

The higher frequency of infant colic among preterm infants may be related to changes in gastrointestinal motility, lower production of gastric acid and proteolytic enzymes and lower concentrations of secretory immunoglobulin A (IgA) and antimicrobial peptides in the gastrointestinal tract, which increase the risk of dysbiosis.[18] Preterm infants also have lower concentrations of lactase in the intestinal villi, compared with term infants.[18] Increased lactose concentration in the large intestine may lead to higher production of lactic acid and gases, which can cause pain and abdominal distension. Both dysbiosis[19] and lactase deficiency[20] are possible factors related to the development of infant colic.

The recent observation that use of antibiotics may cause predisposition to dysbiosis and, thus, to greater odds of developing FGIDs may be included in this context. In our study, we reviewed data on antibiotic use in the neonatal unit: among the 63 preterm infants who used antibiotics during the neonatal period, 21 (33.3%) developed FGID. Neither of the two preterm infants who did not use antibiotics developed any FGID. We used Fisher's exact test to analyze these data and did not find any relationship between antibiotic use during the neonatal period in the preterm group and future development of any FGID ($P = 1.00$).

We found higher frequency of constipation among preterm infants than among term infants (17.2% versus 9.2%), but the difference was not significant ($P = 0.098$). It is worth noting that for a significant difference to be achieved (80% power and 5% alpha error), it would have been necessary to include 361 patients in each group, which would have been unfeasible from an operational point of view. A study conducted in Denmark[17] among 286 preterm infants showed a high rate (approximately 40%) of laxative use among preterm infants up to six months of age.

The only study[9] in the literature that evaluated functional diarrhea among preterm infants showed a prevalence of 3.3%, similar to what was observed in our study. There was also no difference between full and preterm infants. A study conducted in Latin America[21] found that the prevalence of functional diarrhea was 1.9% among infants in the first year of life, regardless of gestational age at birth.

Regarding dyschezia, the findings from our study also contradicted the expectation of higher frequency among preterm infants: the rates found were 9.3% among preterm infants and 7.5% among term infants ($P = 0.735$). Dyschezia is a functional disorder that has been little investigated, with few studies in the literature. It results from lack of coordination between increased abdominal pressure and pelvic floor relaxation during bowel movements.[5] It has been assumed that preterm infants may have a delay in this mechanism that leads to higher rates of dyschezia. However, we were unable to confirm this hypothesis.

We also investigated whether neonatal factors in the group of preterm infants, including invasive diagnostic and therapeutic procedures that were experienced during the neonatal period, could contribute to development of FGIDs. Orotracheal intubation, use of venous or arterial umbilical catheters, use of an orogastric tube, parenteral nutrition, length of hospital stay, type of delivery, history

of sepsis, gestational age, birth weight and weight for gestational age classification were some of the factors analyzed. Although it has been suggested in the literature[7] that these factors could alter the maturation and development of some organs in newborns, thus leading to greater risk of development of FGIDs, we were unable to confirm this relationship in our study.

Our study had some limitations, such as the small number of infants included in the independent analysis on each of the five FGIDs, according to the age ranges recommended through the Rome IV criteria. For example, we included a total of 99 preterm infants in our study, but only 64 were analyzed regarding the presence of regurgitation (infants up to 12 months of age). Moreover, the number of preterm infants with FGIDs was small, which may have compromised the analysis on the relationship between invasive diagnostic and therapeutic procedures and the development of FGIDs. Other limitations were the cross-sectional nature of the study, which did not allow characterization of all FGIDs that had occurred or would occur during the first two years of life, and our use of a sample consisting of all patients consecutively treated at the outpatient clinic, which prevented calculation of the prevalence in a probabilistic sample.

On the other hand, the strength of our study was that it was the first to compare the frequency of FGIDs among preterm infants with their frequency among full-term infants using a comparative design and face-to-face consultations in which the Rome IV criteria were used. These face-to-face consultations decreased the risk of understanding bias, which can occur in studies that use only questionnaires. A physical examination was also performed on all the infants, which enabled a more complete assessment that, in addition to inclusion of weight and length data, helped establish the diagnosis of FGIDs.

CONCLUSIONS

We did not find any evidence of higher frequency of FGIDs among preterm infants than among infants born full term, during the first two years of life. In contrast, we found higher frequency of regurgitation among infants born full term than among preterm infants. In addition, there was no relationship between invasive diagnostic and therapeutic procedures performed during the neonatal period among infants born preterm and development of FGIDs during infancy.

REFERENCES

1. Rasquin-Weber A, Hyman PE, Cucchiara S, et al. Childhood functional gastrointestinal disorders. Gut. 1999;45 Suppl 2(Suppl 2):II60-8. PMID: 10457047; https://doi.org/10.1136/gut.45.2008.ii60.
2. Dhroove G, Chogle A, Saps M. A million-dollar work-up for abdominal pain: is it worth it? J Pediatr Gastroenterol Nutr. 2010;51(5):579-83. PMID: 20706149; https://doi.org/10.1097/MPG.0b013e3181de0639.
3. Vandenplas Y, Hauser B, Salvatore S. Functional Gastrointestinal Disorders in Infancy: Impact on the Health of the Infant and Family. Pediatr Gastroenterol Hepatol Nutr. 2019;22(3):207-16. PMID: 31110953; https://doi.org/10.5223/pghn.2019.22.3.207.
4. Vandenplas Y, Abkari A, Bellaiche M, et al. Prevalence and Health Outcomes of Functional Gastrointestinal Symptoms in Infants From Birth to 12 Months of Age. J Pediatr Gastroenterol Nutr. 2015;61(5):531-7. PMID: 26308317; https://doi.org/10.1097/MPG.0000000000000949.
5. Benninga MA, Faure C, Hyman PE, et al. Childhood Functional Gastrointestinal Disorders: Neonate/Toddler. Gastroenterology. 2016:S0016-5085(16)00182-7. PMID: 27144631; https://doi.org/10.1053/j.gastro.2016.02.016.
6. Bonilla S, Saps M. Early life events predispose the onset of childhood functional gastrointestinal disorders. Rev Gastroenterol Mex. 2013;78(2):82-91. PMID: 23578567; https://doi.org/10.1016/j.rgmx.2013.02.001.
7. Milidou I, Søndergaard C, Jensen MS, Olsen J, Henriksen TB. Gestational age, small for gestational age, and infantile colic. Paediatr Perinat Epidemiol. 2014;28(2):138-45. PMID: 24261325; https://doi.org/10.1111/ppe.12095.
8. Eichenwald EC; Committee on Fetus and Newborn. Diagnosis and Management of Gastroesophageal Reflux in Preterm Infants. Pediatrics. 2018;142(1):e20181061. PMID: 29915158; https://doi.org/10.1542/peds.2018-1061.
9. Salvatore S, Baldassarre ME, Di Mauro A, et al. Neonatal antibiotics and prematurity are associated with an increased risk of functional gastrointestinal disorders in the first year of life. J Pediatr. 2019;212:44-51. PMID: 31201028; https://doi.org/10.1016/j.jpeds.2019.04.061.
10. Velasco-Benitez CA, Axelrod CH, Gutierrez S, Saps M. The relationship between prematurity, method of delivery, and functional gastrointestinal disorders in children. J Pediatr Gastroenterol Nutr. 2020;70(2):e37-e40. PMID: 31978026; https://doi.org/10.1097/MPG.0000000000002543.
11. Steutel NF, Zeevenhooven J, Scarpato E, et al. Prevalence of Functional Gastrointestinal Disorders in European Infants and Toddlers. J Pediatr 2020;221:107-14. PMID: 32446468; https://doi.org/10.1016/j.jpeds.2020.02.076.
12. Miranda A. Early life events and the development of visceral hyperalgesia. J Pediatr Gastroenterol Nutr. 2008;47(5):682-4. PMID: 18955876; https://doi.org/10.1097/01.mpg.0000338958.94313.99.
13. Villar J, Ismail LC, Victora CG, et al. International standards for newborn weight, length, and head circumference by gestational age and sex; the Newborn Cross-Sectional Study for the INTERGROWTH-21st Project. Lancet. 2014;384(9946):857-68. PMID: 25209487; https://doi.org/10.1016/S0140-6736(14)60932-6.
14. Robin SG, Keller C, Zwiener R, et al. Prevalence of Pediatric Functional Gastrointestinal Disorders Utilizing the Rome IV Criteria. J Pediatr. 2018;195:134-9. PMID: 29398057; https://doi.org/10.1016/j.jpeds.2017.12.012.
15. Ferreira-Maia AP, Matijasevich A, Wang YP. Epidemiology of functional gastrointestinal disorders in infants and toddlers: A systematic review. World J Gastroenterol. 2016;22(28):6547-58. PMID: 27605889; https://doi.org/10.3748/wjg.v22.i28.6547.

16. Russo M, Strisciuglio C, Scarpato E, et al. Functional Chronic Constipation: Rome III Criteria Versus Rome IV Criteria. J Neurogastroenterol Motil. 2019;25(1):123-8. PMID: 30646483; https://doi.org/10.5056/jnm18035.
17. Zachariassen G, Fenger-Gron J. Preterm dietary study: meal frequency, regurgitation and the surprisingly high use of laxatives among formula-fed infants following discharge. Acta Paediatr. 2014;103(3):116-22. PMID: 24286180; https://doi.org/10.1111/apa.12524.
18. Lenfestey MW, Neu J. Gastrointestinal Development: Implications for Management of Preterm and Term Infants. Gastroenterol Clin North Am. 2018;47(4):773-91. PMID: 30337032; https://doi.org/10.1016/j.gtc.2018.07.005.
19. de Weerth C, Fuentes S, Puylaert P, de Vos WM. Intestinal microbiota of infants with colic: development and specific signatures. Pediatrics. 2013;131(2):e550-8. PMID: 23319531; https://doi.org/10.1542/peds.2012-1449.
20. Ahmed M, Billoo AG, Iqbal K, Memon A. Clinical Efficacy Of Lactase Enzyme Supplement In Infant Colic: A Randomised Controlled Trial. J Pak Med Assoc. 2018;68(12):1744-7. PMID: 30504935.
21. Chogle A, Velasco-Benitez CA, Koppen IJ, et al. A Population-Based Study on the Epidemiology of Functional Gastrointestinal Disorders in Young Children. J Pediatr 2016;179:139-43.e1. PMID: 27726867; https://doi.org/10.1016/j.jpeds.2016.08.095.

Authors' contributions: Gondim MMBB did the literature search, conceived and designed the study, participated in data collection, conducted the data analysis, wrote the manuscript and performed the review; de Morais MB did the literature search, conceived and designed the study, conducted the data analysis, wrote the manuscript and did writing-review and editing of the manuscript; Goulart AL conceived and designed the study, conducted the data analysis and performed the review. All authors made significant intellectual contributions and approved the final version of the manuscript

Sources of funding: None
Conflict of interest: None

Date of first submission: July 15, 2021
Last received: October 4, 2021
Accepted: October 29, 2021

Address for correspondence:
Marcela Montenegro Braga Barroso Gondim
Av. Nhambiquaras, 1.518
Moema — São Paulo (SP) — Brasil
CEP 04090-011
Tel. (+55 11) 2737-1987
E-mail: marcela_montenegro_@hotmail.com

Clinical diagnosis and treatment of primary thyroid tuberculosis: a retrospective study

Le-Le Sun[I], Su Dong[II], Jia-Lu Xu[III], Jin-Xin Zhu[IV], Jia Liu[V]

First Hospital of Jilin University, Jilin Province, China

[I]MD. Surgeon, Department of Thyroid Surgery, First Hospital of Jilin University, Jilin Province, China.
https://orcid.org/0000-0002-4052-6379

[II]MD, PhD. Anesthesiologist and Professor, Department of Anesthesia, First Hospital of Jilin University, Jilin Province, China.
https://orcid.org/0000-0001-6275-1035

[III]MD. Surgeon, Department of Thyroid Surgery, First Hospital of Jilin University, Jilin Province, China.
https://orcid.org/0000-0003-4295-0592

[IV]MD. Surgeon, Department of Thyroid Surgery, First Hospital of Jilin University, Jilin Province, China.
https://orcid.org/0000-0002-3496-0179

[V]MD, PhD. Surgeon and Professor, Department of Thyroid Surgery, First Hospital of Jilin University, Jilin Province, China.
https://orcid.org/0000-0003-3575-5107

KEY WORDS (MeSH terms):
Thyroiditis.
Tuberculosis.
Diagnosis.

AUTHORS' KEY WORDS:
Thyroid tuberculosis.
Granulomatous inflammation.
Retrospective study.

ABSTRACT

BACKGROUND: Primary thyroid tuberculosis (PTT) is an uncommon type of extrapulmonary tuberculosis, which is caused by *Mycobacterium tuberculosis*. It does not have specific clinical manifestations, and most cases are diagnosed through postoperative histopathological examination.

OBJECTIVE: To evaluate the diagnostic pattern and management strategy among patients with primary thyroid tuberculosis.

DESIGN AND SETTING: Retrospective study on patients with primary thyroid tuberculosis in the First Hospital of Jilin University (Changchun, China).

METHODS: Between March 2015 and June 2020, nine cases of PTT were diagnosed and treated in the Department of Thyroid Surgery of the First Hospital of Jilin University. Age at diagnosis, primary symptoms, preoperative biopsy, operation method, pathological classification, acid-fast staining test, anti-TB therapy and prognosis were registered in order to explore the appropriate protocol for diagnosis and treatment of this disease.

RESULTS: None of the patients was diagnosed with thyroid tuberculosis before surgery. All the patients underwent surgery. Granulomatous changes or caseous necrosis in thyroid tissue were found through postoperative histopathological evaluation. Polymerase chain reaction (PCR) results for *Mycobacterium tuberculosis* were positive in all patients. Most patients had a good prognosis after surgery and anti-tuberculosis drug therapy.

CONCLUSION: PTT is a rare disease. It is important to improve the preoperative diagnosis. Preoperative diagnostic accuracy relies on increased awareness of the disease and appropriate use of preoperative diagnostic methods, such as PCR detection, fine-needle aspiration cytology, acid-fast bacillus culture, ultrasound and blood sedimentation. PCR detection of *M. tuberculosis* is recommended as the gold standard for diagnosis.

INTRODUCTION

The World Health Organization (WHO) reported in 2009 that there were 9 million new cases of tuberculosis (TB) in the world every year. In 2011, it was estimated that there were about 8.7 million cases worldwide. It can be seen that the incidence of TB remains high and is spreading rapidly throughout the world.[1] Thyroid tuberculosis (TT), also known as tuberculous thyroiditis, can be divided into two types: primary and secondary. Secondary thyroid tuberculosis occurs after infection with tuberculosis in any other parts of the body. Primary thyroid tuberculosis (PTT) is mostly caused by direct infection of the thyroid by *Mycobacterium tuberculosis*. Due to the lack of obvious specificity of clinical manifestations, signs and laboratory and imaging examinations, PTT can be easily misdiagnosed clinically.

OBJECTIVE

The objective of this study was to evaluate the diagnostic pattern and management strategy among patients with primary thyroid tuberculosis.

METHODS

In this study, the clinical data of nine patients with PTT who were diagnosed in the Department of Thyroid Surgery of the First Hospital of Jilin University between March 2015 and June 2020 were retrospectively analyzed. Age at diagnosis, primary symptoms, preoperative biopsy, operation method, pathological classification, acid-fast staining test, anti-TB therapy and prognosis

were registered in order to explore the appropriate protocol for diagnosis and treatment of this disease.

General data

Between March 2015 and June 2020, nine cases of PTT were diagnosed in the Department of Thyroid Surgery of the First Hospital of Jilin University. There were five women and four men, with a median age of 50 years (range 43-64 years) (**Table 1**). None of the nine patients had any history of pulmonary or extrapulmonary TB.

Clinical manifestations

Four of the nine patients were admitted with a self-evident neck mass, and five were admitted because of thyroid nodules (nature to be determined), which had been found through outpatient physical examination. One patient presented with tenderness of the mass, but there was no obvious specific manifestation in the other eight cases. There were none of the common TB symptoms such as low fever, fatigue, night sweats, emaciation or loss of appetite (**Table 1**).

Auxiliary examinations

After admission, all patients underwent routine examinations such as thyroid color Doppler ultrasonography, thyroid function tests and computed tomography (CT) scan of the lungs. Thyroid nodules were examined by means of fine-needle aspiration in some patients (3/9).

Thyroid color Doppler ultrasonography showed that five patients were initially suspected of having thyroid malignancy, among whom two cases showed fine-dot calcification inside the thyroid nodule, and one case showed arc calcification at the edge of the nodule (**Figure 1**). The other four patients tended to be benign.

Three patients underwent fine-needle puncture cytological examination, which indicated the presence of atypical epithelial cells. The possibility of thyroid papillary carcinoma was not ruled out. No mutation of *BRAF* gene exon 15 point (V600E) was found in any of the genetic tests. The remaining six patients refused to undergo puncture examination for personal reasons, and required surgical treatment.

Table 1. Clinical data on nine patients with primary thyroid tuberculosis

Serial number	Sex	Age (years)	Symptoms of TB	Preoperative biopsy	Glandular lobe	Concomitant thyroid disease	Operation method	Pathological classification	Acid-fast staining test	Anti-TB therapy	Follow-up (months)	Prognosis
1	Female	58	(-)	(-)	Right	Nodular goiter	Right lobectomy + isthmus excision	Granulomatous type	(+)	Yes	70	No recurrence
2	Female	50	(-)	(-)	Left	None	Left partial resection	Granulomatous type	(+)	Yes	33	Pulmonary tuberculosis occurred
3	Male	64	(-)	(-)	Right	Nodular goiter	Right near total resection + left partial resection	Caseation type	(-)	Yes	41	No recurrence
4	Female	43	(-)	(+)	Both lobes	PTMC + Nodular goiter	Total thyroidectomy	Granulomatous type	(+)	No	52	No recurrence
5	Male	48	(-)	(-)	Right	PTMC	Right lobectomy + isthmus excision	Granulomatous type	(+)	Yes	59	No recurrence
6	Female	62	(-)	(-)	Right	None	Right partial resection	Granulomatous type	(+)	Yes	7	Sonographic features of PTT infection remain
7	Male	77	(-)	(+)	Right	Nodular goiter + lymphocytic thyroiditis	Right lobectomy + isthmus excision	Granulomatous type	(-)	Yes	22	No recurrence
8	Male	52	(-)	(-)	Right	None	Right lobectomy	Diffuse type	(+)	No	16	No recurrence
9	Female	37	(-)	(+)	Left	PTMC	Left lobectomy + isthmus excision	Caseation type	(+)	No	34	No recurrence

TB = tuberculosis; PTMC = papillary thyroid microcarcinoma; PTT = primary thyroid tuberculosis.

Serum tri-iodothyronine, thyroxine, free tri-iodothyronine, free thyroxine and thyroid-stimulating hormone levels were normal in all patients. Lung CT examination showed no obvious abnormality.

For all nine patients, intraoperative rapid frozen section examination, postoperative pathological examination of paraffin sections, acid-fast staining and polymerase chain reaction (PCR) detection of *M. tuberculosis* genes were performed.

Treatment

None of the nine patients was diagnosed with TT before surgery and all the patients underwent surgery. Five patients were suspected of having malignancy preoperatively and underwent unilateral/bilateral lobectomy and isthmus resection (four and one cases, respectively).

In patients who underwent total thyroidectomy, rapid intraoperative pathological evaluation indicated the presence of bilateral papillary thyroid carcinoma with multiple lesions, 0.1–1.1 cm in diameter, with granulomatous inflammation (atypical epithelial cells were observed in preoperative puncture examination). Two patients underwent unilateral partial thyroidectomy after rapid intraoperative pathological evaluation indicated the presence of granulomatous thyroiditis.

Another two patients had large masses. A hypothesis of nodular goiter was considered preoperatively, and granulomatous inflammation accompanied by nodular goiter was indicated through rapid intraoperative pathological evaluation. Thus, right lobectomy resection and right near total resection + left partial resection was performed, respectively (**Table 1**).

Ethics statement

These studies involving human participants were reviewed and approved by the ethics committee of the First Hospital of Jilin University (2021-087). The patients/participants provided their written informed consent to participate in this study. Written informed consent was obtained from the individual(s) for the publication of any potentially identifiable images or data included in this article.

RESULTS

Presence of granulomatous changes or caseous necrosis in thyroid tissue were confirmed through postoperative histopathological evaluations on all nine patients (**Figure 2**). Among them, seven cases were positive for acid-fast staining and two were negative. The PCR results for *M. tuberculosis* genes were positive in all patients.

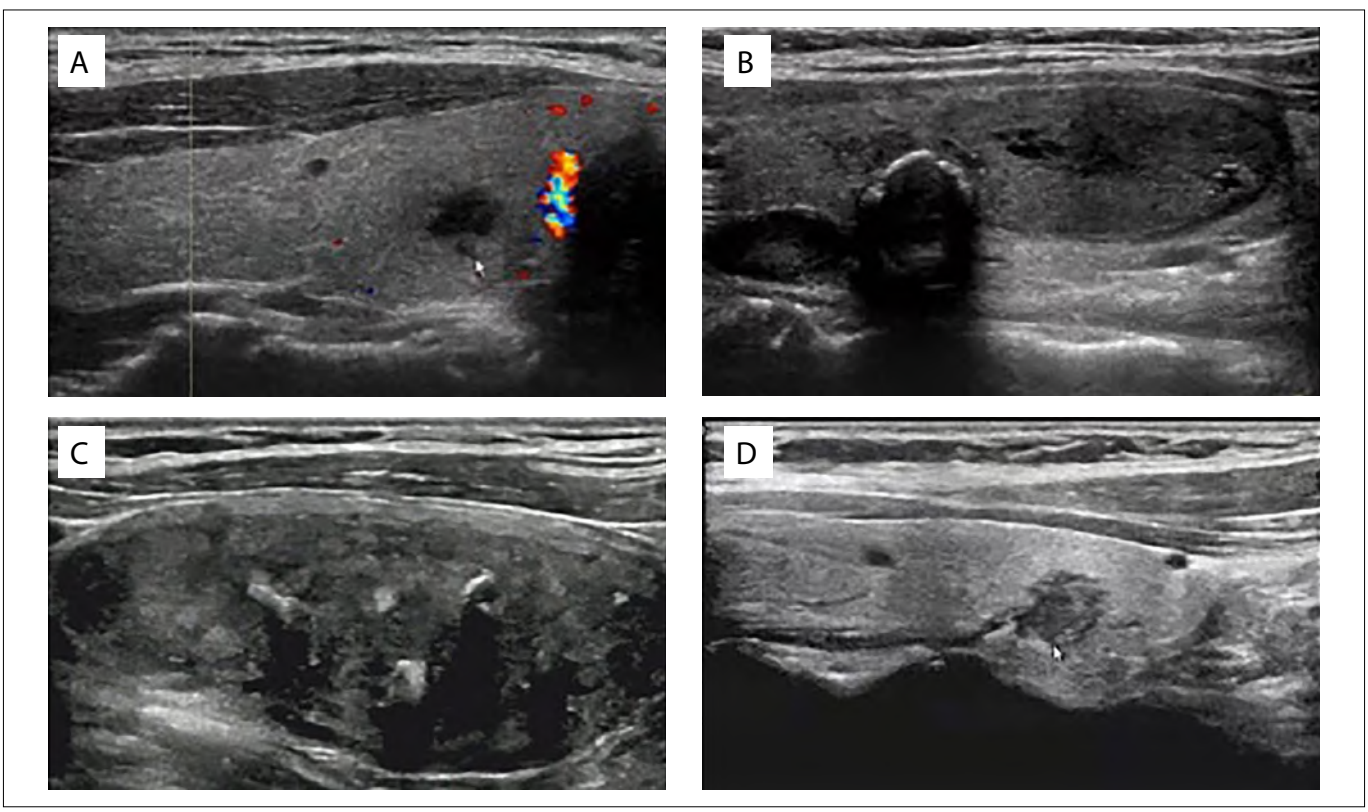


Figure 1. Characteristic ultrasonographic changes of primary thyroid tuberculosis. Ultrasound indicated that the thyroid mass had unclear boundaries and no obvious blood flow signal inside the mass (A); or was surrounded by a strong echo (B); or by a mostly mixed echo (C); or by a scattered strong echo in some parts (D).

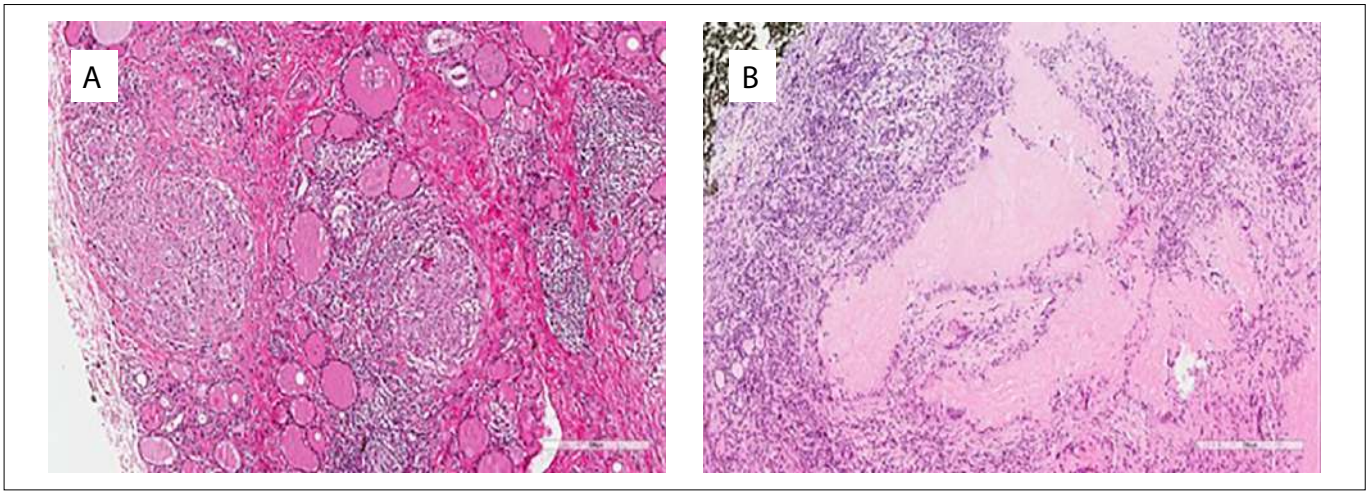


Figure 2. Pathological changes characteristic of primary thyroid tuberculosis. A: Diffuse multifocal irregular granuloma formation was observed in the thyroid gland. (HE 10×). B: Granuloma formation in the thyroid with caseous necrosis in the center. (HE 10×).

All the patients had good wound healing and were discharged after recovery. One patient who underwent total thyroidectomy and had no TB lesions in other parts of the body was only followed up closely after the operation, but the other patients were given systemic anti-TB therapy after the operation. All nine patients were followed up for 7-70 months. The disease was found to be not completely controlled in one patient, and there was recurrence of pulmonary TB in another patient. However, no recurrence was seen in the remaining seven patients (**Table 1**).

DISCUSSION

PTT is a fairly rare disease and the incidence of all forms of thyroid tuberculosis (TT) is only 0.4%-0.76% in China.[2] Here, we reported nine cases of PTT that we saw within a five-year period in our hospital. PTT is caused by *M. tuberculosis* infection and occurs when the systemic immune function is weakened.[3]

It has been reported that human immunodeficiency virus (HIV) infection or extrapulmonary TB can greatly increase the incidence of PTT, to 45%-75%.[4,5] However, in the nine cases assessed here, there was no HIV infection or extrapulmonary TB, according to the preoperative examinations.

Misdiagnosis and missed diagnosis are common among PTT cases before surgery, and high clinical standards and experience are needed for making the diagnosis. Among our cases, the male-to-female ratio was 4:5 and the median age was 50 years old. These characteristics are not specific and are similar to what is seen regarding the incidence of thyroid disease. PTT is most frequent in the lower right lobe of the thyroid[6,7] and the cases of our study were consistent with this (6/9).

Tuberculous nodules are often accompanied by thyroid adenoma, diffuse goiter, acute abscess and cervical lymph node lesions, and are sometimes manifested as sudden enlargement of the original thyroid nodules.[8] Some cases are accompanied by neck compression symptoms.[9] In a few cases, thyroid damage has been found to be caused by *M. tuberculosis* or even by thyrotoxicosis or mucoedema.[10] Most researchers believe that the granulomatous type is the most common type in clinical practice, while a few researchers believe that the caseous type is the most common. Among the nine patients with PTT in our study, six were considered to be the granulomatous type; two, the caseous type; and one, the diffuse type.

Many studies have emphasized the importance of ultrasound in making the diagnosis of PTT. Chan et al.[11] described the ultrasound features of a mixed cystic and solid hypoechoic mass in the right lobe. Kang et al.[12] performed an ultrasound examination on one patient that showed enlargement of the right thyroid gland, with nodules that were mainly anechoic, with some internal echoes and irregular margins. In another patient, the left lobe showed a large, heterogeneous, mostly anechoic lesion with irregular vascular walls and a small amount of internal echo. Yang et al.[13] carried out dynamic ultrasound monitoring on a PTT patient, and the initial ultrasound examination showed an uneven fluid-filled nodule with internal bleeding.

In the present study, all of the nine cases underwent thyroid color doppler ultrasonography, from which five patients were suspected of having thyroid malignancy and four patients tended to be benign. A single ultrasound examination was not specific for PTT in our clinical practice. Yang et al.[13] reported that repeated ultrasound examination during disease progression showed gradual changes when the nodule was solid and hyperechoic with blurred edges.

Enhanced computed tomography (CT) scanning also plays an important role in making the diagnosis of PTT. CT may detect signs of thyroid cartilage plate destruction and laryngeal cavity narrowing and is helpful for locating caseous necrosis. Laitman et al.[14] reported that on enhanced CT, central necrotic foci and marginal enhancement were seen in thyroid tuberculous nodules.

Some research has also described the magnetic resonance imaging (MRI) features of TT.[15] However, we did not perform either enhanced CT or MRI on the thyroid because of their high price and narrow scope of application. Additionally, chest X-rays and abdominal ultrasonography can be used to detect TB in other parts of the body. In our study, all patients underwent CT scans of the lungs to rule out pulmonary tuberculosis.

At present, fine-needle aspiration cytology (FNAC), acid-fast bacillus culture and PCR detection of *M. tuberculosis* are the most important means for preoperative diagnosis. On the other hand, acid-fast staining in PTT patients has been found to present a high false-negative rate.[16] Therefore, PCR detection of *M. tuberculosis* is now recommended as the gold standard for diagnosis. However, among our cases, six patients out of nine refused to undergo FNAC before surgery because they were prone to excessive anxiety or worried about malignant changes and insisted on undergoing the operation directly.

For patients without a definite preoperative diagnosis, rapid intraoperative frozen section examination should be performed, so as to facilitate selection of surgical methods and avoid excessive surgery. In cases of PTT that undergo total thyroidectomy, the examination must be performed to rule out the presence of other focal infections throughout the body. If no other lesions are found, close follow-up is recommended, and additional anti-TB therapy is not required.[17] However, if other lesions are present, at least six months of anti-TB therapy should be given, even if total thyroidectomy is performed. If TB is found in patients who have undergone subtotal or near-total thyroidectomy and thyroid lobectomy, anti-TB therapy should be given for at least six months, regardless of the presence of any additional lesions. Among our patients, only one patient underwent total thyroidectomy without anti-TB therapy, and the remaining eight received postoperative anti-TB drug therapy. The follow-up showed no recurrence in any of the patients.

For patients with complications such as abscesses or sinus passages due to TB, drainage or complete thyroidectomy with medication is recommended. This medication should be continued for at least an average of four months after the last operation. The appropriate follow-up for patients with PTT includes ultrasonography every three months for the first six months, followed by ultrasonography every six months for two years, and then annually thereafter.[17] Among our patients, only one patient underwent total thyroidectomy without anti-TB therapy, and the remaining eight received postoperative anti-TB drug therapy. The follow-up showed no recurrence in any of the patients within follow-up periods ranging from 7 to 70 months.

CONCLUSION

Primary thyroid tuberculosis is a rare thyroid disease and it is easy to misunderstand the diagnosis, thus resulting in delayed treatment. Here, we presented our diagnosis and treatment experiences relating to nine cases that were confirmed as primary thyroid tuberculosis through postoperative histopathological evaluations. We believe that with further accumulation of cases and experience in the future, our understanding of PTT will become enhanced, and the diagnosis and treatment of this disease will be improved.

REFERENCES

1. Kibirige D. Endocrine dysfunction among adult patients with tuberculosis: An African experience. Indian J Endocrinol Metab. 2014;18(3):288-94. PMID: 24944920; https://doi.org/10.4103/2230-8210.131136.
2. Salerno T, Peca D, Menchini L, et al. Respiratory insufficiency in a newborn with congenital hypothyroidism due to a new mutation of TTF-1/NKX2.1 gene. Pediatr Pulmonol. 2014;49(3):E42-4. PMID: 23997037; https://doi.org/10.1002/ppul.22788.
3. Cuesta Hernández M, Gómez Hoyos E, Agrela Rojas E, Téllez Molina MJ, Díaz Pérez JÁ. Tuberculosis tiroidea: causa excepcional de bocio compresivo [Thyroid tuberculosis: a rare cause of compressive goiter]. Endocrinol Nutr. 2013;60(8):e11-e3. PMID: 23410708; https://doi.org/10.1016/j.endoen.2012.10.005.
4. Kaur A, Kucheria M, Gupta R, Thami GP, Kundu R. Extensive Multisystemic Disseminated Tuberculosis in an Immunocompetent Patient. J Clin Aesthet Dermatol. 2018;11(9):42-6. PMID: 30319731.
5. Darre T, Amana B, Pegbessou E, et al. Tuberculosis of the thyroid in Togo: a clinicopathologic study of 11 presumed cases. Trop Doct. 2018;48(4):313-6. PMID: 30114986; https://doi.org/10.1177/0049475518789555.
6. Neki N. Thyroid tuberculosis. J Mahatma Gandhi Inst Med Sci. 2017;22(1):29-30. https://doi.org/10.4103/0971-9903.202002.
7. Chan Shin Jie S, Tan CC. A rare case of primary tuberculosis in a solitary thyroid nodule. Indian J Tuberc. 2020;67(3):360-2. PMID: 32825868; https://doi.org/10.1016/j.ijtb.2019.08.001.
8. Oueslati I, Sakka I, Ismail O, et al. Tuberculosis of the Thyroid Gland Presented as a Rapid Enlargement of a Preexisting Goiter. Case Rep Endocrinol. 2018;2018:4369531. PMID: 30538870; https://doi.org/10.1155/2018/4369531.
9. Baidya A, Singha A, Bhattacharjee R, Dalal BS. Tuberculosis of the thyroid gland: two case reports. Oxf Med Case Reports. 2015;2015(4):262-4. PMID: 26634141; https://doi.org/10.1093/omcr/omv028.
10. Majumder A, Sen D. Uncommon affliction of a common disease - primary tuberculosis of thyroid gland. Indian J Pathol Microbiol. 2020;63(1):83-5. PMID: 32031128; https://doi.org/10.4103/IJPM.IJPM_719_18.
11. Sharma S, Girhotra M, Zafar N, Gupta R. Tuberculosis of the Thyroid in a Child: A Rare cause of Thyromegaly. APSP J Case Rep. 2016;7(1):5. PMID: 26816678.
12. Kang BC, Lee SW, Shim SS, et al. US and CT findings of tuberculosis of the thyroid: three case reports. Clinical Imaging. 2000;24(5):283-6. PMID: 11331157; https://doi.org/10.1016/s0899-7071(00)00194-7.

13. Yang GY, Zhao D, et al. Role of ultrasound evaluation for the diagnosis and monitoring of thyroid tuberculosis: A case report and review of the literature. Oncol Lett. 2015;9(1):227-30. PMID: 25435964; https://doi.org/10.3892/ol.2014.2652.
14. Laitman BM, Samankan S, Hwang S, Chai RL. Primary Thyroid Tuberculosis: An Uncommon Presentation of a Thyroid Mass. Ear Nose Throat J. 2020:145561320949481. PMID: 32791901; https://doi.org/10.1177/0145561320949481.
15. Madhusudhan KS, Seith A, Khadgawat R, Das P, Mathur S. Tuberculosis of the thyroid gland: magnetic resonance imaging appearances. Singapore Med J. 2009;50(7):e235-8. PMID: 19644607.
16. Ortiz-Flores A, Gioia F, Montanez-Fernandez L, et al. Incidental finding of a primary thyroid tuberculosis. Oxf Med Case Reports. 2017;2017(6):omx022. PMID: 28580157; https://doi.org/10.1093/omcr/omx022.
17. Akbulut S, Sogutcu N, Arikanoglu Z, Bakir S, Ulku A, Yagmur Y. Thyroid tuberculosis in southeastern Turkey: is this the resurgence of a stubborn disease? World J Surg. 2011;35(8):1847-52. PMID: 31523497; https://doi.org/10.1007/s00268-011-1118-3.

Authors' contributions: Liu J and Sun LL performed the surgery, reviewed the literature and contributed to manuscript drafting; Dong S reviewed the literature and was responsible for reviewing the manuscript for important intellectual content; Xu JL and Zhu JX analyzed and interpreted the imaging findings; all authors issued final approval for the version to be submitted

Sources of funding: None
Conflicts of interest: None

Date of first submission: May 4, 2021
Last received: September 14, 2021
Accepted: October 29, 2021

Address for correspondence:
Jia Liu
Department of Thyroid Surgery, First Hospital of Jilin University
Changchun 130021 – Jilin Province, China
Tel. (+86) 431-88782331
E-mail: liu_jia@jlu.edu.cn

Prevalence of burnout among healthcare workers in six public referral hospitals in northeastern Brazil during the COVID-19 pandemic: a cross-sectional study

Ana Irene Carlos de Medeiros[I], Rafael Barreto de Mesquita[II], Felipe de Souza Macêdo[III], Antonio George de Calvacante Matos[IV], Eanes Delgado Pereira[V]

Universidade Federal do Ceará (UFC), Fortaleza (CE), Brazil

[I]PT. Doctoral Student, Universidade Federal do Ceará (UFC), Fortaleza (CE), Brazil.
https://orcig.org/0000-0003-2958-6079

[II]PT, PhD. Adjunct Professor, Department of Physiotherapy, Universidade Federal do Ceará (UFC), Fortaleza (CE), Brazil.
https://orcig.org/0000-0002-8048-3393

[III]MD, MSc. Physiotherapist, Department of Clinical Medicine, Universidade Federal do Ceará (UFC), Fortaleza (CE), Brazil.
https://orcig.org/0000-0001-6592-0789

[IV]MD, PhD. Assistant Professor, Department of Clinical Medicine, Universidade Federal do Ceará (UFC), Fortaleza (CE), Brazil.
https://orcid.org/0000-0001-6981-3462

[V]MD, PhD. Adjunct Professor, Department of Clinical Medicine, Universidade Federal do Ceará (UFC), Fortaleza (CE), Brazil.
https://orcid.org/0000-0002-4414-3164

KEY WORDS (MeSH terms):
Burnout, professional.
Intensive care units.
COVID-19.

AUTHORS' KEY WORDS:
Burnout syndrome.
Prevalence
Healthcare workers

ABSTRACT

BACKGROUND: The coronavirus disease 2019 (COVID-19) pandemic has placed considerable psychological stress on frontline healthcare workers (HCWs).

OBJECTIVE: To evaluate the prevalence of burnout syndrome among HCWs facing the COVID-19 outbreak.

DESIGN AND SETTING: Cross-sectional study conducted in six public intensive care units (ICUs) in the city of Fortaleza, Brazil.

METHODS: An online survey was conducted among HCWs to measure the three dimensions of burnout.

RESULTS: A total of 62 physicians (23.4%), 65 nurses (24.5%), 58 nurse technologists (21.9%) and 80 physiotherapists (30.2%) completed the questionnaire. Nearly half of the participants (48.6%) had high levels of emotional exhaustion, and almost one-third of them (29.4%) had high levels of depersonalization. Low levels of professional efficacy were observed in 18.1% of the sample. The independent determinants of depersonalization burnout were age < 33 years (odds ratio, OR 2.03; 95% confidence interval, CI 1.15-3.56; P = 0.01) and female gender (OR 0.33; 95% CI 0.18-0.62; P = 0.01). Increased workload was associated with both depersonalization (OR 2.37; 95% CI 2.02-5.50; P = 0.04) and emotional exhaustion (OR 1.89; 95% CI 1.04-3.58; P = 0.030).

CONCLUSION: The COVID-19 pandemic has had a great impact on the dimensions of depersonalization and emotional exhaustion. Consideration of these dimensions is important when designing future burnout prevention programs for frontline personnel.

INTRODUCTION

Burnout syndrome is defined as a set of psychological symptoms resulting from the interaction between chronic occupational stress and individual factors. These symptoms include emotional exhaustion, depersonalization and decreased professional satisfaction. Maslach and Jackson created the Maslach Burnout Inventory (MBI), which is currently the most commonly used scale for assessing the syndrome.[1]

The impact of the coronavirus disease 2019 (COVID-19) pandemic on frontline healthcare workers (HCWs) has been enormous and has resulted in high prevalence of burnout.[2-4] This pandemic has exacerbated stressors at workplaces and increased occurrence of burnout syndrome among HCWs.[5] A study on HCWs in Italy showed that at least one out of three exhibited high levels of the domain of emotional exhaustion, and one out of four reported high levels of the domain of depersonalization.[6]

The MBI is composed of three domains: emotional exhaustion, depersonalization and personal fulfillment. There is a lack of consensus regarding whether high scores are needed in one, two or all three domains to be able to state that HCWs are classified as burned out or non-burned out.[7,8]

It is recommended that each of the three MBI domains should be evaluated because the symptoms differ between individuals, and exhaustion can manifest itself as cynicism or anger in some and withdrawal and silence in others. Absence of any of the domains can lead to an erroneous assessment of the problem and consequent errors in healthcare policies and actions.

OBJECTIVE

We conducted an online survey among HCWs at six public intensive care units (ICUs) in the city of Fortaleza, Brazil, in order to document the prevalence of each domain of burnout and the factors associated with these domains, during the COVID-19 outbreak.

METHODS

In this cross-sectional study, we measured the prevalence of burnout among HCWs facing the COVID-19 pandemic during June and July 2020, while working in six public ICUs in tertiary-level referral hospitals for treatment of COVID-19 in the city of Fortaleza. We selected HCWs such that the sample included physicians, nurses, nurses technologists and physiotherapists. Anonymity of all the participants was guaranteed. All participants read and signed a written consent statement so that we could ensure that they understood the terms and agreed to participate in the study. The ethical procedures of the study were analyzed and approved by the independent Ethics Committee of the Universidade Federal do Ceará on February 27, 2019, under the number 04582818.6.00005054. This research project was written and approved for evaluation of burnout and its correlation with resilience among healthcare professionals working in ICUs in 2019. Thus, the project was designed before the beginning of the COVID-19 pandemic. However, with the onset of the pandemic, we decided to apply the burnout questionnaire online among healthcare workers in ICUs.

The survey was conducted through a questionnaire built on the Google platform and sent out through social networks. The questionnaire included questions about the participants' demographic characteristics (age, gender and marital status), professional history (job category and years of experience), work characteristics (average weekly hours worked, how many hospitals they worked at, etc.) and habits (drinking alcohol, etc.).

The prevalence of burnout among HCWs in the ICU was measured using the Brazilian version of the Maslach Burnout Inventory-Human Service Survey (MBI-HSS).[9,10]

The questionnaire consisted of 22 questions: five items on depersonalization, nine items on emotional exhaustion and eight items on reduced professional satisfaction. The score for each item in the MBI-HSS was obtained using a seven-point Likert scale, which ranged from zero (never) to six (every day). The results were determined by summing the scores for each domain. This 22-item questionnaire contains three subscales that evaluate what are considered to be the three major domains of burnout. First, emotional exhaustion burnout is characterized by high scores (≥ 26). Second, depersonalization burnout is characterized by high scores (≥ 9). Third, professional efficacy burnout is characterized by low scores (≤ 33).[9]

Sample size

Previous studies showed that the prevalence of burnout among HCWs ranged from 6% to 47%.[11] To compare the rates of burnout between physicians and other HCWs, we assumed rates of 15% and 30%, respectively. By defining α and β as 0.05 and 0.20, respectively, at least 133 participants were required for one arm of the study, i.e. physicians versus other HCWs.

Data analysis

Data from Google Forms were exported to a Microsoft Excel 2016 spreadsheet (Microsoft, Redmond, Washington, United States), and all statistical analyses were performed using SPSS Statistics, version 26.0 (SPSS Inc., Chicago, Illinois, United States). Absolute and relative frequencies (n, %) were used to describe the categorical variables. Continuous variables were described as medians and interquartile ranges.

First, we compared the baseline characteristics of those who did and did not have each domain of burnout using the χ^2 difference test for categorical variables. Normality was verified using the Shapiro-Wilk test.

Logistic regression analyses were then performed using emotional exhaustion (≥ 26; yes/no), depersonalization (≥ 9; yes/no) and professional efficacy (≤ 33; yes/no) as dependent variables. The association between each burnout domain and each potential risk factor was explored by estimating the odds ratio (OR) and 95% confidence interval (CI), using bivariate analysis. The factors were selected *a priori* on clinical or empirical grounds, or were derived from the relevant literature. Predictors presenting $\alpha < 0.05$ in the bivariate analysis were included in the multivariable logistic regression model.

RESULTS

A total of 265 HCWs completed the questionnaire. The participants included 62 physicians (23.4%), 65 nurses (24.5%), 58 nurse technologists (21.9%) and 80 physiotherapists (30.2%). Nearly half of the participants (48.6%) had high levels of emotional exhaustion, and almost one-third of them (29.4%) had high levels of depersonalization. Low levels of professional efficacy were observed in 18.1% of the sample (**Table 1**).

The emotional exhaustion group had more respondents with increased workload than did the group without emotional exhaustion (86% versus 76.4%; P = 0.04) (**Table 2**). The depersonalization group had a significantly higher number of physicians (32% versus 19%; P = 0.03), a lower number of women (62.8% versus 82.9%; P = 0.01), a higher number of professionals younger than 33 years old (61.5% versus 42.1%; P = 0.04), a higher number of unmarried professionals (57.7% versus 41.2%) and higher numbers of HCWs who were working in two or more hospitals (52.6% versus 34.5%; P = 0.007) and with increased workload (89.7% versus 77.5%; P = 0.02), compared with the group without depersonalization (**Table 3**).

A multiple logistic regression analysis showed that depersonalization burnout among women was lower than that among men (OR 0.33; 95% CI 0.18-0.62; P = 0.01) and was higher among professionals

younger than 33 years old (OR 2.03; 95% CI 1.15-3.56; P = 0.01) P = 0.01) (**Table 4**). Increased workload was associated with both depersonalization (OR 2.37; 95% CI 2.02-5.50; P = 0.04) and emotional exhaustion (OR 1.89; 95% CI 1.04-3.58; P = 0.030). No factors were associated with professional efficacy (**Table 5**).

Table 1. Characteristics of the sample

	n	%
Characteristics		
Women	204	67
Age in years, median (interquartile range)	33 (29-38)	
Age < 33 years	127	48
Married	143	54
Professional history		
Physicians	62	23.4
Other healthcare workers	203	76.6
Occupation		
Physicians	62	23.4
Nurses	65	24.5
Nurse technologists	58	21.9
Physiotherapists	80	30.2
Working in ≥ 2 hospitals	106	40
Increased workload	215	81.1
Increased income source	213	80.4
Increased drinking of alcohol	72	27.2
Working for more than 30 hours/week	246	92.8
Length of experience less than six years	200	75.5
Burnout subdomains		
Emotional exhaustion	129	48.6
Depersonalization	78	29.4
Professional efficacy	48	18.1

DISCUSSION

The results from this study were concordant with those from studies carried out in other countries.[3,4,12-14] The proportions with emotional exhaustion, affecting nearly half (48.6%) of the HCWs, with depersonalization in almost one-third (29%) and with low levels of professional effectiveness in less than one-fifth (18%) were similar to the results found by Barello et al.[6]

The contributions of sociodemographic variables to the three burnout domains were explored using multivariate logistic regression analysis. Our findings suggested that female gender is associated with lower levels of depersonalization burnout. This can be explained by the burnout/resilience balance. Duarte et al.[3] observed that resilience is a potentially protective factor against burnout. There is evidence that women are more resilient and have better coping skills, which in turn reduces work stress and allows them to deal with work-related issues more effectively.[15]

A recent meta-analysis on the relationship between gender and burnout showed that women are slightly more emotionally exhausted than men, while men are slightly more depersonalized than women.[16]

Lower age was associated with depersonalization burnout, which is in line with previous research.[3,4] This result can at least partly be explained by the imbalance between expectations about attributions and the reality of the challenges and stressors of the ICU for young professionals. These HCWs, including junior doctors and residents, have formed an important pillar of the effort involved in managing and treating patients during the COVID-19 pandemic.[17] Because of the large number of patients and the heavy burden of the COVID-19 pandemic, many healthcare units,

Table 2. Comparison of characteristics of participants with and without emotional exhaustion

Characteristics	With emotional exhaustion (129) n (%)	Without emotional exhaustion (136) n (%)	Overall (265) n (%)	P
Women	102 (75)	102 (79)	204 (77)	0.43
Age < 33	66 (51.2)	61 (44.9)	127 (47.9)	0.40
Married	76 (58.9)	67 (49.3)	143 (54)	0.15
Professional history				
Physicians	32 (24.8)	30 (22.1)	62 (23.4)	
Other healthcare workers	97 (75.2)	106 (77.9)	203 (76.6)	0.57
Occupation				
Physician	32 (24.8)	30 (22.1)	62 (23.4)	
Nurse	29 (22.5)	36 (26.5)	65 (24.5)	
Nurse technologist	21 (16.3)	37 (27.2)	58 (21.9)	
Physiotherapist	47 (36.4)	33 (24.3)	80 (30.2)	0.05
Working in ≥ 2 hospitals	57 (36)	49 (44.2)	106 (40)	0.17
Changes in relation to pre-pandemic period				
Increased workload	111 (86)	104 (76.4)	215 (81.1)	0.04
Increased income source	99 (76.7)	114 (83.8)	213 (80.4)	0.14
Increased drinking of alcohol	32 (24.8)	40 (29.4)	72 (27.2)	0.40
Working than 30 hours/week	122 (91.2)	124 (94.6)	246 (92.8)	0.28
Length of experience less than six years	96 (74.4)	104 (76.5)	200 (75.5)	0.69

including ICUs, have had to hire young HCWs who, contrary to what was previously thought, are not immune to burnout.

Increased workload is associated with depersonalization and emotional exhaustion. Our findings are consistent with previous research.[4] Work overload is one of the most important risk factors for burnout among healthcare professionals.[18,19] According to Leiter's burnout model, there is evidence to suggest that emotional exhaustion caused by work overload may lead to depersonalization and cynical attitudes.[20-21]

There were no covariables associated with the HCWs' performance. This can be explained by the fact that only 18.1% of the HCWs in the sample had low levels of performance. Empirical evidence points towards exhaustion and cynicism as the core of burnout.[22] In our sample, these two domains had high prevalences.

This study had several limitations. The sample size actually achieved may have been insufficient. It was a cross-sectional online survey, which may have limited its accessibility for individuals with little or no skill regarding the internet. Because this was a cross-sectional study, no data were collected before the pandemic, thus making comparison impossible. Other variables, such as depression and anxiety, have not yet been studied. Longitudinal studies will be needed to clarify the long-term effects of physical and psychological variables on HCWs during the COVID-19 pandemic.

This is an important study that highlights the multidimensionality of burnout syndrome among several types of healthcare professionals in six public ICUs. Indeed, the two burnout domains were associated with specific variables. Previous studies have emphasized the importance of identifying potential factors leading to burnout among HCWs in order to be able to implement remedies for management and prevention of burnout syndrome. These interventions should be at both the individual and the organizational level, and could involve scheduling of activities to enable a healthy work-life balance, strengthening of relationships with family and

Table 4. Logistic regression on factors associated with burnout subscales

Variables	Emotional exhaustion OR (95% CI)	Depersonalization OR (95% CI)
Gender		
Male		Reference
Female		0.33 (0.18-0.62)
Age in years		
≥ 33		Reference
< 33		2.03 (1.15-3.56)
Increased workload	1.89 (1.04-3.58)	2.37 (2.02-5.50)

OR = odds ratio; CI = confidence interval.

Table 3. Comparison of characteristics of participants with and without depersonalization

Characteristics	With depersonalization (78) n (%)	Without depersonalization (187) n (%)	Overall (265) n (%)	P
Women	49 (62.8)	155 (82.9)	204 (77)	0.01
Age years < 33	48 (61.5)	79 (42.2)	127 (49.7)	0.04
Married	33 (42.3)	110 (58.8)	122 (46)	0.01
Professional history				
Physicians	25 (32)	37 (19.0)	62 (23.4)	
Other healthcare workers	53 (67.9)	150 (80.2)	203 (76.6)	0.03
Occupation				
Physician	25 (32.1)	37 (19.8)	62 (23.4)	
Nurse	14 (17.9)	51 (27.3)	65 (24.5)	
Nurse technologist	17 (21.8)	41 (21.9)	58 (21.9)	
Physiotherapists	22 (28.2)	58 (31)	80 (30.2)	0.13
Work in ≥ 2 hospitals	41 (52.6)	65 (34.5)	106 (40)	0.007
Changes in relation to pre-pandemic period				
Increased workload	70 (89.7)	145 (77.5)	215 (81.1)	0.02
Increased income source	66 (84.6)	147 (78.6)	213 (80.4)	0.26
Increased drinking of alcohol	25 (32.5)	47 (25.1)	72 (27.2)	0.27
Working more than 30 hours/week	77 (98.7)	169 (90.4)	246 (92.8)	0.01
Length of experience less than six years	59 (75.6)	141 (75.4)	200 (75)	0.96

Table 5. Comparison of characteristics of participants with and without professional efficacy

Characteristics	With professional efficacy (217) n (%)	Without professional efficacy (48) n (%)	Overall (265) n (%)	P
Women	165 (76)	39 (81.3)	204 (77)	0.43
Age < 33 years	104 (47.9)	23(47.2)	127 (49.3)	0.99
Married	123 (56.7)	20 (41.7)	143 (54)	0.07
Professional history				
Physicians	49 (22.6)	13 (27.1)	62 (23.4)	
Other healthcare workers	168 (77.4)	35 (72.9)	203 (76.6)	0.50
Occupation				
Physician	49 (22)	13 (27.1)	62 (23.4)	
Nurse	53 (24.4)	12 (25)	65 (24.5)	
Nurse technologist	48 (22.1)	10 (20)	58 (21.9)	
Physiotherapists	67 (30.9)	13 (27)	80 (30.2)	0.90
Working in ≥ 2 hospitals	57 (44.2)	49 (36)	106 (40)	0.94
Changes in relation to pre-pandemic period				
Increased workload	173 (79.7)	42 (87.5)	215 (81.2)	0.21
Increased income source	173 (79)	40 (83)	213 (80)	0.56
Increased drinking of alcohol	64 (29.5)	8 (16.7)	72 (27.2)	0.07
Work more than 30 hours/week	199 (91.7)	47 (97.9)	246 (92.8)	0.13
Length of experience less than six years	161 (72.4)	39 (81.3)	200 (75)	0.30

friends, fulfillment of personal goals and ensuring organizational support from the hospital.[23]

We believe that the results from this study contribute to better understanding of the factors associated with burnout among HCWs and should be considered in designing future programs and guidelines to promote protective actions and increase the psychological wellbeing of these professionals. The idea of "burnout contagion" can be useful for "emotional decontamination" in workplaces, among workers who have already been affected by this syndrome.

CONCLUSION

HCWs experience high levels of emotional exhaustion and depersonalization burnout, which warrant attention and support from policymakers.

REFERENCE

1. Maslach C, Jackson SE. The measurement of experienced burnout. J Occup Behav 1981;2(2):99-113. https://doi.org/10.1002/job.4030020205.
2. Albott CS, Wozniak JR, McGlinch B, et al. Battle buddies: rapid deployment of a psychological resilience intervention for health care workers during the COVID-19 pandemic. Anesth Analg. 2020;131(1):43-54. PMID: 32345861; https://doi.org/10.1213/ANE.0000000000004912.
3. Duarte I, Teixeira A, Castro L, et al. Burnout among Portuguese healthcare workers during the COVID-19 pandemic. BMC Public Health. 2020;20(1):1885. PMID: 33287794; https://doi.org/10.1186/s12889-020-09980-z.
4. Matsuo T, Kobayashi D, Taki F, et al. Prevalence of Health Care Worker Burnout During the Coronavirus Disease 2019 (COVID-19) Pandemic in Japan. JAMA Netw Open. 2020;3(8):e2017271. PMID: 32749466; https://doi.org/10.1001/jamanetworkopen.2020.17271.
5. Restauri N, Sheridan AD. Burnout and posttraumatic stress disorder in the coronavirus disease 2019 (COVID-19) pandemic: intersection, impact and interventions. J Am Coll Radiol. 2020;17(7):921-6. PMID: 32479798; https://doi.org/10.1016/j.jacr.2020.05.021.
6. Barello S, Palamenghi L, Graffigna G. Burnout and somatic symptoms among frontline healthcare professionals at the peak of the Italian COVID-19 pandemic. Psychiatry Res. 2020;290:113129. PMID: 32485487; https://doi.org/10.1016/j.psychres.2020.113129.
7. Ricou B, Zampieri FG, Brown SM. Should all ICU clinicians be regularly tested for burnout? No. Intensive Care Med. 2018;44(5):684-6. PMID: 29736792; https://doi.org/10.1007/s00134-018-5139-3. Erratum in: Intensive Care Med. 2018;44(7):1199.
8. Brindley PG, Olusanya S, Wong A, Crowe L, Hawryluck L. Psychological 'burnout' in healthcare professionals: Updating our understanding, and not making it worse. J Intensive Care Soc. 2019;20(4):358-62. PMID: 31695741; https://doi.org/10.1177/1751143719842794.
9. Benevides-Pereira AMT, Gonçalves MB. Transtornos emocionais e a formação em medicina: um estudo longitudinal. Rev Bras Educ Med. 2009;33(1):10-23. https://doi.org/10.1590/S0100-55022009000100003.
10. Carlotto MS, Câmara SG. Propriedades psicométricas do Maslach Burnout Inventory em uma amostra multifuncional. Estud Psicol (Campinas) [online]. 2017;34(3):449. http://doi.org/10.1590/1982-02752017000300012.
11. Chuang CH, Tseng PC, Lin CY, Lin KH, Chen YY. Burnout in the intensive care unit professionals A systematic review. Medicine (Baltimore).

2016;95(50):e5629. PMID: 27977605; https://doi.org/10.1097/MD.0000000000005629.

12. Morgantini L, Naha U, Wang H, et al. Factors contributing to healthcare professional burnout during the COVID-19 pandemic: a rapid turnaround global survey. MedRxiv [Preprint]. 2020:202005.17.20101915. PMID: 32511501; https://doi.org/10.1101/2020.05.17.20101915.
13. Azoulay E, De Waele J, Ferrer R, et al. Symptoms of burnout in intensive care unit specialists facing the COVID-19 outbreak. Ann. Intensive Care. 2020;10(1):110. PMID: 32770449; https://doi.org/10.1186/s13613-020-00722-3.
14. Lasalvia A, Amaddeo F, Porru S, et al. Levels of burn-out among healthcare workers during the COVID-19 pandemic and their associated factors: a cross-sectional study in a tertiary hospital of a highly burdened area of north-east Italy. BMJ Open. 2021;11(1):e045127. PMID: 33455940; https://doi.org/10.1136/bmjopen-2020-045127.
15. Lakomý M, Kafková MP. Resilience as a Factor of Longevity and Gender Differences in Its Effects. Czech Sociological Review. 2017;53(3):369-92. https://doi.org/10.13060/00380288.2017.53.3.336.
16. Purvanova RK, Muros JP. Gender differences in burnout: a meta-analysis. J Vocat Behav. 2010;77(2):168-85. https://doi.org/10.1016/j.jvb.2010.04.006.
17. Ruparelia J, Gosal JS, Garg M, Bhaskar S, Jha DK. Letter to the Editor: Challenges to Neurosurgical Residency Training During COVID-19 Pandemic: An Indian Perspective. World Neurosurg. 2020;140:464-6. PMID: 32474090; https://doi.org/10.1016/j.wneu.2020.05.178.
18. Greenglass ER, Burke RJ, Fiksenbaum L. Workload and burnout in nurses. J Community Appl Soc Psychol. 2001;11(3):211-5. https://doi.org/10.1002/casp.614.
19. Barbosa FT, Leão BA, Tavares GM, Santos JG. Burnout syndrome and weekly workload of on-call physicians: cross-sectional study. Sao Paulo Med J. 2012;130(5):282-8. PMID: 23174866; https://doi.org/10.1590/S1516-31802012000500003.
20. Leiter MP. Burnout as a developmental process: consideration of models. In: Schaufeli WB, Maslach C, Marek T, editors. Professional burnout: recent developments in theory and research. Washington, DC: Taylor & Frances; 1993. p. 237-50.
21. Adams S, Mohos A, Kalabay L, Torzsa P. Potential correlates of burnout among general practitioners and residents in Hungary: the significant role of gender, age, dependent care and experience. BMC Fam Pract. 2018;19(1):193. PMID: 30541461; https://doi.org/10.1186/s12875-018-0886-3.
22. Maslach C, Leiter MP. Understanding the burnout experience: recent research and its implications for psychiatry. World Psychiatry. 2016;15(2):103-11. PMID: 27265691; https://doi.org/10.1002/wps.20311.
23. Kaur M, Sethi P, Gupta N, Bhatia P. Burnout during the COVID-19 pandemic: time to ponder. Braz J Anesthesiol. 2021;71(2):190. PMID: 33894864; https://doi.org/10.1016/j.bjane.2020.10.017.

Authors' contributions: Pereira ED: analysis, interpretation of data for the study, original draft, final approval of the written version and agreement to be accountable for all aspects of the study and for ensuring that questions relating to the accuracy or integrity of any part of the study are appropriately investigated and resolved; Medeiros AIC: contributions to the conception of the work, data acquisition, final approval of the written version and agreement to be accountable for all aspects of the study; Mesquita RB and Matos AGC: interpretation of study data, original draft, final approval of the written version and agreement to be accountable for all aspects of the work; and Macêdo FS: design of the work, data acquisition, final approval of the written version and agreement to be accountable for all aspects of the study

Sources of funding: None
Conflicts of interest: None

Date of first submission: April 16, 2021
Last received: September 7, 2021
Accepted: October 29, 2021

Address for correspondence:
Eanes Delgado Pereira
R. Professor Costa Mendes, s/nº
Fortaleza (CE) — Brasil
CEP 60140-000
Tel. (+55 85) 3224-3541
E-mail: eanes@fortalnet.com.br

Risk factors for acute kidney injury after liver transplantation in intensive care unit: a retrospective cohort study

Ana Paula Camargos de Figueirêdo Neves[I], Angélica Gomides dos Reis Gomes[II], Paula Frizera Vassallo[III], Ana Cristina Simões e Silva[IV], Francisco Guilherme Cancela e Penna[V], Fabrício de Lima Bastos[VI], Mateus Rocha Muniz[VII], Guilherme Carvalho Rocha[VIII], Augusto Cesar Soares dos Santos Júnior[IX], Cecilia Gómez Ravetti[X], Vandack Nobre[XI]

School of Medicine, Universidade Federal de Minas Gerais (UFMG), Belo Horizonte (MG), Brazil

[I]MD. Physician and Master's Student, Postgraduate Program on Infectology and Tropical Medicine, Universidade Federal de Minas Gerais (UFMG), Belo Horizonte (MG), Brazil.
https://orcid.org/0000-0003-0649-5510

[II]MD. Physician and Master's Student, Postgraduate Program on Infectology and Tropical Medicine, Universidade Federal de Minas Gerais (UFMG), Belo Horizonte (MG), Brazil.
https://orcid.org/0000-0002-4568-0738

[III]MD, PhD. Physician in the Intensive Care Unit, Hospital das Clínicas, Universidade Federal de Minas Gerais (UFMG), Belo Horizonte (MG), Brazil.
https://orcid.org/0000-0002-7531-0607

[IV]MD, PhD. Physician, Department of Pediatrics, Universidade Federal de Minas Gerais (UFMG), Belo Horizonte (MG), Brazil.
https://orcid.org/0000-0001-9222-3882

[V]MD, PhD. Physician, Instituto Alfa de Gastroenterologia (IAG), Universidade Federal de Minas Gerais (UFMG), Belo Horizonte (MG), Brazil.
https://orcid.org/0000-0002-2338-5367

[VI]MD. Physician, Department of Internal Medicine, School of Medicine, Universidade Federal de Minas Gerais (UFMG), Belo Horizonte (MG), Brazil.
https://orcid.org/0000-0003-0600-8196

[VII]Undergraduate Medical Student, Universidade Federal de Minas Gerais (UFMG), Belo Horizonte (MG), Brazil.
https://orcid.org/0000-0002-9734-1674

[VIII]Undergraduate Medical Student, Universidade Federal de Minas Gerais (UFMG), Belo Horizonte (MG), Brazil.
https://orcid.org/0000-0002-8105-3133

[IX]MD, PhD. Physician, Department of Nephrology, Hospital das Clínicas, Universidade Federal de Minas Gerais (UFMG), Belo Horizonte (MG), Brazil.
https://orcid.org/0000-0001-5864-2338

[X]MD, PhD. Physician, Department of Internal Medicine, Universidade Federal de Minas Gerais (UFMG), Belo Horizonte (MG), Brazil.
https://orcid.org/0000-0002-6349-3063

[XI]MD, PhD. Physician, Postgraduate Program on Infectology and Tropical Medicine, Universidade Federal de Minas Gerais (UFMG), Belo Horizonte (MG), Brazil.
https://orcid.org/0000-0002-7922-0422

KEY WORDS (MeSH terms):
Intensive care units.
Risk factors.
Mortality.

AUTHORS' KEY WORDS:
Acute renal injury.
Acute kidney injury.
Liver transplantation.
Clinical outcome.
Postoperative.
Critically ill patients.

ABSTRACT

BACKGROUND: Acute kidney injury (AKI) is a frequent complication during the postoperative period following liver transplantation. Occurrence of AKI in intensive care unit (ICU) patients is associated with increased mortality and higher costs.

OBJECTIVE: To evaluate occurrences of moderate or severe AKI among patients admitted to the ICU after liver transplantation and investigate characteristics associated with this complication.

DESIGN AND SETTING: Single-center retrospective cohort study in a public hospital, Belo Horizonte, Brazil.

METHODS: Forty-nine patients admitted to the ICU between January 2015 and April 2017 were included. AKI was defined from a modified Kidney Disease Improving Global Outcomes (KDIGO) score (i.e. based exclusively on serum creatinine levels).

RESULTS: Eighteen patients (36.7%) developed AKI KDIGO 2 or 3; mostly KDIGO 3 (16 out of the 18 patients). Lactate level within the first six hours after ICU admission (odds ratio, OR: 1.3; 95% confidence interval, CI: 1.021-1.717; P = 0.034) and blood transfusion requirement within the first week following transplantation (OR: 8.4; 95% CI: 1.687-41.824; P = 0.009) were independently associated with development of AKI. Patients with AKI KDIGO 2 or 3 underwent more renal replacement therapy (72.2% versus 3.2%; P < 0.01), had longer hospital stay (20 days versus 15 days; P = 0.001), higher in-hospital mortality (44.4% versus 6.5%; P < 0.01) and higher mortality rate after one year (44.4% versus 9.7%; P = 0.01).

CONCLUSION: Need for blood transfusion during ICU stay and hyperlactatemia within the first six postoperative hours after liver transplantation are independently associated with moderate or severe AKI. Developing AKI is apparently associated with poor outcomes.

INTRODUCTION

Acute kidney injury (AKI) is a frequent complication during the postoperative period following liver transplantation, with consequent increases in hospital stay, deaths and costs.[1,2] Moreover, it is associated with an increased risk of developing chronic kidney disease,[1-3] acute graft failure,[1,3] sepsis and coagulopathy.[4] The incidence of AKI during the immediate postoperative period following liver transplantation ranges from 17% to 95% in different series,[1,5,6] and 8% to 17% of these patients require renal replacement therapy (RRT).[4] In Brazil, the reported incidence of AKI after liver transplantation has ranged from 32% to 72%, according to the definition criteria used; and the 30-day mortality in this group of patients has ranged from 12% to 25%, but may reach 50% among those requiring RRT.[7-10]

Liver transplant recipients' survival has improved substantially over the last decades. Nevertheless, occurrences of AKI in this population remain correlated with elevated mortality during the postoperative period. Additionally, even successful liver transplant patients seem to be at higher risk of chronic kidney disease, seen at the long-term follow-up, when they developed AKI during the first postoperative days.[11,12] The pathophysiology of AKI in these cases is multifactorial.[9,13] The most likely contributing factors include higher occurrence of hepatic ischemia-reperfusion injury (HIRI),[10,11] increased use of marginal or high-risk grafts and presence of receptors with a high Model of End-Stage Liver Disease (MELD) score.[12,14]

Currently, Brazil is the country with the largest absolute number of liver transplantations in Latin America and the third globally, with more than 1,700 surgeries per year.[15] However, few

studies in this country or in other low to middle-income countries have assessed AKI during the postoperative period following liver transplantation.

OBJECTIVE

Given this scenario, the aim of this study was to evaluate occurrences of moderate or severe AKI among patients undergoing liver transplantation at a reference center in Brazil and to investigate associated factors and consequences of this complication.

METHODS

Study design and setting

A retrospective cohort study was conducted among adult patients (aged 18 years or older) who had undergone orthotopic cadaveric liver transplantation. These patients were admitted to an intensive care unit (ICU) during their immediate postoperative period (IPO), between January 2015 and April 2017. The exclusion criteria were the occurrence of dialytic chronic end-stage renal failure, double transplantation (hepatic-renal; creatinine clearance (CrCl < 30 ml/minutes) and death during the intraoperative period or within the first 24 hours after ICU admission. The adult ICU of Hospital das Clínicas, Universidade Federal de Minas Gerais (HC-UFMG), is a reference center for liver transplantation, with a total of 18 beds.

This study was approved by the local Research Ethics Committee (CAAE: 83336918.2.0000.5149), on October 8, 2018, which waived the requirement to obtain a signed consent form from the participants, due to the retrospective nature of this study.

Clinical outcomes

We assessed occurrences of AKI during the first seven days of follow-up or up to the time of hospital discharge or death, whichever came first. We also investigated associations between AKI and some relevant patient outcomes, namely length of ICU and hospital stay, in-hospital mortality and mortality rate after one year.

Data collection

Data were extracted from the electronic medical records of Hospital das Clínicas, Universidade Federal de Minas Gerais (HC-UFMG), and from the Alfa Institute of Gastroenterology platform (Belo Horizonte, Brazil).[16] The demographic and clinical characteristics of all participants were obtained. The baseline characteristics assessed were age, gender, body mass index (BMI), Sequential Organ Failure Assessment (SOFA)[17] score values, presence of comorbidities, reason for liver transplantation, Model for End-stage Liver Disease (MELD)[18] values, Child-Pugh score values[19] and laboratory data, including hemoglobin, creatinine (pre-transplantation and post-transplantation) and serum lactate levels. Surgical and cold ischemia time, vasopressors and inotropic medication requirement, along with blood component transfusion, were assessed as intraoperative variables. We also assessed data regarding ICU stay, need for surgical reintervention, need for vasopressors and inotropic drugs and renal replacement therapy rate. Donor-related data, including age, gender, use of vasopressors and occurrence of cardiac arrest, were also collected.

AKI was defined as a 1.5-fold increase in baseline serum creatinine (SCr) level during the first seven days or an increase in SCr ≥ 0.3 mg/dl within 48 hours following liver transplantation. We used a modified AKI KDIGO score (without diuresis measurement) to classify the stage of AKI as KDIGO 1, 2 or 3.[20]

Statistical analysis

Categorical variables were expressed as absolute and relative frequencies and were compared using the chi-square test or Fisher's exact test, as indicated. Continuous nonparametric variables were expressed as medians and interquartile ranges (Q1-Q3) and were compared using the Mann-Whitney test.

Patients with AKI were stratified into the subgroups 1, 2 and 3, in accordance with their AKI KDIGO score. Thus, they were classified into two groups: non-AKI and AKI KDIGO 1 (absent or mild) or AKI KDIGO 2/3 (moderate to severe), for further comparative analyses.

Variables with P-value < 0.20 were included in a multivariate analysis (logistic regression model) in order to determine which of the patients' characteristics were independently associated with development of AKI (KDIGO 2 or 3).

A bicaudal P-value < 0.05 was used to determine significance in all analyses. The SPSS 22.0 software, version 20.0 (IBM, New York, United States), was used for data analysis.

RESULTS

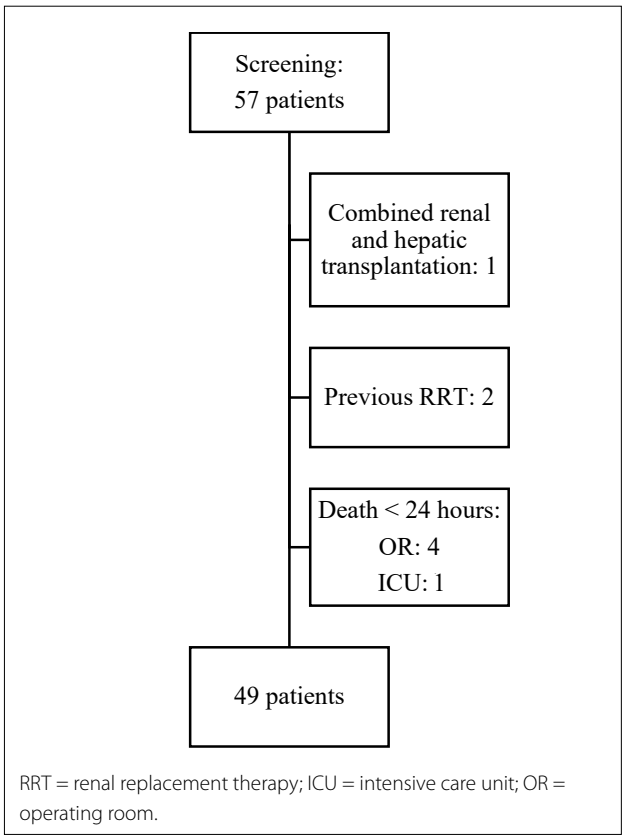
Out of a total of 57 patients who underwent liver transplantation during the study period, 49 were included in the final analyses (**Figure 1**).

The main baseline characteristics of the patients included are shown in **Table 1**. The median (Q1-Q3) age was 54 years (43-65), and 30 patients (61.2%) were male. The median total duration of the surgical procedure was 407 (309-549) minutes. The median cold ischemia time was 466 (405-633) minutes.

No preoperative factor assessed in this study was associated with KDIGO 2/3 development. Forty-one patients (83.6%) developed AKI during the follow-up period; 23 (46.9%) with KDIGO 1, two (4.1%) with KDIGO 2 and 16 (32.7%) with KDIGO 3.

Factors associated with AKI during ICU stay

Vasopressor requirement occurred more frequently in patients with AKI KDIGO 2 or 3 than those with non-AKI/KDIGO 1



RRT = renal replacement therapy; ICU = intensive care unit; OR = operating room.

Figure 1. Flowchart of study selection.

(17 [94.4%] versus 19 [61.3%] patients; P = 0.01). Moreover, the former group received more blood transfusion during the first week of ICU stay (15 [83.3%] versus 13 [41.9%] patients; P < 0.01) and required surgical reintervention more often (8 [44.4%] versus 4 [12.9%] patients; P = 0.01). In addition, the AKI KDIGO 2/3 group had higher creatinine levels (1.5 [1.0-2.39] versus 0.95 [0.71-1.16] mg/dl; P = 0.003) and higher arterial lactate levels within the first six hours after admission (3.31 [2.67-7.28] versus 2.38 [1.78-3.22] mmol/l; P = 0.01) than their counterparts. There was no difference between the two groups with regard to other baseline characteristics (**Table 1**).

In a multivariate analysis, ICU blood transfusion requirement (odds ratio, OR: 8.4; 95% confidence interval, CI: 1.68-41.824; P = 0.009) and higher arterial lactate level measured within the first six hours after ICU admission (OR: 1.32; 95% CI: 1.021-1.717; P < 0.05) were independently associated with development of AKI KDIGO 2 or 3 (**Table 2**).

AKI and patient outcomes

The in-hospital mortality rate was 22.4% (**Table 3**). Patients with AKI KDIGO 2 or 3 throughout the first seven days of follow-up underwent RRT more frequently (13 [72.2%] versus 1 [3.2%] patients; P < 0.01), had a longer hospital stay in days

Table 1. Main characteristics of the patients included in the study, stratified according to the occurrence of acute kidney injury (AKI) KDIGO 0/1 (no AKI or KDIGO 1) or KDIGO 2 or 3

	All (n = 49)	KDIGO 0/1 (n = 31)	KDIGO 2/3 (n = 18)	P-value
Preoperative data				
Age in years	54 (43-65)	53 (41-62)	61 (43-65)	0.24
Sex, male	30 (61.2)	20 (64.5)	10 (55.6)	0.55
Weight in kg	74 (63-82)	72 (63-80)	79.5 (61-86)	0.23
Comorbidities				
SAH	9 (18.4)	6 (19.4)	3 (16.7)	1
DM	9 (18.4)	4 (12.9)	5 (27.8)	0.25
CKD	2 (4.1)	2 (6.5)	0	0.52
Others	21 (42.9)	12 (38.7)	9 (50)	0.55
Reason for transplantation				0.42
HCC	12 (24.5)	5 (16.1)	7 (38.9)	
Hepatitis	11 (22.4)	7 (22.6)	4 (22.2)	
Alcoholism	10 (20.4)	8 (25.8)	2 (11.1)	
Cryptogenic	7 (14.3)	5 (16.1)	2 (11.1)	
Others	9 (18.4)			
Child-Pugh*				0.34
A	12 (24.5)	7 (22.6)	5 (27.8)	
B	13 (26.5)	8 (25.8)	5 (27.8)	
C	18 (36.7)	13 (41.9)	5 (27.8)	
MELD	20 (18.3-24)	20 (18-23)	20 (19.7-24)	0.73
Baseline SCr	0.91 (0.69-1.20)	0.89 (0.66-0.99)	0.98 (0.74-1.35)	0.188
Donor data				
Age in years	338 (24-51)	41 (23-53)	31.5 (26.7-47.2)	0.67
Sex, male	33 (67.3)	22 (71)	11 (61)	0.53
Vasopressor use	29 (59)	16 (51.6)	13 (72.2)	0.23
Surgical/perioperative data				
Surgical time	407 (309-549)	375 (300-467)	453 (331-633)	0.07
Cold ischemia time	466 (405-633)	473 (375-620)	460 (412-661)	0.3
Vasopressor use	32 (65.3)	19 (61.3)	13 (72.2)	0.54
Blood transfusion	27 (55.1)	16 (51.6)	11 (61.1)	0.28
Postoperative data				
Reintervention	12 (24.5)	4 (12.9)	8 (44.4)	0.01
Vasopressor requirement	36 (73.5)	19 (61.3)	17 (94.4)	0.01
Albumin use for more than 24 hours	20 (40.8)	11 (35.5)	9 (50)	0.37
Hemoglobin 6 hours		9.5 (8.5-11.9)	8.5 (7.2-10.4)	0.19
Hemoglobin 24 hours#		8.5 (6.8-11.0)	7.2 (6.7-9.2)	0.969
Creatinine 6 hours	1.04 (0.77-1.67)	0.95 (0.71-1.16)	1.5 (1.0-2.39)	0.003
Lactate within 6 hours	2.8 (1.9-4.3)	2.38 (1.78-3.22)	3.31 (2.67-7.28)	0.01
Lactate 24 hours	2.0 (1.44-3.0)	1.82 (1.25-2.27)	4.0 (1.84-6.0)	< 0.001
Transfusion in ICU	28 (57.1)	13 (41.9)	15 (83.3)	0.01

Data are presented as n (%) or median (Q1-Q3).
*Referring to 45 patients; #Referring to 47 patients; Q1-Q3 = interquartile range; AKI = acute kidney injury; SAH = systemic arterial hypertension; DM = diabetes mellitus; CKD = chronic kidney disease; HCC = hepatocellular carcinoma; MELD = Model of End-Stage Liver Disease; ICU = intensive care unit; SCr = serum creatinine.

Table 2. Univariate and multivariate analysis on factors associated with development of acute kidney injury KDIGO 2 or 3

Characteristics	Univariate		Multivariate	
	P - value	OR	95% CI	P-value
Vasopressor requirement	0.01			
Hemoglobin 6 hours	0.19			
Lactate 24 hours	< 0.001			
Reintervention	0.01			
Transfusion in ICU	0.01	8.400	1.68-41.824	0.009
Lactate within 6 hours	0.01	1.324	1.021-1.717	0.034

Data are presented as n (%) or median and interquartile range (Q1-Q3).
ICU = intensive care unit; OR = odds ratio; CI = confidence interval.

Table 3. Outcomes according to development of acute kidney injury (KDIGO 0/1 and KDIGO 2/3)

Outcomes	All	KDIGO 0/1	KDIGO 2/3	P-value
	(n = 49)	(n = 31)	(n = 18)	
RRT in ICU	14 (28.6)	1 (3.2)	13 (72.2)	< 0.01
Days in ICU	6 (3-9)	5 (3-8)	7.5 (3-12.5)	0.59
Days in hospital	18 (11-30)	15 (11-29)	20 (7.2-31.7)	0.001
In-hospital mortality	10 (20.4)	2 (6.5)	8 (44.4)	< 0.01
One-year mortality	11 (22.4)	3 (9.7)	8 (44.4)	0.01

Data are presented as n (%) or median and interquartile range (Q1-Q3).
RRT = renal replacement therapy; ICU = intensive care unit.

(20 [7.2-31.7] versus 15 [11-29] days; P < 0.01), higher in-hospital mortality (8 [44.4%] versus 2 [6.5%] patients; P < 0.01) and a higher mortality rate after one year of follow-up (8 [44.4%] versus 3 [9.7%] patients; P < 0.01), compared with the non-AKI or KDIGO 1 subgroup (**Table 3**).

DISCUSSION

In this study, occurrence of AKI KDIGO 2 or 3 during the postoperative period following liver transplantation was common (36.7%) and was independently associated with a requirement for blood transfusion during the ICU stay and with higher levels of lactate during the first six hours after ICU admission. Additionally, our exploratory data suggested that patients who developed AKI at these stages had worse outcomes, such as longer ICU and hospital stay and higher short and long-term mortality rates.

Previous studies have suggested that pre-transplantation renal impairment, measured through creatinine levels, plays an essential role in the development of postoperative AKI.[21-23] It is well known that in cirrhotic patients, serum creatinine levels can be falsely low due to malnutrition, reduced muscle mass or decreased creatinine biosynthesis.[24] In order to better identify occurrences of AKI, we did not include patients with dialytic chronic end-stage renal failure and those undergoing double renal-hepatic transplantation in our study. Through this strategy, we intentionally selected individuals with serum creatinine values within the normal range, which thus precluded investigation of the role of pre-transplantation altered creatinine levels for predicting AKI in the postoperative period.

A requirement for vasoactive drugs during the intraoperative period has previously been correlated with AKI development among liver transplantation patients. Karapanagiotou et al. showed that use of vasopressors during the intraoperative period was associated with higher rates of AKI, assessed through the RIFLE and AKIN scores.[25] Other authors found similar results using the KDIGO score.[2,22,26] However, even though the majority of the data speaks in favor of the existence of an association between intraoperative use of vasopressors and AKI, this issue remains a matter of debate.[27] For instance, some authors have suggested that norepinephrine might protect against AKI development, through improving renal blood flow.[28] In our study, a requirement for vasopressors during the ICU stay but not during the preoperative period was shown to be associated with AKI. Similarly, Zhou et al. showed that the need for vasopressors to maintain blood pressure at a minimum of 65 mmHg (mercury millimeters) during the postoperative period resulted in a fivefold increase in AKI incidence.[12]

Knowledge of postoperative risk factors associated with AKI in liver transplantation patients is scarce: this has mostly been studied in the pre and intraoperative periods.[23,27,28-30] It is currently believed that bleeding that leads to transfusion requirements during the surgical procedure is associated with AKI, especially a need for red blood cells and cryoprecipitate.[6,22,30] In our study, the need for blood transfusion at any time during the ICU stay was associated with an odds ratio eight times higher for the development of AKI KDIGO 2 or 3.

Erdost et al. evaluated the three surgical periods among liver transplantation patients and found that only in the intraoperative period was blood transfusion associated with AKI development.[30] Zongyi et al. also evaluated the three surgical periods and identified that transfusion of red blood cells and fresh frozen plasma in the intraoperative period was associated with postoperative AKI development in liver transplantation patients.[29] These authors did not find that the need for transfusion in the postoperative period was a risk factor associated with development of AKI, but they noted that there was an association between postoperative intraperitoneal hemorrhage and AKI.[29] We hypothesize that the need for blood transfusion is an indirect marker of the severity of patients' condition, such that it is more frequent among patients with postoperative complications and among those who need surgical reintervention.

We showed that higher serum lactate levels within the first six hours after ICU admission were independently associated with

development of AKI KDIGO 2/3. In agreement with our findings, Jipa et al. showed that lactate levels greater than 1.5 mmol/l were related to postoperative complications in liver transplantation patients, including AKI, need for surgical reintervention and graft dysfunction.[31] Furthermore, Rueggeberg et al. observed that hyperlactatemia observed at the end of surgery was associated with increased intraoperative bleeding, longer ICU stay and increased mortality.[31,32] Given that lactate is primarily metabolized in the liver, higher levels of this molecule are observed in cases of liver dysfunction, regardless of the etiology. However, in cases of ischemic injuries, such as thrombosis of the vascular graft in liver transplantation, a sharp increase in lactate levels might be observed. In our study, patients with renal impairment showed higher lactate levels than those without kidney injury, thus suggesting that the former group probably had some liver harm or hypoperfusion.

Regarding the consequences of AKI during the postoperative period following liver transplantation, our study showed that patients with KDIGO 2 or 3 required renal replacement therapy (RRT) more often and had longer hospital stays and higher in-hospital mortality, compared with the KDIGO 1 or non-AKI patients. Similarly, Lima et al. found that severe AKI (KDIGO 2 or 3) was associated with RRT therapy, longer hospital and ICU stays and higher mortality over a 60-day period.[9] These are somewhat expected findings, since AKI probably serves as a marker for other types of organ dysfunction and for clinical severity in general.

This study had limitations that need to be considered. Firstly, because of the retrospective design, we were unable to assess diuresis in our definition of AKI, quantify vasopressor use or analyze the use of each vasopressor separately. Also, we did not evaluate early calcineurin therapy in the postoperative period following liver transplantation (e.g. tacrolimus serum levels). Secondly, this was a single-center study, with inclusion of a small number of patients, thus limiting the power of our statistical inferences. Thirdly, we were unable to characterize the severity of illness of the patients included using a severity score (e.g. Acute Physiology and Chronic Health Evaluation II [APACHE II] or Simplified Acute Physiology Score 3 [SAPS 3]), which precluded any adjustment of our associative analyses for this relevant parameter.

CONCLUSION

This study showed that the need for blood transfusion during ICU stay and hyperlactatemia at ICU admission are independently associated with development of AKI KDIGO stages 2 or 3. Furthermore, our findings suggest that AKI patients require RRT more often, have a longer hospital stay and might have higher short and long-term mortality. Prospective studies are needed in order to better identify early factors associated with acute renal function loss during the immediate postoperative period following liver transplantation, thereby enabling more assertive and prompter interventions that might result in better clinical outcomes.

REFERENCES

1. Thongprayoon C, Kaewput W, Thamcharoen N, et al. Incidence and Impact of Acute Kidney Injury after Liver Transplantation: A Meta-Analysis. J Clin Med. 2019;8(3):372. PMID: 30884912; https://doi.org/10.3390/jcm8030372
2. Wyssusek KH, Keys AL, Yung J, et al. Evaluation of perioperative predictors of acute kidney injury post orthotopic liver transplantation. Anaesth Intensive Care. 2015;43(6):757-63. PMID: 26603801; https://doi.org/101177/0310057X1504300614.
3. Chen J, Singhapricha T, Hu KQ, et al. Postliver transplant acute renal injury and failure by the RIFLE criteria in patients with normal pretransplant serum creatinine concentrations: a matched study. Transplantation. 2011;91(3):348-53. PMID: 21127462; https://doi.org/10.1097/TP.0b013e31820437da.
4. Cabezuelo JB, Ramírez P, Ríos A, et al. Risk factors of acute renal failure after liver transplantation. Kidney Int. 2006;69(6):1073-80. PMID: 16528257; https://doi.org/10.1038/sj.ki.5000216.
5. Durand F, Francoz C, Asrani SK, et al. Acute Kidney Injury After Liver Transplantation. Transplantation. 2018;102(10):1636-49. PMID: 29847502; https://doi.org/10.1097/TP.0000000000002305.
6. Caragata R, Wyssusek KH, Kruger P. Acute kidney injury following liver transplantation: a systematic review of published predictive models. Anaesth Intensive Care. 2016;44(2):251-61. PMID: 27029658; https://doi.org/10.1177/0310057X1604400212.
7. Codes L, Souza YG, D´Oliveira RAC, Bastos JLA, Bittencourt PL. Cumulative positive fluid balance is a risk factor for acute kidney injury and requirement for renal replacement therapy after liver transplantation. World J Transplant. 2018;8(2):44-51. PMID: 29696105; https://doi.org/10.5500/wjt.v8.i2.44.
8. Klaus F, Keitel da Silva C, Meinerz G, et al. Acute kidney injury after liver transplantation: incidence and mortality. Transplant Proc. 2014;46(6):1819-21. PMID: 25131045; https://doi.org/10.1016/j.transproceed.2014.05.053.
9. Lima C, de Paiva Haddad LB, de Melo PDV, et al. Early detection of acute kidney injury in the perioperative period of liver transplant with neutrophil gelatinase-associated lipocalin. BMC Nephrol. 2019;20(1):367. PMID: 31615452; https://doi.org/10.1186/s12882-019-1566-9.
10. Narciso RC, Ferraz LR, Mies S, et al. Impact of acute kidney injury exposure period among liver transplantation patients. BMC Nephrol. 2013;14:43. PMID: 23425345; https://doi.org/10.1186/1471-2369-14-43.
11. Kim WH, Lee HC, Lim L, Ryu HG, Jung CW. Intraoperative Oliguria with Decreased SvO2 Predicts Acute Kidney Injury after Living Donor Liver Transplantation. J Clin Med. 2018;8(1)29. PMID: 30597881; https://doi.org/10.3390/jcm8010029.

12. Zhou ZQ, Fan LC, Zhao X, et al. Risk factors for acute kidney injury after orthotopic liver transplantation: A single-center data analysis. J Huazhong Univ Sci Technolog Med Sci. 2017;37(6):861-3. PMID: 29270744; https://doi.org/10.1007/s11596-017-1818-5.
13. Lebrón Gallardo M, Herrera Gutierrez ME, Seller Pérez G, et al. Risk factors for renal dysfunction in the postoperative course of liver transplant. Liver Transplant. 2004;10(11):1379-85. PMID: 15497160; https://doi.org/10.1002/lt.20215.
14. Leithead JA, Rajoriya N, Gunson BK, Muiesan P, Ferguson JW. The evolving use of higher risk grafts is associated with an increased incidence of acute kidney injury after liver transplantation. J Hepatol. 2014;60(6):1180-6. PMID: 24631601; https://doi.org/10.1016/j.jhep.2014.02.019.
15. Bittencourt PL, Farias AQ, Couto CA. Liver Transplantation in Brazil. Liver Transplant. 2016;22(9):1254-8. PMID: 27228568; https://doi.org/10.1002/lt.24487.
16. Instituto alfa de gastroenterologia. Hospital das Clínicas - UFMG. Grupo de transplantes. Available from: http://iag.hc.ufmg.br/. Accessed in 2021 (Sep 9).
17. Vincent JL, Moreno R, Takala J, et al. The SOFA (Sepsis-related Organ Failure Assessment) score to describe organ dysfunction/ failure. On behalf of the Working Group on Sepsis-Related Problems of the European Society of Intensive Care Medicine. Intensive Care Med. 1996;22(7):707-10. PMID: 8844239; https://doi.org/10.1007/BF01709751.
18. Kamath PS, Wiesner RH, Malinchoc M, et al. A model to predict survival in patients with end-stage liver disease. Hepatology. 2001;33:464-70. PMID: 11172350; https://doi.org/10.1053/jhep.2001.22172.
19. Pugh RN, Murray-Lyon IM, Dawson JL, Pietroni MC, Williams R. Transection of the oesophagus for bleeding oesophageal varices. Br J Surg. 1973;60(8):646-9. PMID: 4541913; https://doi.org/10.1002/bjs.1800600817.
20. Kidney Disease: Improving Global Outcomes (KDIGO) Acute Kidney Injury Work Group. KDIGO Clinical Practice Guideline for Acute Kidney Injury. Kidney inter., Suppl. 2012;2:1-138. Available from: https://kdigo.org/wp-content/uploads/2016/10/KDIGO-2012-AKI-Guideline-English.pdf. Accessed in 2021 (Sep 8).
21. de Ataide EC, Perales SR, Bortoto JB, et al. Immunomodulation, Acute Renal Failure, and Complications of Basiliximab Use After Liver Transplantation: Analysis of 114 Patients and Literature Review. Transplant Proc. 2017;49(4):852-7. PMID: 28457410; https://doi.org/10.1016/j.transproceed.2017.01.047.
22. Zongyi Y, Baifeng L, Funian Z, Hao L, Xin W. Risk factors of acute kidney injury after orthotopic liver transplantation in China. Sci Rep. 2017;7:41555. PMID: 28134286; https://doi.org/10.1038/srep41555.
23. Karapanagiotou A, Kydona C, Dimitriadis C, et al. Acute kidney injury after orthotopic liver transplantation. Transplant Proc. 2012;44(9):2727-9. PMID: 23146506; https://doi.org/10.1016/j.transproceed.2012.09.096.
24. Contreras G, Garces G, Quartin AA, et al. An epidemiologic study of early renal replacement therapy after orthotopic liver transplantation. J Am Soc Nephrol. 2002;13(1):228-33. PMID:11752042; https://doi.org/10.1681/ASN.V131228.
25. Karapanagiotou A, Dimitriadis C, Papadopoulos S, et al. Comparison of RIFLE and AKIN Criteria in the Evaluation of the Frequency of Acute Kidney Injury in Post–Liver Transplantation Patients. Transplant Proc. 2014;46(9):3222-7. PMID: 25420865; https://doi.org/10.1016/j.transproceed.2014.09.161.
26. Khwaja A. KDIGO Clinical Practice Guidelines for Acute Kidney Injury. Nephron Clinical Practice. 2012;120(4):c179-84. PMID: 22890468; https://doi.org/10.1159/000339789.
27. Mukhtar A, Mahmoud I, Obayah G, et al. Intraoperative Terlipressin Therapy Reduces the Incidence of Postoperative Acute Kidney Injury After Living Donor Liver Transplantation. J Cardiothorac Vasc Anesth. 2015;29(3):678-83. PMID: 25620766; https://doi.org/10.1053/j.jvca.2014.10.008.
28. Xu X, Ling Q, Wei Q, et al. An effective model for predicting acute kidney injury after liver transplantation. Hepatobiliary Pancreat Dis Int. 2010;9(3):259-63. PMID: 20525552.
29. Zongyi Y, Baifeng L, Funian Z, Hao L, Xin W. Risk factors of acute kidney injury after orthotopic liver transplantation in China. Sci Rep. 2017;7:41555. PMID: 28134286; https://doi.org/10.1038/srep41555.
30. Erdost HA, Ozkardesler S, Akan M, et al. Comparison of the RIFLE, AKIN, and KDIGO Diagnostic Classifications for Acute Renal Injury in Patients Undergoing Liver Transplantation. Transplant Proc. 2016;48(6):2112-8. PMID: 27569955; https://doi.org/10.1016/j.transproceed.2016.03.044.
31. Jipa LN, Tomescu D, Droc G. The interrelation between arterial lactate levels and postoperative outcome following liver transplantation. Rom J Anaesth Intensive Care. 2014;21(2):106-12. PMID: 28913441.
32. Rueggeberg A, Boehm S, Napieralski F, Mueller AR, et al. Development of a risk stratification model for predicting acute renal failure in orthotopic liver transplantation recipients. Anaesthesia. 2008;63(11):1174-80. PMID: 18803627; https://doi.org/10.1111/j.1365-2044.2008.05604.x.

Authors' contributions: Neves APCF: conceptualization, methodology, formal analysis, investigation, resources, data curation and writing review and editing; Gomes AGR: methodology, formal analysis, data curation, investigation, writing original draft and writing review and editing; Vassallo PF: conceptualization, methodology and writing review and editing; Simões e Silva AC: conceptualization, methodology, validation and writing review and editing; Cancela e Penna FG: conceptualization, methodology, validation and writing review and editing; Bastos FL: investigation, resources, methodology and data curation; Muniz MR: investigation, resources, methodology and data curation; Rocha GC: investigation, resources, methodology and data curation; Santos Júnior ACS: conceptualization, methodology, validation and writing review and editing; Ravetti CG: conceptualization, methodology, software, formal analysis, data curation and writing review and editing; and Nobre V: conceptualization, methodology, data curation, writing review and editing and study coordination. All authors actively contributed to the discussion of the study results, reviewing and approving the final version of the manuscript for publication

Acknowledgements: This study was conducted on behalf of the Núcleo Interdiciplinar de Investigação em Medicina Intensiva (NIIMI)

Sources of funding: Conselho Nacional de Desenvolvimento Científico e Tecnológico (CNPq), grant number 311759/2020-3
Conflicts of interest: No conflicts

Date of first submission: July 23, 2021
Last received: October 19, 2021
Accepted: November 12, 2021

Address for correspondence:
Ana Paula Camargos de Figueirêdo Neves
Faculdade de Medicina, Universidade Federal de Minas Gerais (UFMG)
Av. Prof. Alfredo Balena, 190
Santa Efigênia — Belo Horizonte (MG) — Brasil
CEP 30130-100
Tel. (+55 31) 3409-9641
E-mail: anacfneves@hotmail.com

https://doi.org/10.1590/1516-3180.2021.0668.R1.121121

Clinical characteristics and factors associated with acute kidney injury among patients hospitalized with coronavirus disease: an observational retrospective study

Edgar Dehesa-López[I], Adolfo Entzana Galindo[II], Irali María Velasco Santos[III], Michel Alberto Aros-Pérez[IV], Diego Manuel Gómez Rodríguez[V], Erick Ojeda-Mendoza[VI], Brenda Paola Aguilar Ide[VII]

Centro de Investigación y Docencia en Ciencias de la Salud (CIDOCS), Culiacán, Mexico

[I]MD, MSc, PhD. Chief of Department of Internal Medicine, Centro de Investigación y Docencia en Ciencias de la Salud (CIDOCS), Culiacán, Mexico; Nephrologist, Department of Nephrology, Hospital Civil de Culiacán, Tierra Blanca, Culiacán Rosales, Sinaloa, Mexico; and Nephrologist, Instituto Mexicano del Seguro Social, Culiacán, Mexico.
https://orcid.org/0000-0001-8239-061X

[II]MD. Chief of the Hospital Epidemiological Unit, Hospital Civil de Culiacán, Culiacán, Mexico.
https://orcid.org/0000-0002-2437-5267

[III]MD. Internal Medicine Resident, Department of Internal Medicine, Centro de Investigación y Docencia en Ciencias de la Salud (CIDOCS), Culiacán, Mexico.
https://orcid.org/0000-0002-0624-0166

[IV]MD. Internal Medicine Resident, Department of Internal Medicine, Centro de Investigación y Docencia en Ciencias de la Salud (CIDOCS), Culiacán, Mexico.
https://orcid.org/0000-0003-4133-8000

[V]MD. Internal Medicine Resident, Department of Internal Medicine, Centro de Investigación y Docencia en Ciencias de la Salud (CIDOCS), Culiacán, Mexico.
https://orcid.org/0000-0003-2128-9854

[VI]MD. Internal Medicine Resident, Department of Internal Medicine, Centro de Investigación y Docencia en Ciencias de la Salud (CIDOCS), Culiacán, Mexico.
https://orcid.org/0000-0003-2195-3735

[VII]MD. House Staff, Department of Internal Medicine, Centro de Investigación y Docencia en Ciencias de la Salud (CIDOCS), Culiacán, Mexico.
https://orcid.org/0000-0002-6383-1499

KEY WORDS (MeSH terms):
Acute kidney injury.
COVID-19.
Community-acquired infections.
Mortality.
Risk factors.

AUTHORS' KEY WORDS:
Acute renal injuries.
Coronavirus disease 19.
Hospital-acquired AKI.
Community-acquired AKI.

ABSTRACT

BACKGROUND: Coronavirus disease 19 (COVID-19) is a multisystemic disease with high incidence of acute kidney injury (AKI).

OBJECTIVE: To describe the clinical characteristics and factors associated with AKI among patients hospitalized with COVID-19.

DESIGN AND SETTING: Retrospective cohort conducted at Hospital Civil de Culiacan, Mexico.

METHODS: We included 307 patients hospitalized due to COVID-19. AKI was defined and staged based on serum creatinine levels in accordance with the criteria of the Acute Kidney Injury Network (AKIN). Multivariate logistic regression analysis was used to determine factors associated with AKI.

RESULTS: The patients' age was 56 ± 15 years (64.5% male). The incidence of AKI was 33.6% (n = 103). Overall, 53.4% of patients had community-acquired AKI, and 46.6% had hospital-acquired AKI. Additionally, 15.5% of them presented AKIN stage 1; 34% had AKIN stage 2; and 50.5% had AKIN stage 3. Hemodialysis was required for 10.7% of the patients. The factors associated with AKI were chronic kidney disease (odds ratio, OR: 10.8; P = 0.04), use of norepinephrine (OR: 7.3; P = 0.002), diabetes mellitus (OR: 2.9; P = 0.03), C-reactive protein level (OR: 1.005; P = 0.01) and COVID-19 severity index based on chest tomography (OR: 1.09; statistical trend, P = 0.07). Hospital stay (11 ± 7 days; P < 0.001) and mortality (83.5 versus 31.4%; P < 0.05) were greater among patients with AKI.

CONCLUSION: AKI was a frequent and serious complication in our cohort of patients hospitalized with COVID-19, which was associated with high mortality and long hospital stay.

INTRODUCTION

Coronavirus disease 19 (COVID-19) was initially considered to predominantly be a pulmonary disease. However, it is now known that it is actually a disease with a wide spectrum of clinical manifestations and frequent multisystem involvement, especially in severe cases.[1] From a pathophysiological viewpoint, entry of severe acute respiratory syndrome coronavirus-2 (SARS-CoV-2) into cells occurs through the receptor for the angiotensin-converting enzyme 2, which is highly expressed in podocytes and the apical border of epithelial cells of the kidney proximal tubules. This could explain the kidney trophism exhibited by SARS-CoV-2.[2]

The reported incidence of acute kidney injury (AKI) among patients with COVID-19 has been variable, depending on the diagnostic criteria used, geographical region and clinical context. In patients hospitalized due to COVID-19, the reported incidences of AKI range from 0% to 57% in different published studies.[3] Clinical and pathological studies on patients with COVID-19 who developed AKI have documented various clinical and histological findings, such as hematuria, proteinuria, focal and segmental glomerulosclerosis, tubular pigment deposition, tubulointerstitial nephritis, fibrosis and tubular atrophy, evidence of hypoperfusion, thrombotic microangiopathy and acute tubular necrosis.[4-6] On the other hand, the negative effect of AKI on hospitalized patients with COVID-19 has been consistently documented and has been found to be associated with a long hospital stay, mechanical ventilation requirement, high medical care costs and mortality.[3,7,8] The factors associated with the development of AKI among these patients, previously reported in the literature, are male sex, previous diagnosis of chronic kidney disease (CKD), diabetes, hypertension, use of vasopressors, use of mechanical ventilation and presence of markers for disease activity

(ferritin, D-dimer and C-reactive protein [CRP]) and severity (partial pressure of oxygen [PaO2]/fraction of inspired oxygen [FiO2] and Sequential Organ Failure Assessment [SOFA] score).[3,7,9]

OBJECTIVE

Because of the limited information published on this topic in Mexico, the main objective of our study was to describe the clinical presentation, associated factors and prognosis of AKI among patients hospitalized for COVID-19 in this country.

METHODS

Study design and population

This was a single-center, retrospective and observational cohort study. The study protocol was reviewed and approved (registration number: 1/386/193; date: August 31, 2021) by the institutional ethics committee of our hospital; and it fulfilled the international ethical standards of the Declaration of Helsinki. The need for written informed consent was waived because of the observational nature of the study.

We included 307 patients hospitalized due to severe COVID-19 in the internal medicine service between March 18, 2020, and September 11, 2020. Patients older than 18 years of age, of both sexes, and patients with a diagnosis of severe COVID-19 were included. Pregnant women, patients with end-stage CKD, patients on chronic dialysis (hemodialysis or peritoneal dialysis) prior to admission, patients hospitalized for less than 24 hours, cases of mild/moderate COVID-19 and those with incomplete collection of data on the variables studied were excluded (**Figure 1**).

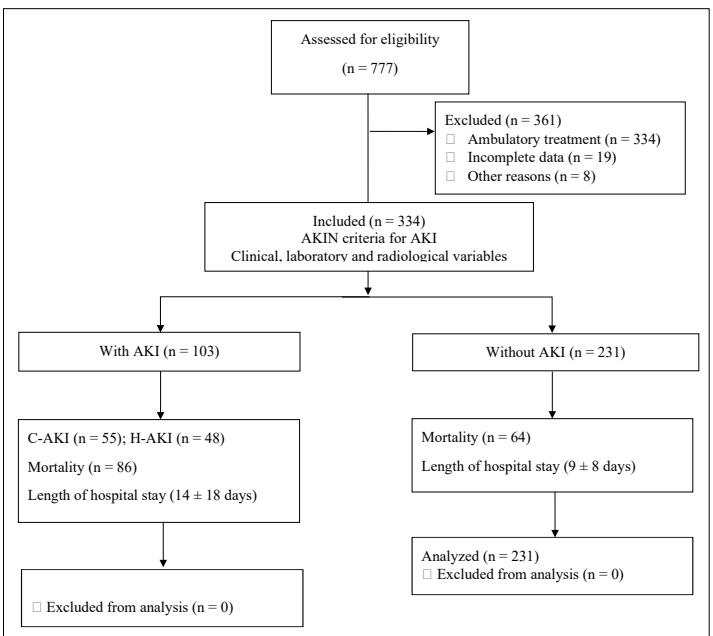
Data collection and definitions

Clinical variables (age, sex, comorbidities, oxygen saturation and type of respiratory support), radiological variables (severity index based on chest computed tomography [CT]) and laboratory variables (glucose, urea, creatinine, hematic biometry, sodium, potassium, arterial blood gas, CRP, ferritin serum, D-dimer and procalcitonin) were collected at admission and during hospitalization every 24 to 48 hours. The definitive diagnosis of COVID-19 was integrated based on the polymerase chain reaction test results, chest CT findings and serum levels of CRP, ferritin, D-dimer and procalcitonin. AKI was diagnosed and staged at admission (community-acquired AKI [C-AKI]) or during hospitalization (hospital-acquired AKI [H-AKI]) based on the serum creatinine level, in accordance with the criteria of the Acute Kidney Injury Network (AKIN).[10] The type of AKI (C-AKI/H-AKI), dialysis requirement and evolution (transitory AKI, persistent AKI or acute kidney disease [AKD]) of each episode of AKI were studied in accordance with the criteria of the Acute Disease Quality Initiative.[11] Transitory AKI was defined as a complete reversal of AKI in accordance with Kidney Disease Improving Global Outcomes (KDIGO) criteria within 48 hours of AKI onset. Persistent AKI was defined as continuance of AKI, using serum creatinine criteria, beyond 48 hours after AKI onset. AKD was defined as a condition in which AKI stage 1 or greater was present for ≥ 7 days after an AKI-initiating event. Kidney recovery was defined as a return to baseline creatinine. CKD was defined in accordance with the KDIGO CKD guidelines, based on previously documented findings or during the evaluation for COVID-19. Oliguria was defined as urinary output < 400 ml/day at AKI diagnosis. The impact of AKI on prognosis was studied by comparing mortality and hospital stay (in days) between patients with and without AKI.

Statistical analysis

Descriptive statistics with means/standard deviations or median/interquartile range were used to describe continuous variables according to distribution data; and frequencies and proportions were used to describe categorical variables. Comparisons between pairs of groups were performed using Student's t test or the Mann-Whitney U test for continuous variables according to distribution data; and the χ^2 test was used for categorical variables. Comparisons between more than two groups were performed using the Kruskal-Wallis test.

The clinical impact of AKI was evaluated based on in-hospital mortality and the length of hospital stay. Factors associated with the development of AKI were analyzed using multivariate logistic regression analysis. All clinically relevant variables with P-values < 0.05 in bivariate analysis were included for entry into



AKI = acute kidney injury; C-AKI = community-acquired; H-AKI = hospital-acquired AKI.

Figure 1. Patient inclusion flowchart.

multivariate modeling. Differences were considered statistically significant at $P < 0.05$.

Data analysis was performed using the IBM SPSS Statistics software for Macintosh, version 22.0 (IBM Corp., Armonk, New York, United States). No formal sample size calculation was carried out, because of the observational and convenience-sampling nature of the study.

RESULTS

General characteristics of the population studied

During the study period, 777 patients were treated for COVID-19 in our hospital, of whom 443 were treated on an outpatient basis and 334 required hospitalization in the internal medicine service. Among the latter patients, who were assessed for eligibility, three patients were excluded because they were younger than 18 years of age and another 24 adult patients were excluded (five who were hospitalized for less than 24 hours and 19 whose data were incomplete). Therefore, 307 patients were included in the final analysis of our study (**Figure 1**).

The patients' age was 56 ± 16 years, and males were more affected (64.5%, n = 198). The most frequently observed comorbidities in our population were hypertension (41.4%; n = 127), diabetes mellitus (30.9%; n = 95) and smoking (16.9%; n = 52). The remaining characteristics are shown in **Table 1**.

Clinical characteristics and evolution of AKI episodes

The frequency of AKI in our population was 33.6% (n = 103), of which 53.4% (n = 55) corresponded to C-AKI and 46.6% (n = 48) corresponded to H-AKI. The most frequently observed stage of severity was AKIN stage 3 in 50.5% (n = 52) of the cases, followed by AKIN stage 2 (34%; n = 35) and AKIN stage 1 (15.5%; n = 16). Among the AKI episodes, 48.5% (n = 50) were oliguric, and 10.7% (n = 11) required renal replacement therapy, which consisted of intermittent hemodialysis in all cases.

At the time of hospital discharge or death, only 35.9% (n = 37) of the patients with AKI had achieved recovery of kidney function. On the other hand, 25.2% (n = 26) of the patients had transitory AKI, 36.9% (n = 38) had persistent AKI and 37.9% (n = 39) had AKD.

In comparing the characteristics according to the type of AKI (transitory AKI, persistent AKI and AKD), we observed that the frequency of oliguria was higher among patients with AKD than among those with either transitory AKI or persistent AKI (65.6% versus 29.6% versus 13.3%, respectively; $P < 0.001$). The frequency of AKIN 3 episodes was also higher among patients with AKD than among those with either persistent AKI or transitory AKI (72.1% versus 33.3% versus 14.8%, respectively; $P < 0.001$). In contrast, the frequency of AKIN 1 episodes was higher in patients with transitory AKI than among those with either persistent AKI or AKD (44.4% versus 20% versus 3.3%, respectively; $P < 0.001$).

Recovery of kidney function was more frequent among patients with transitory AKI than among those with either persistent AKI or AKD (85.2% versus 60% versus 4.9%, respectively; $P < 0.001$). There were no statistically significant differences in the frequency of hemodialysis between patients with transitory AKI, persistent AKI or AKD (7.4% versus 0% versus 14.8%, respectively; $P = 0.253$).

Comparison of clinical and laboratory characteristics between patients with and without AKI

In comparing the general characteristics between the groups, we observed that patients with AKI were older than those without AKI (61 ± 14 versus 54 ± 15 years; $P = 0.001$) and had higher frequencies of diabetes mellitus (44.7% versus 24%; $P < 0.05$), hypertension (58.3% versus 32.8%; $P < 0.05$), CKD (13.6% versus 0.5%; $P < 0.05$) and heart failure (9.7% versus 2.9%; $P < 0.05$). On the other hand, the frequencies of use of invasive mechanical ventilation (65% versus 20.1%; $P < 0.05$) and use of norepinephrine (56.3% versus 10.8%; $P < 0.05$) were also higher among patients with AKI than among those without.

Patients with AKI had higher total leukocyte counts (13,710 versus 10,330 /µl; $P < 0.001$), serum glucose levels (146 versus 125 mg/dl; $P = 0.001$), urea levels (57 versus 34 mg/dl; $P = 0.001$), serum creatinine levels (1.3 versus 0.7 mg/dl; $P < 0.001$), serum potassium levels (4.5 versus 4.2 mEq/l/; $P = 0.019$), serum CRP levels (109 versus 95 mg/dl; $P = 0.025$), ferritin levels (848 versus 615 ng/dl; $P < 0.001$), D-dimer levels (1,420 versus 760 ng/dl; $P < 0.001$) and severity score based on chest CT (24 versus 19; $P < 0.001$) at admission, than patients without AKI. In addition, patients with AKI presented lower pH (7.42 versus 7.46; $P < 0.001$), and PaO2/FiO2 index (124 versus 170; $P = 0.005$) than those without AKI. The remaining characteristics are shown in **Tables 2** and **3**.

Table 1. General population characteristics

Variables	n = 307	%
Age (years)	56 ± 15	
Gender (female/male)	109 (35.5%) / 198 (64.5%)	
Diabetes mellitus	95	30.9%
Hypertension	127	41.4%
Chronic pulmonary obstructive disease	6	2.0%
Chronic kidney disease	15	4.9%
Heart failure	16	5.2%
Smoking	52	16.9%
Respiratory support		
Simple mask	54	17.6%
Reservoir mask	109	35.4%
High-flow nasal cannula	10	3.3%
Non-invasive ventilation	26	8.5%
Invasive ventilation	108	35.2%

Comparison of clinical and laboratory characteristics between patients with C-AKI and those with H-AKI

The frequency of AKI was 33.6% (n = 103), of which 53.4% (n = 55) corresponded to C-AKI and 46.6% (n = 48) to H-AKI. Compared with patients with C-AKI, patients with H-AKI required mechanical ventilation more frequently (81.3% versus 50.9%; P = 0.018). On the other hand, patients with C-AKI had higher total leukocyte counts (13,950 versus 10,940 /µl; P = 0.037), serum glucose levels (164 versus 127 mg/dl; P = 0.001), ferritin levels (854 versus 648 ng/dl; P = 0.009), D dimer levels (1.627 versus 847 ng/dl; P = 0.020), procalcitonin levels (0.5 versus 0.1 ng/dl; P = 0.001) and severity score based on chest CT (24 versus 20; P = 0.003) at admission, than patients with H-AKI.

We did not observe any statistically significant differences in relation to age, comorbidities, disease severity markers, severity of AKI episodes, dialysis requirement or recovery of kidney function, between the C-AKI and H-AKI groups (**Table 4**).

Factors associated with development of AKI among patients hospitalized due to COVID

In our study, the factors independently associated with AKI were as follows: previous diagnosis of CKD (odds ratio, OR: 10.8; 95% confidence interval, CI: 1.02-116.1; P = 0.04), use of norepinephrine (OR: 7.3; 95% CI: 2.1-25.8; P = 0.002), diabetes mellitus (OR: 2.9; 95% CI: 1.05-8.3; P = 0.03), serum CRP level (OR: 1.005; 95% CI: 1.001-1.009; P = 0.01) and COVID severity index based on chest CT (OR: 1.09; 95% CI: 0.99-1.21; statistical trend, P = 0.07) (**Table 5**).

Clinical impact of AKI on the prognosis of patients hospitalized due to COVID-19

Overall mortality was 48.9% (n = 150), and this was higher among patients with AKI than in those without AKI (83.5% versus 31.4%; P = 0.001). No statistically significant difference in mortality was observed between patients with C-AKI and those with H-AKI (80% and 87.5%, respectively; P = 0.42). On the other hand, the median length of hospitalization in our population was 8 days (range: 3-15 days), which was longer among patients with AKI than among those without AKI (11 versus 7 days; P < 0.001), but not between patients with H-AKI and those with C-AKI) (8 versus 8 days; P = 0.918).

In comparing mortality according to the type of AKI (transitory AKI, persistent AKI and AKD), we observed that, among these three types, mortality was only higher among patients with AKD (74.1% versus 66.7% versus 91.8%, respectively; P < 0.015). No statistically significant difference in the length of hospitalization was observed between patients with transitory AKI, persistent AKI and AKD (15 versus 10 versus 10 days, respectively; P = 0.285).

Table 2. Comparison of general characteristics between patients with and without acute kidney injury (AKI)

Variables	Without AKI		With AKI		P
	n = 204	%	n = 103	%	
Age (years)	54 ± 15		61 ± 14		< 0.001
Gender (female/male)	74 (36.3%) / 130 (63.7%)		35 (34%) / 68 (66%)		0.707
Diabetes mellitus	49	24.0%	46	44.7%	< 0.001
Hypertension	67	32.8%	60	58.3%	< 0.001
CPOD	5	2.5%	1	1.0%	0.668
CKD	1	0.5%	14	13.6%	< 0.001
Heart failure	6	2.9%	10	9.7%	0.026
Smoking	31	15.2%	21	20.4%	0.263
Respiratory support					
Simple mask	49	24.0%	5	4.9%	< 0.001
Reservoir mask	92	45.1%	17	16.5%	
HFNC	6	2.9%	4	3.9%	
NIV	16	7.8%	10	9.7%	
IV	41	20.1%	67	65.0%	

CPOD = chronic pulmonary obstructive disease; CKD = chronic kidney disease; HFNC = high-flow nasal canula; NIV = noninvasive ventilation; IV = invasive ventilation.

Table 3. Comparison of clinical and laboratory characteristics at admission between patients with and without acute kidney injury (AKI)

Variables	Without AKI		With AKI		P
	Median	IQR / %	Median	IQR / %	
Hemoglobin (g/dl) (X/SD)	13.7	(12.6-14.8)	13.5	(11.5-14.5)	0.689
White blood cells (/µl) (x1000)	10.3	(7.7-14.8)	13.7	(9.8-19.7)	< 0.001
Total lymphocytes (/µl)	950	(578-1,322)	924	(568-1,551)	0.571
Platelets (/µl) (x1000)	244	(187-307)	263	(210-332)	0.333
Serum glucose (mg/dl)	125	(96-169)	146	(120-210)	0.001
Serum creatinine (mg/dl)	0.7	(0.6-0.8)	1.3	(0.8-2.1)	< 0.001
C-reactive protein (mg/dl)	95	(48-185)	109	(83-192)	0.025
Ferritin (ng/dl)	615	(349-904)	848	(471-1,000)	< 0.001
D-dimer (ng/dl)	760	(365-1,965)	1,420	(670-4,140)	< 0.001
Procalcitonin (ng/dl)	0.10	(0.05-0.26)	0.29	(0.11-1.09)	< 0.001
PaO2/FiO2	170	(101-266)	124	(84-180)	0.005
Index CT severity	19	(14-22)	24	(21-25)	< 0.001
Invasive ventilation	41	20.1%	67	65.0%	< 0.001
Use of norepinephrine	22	10.8%	58	56.3%	< 0.001

IQR = interquartile range; SD = standard deviation; CT = chest tomography; PaO2 = partial pressure of oxygen; FiO2 = fraction of inspired oxygen.

DISCUSSION

COVID-19 is considered to be a lung disease; however, its clinical and systemic spectrum is very broad, from asymptomatic cases to severe cases with multisystemic disease, including kidney damage.

Table 4. Comparison of clinical and laboratory characteristics at admission between patients with community-acquired acute kidney injury (C-AKI) and those with hospital-acquired acute kidney injury (H-AKI)

Variables	C-AKI (n = 55)		H-AKI (n = 48)		P
	n/median	%/IQR	n/median	%/IQR	
General characteristics:					
Age (years) (mean ± SD)	61 ± 15		60 ± 14		0.678
Female	18	32.7%	17	35.4%	0.77
Male	37	67.3%	31	64.6%	
Diabetes mellitus	28	50.9%	18	37.5%	0.17
Hypertension	36	65.5%	24	50.0%	0.11
Chronic kidney disease	7	12.7%	7	14.6%	0.78
Respiratory support:					
Simple mask	4	7.3%	1	2.1%	0.018
Reservoir mask	14	25.5%	3	6.3%	
High-flow nasal canula	2	3.6%	2	4.2%	
NIV	7	12.7%	3	6.3%	
IV	28	50.9%	39	81.3%	
AKI characteristics:					
AKIN 1	10	18.2%	6	12.5%	0.32
AKIN 2	21	38.2%	14	29.2%	
AKIN 3	24	43.6%	28	58.3%	
Hemodialysis	7	12.7%	4	8.3%	0.47
Recovered kidney function	19	34.5%	18	37.5%	0.75
Laboratory characteristics:					
Hemoglobin (g/dl)	12.5	(10.4-14.1)	13.8	(12.5-14.8)	0.027
Total leucocytes (/µl) (x1000)	13.9	(9.8-20.9)	10.9	(7.9-15.6)	0.037
Total lymphocytes (/µl)	857	(488-1,256)	961	(595-1,382)	0.571
Platelets (/µl) (x1000)	250	(221-318)	253	(188-311)	0.999
Serum creatinine (mg/dl)*	1.8	(1.3-2.8)	1.4	(1.3-2.1)	0.256
C-reactive protein (mg/dl)	120	(48-192)	96	(48-192)	0.173
Ferritin (ng/dl)	854	(453-1,000)	648	(361-964)	0.009
D-dimer (ng/dl)	1627	(755-3,970)	847	(390-2,090)	0.020
PaO2/FiO2 at admission	140	(102-244)	142	(100-236)	0.875
Index CT severity	24	(21-25)	20	(15-24)	0.003
Use of norepinephrine	28	50.9	30	62.5	0.320

IQR = interquartile range; SD = standard deviation; NIV = noninvasive ventilation; IV = invasive ventilation; AKIN = acute kidney injury network. PaO2 = partial pressure of oxygen; FiO2 = fraction of inspired oxygen. *Serum creatinine at the time of AKI diagnosis.

Table 5. Multivariate analysis on factors associated with acute kidney injury among patients hospitalized due to coronavirus disease

Variables	OR	95% CI		P
		Lower	Upper	
Age (years)	1.030	0.991	1.071	0.133
Gender (male/female)	1.692	0.619	4.627	0.305
Diabetes mellitus (yes/no)	2.978	1.058	8.385	0.039
Hypertension (yes/no)	0.943	0.322	2.762	0.914
Chronic kidney disease (yes/no)	10.892	1.022	116.112	0.048
Invasive ventilation (yes/no)	1.496	0.416	5.375	0.537
Use of norepinephrine (yes/no)	7.369	2.104	25.816	0.002
C-reactive protein (mg/dl)	1.005	1.001	1.009	0.010
Index CT severity (points)	1.099	0.991	1.218	0.073

OR = odd ratio; CT = chest tomography; CI = confidence interval.

As in the rest of the world, in our retrospective cohort of patients hospitalized due to COVID-19, AKI was a frequent complication, observed in 33.6% of the cases.

The incidence of AKI among patients hospitalized due to COVID-19 reported by other authors has varied according to the diagnostic criteria for AKI, geographical region and clinical context studied. In a meta-analysis by Lin et al. on 79 studies that included 49,692 patients with COVID-19 from Asia, Europe and North America, the incidences of AKI were 22.6% in North America, 11.6% in Europe and 4.3% in Asia.[3] In contrast, Chen et al. conducted a systematic review of 20 studies with 6,495 patients hospitalized due to COVID-19 in China, Italy, the United Kingdom and the United States. The reported incidence of AKI was 8.9% (95% CI: 4.6-14.5%) with a range from 0 to 57.1% in the different

studies included.[12] In another meta-analysis on 40 studies with 24,377 patients hospitalized due to COVID-19, Shao et al. reported that the incidence of AKI was 10% (95% CI: 8-13%) with a range from 0.5 to 49.3%.[8] Lastly, Martinez-Rueda et al. reported that the incidence of AKI was 30% in a cohort of 1,170 Mexican patients hospitalized due to COVID-19.[9]

Another important finding from our study was that AKIN stage 3 of AKI occurred most frequently, followed by stage 2 and stage 1, which indicates that AKI was a frequent and serious complication in our population. Regarding the severity of AKI episodes, the data published by other authors have varied according to the region and the clinical context studied. In a study by Chan et al. on 3,993 patients hospitalized due to COVID-19 in five hospitals in New York, the incidences of AKI were 46% in the general hospitalized population and 76% in patients in the intensive care unit. AKIN stage 3 occurred most frequently overall (AKIN stage 3 = 42%; AKIN stage 2 = 19%; and AKIN stage 1 = 39%) and among intensive care patients (AKIN stage 3 = 56%; AKIN stage 2 = 17%; and AKIN stage 1 = 28%).[13] However, in one of the largest cohorts of patients hospitalized due to COVID-19 (n = 5,449), the incidence of AKI was 36.6%. AKIN stage 1 occurred most frequently (46.5%), followed by AKIN stage 2 (22.4%) and AKIN stage 3 (31.1%).[7]

Recently, there has been great interest in differentiating between C-AKI and H-AKI among patients hospitalized due to COVID-19, given the different etiology and prognosis between these two types of AKI.[9,14] In our cohort, patients with H-AKI had respiratory failure more frequently and patients with C-AKI had higher levels of activity markers (D-dimer and ferritin) and severity markers (index CT severity) for the disease. We did not observe any statistically significant difference in relation to age, comorbidities, severity of AKI episodes, dialysis requirement, recovery of kidney function or mortality, between patients with C-AKI and those with H-AKI. Our findings contrast with those reported by Martinez-Rueda et al. in their cohort of Mexican patients hospitalized due to COVID-19. Although C-AKI (64.1%) was also the more frequent type in their study and they did not observe any differences in mortality between patients with C-AKI and those with H-AKI (53% and 50%, respectively; P = 0.65), the patients with C-AKI were older and had greater levels of comorbidities (based on the Charlson index) than the patients with H-AKI, who were younger, had greater multiorgan failure (higher SOFA score), greater respiratory failure (lower PaO2/FiO2 index), greater severity of AKI episodes (AKIN stages 2-3), and greater dialysis requirement (27% versus 7%; P = 0.001).[9]

In our population, the overall frequency of dialysis required was 10.7%, with no statistically significant difference between the C-AKI and H-AKI groups. The frequency reported by other researchers has varied widely worldwide, from 0.4% to 22.3%.[3,8,15] This variability in dialysis requirement worldwide could partly be explained by differences in the severity of AKI episodes and the clinical context studied, as well as in the availability and prioritization of dialysis treatment assignments during the pandemic, due to oversaturation of medical services and the poor prognosis of patients with COVID-19 and AKI, which may have underestimated the true frequency of the dialysis requirement among these patients.

In our study, the history of CKD, use of norepinephrine, presence of diabetes mellitus, serum CRP level and COVID severity index based on chest CT were the factors associated with development of AKI. In this regard, multiple factors have been associated with development of AKI, as referenced by other authors. In a retrospective cohort on 5,449 patients hospitalized due to COVID-19 in New York, Hirsch et al. reported that age, black race, presence of diabetes mellitus, arterial hypertension, cardiovascular disease, mechanical ventilation use and vasopressor use were factors associated with development of AKI.[7] Hamilton et al., in a retrospective cohort of 1,032 patients hospitalized due to COVID-19 in the United Kingdom, reported that male sex, presence of CKD, presence of diabetes mellitus and serum CRP level were factors associated with AKI.[16] In a meta-analysis on 26 studies with 5,497 patients hospitalized due to COVID-19, Hansrivijit et al. reported that age, hypertension, presence of diabetes mellitus and serum creatinine level were risk factors associated with AKI.[15] Lastly, Martínez-Rueda et al., in a prospective cohort of 1,170 Mexican patients hospitalized due to COVID-19, reported that certain factors were specific for the type of AKI. The Charlson index, CKD, SOFA score, serum glucose level, creatinine level, CRP level and troponin level were factors associated with C-AKI, while the body mass index, glucose level, troponin level and intubation were factors associated with development of H-AKI.[9]

The overall fatality rate in our population was 48.9%, and it was higher among patients with AKI than among those without AKI. In addition, the median hospital stay was longer among patients with AKI than among those without AKI. It has been consistently demonstrated that AKI has a negative impact on the prognosis of patients hospitalized due to COVID-19 and is associated with a long hospital stay, high mechanical ventilation requirements and fatality. In a meta-analysis on 40 studies with 24,527 patients, Shao et al. reported that the overall fatality rate was 20.3%, and that it was higher among patients with AKI than among those without AKI (63.1% versus 12.9%; P < 0.01), with an OR for mortality of 14.6 (95% CI: 9.94-21.5; P < 0.00001).[8] On the other hand, similar to the findings of Martínez-Rueda et al.,[9] we did not observe any statistically significant difference in mortality between patients with C-AKI and those with H-AKI. However, our fatality rate was above the overall fatality rate (48.9% versus 27%), C-AKI fatality rate (80% versus 53%) and H-AKI fatality rate (87.5% versus. 50%) reported by Martínez-Rueda et al.[9]

The great variability in the prognosis of these patients observed worldwide might be partially explained by differences in the severity of the patients' conditions, the clinical contexts studied, the hospital resources and infrastructure and the availability of trained and specialized personnel for caring for these patients, among different hospitals during the pandemic.

The present study had some limitations. Firstly, it was a retrospective study conducted in a single center. Therefore, it was not possible to include the criterion of urinary volume for diagnosing AKI, which could have underestimated the frequency of AKI in our population. Moreover, the precise cause of each AKI episode could not be determined. Secondly, we did not include variables relating to treatment in our analysis because of the great variability and modifications of the drugs used during the pandemic. Lastly, it was not possible to construct a specific logistic regression model of factors associated with C-AKI and H-AKI because of the small number of cases. Nevertheless, despite these deficiencies, we believe that the results from our study are valid and useful for improving the characterization of AKI episodes among patients hospitalized due to COVID-19.

CONCLUSION

AKI was a frequent and serious complication in our cohort of patients hospitalized due to COVID-19, which was associated with high mortality and long hospital stay. This highlights the importance of close nephrological surveillance for early detection of patients at high risk of developing AKI.

REFERENCES

1. Nadim MK, Forni LG, Mehta RL, et al. COVID-19-associated acute kidney injury: consensus report of the 25th Acute Disease Quality Initiative (ADQI) Workgroup. Nat Rev Nephrol. 2020;16(12):747-64. PMID: 33060844; https://doi.org/10.1038/s41581-020-00356-5.
2. Batlle D, Soler MJ, Sparks MA, et al. Acute Kidney Injury in COVID-19: Emerging Evidence of a Distinct Pathophysiology. J Am Soc Nephrol. 2020;31(7):1380-3. PMID: 32366514; https://doi.org/10.1681/ASN.2020040419.
3. Lin L, Wang X, Ren J, et al. Risk factors and prognosis for COVID-19-induced acute kidney injury: a meta-analysis. BMJ Open. 2020;10(11):e042573. PMID: 33172950; https://doi.org/10.1136/bmjopen-2020-042573.
4. Rivero J, Merino-López M, Olmedo R, et al. Association between Postmortem Kidney Biopsy Findings and Acute Kidney Injury from Patients with SARS-CoV-2 (COVID-19). Clin J Am Soc Nephrol. 2021;16(5):685-93. PMID: 33782033; https://doi.org/10.2215/CJN.16281020.
5. Su H, Yang M, Wan C, et al. Renal histopathological analysis of 26 postmortem findings of patients with COVID-19 in China. Kidney Int. 2020;98(1):219-27. PMID: 32327202; https://doi.org/10.1016/j.kint.2020.04.003.
6. Santoriello D, Khairallah P, Bomback AS, et al. Postmortem Kidney Pathology Findings in Patients with COVID-19. J Am Soc Nephrol. 2020;31(9):2158-67. PMID: 32727719; https://doi.org/10.1681/ASN.2020050744.
7. Hirsch JS, Ng JH, Ross DW, et al. Acute kidney injury in patients hospitalized with COVID-19. Kidney Int. 2020;98(1):209-18. PMID: 32416116; https://doi.org/10.1016/j.kint.2020.05.006.
8. Shao M, Li X, Liu F, et al. Acute kidney injury is associated with severe infection and fatality in patients with COVID-19: A systematic review and meta-analysis of 40 studies and 24,527 patients. Pharmacol Res. 2020;161:105107. PMID: 32739424; https://doi.org/10.1016/j.phrs.2020.105107.
9. Martínez-Rueda AJ, Álvarez RD, Méndez-Pérez RA, et al. Community- and Hospital-Acquired Acute Kidney Injury in COVID-19: Different Phenotypes and Dismal Prognosis. Blood Purif. 2021:50(6):931-41. PMID: 33744901; https://doi.org/10.1159/000513948.
10. Work Group Membership. Kidney Int Suppl (2011). 2012;2(1):2. PMID: 25028631; https://doi.org/10.1038/kisup.2012.2.
11. Chawla LS, Bellomo R, Bihorac A, et al. Acute kidney disease and renal recovery: consensus report of the Acute Disease Quality Initiative (ADQI) 16 Workgroup. Nat Rev Nephrol. 2017;13(4):241-57. PMID: 28239173; https://doi.org/10.1038/nrneph.2017.2.
12. Chen YT, Shao SC, Hsu CK, et al. Incidence of acute kidney injury in COVID-19 infection: a systematic review and meta-analysis. Crit Care. 2020;24(1):346. PMID: 32546191; https://doi.org/10.1186/s13054-020-03009-y.
13. Chan L, Chaudhary K, Saha A, et al. AKI in Hospitalized Patients with COVID-19. J Am Soc Nephrol. 2021;32(1):151-60. PMID: 32883700; https://doi.org/10.1681/ASN.2020050615.
14. Pelayo J, Lo KB, Bhargav R, et al. Clinical Characteristics and Outcomes of Community- and Hospital-Acquired Acute Kidney Injury with COVID-19 in a US Inner City Hospital System. Cardiorenal Med. 2020;10(4):223-31. PMID: 32554965; https://doi.org/10.1159/000509182.
15. Hansrivijit P, Qian C, Boonpheng B, et al. Incidence of acute kidney injury and its association with mortality in patients with COVID-19: a meta-analysis. J Investig Med. 2020;68(7):1261-70. PMID: 32655013; https://doi.org/10.1136/jim-2020-001407.
16. Hamilton P, Hanumapura P, Castelino L, et al. Characteristics and outcomes of hospitalised patients with acute kidney injury and COVID-19. PLoS One. 2020;15(11):e0241544. PMID: 33141867; https://doi.org/10.1371/journal.pone.0241544.

Authors' contributions: Dehesa-López E: conceptualization (equal), data curation (equal), formal analysis (equal), methodology (equal), project administration (equal), supervision (equal), validation (equal), visualization (equal), writing-original draft (equal) and writing-review and editing; Galindo AE: conceptualization (equal), data curation (equal), supervision (equal) and validation (equal); Velasco Santos IM: conceptualization (equal), data curation (equal), supervision (equal)

and validation (equal); Aros-Pérez MA: conceptualization (equal), data curation (equal), supervision (equal) and validation (equal); Gómez Rodríguez DM: conceptualization (equal), data curation (equal), supervision (equal) and validation (equal); Ojeda-Mendoza E: conceptualization (equal), data curation (equal), supervision (equal) and validation (equal); Aguilar Ide BP: conceptualization (equal), data curation (equal), supervision (equal) and validation (equal). All authors critically reviewed the manuscript and agree to be fully accountable for ensuring the integrity and accuracy of the work, and they all read and approved the final manuscript

Sources of funding: None
Conflicts of interest: The authors declare that they did not have any conflicts of interest

Date of first submission: September 21, 2021
Last received: October 23, 2021
Accepted: November 12, 2021

Address for correspondence:
Edgar Dehesa-López
Eustaquio Buelna No. 91
Col. Gabriel Leyva
Culiacán — Sinaloa — México
80030
Tel. (+52 667) 7132606/7137978
E-mail: edgar.lopez@uas.edu.mx

https://doi.org/10.1590/1516-3180.2021.0601.R1.121121

Liver cancer in Hidalgo State, Mexico: analysis of the status, risk factors and regional public health policy requirements: a cross-sectional correlational study

Rosa Isela Barrera-Cortés[I], Erika Elizabeth Rodriguez-Torres[II], Enrique Vázquez-Mendoza[III], Jesús Carlos Ruvalcaba-Ledezma[IV], Luis Enrique Soria-Jasso[V], Mario Isidoro Ortiz[VI], Eduardo Fernández-Martínez[VII]

Universidad Autónoma del Estado de Hidalgo (UAEH), Pachuca, Hidalgo, Mexico

[I]MD, MPH. Family Medicine Specialty Student, Department of Medicine, School of Health Sciences, Universidad Autónoma del Estado de Hidalgo (UAEH), Pachuca, Hidalgo, Mexico.
https://orcid.org/0000-0002-9849-3178

[II]BSc, MSc, PhD. Full Professor, Department of Mathematics and Physics, School of Basic Sciences and Engineering, Universidad Autónoma del Estado de Hidalgo (UAEH), Pachuca, Hidalgo, Mexico.
https://orcid.org/0000-0002-7738-1863

[III]BSc, MSc. Doctoral Student, Department of Mathematics and Physics, School of Basic Sciences and Engineering, Universidad Autónoma del Estado de Hidalgo (UAEH), Pachuca, Hidalgo, Mexico.
https://orcid.org/0000-0002-4244-6161

[IV]MD, PhD. Full Professor, Department of Medicine, School of Health Sciences, Universidad Autónoma del Estado de Hidalgo (UAEH), Pachuca, Hidalgo, Mexico.
https://orcid.org/0000-0002-5593-3946

[V]MD, PhD. Full Professor, Department of Medicine, School of Health Sciences, Universidad Autónoma del Estado de Hidalgo (UAEH), Pachuca, Hidalgo, Mexico.
https://orcid.org/0000-0002-6581-7295

[VI]MD, MSc, PhD. Full Professor, Department of Medicine, School of Health Sciences, Universidad Autónoma del Estado de Hidalgo (UAEH), Pachuca, Hidalgo, Mexico.
https://orcid.org/0000-0003-1047-6304

[VII]BSc, MSc, PhD. Full Professor, Department of Medicine, School of Health Sciences, Universidad Autónoma del Estado de Hidalgo (UAEH), Pachuca, Hidalgo, Mexico.
https://orcid.org/0000-0003-3280-1323

KEY WORDS (MeSH terms):
Alcoholism.
Health policy.
Liver neoplasms.
Regional medical programs.
Risk factors.
Public health.

AUTHORS' KEY WORDS:
Cirrhosis.
Hepatocellular carcinoma.
Marginalization.
Non-alcoholic steatohepatitis.
Regional strategies.

ABSTRACT

BACKGROUND: In Latin America, liver cancer is one of the top causes of cancer mortality. It is the fifth most common cause of death among malignant tumors in Mexico and is the leading cause in Hidalgo State (43.8% of the population living in poverty).

OBJECTIVE: To conduct a correlational analysis on the main risk factors for liver cancer in Hidalgo State, Mexico, including municipal disaggregation and comparison with the national level.

DESIGN AND SETTING: Cross-sectional, correlational, descriptive and comparative epidemiological study using Mexican governmental databases covering 1990-2019.

METHODS: A comprehensive review of the databases of the General Directorate of Health Information (DGIS) was performed to analyze official death figures, hospital discharges and national and municipal population projections, using specific search criteria defined in the Global Burden of Disease classification, based on the risk factors for liver cancer.

RESULTS: Liver cancer rates showed an evident rise in Hidalgo (183%), moving from 21st place in Mexico in 1990 to 9th place in 2019. This increase was correlated with alcoholism. An increasing trend for liver cancer deaths, of 133.89%, is projected for 2030. Females and the population over 60 years of age are more affected. There are some critical regions with liver cancer death rates twice the national rate or more.

CONCLUSION: Targeted effective public health strategies should be structured by identifying, characterizing and regionalizing critical marginalized municipalities that are vulnerable to alcoholism and other risk factors for liver cancer. This approach may be helpful for other states in Mexico or similar countries.

INTRODUCTION

There has been an increase in the global incidence of liver cancer, which became the sixth most common cancer and the third leading cause of cancer death in the world in 2020.[1] This has also raised interest in studying its clinical and epidemiological aspects in Latin America.[2-4] Hepatocellular carcinoma (HCC) is the most frequent form of liver cancer, accounting for 75% to 85% of primary hepatic neoplasms.[1] It is also between the second and fourth most important cause of cancer-related mortality worldwide and is the leading cause of cancer among patients with cirrhosis.[2,3,5] HCC occurs more frequently in men than in women, and about one million new cases are diagnosed every year.[3,6,7]

In Mexico, complications from liver cirrhosis have remained the third most common cause of death over the last decades, and the future trend is worrying. The incidence of HCC continues to rise in Mexico, especially affecting older people in the sixth decade of life, and the mortality rate used to be higher among males. The most common underlying chronic liver diseases that cause HCC in the Mexican population are alcoholic liver disease (ALD) and hepatitis C virus (HCV). However, non-alcoholic steatohepatitis (NASH) is increasingly a cause of HCC: the incidence of this disease is rising at an alarming rate because of complications from metabolic syndrome (MetS), which is present in a high proportion of Mexicans.[8,9] Although the epidemiological characteristics of HCC in Mexico are similar to those in other Latin American countries, such as Argentina, Brazil and Colombia,[4] comprehensive information concerning the diagnosis, treatment and surveillance of HCC in Mexico is scarce. Better information might improve early detection and thus decrease morbidity and mortality among HCC patients.[7,8,10]

Hidalgo State, Mexico, had an economic complexity index (ECI) of -0.68 in 2021 and ranked 21st among the country's 32 states, while the overall ECI for Mexico was 1.31 in 2020. Over 43.8% of Hidalgo's population live in poverty, and the average illiteracy rate in 2020 was 6.6%. The average social marginalization of Hidalgo in 2015, according to the GINI index, was 0.421. The medical attention options and healthcare coverages for inhabitants of Hidalgo are hospitals and care clinics belonging to the Ministry of Health (Secretaría de Salud, SS) and the Mexican Institute of Social Security (Instituto Mexicano del Seguro Social, IMSS) with coverages of 43.3% and 20.5%, respectively.[11]

In Hidalgo, recent epidemiological data on cancer from the General Directorate of Health Information (DGIS) and the Ministry of Health (Secretaría de Salud, SS) of Mexico have revealed that HCC is the leading cause of death in this state, and this has attracted attention as a critical public health problem. In this state, the percentage of deaths caused by malignant liver tumors (MLTs) increased alarmingly from 1990 to 2013, by 152%. This contrasted with the national increase of 97.5% over the same period. The liver cancer mortality rate in Hidalgo almost doubled in 23 years, from 3.1 to 6.1 deaths per 100,000 inhabitants, while this rate was 1.6 deaths per 100,000 inhabitants in Mexico. Importantly, this cause of mortality in Hidalgo is higher than the national average.

OBJECTIVE

The aims of this study were to conduct a correlational and descriptive analysis on the main risk factors for liver cancer in Hidalgo State (hepatic fibrosis/cirrhosis, ALD and HCV), including municipal disaggregation and comparison with the national level; and to study trends of liver cancer deaths and projections to 2030, using data covering the period from 1990-2019.

METHODS

Study design

This study was designed as a correlational, descriptive, cross-sectional and comparative epidemiological study. This work did not require institutional review board (IRB) approval, given that it used anonymized and publicly available data.

Data sources

A comprehensive review of the databases of the DGIS was performed using specific search criteria for the analysis. The items were: a) deaths, according to definitive official figures for the period from 1979 to 2019 that were obtained from the National Institute of Statistics, Geography and Informatics (INEGI) and the SS of Mexico; b) hospital discharges, according to definitive official figures reported by the medical units of the SS for the period from 2000 to 2016; c) data from the National Population Council (Consejo Nacional de Población, CONAPO) and the 2010 National Population and Housing Census for 1990-2030 population projections in Mexico; and d) data from CONAPO for municipal population projections for 2010-2019.

Variables

Records with a diagnosis of liver disease that was in accordance with the codes of the 10th Revision of the International Classification of Diseases (ICD-10) were selected. The corresponding figures for the study variables were obtained from the databases by applying the Global Burden of Disease (GBD) classification to analyze deaths and hospital discharges, based on the risk factors for HCC described in the literature.[2,6,8] Thus, for chronic viral hepatitis (CVH) B or C, the code was B18; for MLT, C220-C224, C227 and C229; for ALD, K70; and for liver cirrhosis, K74. NASH and MetS were not considered because of limited availability of information.

Study size, eligibility criteria, calculations and statistical analysis

The sample size depended on inclusion of consecutive cases sampled from the total figures in the databases according to year, after applying the exclusion criteria. The mortality rates were calculated annually from 1990 to 2019, with regard to reports of deaths in municipalities of Hidalgo State (towns and their areas), and were analyzed according to sex and age groups. The mortality rate in Hidalgo was compared with that of other Mexican states. The DGIS records of death due to MLT as the primary cause over the 34-year period from 1985 to 2019 were used to run functional models for data trend projections. These revealed a positive association between time and death due to liver cancer; the actual figures were compared with those projected using the Student t test.

To determine whether the hospital discharges relating to liver cancer were correlated with the hospital discharges relating to pathological conditions that were considered to be causes of HCC (which was our hypothesis), data from all municipalities were studied using the Spearman correlation test. However, the data did not follow normal distribution ($P < 0.0001$). Since not every municipality had similar hospital discharge relating to liver cancer, that hypothesis was tested again but considering only the municipalities in which the death rate was higher than the mean (5.02) + one standard deviation (5.49). These corresponded to municipalities with at least twice the national death rate due to HCC. These data followed normal distribution ($P > 0.05$), and the Spearman correlation test was thus applied. Finally, normality was tested using the Shapiro-Wilk test. These analyses were performed using the GraphPad Prism 6.01 software (California, United States).

The inclusion criteria were that these municipalities of Hidalgo State needed to have the following: a) records of MLT as the primary

cause of death; and b) records of hospital discharges from the SS of Hidalgo relating to liver diseases. The exclusion criteria were situations of the following: a) death and hospital discharge records that stated a country of residence other than Mexico or reported the country as unspecified; and b) for data analysis at the state level, death and hospital discharge records declaring a state of residence other than Hidalgo or reporting this as unspecified.

Descriptive analysis on the data was carried out by determining the relative weight and mortality rate (national or state), and by numbering the position occupied by each tumor as a cause of death due to malignant neoplasm. Crude or cumulative death rates were calculated to compare the mortality rate in Hidalgo State with the rates in other Mexican states and the MLT mortality rate for the country over the period 1990-2019. Crude or cumulative death rates were estimated to compare the 84 municipalities of Hidalgo State from 1990 to 2019. The 1990-2030 population projections for Mexico compiled by CONAPO were used.

After the municipal mortality rates for liver cancer had been calculated, differential mapping was used to identify regions of Hidalgo with higher liver cancer rates. In addition, the 2010-2019 municipal population projections for Mexico compiled by CONAPO were used.

RESULTS

The relative weight (%), mortality rates for malignant tumors and their ranks as the primary cause of mortality were calculated for Mexico and Hidalgo based on the death figures for malignant tumors according to the GBD classification (**Table 1**). MLTs are a public health problem at both the national and the state level, considering that they are the fifth largest cause of death in Mexico and the leading cause in Hidalgo. This state's liver cancer mortality rate is 6.4 deaths per 100,000 inhabitants, which is 1.1 points greater than the national rate; its relative weight is at least 1.4% higher than that of other tumors in the state and Mexico.

Table 2 shows the ten states of Mexico that had the highest MLT mortality rates over the period 1990-2019. The increase in the ranking of the Hidalgo figures is evident: from the 21st place in 1990 to ninth place in 2019. Hidalgo occupied the sixth place in 2005;

Table 1. The six malignant tumors with the highest mortality rates in Mexico and Hidalgo in 2019

Tumor	Deaths in Mexico	Relative weight (%)	Rate	National rank	Deaths in Hidalgo	Relative weight (%)	Rate	State rank
Breast	7,419	8.5	5.9	1	152	7.7	5.0	3
Colorectal	6,978	8.0	5.5	2	142	7.2	4.7	4
Trachea, bronchi and lung	6,774	7.8	5.4	3	112	5.7	3.7	7
Prostate	6,760	7.8	5.34	4	160	8.1	5.2	2
Liver	6,727	7.8	5.3	5	194	9.9	6.4	1
Stomach	6,327	7.3	5.0	6	141	7.2	4.6	5
Total	**40,985**	**47.2**	**32.44**		**901**	**45.8**	**29.6**	

General Directorate of Health Information (DGIS), Institute of Statistics, Geography and Informatics (INEGI), Ministry of Health (Secretaría de Salud, SS) of Mexico and National Population Council (Consejo Nacional de Población, CONAPO). Definitive official death figures in 2019. Rates are calculated per 100,000 inhabitants within the total population for the period and were consulted in September 2021.

Table 2. The current ten states of Mexico with the highest mortality rates for malignant liver tumors, 1990-2019

State	1990	R	1995	R	2000	R	2005	R	2010	R	2015	R	2019	R	ECI 2021
Veracruz	4.34	4	5.85	3	6.73	3	8.29	1	8.56	1	10.08	1	9.13	1	-0.95
Oaxaca	2.47	25	3.65	15	4.36	9	4.85	9	5.82	6	6.68	4	7.96	2	-1.97
Yucatan	6.23	1	8.57	1	7.26	1	6.49	3	6.36	3	7.13	3	7.97	3	0.06
Tabasco	3.85	12	4.52	7	4.25	11	4.53	12	5.15	11	5.91	11	7.00	4	-0.75
Chiapas	3.59	14	4.42	8	4.54	8	4.99	8	5.79	7	6.43	7	6.92	5	-1.77
Campeche	2.35	26	4.92	5	4.14	14	4.43	13	4.42	16	7.16	2	6.91	6	-0.43
San Luis Potosi	3.13	20	3.84	13	4.81	7	5.53	5	6.15	4	6.14	9	6.75	7	0.64
Mexico City	3.59	15	4.53	6	5.02	6	5.72	4	5.94	5	6.54	5	6.65	8	0.95
Hidalgo	3.08	21	3.64	16	3.1	27	5.51	6	5.39	9	6.43	8	6.36	9	-0.68
Tamaulipas	5.5	3	5.63	4	5.52	4	5.27	7	7.32	2	6.43	6	5.83	10	0.81

ECI = economic complexity index 2021.[11]

General Directorate of Health Information (DGIS), Institute of Statistics, Geography and Informatics (INEGI), Ministry of Health (Secretaría de Salud, SS) of Mexico and National Population Council (Consejo Nacional de Población, CONAPO). R: The annual national rank of the state in mortality rates for malignant liver tumors calculated per 100,000 inhabitants. Definitive official death figures (1990-2019) were consulted in September 2021.

since then, it has always been among the top ten. Hidalgo occupies the ninth place in the national ranking of liver cancer deaths considering the cumulative death rate of 2010-2019 as the period analyzed for mortality. Furthermore, the ECI index in 2021 for each state is presented to contextualize their economic development. As observed, the situation of the financial resources of most of these states has the implication that their ability to improve their healthcare services and prevention programs may be limited.

The MLT mortality rate was 31.43% higher than the national rate between 1990 and 2019 (151.42% for Mexico and 182.85% for Hidalgo). Since 2005, the mortality rates in Hidalgo have always been higher than national rates (**Figure 1A**). The death records comprising the period from 1985 to 2019 formed the basis to construct a functional linear model of data trend (**Figure 1B**), which showed a positive association between time and liver cancer death ($y = 4.4667x - 8825.5$; $R^2 = 0.935$), as well as a noticeable increase in the number of deaths due to this cause over time. This relationship was corroborated by comparing real and theoretical figures ($t_{64} = 0.0002$; $P = 0.99$), which were statistically similar. This model projected 237 deaths (95% confidence interval, CI, 223 to 251) due to MLT by 2030, in contrast to 194 deaths recorded in 2019 (122.16% increase). **Figure 1C** depicts an increasing trend in deaths for both men ($y = 0.0364x^2 - 143.28x + 141082$; $R^2 = 0.921$) and women ($y = 0.0152x^2 - 58.808x + 56835$; $R^2 = 0.903$) from 1985-2019 through a quadratic trend model. A larger number of deaths among women can be seen, although more men died in some years; however, these figures are similar when the data are compared according to mortality rates. The distribution according to age group with liver cancer as the cause of death (1985-2019) showed a linear trend (< 60 years old, $y = 0.7958x - 1562.8$, $R^2 = 0.713$; > 60 years old, $y = 3.6821x - 7285.5$, $R^2 = 0.928$), in which a greater increase over time was observed for the group aged > 60 years (**Figure 1D**).

Adjusted liver cancer mortality rates according to sex and age in 2010-2019 were calculated to compare Mexico with Hidalgo, but only the 2019 figures are presented because the trend over time was similar. For individuals > 60 years old in Mexico (rate 37.8 per 100,000 inhabitants), the rate for females was 34.2 and for males, 41.9; in Hidalgo (rate 42.1), the rate for females was 38.0 and for males, 47.0. For individuals < 60 years old in Mexico (rate 1.2), the rate for females was 1.1 and for males, 1.2; in Hidalgo (rate 1.8), the rate for females was 2.2 and for males, 1.4. Thus, Hidalgo had higher mortality rates for both sexes and both age groups than those of Mexico. Standardized rates were greater for males and > 60 years in both Hidalgo and Mexico, except for females < 60 in Hidalgo.

Given the high prevalence of MLT in the state, municipal disaggregation was a necessity in order to analyze their death rates over

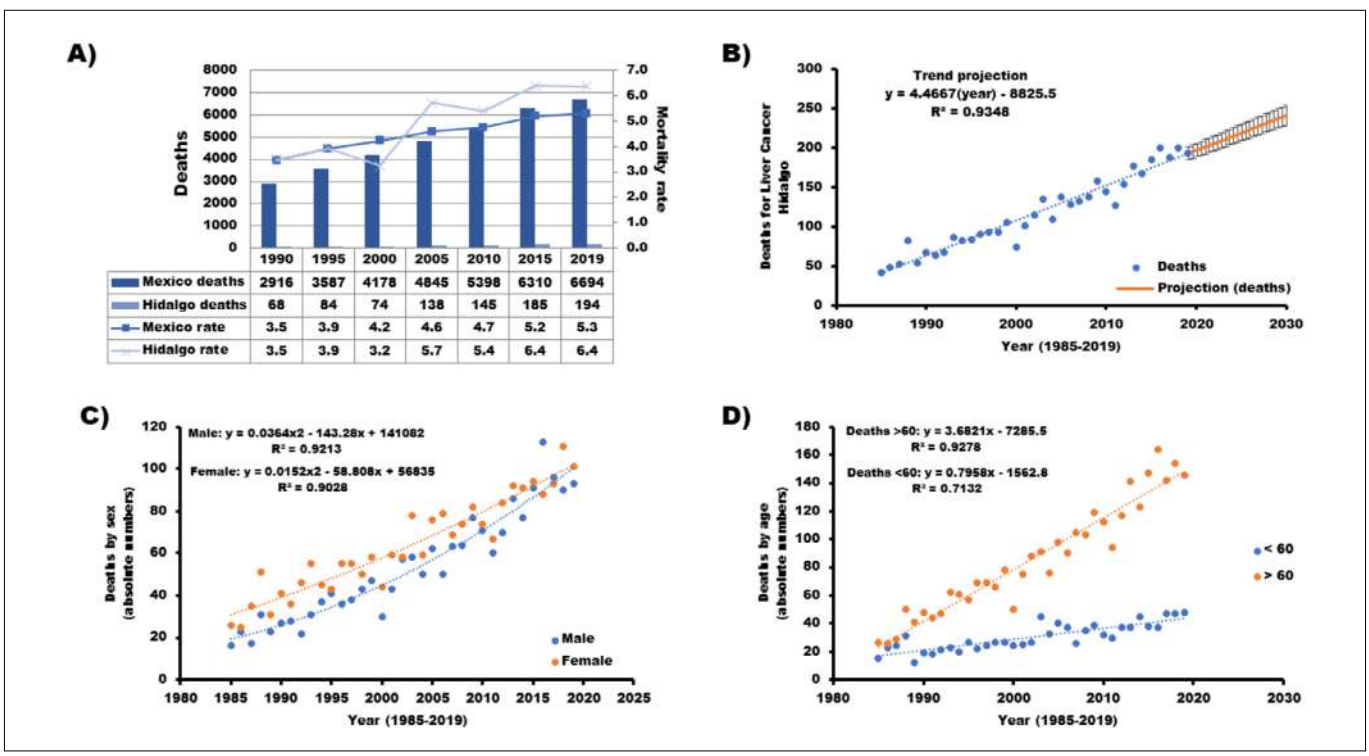
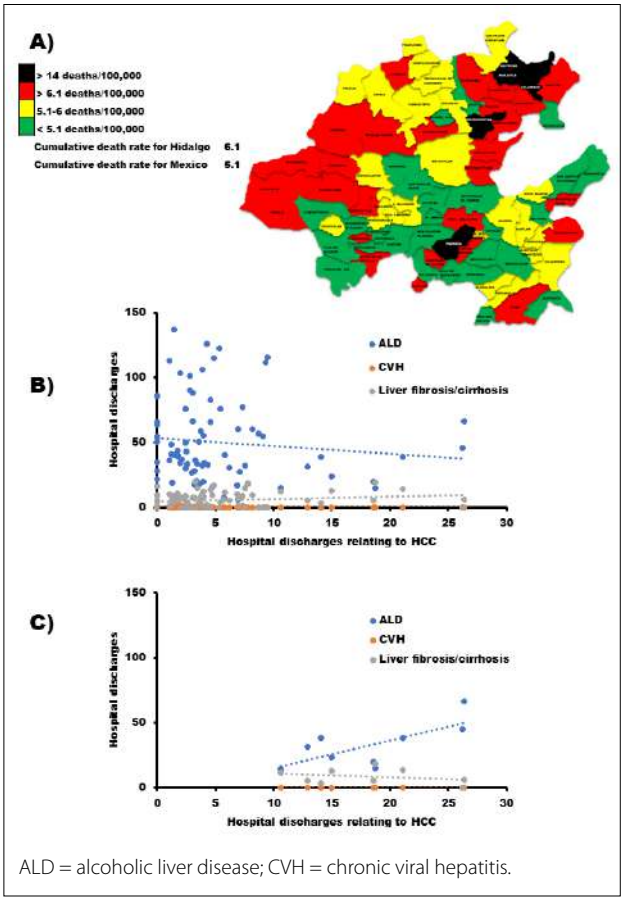


Figure 1. A) Comparison of mortality rates for malignant liver tumors between Hidalgo State and Mexico, 1990-2019. **B)** Deaths due to liver cancer in the Hidalgo State population, 1985-2019, and 2018-2030 projections. Error bars represent the 95% confidence interval. **C)** Quadratic trend according to sex of liver cancer deaths, 1985-2019. **D)** Linear trend according to age group (< 60 years or > 60 years) of liver cancer deaths, 1985-2019.

the period 2010-2019. **Figure 2A** shows a map of Hidalgo State in which the municipalities are color-coded as follows: municipalities with a liver cancer death rate lower than the national rate are shown in green; those with a death rate between 5.1 and 6.1, which are the national and state cumulative rates respectively, are shown in yellow; those with a rate higher than the state rate are shown in red, and those with the highest rates (twice the state rate or more) are shown in black. Huejutla was the municipality with the largest number of deaths (187) due to MLT and had the third highest mortality rate. Jaltocan ranked first in mortality rate despite its small population and just 20 deaths. These two municipalities are considered socially marginalized; surprisingly, Pachuca, the state capital municipality, had a mortality rate of 14 with 141 deaths. The population > 60 years exhibited the largest number of deaths; however, there were reports of deaths among young patients (23-39 years of age) in critical municipalities. In the five municipalities with the highest mortality rate, the percentage of death among women was slightly higher than that among men (52.8% versus 47.2%), although some municipalities registered more male deaths.

The hospital discharge rates were calculated considering the SS records over the period 2010-2019 relating to patients either attended in Hidalgo or from Hidalgo attended in other states, who were diagnosed with CVH, ALD, liver fibrosis/cirrhosis or hepatic cancer. **Table 3** shows the 15 municipalities in Hidalgo with the highest hospital discharge rates relating to MLT, according to risk factor for the disease during that period. Figures for the hospital discharge rates of these municipalities can be compared with the state figures.

The relationship between hospital discharge rates relating to HCC and hospital discharge rates relating to ALD, CVH and fibrosis/cirrhosis as the leading risk factor for the disease in Hidalgo (2010-2019) was studied. The correlation analysis did not show any significant difference between hospital discharges relating to HCC and hospital discharges relating to ADL ($\rho = -0.13$, $P > 0.05$), CVH ($\rho = -0.19$, $P > 0.05$) or fibrosis/cirrhosis ($\rho = 0.16$, $P > 0.05$) (**Figure 2B**). Nevertheless, among the municipalities with the highest HCC death rates, only nine with a mean hospital discharge rate for HCC + one standard deviation were considered for calculating Pearson's coefficient. This analysis revealed that there was a significant positive correlation between HCC and ALD ($R^2 = 0.49$, $P < 0.05$) in these critical municipalities (**Figure 2C**).



ALD = alcoholic liver disease; CVH = chronic viral hepatitis.

Figure 2. A) Map of distribution of deaths due to hepatocellular carcinoma (HCC) according to municipality and cumulative death rates in Hidalgo State, using data from the General Directorate of Health Information (DGIS) and Ministry of Health (Secretaría de Salud, SS) of Hidalgo, 2010-2019. B) Correlation between hospital discharges relating to HCC and hospital discharges relating to risk factors for this disease in the municipalities of Hidalgo State. C) Correlation between hospital discharges relating to HCC and hospital discharges relating to risk factors for this disease in the nine municipalities of Hidalgo with the highest HCC death rates.

DISCUSSION

In Mexico (ECI index of 1.31 in 2020 and GINI index of 0.45 in 2018), liver cancer is among the five leading types of malignant tumor causing death. This is consistent with the third place that was identified in a review of official death certificates in Mexico over the period 2000-2006, in which a national increase in HCC deaths of 14% was found (4.16 deaths in 2000 versus 4.74 in 2005, both per 100,000 inhabitants); and with the ranking of liver cancer as the third largest cause of mortality due to cancer in GLOBOCAN 2020.[7,12] The trend projections obtained for HCC as a mortality cause are a helpful tool for proposing the strengthening of healthcare strategies to diminish liver cancer cases in Mexico and Hidalgo, since no up-to-date or previous state projections were found.[9] Cancer is a growing health problem, just like other non-communicable diseases, and reducing deaths caused by such diseases is a goal set by the World Health Organization (WHO).[13] Similar countries in Latin America, such as Argentina (-0.29 ECI, 0.42 GINI), Brazil (0.10 ECI, 0.53 GINI)

Table 3. The fifteen municipalities in Hidalgo State with the highest hospital discharge rates relating to malignant liver tumors according to risk factors for this disease, 2010-2019

Municipality	Liver cancer	CVH	ALD	Liver fibrosis/cirrhosis
Eloxochitlán	176.4	0.0	52.9	0.0
Pisafores	62.8	0.0	21.8	10.9
Xochicoatlán	40.5	0.0	8.1	8.1
Xochiatipan	30.1	0.0	12.5	10.0
Agua Blanca de Iturbide	20.1	0.0	48.2	4.0
Jacala de Ledezma	19.0	0.0	61.0	9.5
San Agustín Metzquititlán	17.1	0.0	17.1	0.0
Tianguistengo	16.7	0.0	22.3	16.7
Huazalingo	15.0	0.0	5.0	10.0
Tepetitlán	14.7	0.0	33.0	0.0
Nicolás Flores	13.7	0.0	68.3	0.0
Huichapan	13.6	0.5	70.7	1.1
Tlahuelilpan	12.6	0.0	28.7	9.0
Pacula	11.1	0.0	55.5	0.0
Omitlán de Juárez	10.7	0.0	24.9	0.0
Unspecified	10.5	5.3	982.3	124.3
Hidalgo's hospital discharge rate	0.9	0.1	27.4	4.4

ALD = alcoholic liver disease; CVH: chronic viral hepatitis.

General Directorate of Health Information (DGIS), Institute of Statistics, Geography, and Informatics (INEGI), Ministry of Health (Secretaría de Salud, SS), and National Population Council (Consejo Nacional de Población CONAPO). Definitive official hospital discharge rates calculated per 10,000 inhabitants, 2010-2019. Consulted in September 2021.

and Colombia (0.09 ECI, 0.51 GINI), have lower mortality rates for liver cancer, which was ranked between sixth and tenth place in 2020.[12]

MLTs are the leading cause of death in Hidalgo; identification and characterization of critical municipalities provide better understanding of the current situation of this disease in the state. In the population studied, the highest mortality rates were observed in the group aged > 60 years, which agrees with earlier data for Mexico.[8,10] In addition, both sexes seemed to suffer equally from HCC in 2014,[8] although most authors have reported higher mortality rates for men in Mexico[5,6] and Latin America.[2] In the present study in 2019, a higher death rate among women aged < 60 years was found in Hidalgo, although men were more affected than women in the three municipalities with the highest HCC death figures. Epidemiological reports have shown an equal ratio of male/female mortality due to HCC in countries like Mexico; however, current trends indicate a rise in the number of female deaths, such that in Mexico liver cancer was the third largest cause of death among women and the fifth among men in 2020.[9,12,14] Conversely, the estimated death rates due to liver cancer in Argentina, Brazil and Colombia for both sexes ranked sixth to tenth among cancers in 2020.[12]

Scientific evidence confirms that ALD, CVH and fibrosis/cirrhosis are the major risk factors for developing liver cancer.[1-3] Several studies carried out in South America have reported that HCV infection is the most frequent risk factor, but also that HCV/HBV coinfection, alcoholic cirrhosis and non-alcoholic fatty liver disease (NAFLD) are also widespread risk factors.[4] Indeed, the Mexican population has been found to be more susceptible to ALD because of genetic and environmental factors.[15]

In addition to the mortality data, our analysis on hospital discharges among Hidalgo inhabitants provided a gross indicator of morbidity. Hospital discharges can represent either demand for or provision of healthcare services, thus providing a valuable tool for identifying the morbidity profile. Moreover, hospital discharges indicate the level of hospital services for resolving the needs of patients.[16] For the present study, hospital discharges in which the municipality of residence was not specified were eliminated from the results, given that the objective was to analyze municipalities; otherwise, precise information might improve the municipal analysis.

A significant increase in hospital discharges among cirrhosis patients was observed in Hidalgo from 2010 to 2019. Other authors have also reported high incidence and prevalence of cirrhosis over a similar period, which was related to high alcohol consumption and viral infections.[9,17] Hospital discharges relating to HCV also increased in this state, since chronic HCV infection has emerged as a health problem in Mexico[18,19] and Latin America.[3,4] ALD is the most important cause of chronic liver disease and accounts for one-third of all HCC cases globally.[20] Furthermore, the increase in alcohol consumption in the young Mexican population is alarming, while

demand for its medical treatment is diminishing.[21-23] Moreover, there is an increasing trend of injectable drug abuse.[19,24] This information may explain the increase in the rate of hospital discharges relating to ALD in Hidalgo. These data support the existence of a correlation between HCC in Hidalgo and the risk factors of ALD, CVH and cirrhosis.

Studies on HCC epidemiology in Argentina, Brazil and Chile, among other countries, have pointed out the importance of NAFLD/NASH as a new leading cause of liver cancer.[4] In Mexico, specific information about HCC caused by NAFLD/NASH is scarce.[7-9] The lack of data on the prevalences of NASH, MetS and alcoholism in the municipalities of Hidalgo hinders implementation of effective public health strategies and policies. Therefore, enhanced prevention programs to decrease the acquisition of modifiable risk factors are essential, including hepatitis B vaccination. Likewise, there is a need for programs promoting healthy nutrition and safe sex and programs aimed at stopping injection drug use to prevent HCV infection and aimed at reducing alcohol consumption. Moreover, early diagnosis and treatment adherence are needed.[2,8,19,23,24]

The municipal cumulative MLT mortality rates revealed the presence of a critical zone in the north of Hidalgo, with a rate that was almost three times higher than the national rate. Indeed, some municipalities with high hospital discharge rates regarding HCC also show many hospital discharges relating to ALD and cirrhosis. Therefore, a significant correlation between HCC and ALD was found in these municipalities. Notably, in Hidalgo State, 43.8% of the population lives in poverty and 6.1% under conditions of extreme poverty.[11,25] The northern region exhibits high poverty indicators, dispersion of small communities, underserved populations and indigenous residents, according to DGIS 2019 data. In addition, it has a high illiteracy rate (6% to 20% in 2020) and high social inequality according to the GINI index (0.435-0.505 in 2015).[11]

Unexpectedly, the municipality of Pachuca, the state capital of Hidalgo, had a high mortality rate for liver cancer and was ranked third. Pachuca had a GINI index of 0.397 in 2015 and an illiteracy rate of 1.59% in 2020. Use of alcohol and illegal drugs is increasing in Pachuca, although 54.8% of the Hidalgo population has been exposed to prevention programs.[22] Hence, these municipalities require a profound status analysis and regional strategies to improve future public health policies.

These findings suggest that national or state prevention programs aimed at reducing alcohol and drug consumption or at providing care for underserved communities have not significantly improved the social and health conditions in those municipalities. This may be considered to be a social failure despite the many governmental strategies that have been implemented to improve Mexico's poverty and social lag indicators.[22-25] Consequently, the prevalence of non-communicable diseases is high among marginalized communities. Moreover, these communities are exposed to unhealthy environments, and the socioeconomic inequalities and exclusion from formal labor markets to which these communities are exposed in Mexico and Latin America restrict their access to healthcare services.[26] Although local or regionalized public health policies are often overdue, application of such policies is required urgently because they can have profound positive effects on community health and can ameliorate health disparities, lessen administrative paperwork within healthcare systems and diminish governmental dysfunction.[27] Two areas of opportunity and challenges are recognized: implementation of a population-based cancer registry with reliable data; and creation of a national cancer plan to guide control programs and strategies.[28,29] Unfortunately, local or regional healthcare policy strategies depend on government budgets at the state or national level, but community and municipal populations cannot quickly manage these resources and demand their uncorrupted use.

CONCLUSION

This study provided a detailed epidemiological view of the status of liver cancer in Hidalgo State through projections, trends, and cause analysis. This information may serve as a helpful example with regard to identifying a local health issue that requires establishment of preventive actions to diminish recognized and correlated risk factors, particularly in marginalized municipalities. In this regard, increased recording and surveillance of NASH and MetS are mandatory since these are currently the second most common risk factors for HCC. Lastly, there is an urgent need for effective regional health policies and strategies in Hidalgo State, Mexico, and throughout Latin America and in other countries with similar epidemiological and socioeconomic conditions, in order to prevent the expansion of liver cancer to populations that are more vulnerable to alcoholism and other risk factors for liver cancer.

REFERENCES

1. Sung H, Ferlay J, Siegel RL, et al. Global cancer statistics 2020: GLOBOCAN estimates of incidence and mortality worldwide for 36 cancers in 185 countries. CA Cancer J Clin. 2021;71(3):209-49. PMID: 33538338; https://doi.org/10.3322/caac.21660.
2. Piñero F, Poniachik J, Ridruejo E, Silva M. Hepatocellular carcinoma in Latin America: Diagnosis and treatment challenges. World J Gastroenterol. 2018;24(37):4224-9. PMID: 30310255; https://doi.org/10.3748/wjg.v24.i37.4224.
3. Galicia-Moreno M, Monroy-Ramirez HC, Campos-Valdez M, et al. Hepatocellular carcinoma and hepatitis C virus infection in Latin America: epidemiology, diagnosis and treatment. Hepatoma Res. 2020;6:20. https://doi.org/10.20517/2394-5079.2019.36.
4. Carrilho FJ, Paranaguá-Vezozzo DC, Chagas AL, Alencar RSSM, da Fonseca LG. Epidemiology of liver cancer in Latin America: Current and future

trends. Semin Liver Dis. 2020;40(2):101-10. PMID: 31711252; https://doi.org/10.1055/s-0039-3399561.

5. Castells Fusté L. Virus de la hepatitis B y carcinoma hepatocelular. Gastroenterol Hepatol. 2006;29:86-92. https://doi.org/10.1157/13097585.
6. Mittal S, El-Serag HB. Epidemiology of hepatocellular carcinoma: consider the population. J Clin Gastroenterol. 2013;47 Suppl(0):S2-S6. PMID: 23632345; https://doi.org/10.1097/MCG.0b013e3182872f29.
7. Méndez-Sánchez N, Villa AR, Vázquez-Elizondo G, Ponciano-Rodríguez G, Uribe M. Mortality trends for liver cancer in Mexico from 2000 to 2006. Ann Hepatol. 2008;7(3):226-9. PMID: 18753989; https://doi.org/10.1016/S1665-2681(19)31852-6.
8. Cisneros-Garza LE, González-Huezo MS, López-Cossio JA, Kuljacha-Gastelum AL. Characterization of hepatocellular carcinoma in Mexico. Rev Gastroenterol Mex. 2018;83(3):223-7. PMID: 29801665; https://doi.org/10.1016/j.rgmx.2017.06.003.
9. Méndez-Sánchez N, Villa AR, Chávez-Tapia NC, et al. Trends in liver disease prevalence in Mexico from 2005 to 2050 through mortality data. Ann Hepatol. 2005;4(1):52-5. PMID: 15798662; https://doi.org/10.1016/S1665-2681(19)32086-1.
10. González-Huezo MS, Sánchez-Ávila JF. Mexican consensus on the diagnosis and management of hepatocellular carcinoma. Rev Gastroenterol Mex. 2014;79(4):250-62. PMID: 25487133; https://doi.org/10.1016/j.rgmx.2014.09.004.
11. DataMéxico: Hidalgo entidad federativa. Datawheel. 2021. Available from: https://datamexico.org/es/profile/geo/hidalgo-hg. Accessed in 2021 (Nov 19).
12. World Health Organization. International Agency for Research on Cancer; 2020. Available from: https://gco.iarc.fr/. Accessed in 2021 (Nov 19).
13. Córdova-Villalobos JA, Barriguete-Meléndez JA, Lara-Esqueda A, et al. Las enfermedades crónicas no transmisibles en México: sinopsis epidemiológica y prevención integral [Chronic non-communicable diseases in Mexico: epidemiologic synopsis and integral prevention]. Salud Publica Mex. 2008;50(5):419-27. PMID: 18852939; https://doi.org/10.1590/s0036-36342008000500015.
14. Nordenstedt H, White DL, El-Serag HB. The changing pattern of epidemiology in hepatocellular carcinoma. Dig Liver Dis. 2010;42 Suppl 3(Suppl 3):S206-14. https://doi.org/10.1016/s1590-8658(10)60507-5.
15. Roman S, Zepeda-Carrillo EA, Moreno-Luna LE, Panduro A. Alcoholism and liver disease in Mexico: genetic and environmental factors. World J Gastroenterol. 2013;19(44):7972-82. https://doi.org/10.3748/wjg.v19.i44.7972.
16. Schoenman JA, Sutton JP, Elixhauser A, Love D. Understanding and enhancing the value of hospital discharge data. Med Care Res Rev. 2007;64(4):449-68. PMID: 17684112; https://doi.org/10.1177/1077558707301963.
17. Fajardo González M, Arce Nuñez M, Medina Garrido Y, Esteva Carral L, Osorio Pagola M. Comportamiento de la cirrosis hepática en el hospital "Arnaldo Milián Castro" de julio de 2007 a marzo de 2009. MediSur. 2010;8:40-8. Available from: http://scielo.sld.cu/scielo.php?script=sci_arttext&pid=S1727-897X2010000400007&lng=es&nrm=iso&tlng=es. Accessed in 2021 (Nov 19).
18. Valdespino J, Conde-González C, Olaiz-Fernández G. Seroprevalencia de la hepatitis C en adultos de México: ¿un problema de salud pública emergente? [Seroprevalence of hepatitis C among Mexican adults: an emerging public health problem?]. Salud Publica Mex. 2007;49(3):395-403. Available from: https://scielosp.org/article/spm/2007.v49suppl3/s395-s403/es/#ModalArticles. Accessed in 2021 (Nov 19).
19. Sedeño-Monge V, Laguna-Meraz S, Santos-López G, et al. A comprehensive update of the status of hepatitis C virus (HCV) infection in Mexico-A systematic review and meta-analysis (2008-2019). Ann Hepatol. 2021;20:100292. PMID: 33259949; https://doi.org/10.1016/j.aohep.2020.100292.
20. Ganne-Carrié N, Nahon P. Hepatocellular carcinoma in the setting of alcohol-related liver disease. J Hepatol. 2019;70(2):284-93. PMID: 30658729; https://doi.org/10.1016/j.jhep.2018.10.008.
21. González-Bautista E, Zavala-Arciniega L, Rivera-Rivera L, Leyva-López A, Natera-Rey G, Reynales-Shigematsu LM. Factores sociales asociados con el consumo de tabaco y alcohol en adolescentes mexicanos de poblaciones menores a 100 000 habitantes [Social factors associated with tobacco and alcohol consumption in Mexican adolescents from populations under 100 000 inhabitants.]. Salud Publica Mex. 2019;61(6):764-74. PMID: 31869541; https://doi.org/10.21149/10563.
22. CIJ. Estudio básico de comunidad objetivo 2018: Diagnóstico del consumo de drogas del área de influencia del CIJ Pachuca, Hidalgo. 2018 ed: Centros de Integración Juvenil; 2018. p. 1-9. Available from: http://www.cij.gob.mx/ebco2018-2024/9010/CD/9010_CD_Dx.pdf. Accessed in 2021 (Nov 19).
23. CONADIC. Informe sobre la situación de la salud mental y el consumo de sustancias psicoactivas en México. In: SSA, editor. Mexico: Comisión Nacional Contra las Adicciones; 2021. p. 1-63. Available from: https://www.gob.mx/cms/uploads/attachment/file/648021/INFORME_PAIS_2021.pdf. Accessed in 2021 (Nov 19).
24. Magis-Rodríguez C, García-Sánchez JA, Marín-Navarrete R. Harm reduction among people who inject drugs in Mexico. Salud Mental. 2018;41(4):153-6. https://doi.org/10.17711/sm.0185-3325.2018.023.
25. CONEVAL. Pobreza Municipal: Hidalgo Mexico: CONEVAL; 2018. Available from: https://www.coneval.org.mx/coordinacion/entidades/Hidalgo/Paginas/principal.aspx. Accessed in 2021 (Nov 19).
26. Machado CV, Lima LD. Health policies and systems in Latin America: regional identity and national singularities. Cad Saude Publica. 2017;33Suppl 2 (Suppl 2):e00068617. PMID: 28767811; https://doi.org/10.1590/0102-311X00068617.
27. Bishai DM, Frattaroli S, Pollack KM. Public health policies: Go local! Am J Public Health. 2017;107(5):672-4. PMID: 28398793; https://doi.org/10.2105/AJPH.2017.303682.

28. Lazcano-Ponce E, Mohar-Betancourt A, Meneses-García A, Hernández-Ávila M. Cancer burden in Mexico: urgent challenges to be met. Salud Publica Mex. 2016;58(2):101-3. PMID: 27557368; http://doi.org/10.21149/spm.v58i2.7778.
29. Leal YA, Fernández-Garrote LM, Mohar-Betancourt A, Meneses-García A. The importance of registries in cancer control. Salud Publica Mex. 2016;58(2):309-16. PMID: 27557391; http://doi.org/10.21149/spm.v58i2.7802.

Authors' contributions: Barrera-Cortés RI: conceptualization (lead), data curation (lead), formal analysis (lead), investigation (equal), methodology (lead), resources (equal) and software (lead); Rodríguez-Torres EE: conceptualization (lead), formal analysis (lead), investigation (supporting), methodology (lead), software (lead) and supervision (lead); Vázquez-Mendoza E: data curation (supporting), formal analysis (supporting), methodology (supporting), software (lead) and validation (lead); Ruvalcaba-Ledezma JC: formal analysis (lead) investigation (supporting), methodology (lead), supervision (supporting) and visualization (lead); Soria-Jasso LE: data curation (equal), investigation (equal), methodology (equal), resources (supporting) and software (supporting); Ortiz MI: formal analysis (supporting), investigation (equal), methodology (equal), software (equal) and writing-review and editing (equal); Fernández-Martínez E: conceptualization (lead), formal analysis (lead), investigation (equal), project administration (lead), resources (lead), supervision (lead), visualization (lead), writing-original draft (lead) and writing-review and editing (lead)

Acknowledgements: The authors would like to thank M.C.Esp. Luis Carlos Romero Quezada for administrative support and Consejo Nacional de Ciencia y Tecnología (CONACyT), Mexico, for the master's degree fellowship granted to Rosa I. Barrera-Cortés (number 709901)

Sources of funding: This work did not require any financial support
Conflicts of interest: The authors declare that there were no conflicts of interest

Date of first submission: July 8, 2021
Last received: October 4, 2021
Accepted: November 12, 2021

Address for correspondence:
Eduardo Fernández-Martínez
Laboratory of Medicinal Chemistry and Pharmacology, Biology Research Center in Reproduction, Department of Medicine, School of Health Sciences, Universidad Autónoma del Estado de Hidalgo (UAEH)
Calle Dr. Eliseo Ramírez Ulloa, 400
Colonia Doctores, Pachuca Hidalgo, México
42090
Tel. (+52) 771 717 2000 ext. 2368.
E-mail: efernan@uaeh.edu.mx

Intermediate-term follow-up of laparoscopic pectopexy cases and their effects on sexual function and quality of life: a cross-sectional study

Selami Erdem[I]

Department of Gynecology and Obstetrics, Özel Bağlar Hastanesi, Diyarbakır, Turkey

[I]MD. Physician, Department of Gynecology and Obstetrics, Özel Bağlar Hastanesi, Diyarbakır, Turkey
https://orcid.org/0000-0002-8517-5787

KEY WORDS (MeSH terms):
Pelvic organ prolapse.
Quality of life.
Laparoscopy.

AUTHORS' KEY WORDS:
Pectopexy.
Prolapsus.
Laparoscopic surgery.

ABSTRACT

BACKGROUND: Apical prolapsus refers to downward displacement of the vaginal apex, uterus or cervix. Pelvic organ prolapse (POP) can significantly affect women's daily activities and sexuality.

OBJECTIVE: To investigate, at the mid-term follow-up after laparoscopic pectopexy surgery, whether this procedure improved the patients' quality of life and sexual function.

DESIGN AND SETTING: In this cross-sectional study, data on patients who underwent laparoscopic pectopexy in the Gazi Yasargil Education and Research Hospital were evaluated.

METHODS: Thirty-five patients with symptomatic apical prolapse and POP quantification stage II and higher were included in this study. We used the Turkish version of the female sexual function index (FSFI) questionnaire to assess preoperative and postoperative sexual dysfunction, and the Turkish version of the Prolapse Quality of Life Questionnaire (P-QOL) to evaluate the severity of POP and its impact on quality of life.

RESULTS: The mean age, parity and length of follow-up of the patients were 36.08 ± 9.04 years, 4.00 ± 1.86 and 28.88 ± 5.88 months, respectively. The most common complications were de novo rectocele in three patients (8.6%) and de novo cystocele in two patients (5.7%). All the FSFI and P-QOL scores were statistically significantly improved in the postoperative period ($P < 0.001$ for all scores of both FSFI and P-QOL).

CONCLUSION: The quality of life and sexual function of the patients who underwent laparoscopic pectopexy were found to have become statistically improved at the midterm follow-up. Laparoscopic pectopexy was found to be a viable, effective and safe procedure.

INTRODUCTION

Apical prolapse refers to downward displacement of the vaginal apex, uterus or cervix. Pelvic organ prolapse (POP) affects 50% of parous women, and this rate increases with age, menopause and parity. However, POP can be asymptomatic and may only be noticed when patients are examined for another reason.[1] POP can significantly affect women's daily activities and sexuality. Many studies have reported that sacropexy is the most appropriate approach for providing a physiological axis for the vagina in terms of size, depth and inclination.[2-4] However, defecation disorders and urinary problems are common after sacropexy.

The pectopexy procedure, defined as a new endoscopic prolapse surgery method, was developed especially for obese patients by Banerjee and Noe in 2007. In this, mesh fixation is performed on both sides of the descending lateral parts of the iliopectineal ligament, for suspension of the cervix or vagina. This segment of the ligament is located at the level of the second sacral vertebra (S2), which is the most suitable level for the physiological axis of the vagina. In this method, because the mesh does not cross the ureter or intestine and passes through the broad ligament, it does not cause problems with the ureter and intestine. In addition, the hypogastric vessels are at a safe distance from any danger. This new method is a simpler and safer procedure, especially in patients for whom surgery is difficult.[5]

OBJECTIVE

In this study, our aim was to investigate, at the mid-term follow-up after laparoscopic pectopexy surgery, whether this procedure improved the patients' quality of life and sexual function; and to determine the reliability, applicability and effectiveness of the surgery by using the

female sexual function index (FSFI) and Prolapse Quality of Life (P-QOL) questionnaires.

METHODS

Study design and patients

Data on patients who underwent laparoscopic pectopexy in our hospital between January 2016 and June 2018 were collected from the registry system of our hospital. Approval was obtained from the Ethics Committee of Gazi Yasargil Education and Research Hospital (decision no. 507; date: March 7, 2020). In this study, which we conducted in accordance with the Declaration of Helsinki, we obtained written informed consent from all participants. All the surgical operations were performed by three gynecological surgeons with advanced laparoscopic experience.

The patients with apical prolapse were evaluated in terms of their feeling of pressure in the vagina, bloated/bulging sensation, urinary symptoms, constipation and sexual dysfunction, and the results were recorded. Genital prolapse was evaluated using both physical examination and ultrasonography.

The pelvic organ prolapse quantification system (POP-Q) was used for prolapse evaluation. Only patients with symptomatic prolapse (POP-Q stage II and higher) were included in this study. Patients with pelvic inflammatory disease, genital malignancy, pregnancy or previous POP surgery were excluded from the study.

The Turkish version of the FSFI questionnaire, evaluating six sexual desire domains (sexual desire, sexual arousal, lubrication, orgasm, satisfaction and pain), was used to evaluate preoperative and postoperative sexual dysfunction. In this questionnaire, the lowest score is 2, and the highest score is 36. Total scores < 26.55 were considered indicative of impaired sexual function.[6,7]

The Turkish version of the P-QOL questionnaire, which is a reliable, consistent and valid tool, was used to evaluate the severity of POP and its effect on quality of life. A high P-QOL score represents poor quality of life.

Surgical procedure

All the operations were performed under endotracheal general anesthesia in the dorsal lithotomy position. After the operation had been started and trocars had been placed, the patient was placed in the Trendelenburg position. Cephazolin sodium (1 g) was administered to all the patients preoperatively, and a Foley catheter was placed in the bladder.

Firstly, a camera was inserted through a 10-mm periumbilical trocar. Pneumoperitoneum was created until an intra-abdominal pressure of 13 mmHg was achieved. Then, two 5-mm trocars were placed ipsilaterally on the left side of the patient; and one 5-mm trocar, on the right side. During the operation, the surgeon stood on the left side of the patient, and the assistant stood on the right side. A uterine manipulator was used in all the patients, to position the uterus. Monopolar cautery was used for the dissection. The bladder was dissected starting from the uterus, using sharp and blunt dissection. On both sides, the lateral part of the iliopectineal ligament was reached, up to the area bounded by the ligamentum rotundum, external iliac vein and obturator nerve (**Figure 1**).

The polypropylene mesh that was brought into the abdomen from a 10-in trocar was first fixed with a non-absorbable polypropylene monofilament suture on the lateral part of both iliopectineal ligaments, in a tension-free manner. Then, the mesh was fixed to the lower anterior segment of the uterus with three non-absorbable polypropylene monofilament sutures. The operation was completed by closing the peritoneal layer with no. 0 absorbable sutures (**Figure 2**).

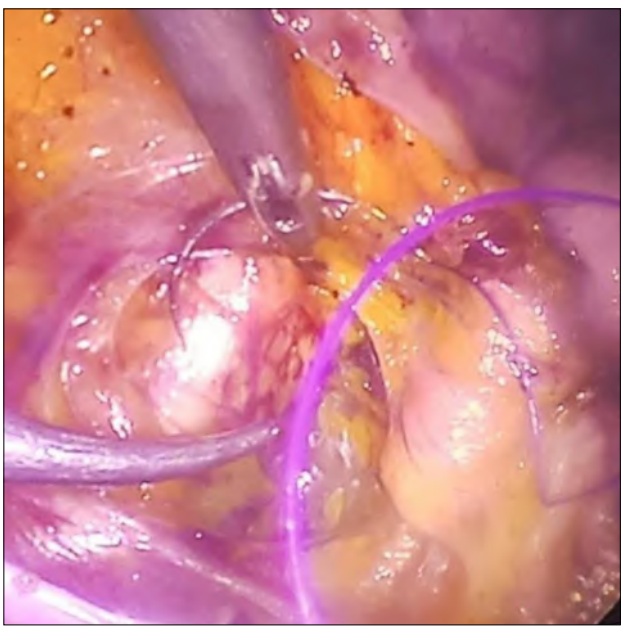


Figure 1. Iliopectineal ligament fixation.

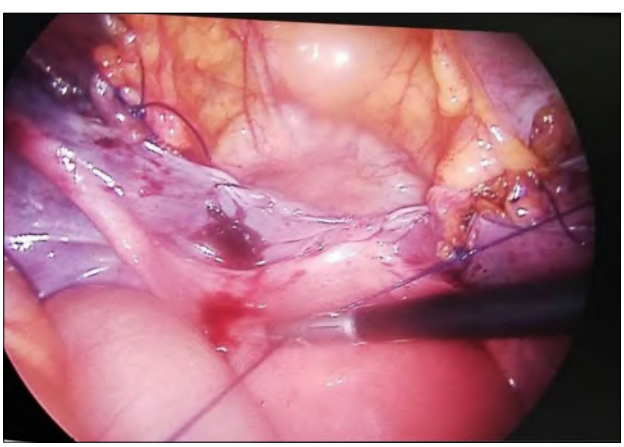


Figure 2. Closing the peritoneal layer.

Statistical analysis

We performed all the statistical analyses using the SPSS software (version 26.0; SPSS Inc., Chicago, Illinois, United States). Demographic data were calculated using descriptive statistics. Means and standard deviations were used to describe the data. The Kolmogorov-Smirnov test was used to verify whether an assumption of normal distribution of variables could be made. Paired t tests were used to compare P-QOL and FSFI scores before and after the pectopexy.

RESULTS

The mean age, parity and length of follow-up of the patients included in the study were 36.08 ± 9.04 years, 4.00 ± 1.86 and 28.88 ± 5.88 months, respectively (**Table 1**). The duration of surgery (mean ± standard deviation, SD) was 71.34 ± 18.33 minutes, while the mean blood loss was 94.00 ± 74.36 ml. Except for three patients, all the cases were stages 2 and 3, and the most common additional procedure was anterior colporrhaphy, which was performed in 45.7% of all the cases (**Table 2**).

In the postoperative period, de novo rectocele was found in three patients (8.6%); and de novo cystocele, in two patients (5.7%). Only one patient (2.9%) had complications, namely urinary infection, de novo stress urinary incontinence, relapse, de novo urgency and de novo constipation (**Table 3**).

All the FSFI and P-QOL scores were found to have become statistically significantly improved in the postoperative period ($P < 0.001$ for all scores of both FSFI and P-QOL). In addition, the total FSFI score was 28.47 ± 2.40 in the postoperative period, which exceeded the cutoff score of 26.5 (**Tables 4** and **5**).

Table 1. Demographic and clinical characteristics of the patients

Characteristics	(Mean ± standard deviation)
Age (years)	36.08 ± 9.04
Parity	4.00 ± 1.86
Length of follow-up (months)	28.88 ± 5.88

Table 2. Clinical characteristics of the subjects included in the study

Characteristics	
Duration of surgery (min), mean ± SD	71.34 ± 18.33
Blood loss (ml), mean ± SD	94.00 ± 74.36
Preoperative POP-Q, n (%)	
Stage 2	16 (45.7)
Stage 3	16 (45.7)
Stage 4	3 (8.60)
Additional procedures, n (%)	
Anterior colporrhaphy	16 (45.7)
Posterior colporrhaphy	9 (25.7)
Sling operation	7 (20.0)
Tubal ligation	3 (8.6)

POP-Q = pelvic organ prolapse quantification system; min = minute; ml = milliliter; SD = standard deviation.

DISCUSSION

In this study, we investigated at the mid-term follow-up after laparoscopic pectopexy surgery whether this procedure improved the patients' quality of life and sexual function; and determined the reliability, applicability and effectiveness of the surgery. We detected that all the FSFI and P-QOL scores of the patients included in the study became statistically significantly improved in the postoperative period.

Table 3. Complications observed in patients in the postoperative period

Characteristics	n (%)
Urinary infection	1 (2.9)
De novo stress urinary incontinence	1 (2.9)
Relapse	1 (2.9)
De novo urgency	1 (2.9)
De novo cystocele	2 (5.7)
De novo rectocele	3 (8.6)
De novo constipation	1 (2.9)

Table 4. Female sexual function index (FSFI) scores

Characteristics	Preoperative (Mean ± SD)	Postoperative (Mean ± SD)	Significant (P-value)
Desire	2.69 ± 0.87	4.83 ± 0.62	< 0.001
Arousal	2.82 ± 1.12	4.90 ± 0.63	< 0.001
Lubrication	2.70 ± 0.95	5.00 ± 0.40	< 0.001
Orgasm	2.44 ± 0.93	4.52 ± 0.43	< 0.001
Satisfaction	3.02 ± 0.64	4.54 ± 0.69	< 0.001
Pain	3.47 ± 0.50	4.66 ± 0.69	< 0.001
Total score	16.95 ± 4.45	28.47 ± 2.40	< 0.001

SD = standard deviation.

Table 5. Prolapse Quality of Life (P-QOL) scores observed in the patients included in the study

Characteristics	Preoperative Mean ± SD	Postoperative Mean ± SD	Significant P-value
GHP	5.94 ± 0.58	3.35 ± 0.37	< 0.001
PI	23.68 ± 4.65	8.00 ± 2.75	< 0.001
RL	3.16 ± 0.86	1.82 ± 1.42	< 0.001
PL	4.50 ± 1.45	1.80 ± 0.86	< 0.001
SL	3.51 ± 0.71	1.39 ± 0.70	< 0.001
PR	6.20 ± 1.78	1.79 ± 1.18	< 0.001
EM	6.25 ± 1.47	2.90 ± 0.96	< 0.001
SE	2.70 ± 0.43	1.50 ± 0.80	< 0.001
SM	6.43 ± 1.14	2.04 ± 0.93	< 0.001
GS	62.41 ± 12.25	24.62 ± 7.04	< 0.001

SD = standard deviation; GHP = general health perceptions; PI = prolapse impact; RL = role limitations; PL = physical limitations; SL = social limitations; PR = personal relationships; EM = emotions; SE = sleep/energy; SM = severity measurements; GS = general score.

Laparoscopic pectopexy is a new type of endoscopic prolapse surgery. Both abdominal and laparoscopic sacrocolpopexy for apical prolapse surgery have been reported to be associated with excellent anatomical and functional outcomes over the long term.[8–10] However, potential problems may be observed, including pelvic outlet stenosis, hypogastric nerve damage, sigmoid colon damage, ureter damage, osteomyelitis and sacrohysteropexy. As the lateral parts of the iliopectineal ligament are used in mesh fixation in pectopexy, fewer long-term problems are expected.[11] In addition, pelvic outlet stenosis, ureteral and hypogastric nerve damage and de novo constipation are not expected with this method.

In a previous study, de novo constipation was detected in the pectopexy group, while constipation was found in 19.5% of the patients in the sacropexy group. In that study, no statistically significant difference was found between the pectopexy and sacropexy groups in terms of the incidence of de novo rectocele (9.5% versus 9.8%, respectively).[12] Similarly to the reason for the low de novo constipation rate in our study, the possible reason for the absence of de novo constipation in that study may have been the absence of pelvic outlet stenosis and hypogastric nerve damage. Pregnancy does not affect the success of pectopexy, which is thus a safe method for women who desire fertility.[13]

Pectopexy may be protective against de novo anterior and lateral defects owing to the lateral location of the mesh.[12] Similarly, we found a low incidence rate for de novo cystocele in our study (5.7%) and did not observe any de novo lateral defects. Although many studies have reported high incidence rates (> 25%) of de novo stress urinary incontinence (SUI) after sacrocolpopexy, we found that the incidence rate of de novo SUI was low (2.9%) in our study.[14–16] It has been have reported that pectopexy is not associated with increased intraoperative risk.[11] Similarly, in our study, no intraoperative complications developed, except in one patient who underwent laparotomy due to intraoperative bleeding.

Similar to the low recurrence rates reported in cases of laparoscopic sacrocolpopexy, recurrence was only found in one patient at our midterm follow-up.[14,17] Use of a mesh in surgical treatments for cystocele and POP may cause dyspareunia and worsen sexual function.[18,19] It has been suggested in some studies that patients' quality of life and sexual function rarely improve after POP surgery.[18,20] However, we detected that the quality of life and sexual function of our patients improved.

Unlike in a previous study in which the mesh was fixed to both iliopectineal ligaments with two stitches, we provided fixation to each ligament with one suture. We observed that this could be an effective, safe and applicable method.[5]

The limitations of our study were that it was conducted at a single center and that the number of cases was small. On the other hand, the strength of our study was that laparoscopic pectopexy was presented as an easily applicable, effective and safe procedure that at the midterm follow-up can be seen to have improved the quality of life and sexual function of patients with POP.

CONCLUSION

In this study, we detected at the midterm follow-up that the quality of life and sexual function of patients who underwent laparoscopic pectopexy were statistically improved. In addition, laparoscopic pectopexy was found to be a viable, effective and safe procedure. Therefore, it can be considered to be an alternative treatment method for sacropexy in suitable patients with POP.

REFERENCES

1. Masenga GG, Shayo BC, Rasch V. Prevalence and risk factors for pelvic organ prolapse in Kilimanjaro, Tanzania: A population-based study in Tanzanian rural community. PLoS One. 2018;13(4):e0195910. PMID: 29694427; https://doi.org/10.1371/journal.pone.0195910.
2. Beer M, Kuhn A. Surgical techniques for vault prolapse: a review of the literature. Eur J Obstet Gynecol Reprod Biol. 2005;119(2):144-55. PMID: 15808370; https://doi.org/10.1016/j.ejogrb.2004.06.042.
3. Nygaard IE, McCreery R, Brubaker L, et al. Abdominal sacrocolpopexy: a comprehensive review. Obstet Gynecol. 2004;104(4):805-23. PMID: 15458906; https://doi.org/10.1097/01.AOG.0000139514.90897.07.
4. Maher C, Feiner B, Baessler K, Schmid C. Surgical management of pelvic organ prolapse in women. Cochrane Database Syst Rev. 2013(4):CD004014. PMID: 23633316; https://doi.org/10.1002/14651858.CD004014.pub5.
5. Banerjee C, Noé KG. Laparoscopic pectopexy: a new technique of prolapse surgery for obese patients. Arch Gynecol Obstet. 2011;284(3):631-35. PMID: 20941503; https://doi.org/10.1007/s00404-010-1687-7.
6. Rosen R, Brown C, Heiman J, et al. The Female Sexual Function Index (FSFI): a multidimensional self-report instrument for the assessment of female sexual function. J Sex Marital Ther. 2000;26(2):191-208. PMID: 10782451; https://doi.org/10.1080/009262300278597.
7. Wiegel M, Meston C, Rosen R. The female sexual function index (FSFI): cross-validation and development of clinical cutoff scores. J Sex Marital Ther. 2005;31(1):1-20. PMID: 15841702; https://doi.org/10.1080/00926230590475206.
8. Beer M, Kuhn A. Surgical techniques for vault prolapse: a review of the literature. Eur J Obstet Gynecol Reprod Biol. 2005;119(2):144-55. PMID: 15808370; https://doi.org/10.1016/j.ejogrb.2004.06.042.
9. Nygaard IE, McCreery R, Brubaker L, et al. Abdominal sacrocolpopexy: a comprehensive review. Obstet Gynecol. 2004;104(4):805-23. PMID: 15458906; https://doi.org/10.1097/01.AOG.0000139514.90897.07.
10. Sarlos D, Kots LV, Ryu G, Schaer G. Long-term follow-up of laparoscopic sacrocolpopexy. Int Urogynecol J. 2014;25(9):1207-12. PMID: 24700356; https://doi.org/10.1007/s00192-014-2369-y.
11. Noé KG, Spüntrup C, Anapolski M. Laparoscopic pectopexy: a randomised comparative clinical trial of standard laparoscopic sacral

colpo-cervicopexy to the new laparoscopic pectopexy. Short-term postoperative results. Arch Gynecol Obstet. 2013;287(2):275-80. PMID: 22945837; https://doi.org/10.1007/s00404-012-2536-7.

12. Noé KG, Schiermeier S, Alkatout I, Anapolski M. Laparoscopic pectopexy: a prospective, randomized, comparative clinical trial of standard laparoscopic sacral colpocervicopexy with the new laparoscopic pectopexy-postoperative results and intermediate-term follow-up in a pilot study. J Endourol. 2015;29(2):210-5. PMID: 25350228; https://doi.org/10.1089/end.2014.0413.
13. Bagli I, Tahaoglu AE. Pregnancy outcomes after laparoscopic pectopexy surgery: A case series. J Obstet Gynaecol Res. 2020;46(8):1364-1369. PMID: 32483826; https://doi.org/10.1111/jog.14337.
14. Sarlos D, Brandner S, Kots LV, Gygax N, Schaer G. Laparoscopic sacrocolpopexy for uterine and post-hysterectomy prolapse: anatomical results, quality of life and perioperative outcome-a prospective study with 101 cases. Int Urogynecol J Pelvic Floor Dysfunct. 2008;19(10):1415-22. PMID: 18536861; https://doi.org/10.1007/s00192-008-0657-0.
15. Leruth J, Fillet M, Waltregny D. Incidence and risk factors of postoperative stress urinary incontinence following laparoscopic sacrocolpopexy in patients with negative preoperative prolapse reduction stress testing. Int Urogynecol J. 2013;24(3):485-91. PMID: 22825418; https://doi.org/10.1007/s00192-012-1888-7.
16. Chan CMY, Liang HHX, Go WW, To WW, Mok KM. Laparoscopic sacrocolpopexy for uterine and posthysterectomy prolapse: Anatomical and functional outcomes. Hong Kong Med J. 2011;17(4):301-5. PMID: 21813899.
17. Bojahr B, Tchartchian G, Waldschmidt M, Schollmeyer T, De Wilde RL. Laparoscopic sacropexy: a retrospective analysis of perioperative complications and anatomical outcomes. JSLS. 2012;16(3):428-36. PMID: 23318069; https://doi.org/10.4293/108680812X13462882736132.
18. Liang CC, Lin YH, Chang YL, Chang SD. Urodynamic and clinical effects of transvaginal mesh repair for severe cystocele with and without urinary incontinence. Int J Gynecol Obstet. 2011;112(3):182-6. PMID: 21238966; https://doi.org/10.1016/j.ijgo.2010.09.011.
19. Vitale SG, Caruso S, Rapisarda AMC, et al. Biocompatible porcine dermis graft to treat severe cystocele: impact on quality of life and sexuality. Arch Gynecol Obstet. 2016;293(1):125-131. PMID: 26193956; https://doi.org/10.1007/s00404-015-3820-0.
20. Helström L, Nilsson B. Impact of vaginal surgery on sexuality and quality of life in women with urinary incontinence or genital descensus. Acta Obstet Gynecol Scand. 2005;84(1):79-84. PMID: 15603572; https://doi.org/10.1111/j.0001-6349.2005.00668.x.

Authors' contributions: Erdem, S: conceptualization (lead), data curation (lead), formal analysis (lead), funding acquisition (lead), investigation (lead), methodology (lead), project administration (lead), resources (lead), software (lead), supervision (lead), validation (lead), visualization (lead), writing-original draft (lead) and writing-review and editing (lead)

Sources of funding: None
Conflicts of interest: None

Date of first submission: June 06, 2021
Last received: September 12, 2021
Accepted: November 17, 2021

Address for correspondence:
Selami Erdem
Department of Gynecology and Obstetrics, Özel Bağlar Hastanesi, 21080 Diyarbakır, Turkey
Tel. +90 5535967692
E-mail: serdem2109@gmail.com

https://doi.org/10.1590/1516-3180.2021.0522.R1.22112021

Severe oral mucositis relating to pain and worse oral condition among patients with solid tumors undergoing treatment with FOLFIRI and 5-FU: a retrospective study

Laura Costa de Almeida[I], Bernardo da Fonseca Orcina[II], Aloizio Premoli Maciel[III], Dayanne dos Santos[IV], Brena Rodrigues Manzano[V], Paulo Sérgio da Silva Santos[VI]

Faculdade de Odontologia de Bauru (FOB), Universidade de Sao Paulo (USP), Bauru (SP), Brazil

[I]DDS. Dental Surgeon, Private Practice, Bauru (SP), Brazil.
https://orcid.org/0000-0002-8403-5141

[II]DDS. Master's Student, Department of Surgery, Stomatology, Pathology and Radiology, Faculdade de Odontologia de Bauru (FOB), Universidade de Sao Paulo (USP), Bauru (SP), Brazil.
https://orcid.org/0000-0003-3367-483X

[III]DDS, MSc. Doctoral Student, Department of Surgery, Stomatology, Pathology and Radiology, Faculdade de Odontologia de Bauru (FOB), Universidade de Sao Paulo (USP), Bauru (SP), Brazil.
https://orcid.org/0000-0002-7062-0630

[IV]DDS. Master's Student, Department of Surgery, Stomatology, Pathology and Radiology, Faculdade de Odontologia de Bauru (FOB), Universidade de Sao Paulo (USP), Bauru (SP), Brazil.
https://orcid.org/0000-0002-1899-3499

[V]DDS, MSc. Doctoral Student, Department of Surgery, Stomatology, Pathology and Radiology, Faculdade de Odontologia de Bauru (FOB), Universidade de Sao Paulo (USP), Bauru (SP), Brazil.
https://orcid.org/0000-0003-0412-2243

[VI]DDS, PhD. Associate Professor, Department of Surgery, Stomatology, Pathology and Radiology, Faculdade de Odontologia de Bauru (FOB), Universidade de Sao Paulo (USP), Bauru (SP), Brazil.
https://orcid.org/0000-0002-0674-3759

KEYWORDS (MeSH terms):
Stomatitis.
Dental service, hospital.
Drug therapy.
Oral health.
Oral medicine.
Pathology, oral.

AUTHORS' KEYWORDS:
Chemotherapy.
Oral mucositis.
Stomatology.

ABSTRACT

BACKGROUND: There is a need for studies that correlate the severity of oral mucositis (OM) with chemotherapy protocols, transient myelosuppression and oral health.

OBJECTIVE: To analyze the severity of OM among individuals with solid tumors during hospitalization and its correlation with the type of chemotherapy, myelosuppression and oral health condition.

DESIGN AND SETTING: Retrospective study at a public hospital in Bauru, state of São Paulo, Brazil, that is a regional referral center.

METHODS: Individuals diagnosed with solid malignant tumors who received chemotherapy during hospitalization for completion of the antineoplastic treatment cycle or who presented complications resulting from this were assessed.

RESULTS: Twenty-eight individuals (24.3%) manifested some degree of OM. The most prevalent degrees of OM according to the World Health Organization (WHO) and modified WHO classification were grades 2 (11.3%) and 5 (4.3%), respectively. It was observed that the higher the OM-WHO ($P < 0.001$; $r = 0.306$) and modified OM-WHO ($P < 0.001$; $r = 0.295$) classifications were, the greater the oral pain reported by the individuals was. Presence of mucositis in the upper lip and buccal mucosa contributed to increased severity of OM and worsening of swallowing during hospitalization. Thus, severe OM was associated with use of the FOLFIRI protocol (folinic acid, fluorouracil and irinotecan).

CONCLUSION: Individuals with tumors who presented severe OM had greater severity of oral pain and worse oral health. Use of the FOLFIRI protocol was associated with higher prevalence of severe OM, while use of 5-fluorouracil (5-FU) was correlated with worse oral condition.

INTRODUCTION

Oral mucositis (OM) is an inflammatory process caused by the cytotoxic effect of antineoplastic treatments (AnTs). This adverse effect has a large impact on individuals following certain chemotherapy protocols for treatment of solid tumors, such as cytarabine, 5-fluorouracil (5-FU) and alkylating and platinum derivatives.[1,2] During these chemotherapy protocols, OM affects both the mouth and the entire gastrointestinal tract.[3]

OM occurs mainly in the mucosa and is not keratinized in the form of erythematous lesions and/or ulcers. It may or may not be associated with edema, burning and intense pain. These signs and symptoms significantly impair the quality of life of individuals under hospitalization and affect speech, swallowing and chewing. Therefore, worse nutritional status often indicates enteral or parenteral nutrition, use of systemic analgesics, increased inpatient hospital time and interruption of AnT.[1,4,5]

Certain forms of chemotherapy, besides causing OM, lead to transient myelosuppression and blood pancytopenia. Thus, aside from direct health-related problems, these cause decreased leukocyte counts and are associated with a high risk of opportunistic infections and exacerbation of infections.[6,7]

In the literature, few studies have correlated the severity of OM with the chemotherapy protocols used, its relationship with transient myelosuppression or the oral health of individuals under hospitalization.[1,7-9] In addition, there is a lack of studies comparing the severity of OM with the use of oral health indicators and pain assessment by means of an OM-related visual analogue scale (VAS). Moreover, the relationship of these variables with transient myelosuppression has not been assessed.

OBJECTIVE

The aim of this study was to assess the severity of OM in relation to the type of chemotherapy, oral health condition and myelosuppression among individuals with solid tumors who had been hospitalized for treatment.

METHODS

Characterization of the study and sample, and ethical matters

This retrospective cross-sectional study included individuals diagnosed with solid malignant tumors who were undergoing chemotherapy and who had been hospitalized for a single cycle or who had been hospitalized due to oral complications from the previous chemotherapy cycle utilized, at a public hospital between 2015 and 2017.

Patients for whom insufficient data were available in the electronic medical records or who were not receiving dental care were excluded.

This study was approved by the Human Research Ethics Committee at the institution where the research was carried out (registration no. CAAE 74449317.1.0000.5417; September 11, 2017).

Data collected and study group characteristics

The following data on demographic and treatment characteristics were collected from the hospital's electronic medical records: age, sex, diagnosis of cancer, evolution of cancer, comorbidities, complete blood count and chemotherapy regimen. These regimens included FOLFOX (oxaliplatin + calcium folinate + fluorouracil), TAXOL (paclitaxel), MTX (methotrexate), Gemzar, FOLFIRI (folinic acid, fluorouracil and irinotecan), CARBOTAXOL (carboplatin + paclitaxel), 5-FU (fluorouracil) and others (vinorelbine, ifosfamide, etoposide, cisplatin, capecitabin, bicalutamide, vincristine, vinblastine, irinotecan, cyclophosphamide and doxorubicin).

The following data from the dental evaluation were collected: oral regions with OM, classification of the OM and oral health of the individuals during hospitalization.

Individuals with OM were evaluated with regard to the number of oral regions affected, presence of erythema and ulcers, duration of manifested OM and oral pain (assessed using a VAS).[10] OM was classified in accordance with the World Health Organization categories (OM-WHO) and the modified WHO scale (mOM-WHO).[11,12] To assess the oral health involvement of the individuals included in this study, we used the Bedside Oral Examination (BOE), which classifies the oral condition as normal oral condition (score of 8 to 10), moderately impaired oral condition (score of 11 to 14) or very impaired oral condition (score of 15 to 24).[13]

All individuals seen by an oncologist were also evaluated with regard to their need for dental evaluation. Through this perception, consultations were requested by the dental team during these patients' hospitalization. All individuals examined by dentists were under dental care during hospitalization and received the same treatment for OM.

The therapeutic strategies used in relation to OM depended on the degree of OM and its associated comorbidities, such as hypertension, diabetes and other conditions. For grades 1 and 2, low-power laser therapy at 660 nm (100 mW) with E = 2 J, at a dose of 20 J/cm^2, was used. For grades 3 and 4, the same laser therapy dose with benzydamine hydrochloride (1.5 mg/ml) was used. In cases in which a focus of infection was found associated with OM grade 1 and 2, 0.12% chlorhexidine without alcohol administered every 12 hours was prescribed; and in cases of OM grades 3 and 4, this topical antibiotic was indicated for administration between meals. In the presence of labial dryness in cases of OM grades 1 and 2, *Chamomilla recutita* Rauschert extract (100 mg) was applied; in cases of OM grades 3 and 4, it was applied after laser therapy and before intraoral manipulation.

Transient myelosuppression was evaluated by analyzing the complete blood count performed at the time of the most severe OM. Red blood cell, leukocyte, neutrophil and platelet counts were also evaluated. The degree of myelosuppression and the respective ratings and references for men and women are shown in **Table 1**.

Statistical analysis

To analyze the data distribution, the Shapiro-Wilk test was applied. Descriptive analysis was performed based on the prevalence and

Table 1. Reference values for transient myelosuppression

Anemia	Hemoglobin Men	Hemoglobin Women	Thrombocytopenia	Platelets
Grade I	≥ 13	≥ 12	Grade I	≥ 151,000
Grade II	10.1-12.9	10.1-11.9	Grade II	81000-150,000
Grade III	9.1-10	9.1-10	Grade III	51,000-80,000
Grade IV	7.1-9	7.1-9	Grade IV	31,000-50,000
Grade V	0-7	0-7	Grade V	0-30,000
Leukopenia	**Leukocytes**		**Neutropenia**	**Neutrophils**
Grade I	≥ 3,501		Grade I	≥ 2,001
Grade II	2,001-3,500		Grade II	1,001-2,000
Grade III	1,001-2,000		Grade III	501-1,000
Grade IV	0-1,000		Grade IV	0-500

average. Comparisons between variables were analyzed using the Mann-Whitney and Kruskal-Wallis tests, and correlations were performed using Spearman's correlation. The level of significance was set at 5% ($P < 0.005$).

RESULTS

Patients' demographic data and characteristics

A total of 115 medical records were evaluated. These individuals had a mean age of 47.5 years (range: 2 to 90 years) and comprised 63 males (54.8%) and 52 females (45.2%). Gastric tumors (33.9%) and osteosarcoma (15.7%) were the most prevalent conditions, and the most prevalent chemotherapy protocols were MTX (12.2%) and FOLFOX (12.2%). The prevalences of other tumors and certain chemotherapy protocols are shown in **Tables 2 and 3**, respectively.

No therapeutic measures that could potentiate OM were used. Out of the 115 patients, 24 underwent associated radiotherapy treatment. Of these, only one patient underwent radiotherapy in the head and neck region, while the others had indications for the lower respiratory tract, prostate, uterus, breast, pelvis and digestive tract regions.

Oral mucositis

Regarding OM, 28 individuals (24.3%) presented with some clinical manifestations of OM. The most prevalent degrees of OM were degree 2 (11.3%) according to the OM-WHO classification and grades 1 and 5 according to mOM-WHO (4.3%) (**Table 4**).

It was observed that the regions most affected by OM (**Table 5**) were the tongue, lower lip, upper lip and buccal mucosa in equal proportions (64.3%). Moreover, OM was manifested in these regions primarily when the chemotherapy protocols used were FOLFIRI, FOLFOX, MTX and gemcitabine hydrochloride. Higher degrees of OM-WHO ($P = 0.009$) and mOM-WHO ($P = 0.004$) were observed when the FOLFIRI protocol was used for AnT. **Figure 1** shows the relationship between chemotherapy protocols and the prevalence of OM.

With regard to the ratio between OM and pain, the higher the degrees of OM-WHO ($P < 0.001$; $r = 0.306$) and mOM-WHO were ($P < 0.001$; $r = 0.295$), the higher the level of mouth pain reported by individuals was. In addition, manifestation of OM on the upper lip ($P < 0.044$) and jugal mucosa ($P = 0.005$) contributed to increased severity of OM-WHO.

Mouth condition

In the BOE assessment, 58 individuals (50.4%) had a normal oral condition, 53 (46.3%) had a moderately impaired oral condition and only 4 (3.5%) had a very impaired oral condition.

By analyzing the relationship between oral conditions and OM, it was observed that worse oral condition was significantly associated with greater degrees of OM-WHO ($P = 0.025$; $r = 0.208$) and mOM-WHO ($P < 0.001$; $r = 0.228$).

The oral condition of individuals who received certain types of chemotherapy was significantly correlated with more severe manifestations of OM-WHO ($P = 0.025$; $r = 0.208$) and mOM-WHO

Table 2. Prevalence of solid tumors (n = 115)

Diagnosis	n (%)
Gastric tumors	39 (33.9%)
Osteosarcoma	18 (15.7%)
Breast cancer	15 (13.01%)
Lung cancer	12 (10.4%)
Urinary tract cancer	11 (9.6%)
Gynecological cancer	6 (5.2%)
Tumors of the nervous system	4 (3.5%)
Others	10 (8.7%)

Table 3. Prevalence of chemotherapy protocols (n = 115)

CT protocol	n (%)
MTX	16 (13.9%)
FOLFOX	14 (12.2%)
Gemcitabine hydrochloride	13 (11.3%)
FOLFIRI	10 (8.7%)
Taxol + Carbo	7 (6.1%)
5-FU	6 (5.2%)
Others	49 (42.6%)

MTX = methotrexate; FOLFOX = oxaliplatin + calcium folinate + fluorouracil; gemcitabine hydrochloride = gemcitabine + diphenhydramine; FOLFIRI = irinotecan + fluorouracil + calcium folinate; Taxol + Carbo = carboplatin + paclitaxel; 5-FU = fluorouracil.

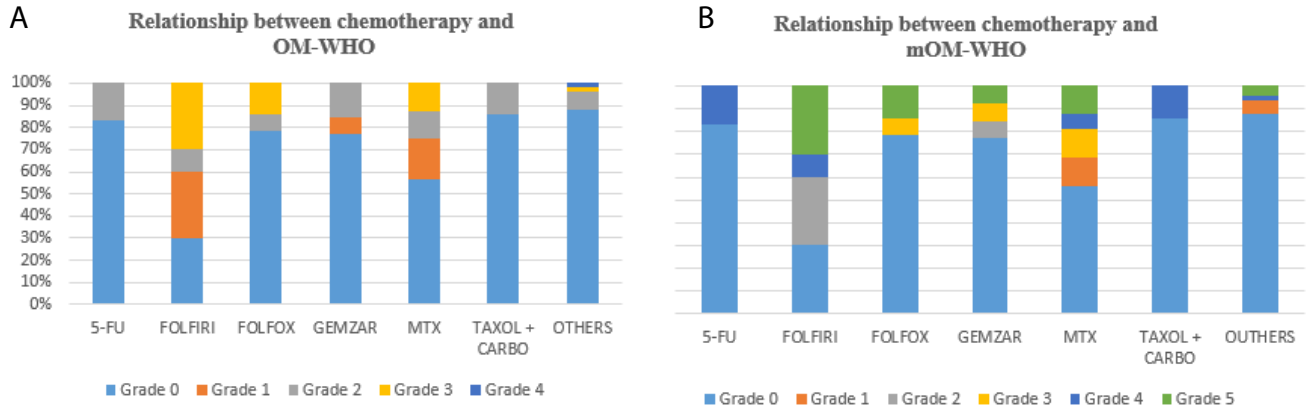
Table 4. Prevalence severity of OM-WHO and mOM-WHO

Degree	WHO mucositis	Modified WHO mucositis
0	87 (75.6%)	87 (75.6%)
1	7 (6.1%)	5 (4.3%)
2	13 (11.3%)	4 (3.5%)
3	7 (6.1%)	4 (3.5%)
4	1 (0.9%)	5 (4.3%)
5	NA	10 (8.7%)

OM-WHO = oral mucositis according to the World Health Organization classification; mOM-WHO = oral mucositis according to the modified World Health Organization classification; NA = not applicable.

Table 5. Prevalence of oral regions with oral mucositis

Oral regions	n (%)
Language	18 (64.3%)
Bottom lip	18 (64.3%)
Jugal mucosa	18 (64.3%)
Upper lip	14 (50%)
Soft palate	5 (17.8%)
Hard palate	3 (10.7%)
Gum	2 (7.1%)
Alveolar mucosa	2 (7.1%)
Oral floor	1 (3.6%)
Throat	1 (3.6%)
Retromolar region	0 (0%)



OM-WHO = oral mucositis according to the World Health Organization; mOM-WHO = oral mucositis according to the modified World Health Organization classification; 5-FU = fluorouracil; FOLFIRI = folinic acid, fluorouracil and irinotecan; FOLFOX = oxaliplatin + calcium folinate + fluorouracil; MTX = methotrexate; Taxol + Carbo = carboplatin + paclitaxel; Others = vinorelbine, ifosfamide, etoposide, cisplatin, capecitabin, bicalutamide, vincristine, vinblastine, irinotecan, cyclophosphamide and doxorubicin.

Figure 1. Relationship between chemotherapy protocols and OM prevalence on the OM-WHO and mOM-WHO scales.

($P < 0.001$; $r = 0.228$). Individuals under the 5-FU regimen presented worsening of their oral condition (BOE) ($P = 0.038$), especially when OM was present in the lips, tongue and gums. **Figure 2** shows the relationship between chemotherapy protocols and VAS and BOE.

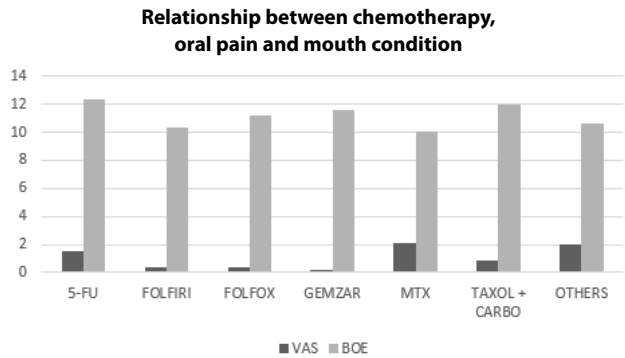
Evaluation of myelosuppression

Complete blood count examinations revealed that 104 patients (90.44%) had anemia, 23 (19.93%) had thrombocytopenia, 30 (26.09%) had leukocytosis and 32 (27.83%) had neutropenia (**Table 6**). However, there were no significant correlations between specific chemotherapy protocols and the severity of OM-WHO and mOM-WHO. Nor were there any statistically significant correlations between chemotherapy protocols and myelosuppression reference values ($P > 0.05$). **Figure 3** shows four graphs correlating the chemotherapy protocols with anemia, thrombocytopenia, leukopenia and neutropenia.

DISCUSSION

Individuals under AnT for solid tumors have risk factors that contribute to manifestation of severe OM. These factors may be related to systemic conditions, such as certain types of chemotherapy (CT); or to local conditions, such as damage to the oral cavity. In the present study, a relationship was observed between damage to the oral cavity and manifestation of severe OM.[14,15]

Due to the intense discomfort, buccal pain and significant worsening of oral condition in relation to OM among individuals under hospitalization for AnT, it is important and necessary to trace individuals who are at higher risk of OM.[16]



VAS = visual analogue scale; BOE = Bedside Oral Examination; 5-FU = fluorouracil; FOLFIRI = folinic acid, fluorouracil and irinotecan; FOLFOX = oxaliplatin + calcium folinate + fluorouracil; MTX = methotrexate; Taxol + Carbo = carboplatin + paclitaxel; Others = vinorelbine, ifosfamide, etoposide, cisplatin, capecitabin, bicalutamide, vincristine, vinblastine, irinotecan, cyclophosphamide and doxorubicin.

Figure 2. Relationship between chemotherapy protocols and oral pain (from visual analogue scale, VAS) and oral mouth condition (from bedside oral examination, BOE).

In this study, OM was observed in 24.3% of the individuals. This proportion was similar to what was found in other studies that evaluated OM in individuals who underwent certain types of chemotherapy for solid tumors. In one such study, the prevalence of OM was 24% among individuals who underwent a second cycle of certain types of chemotherapy; and in another, it was 31% under the same treatment.[17,18]

When 5-FU is used in protocols such as TPF, CAF or FOLFIRI, the incidence rate of OM can reach more than 15%, causing

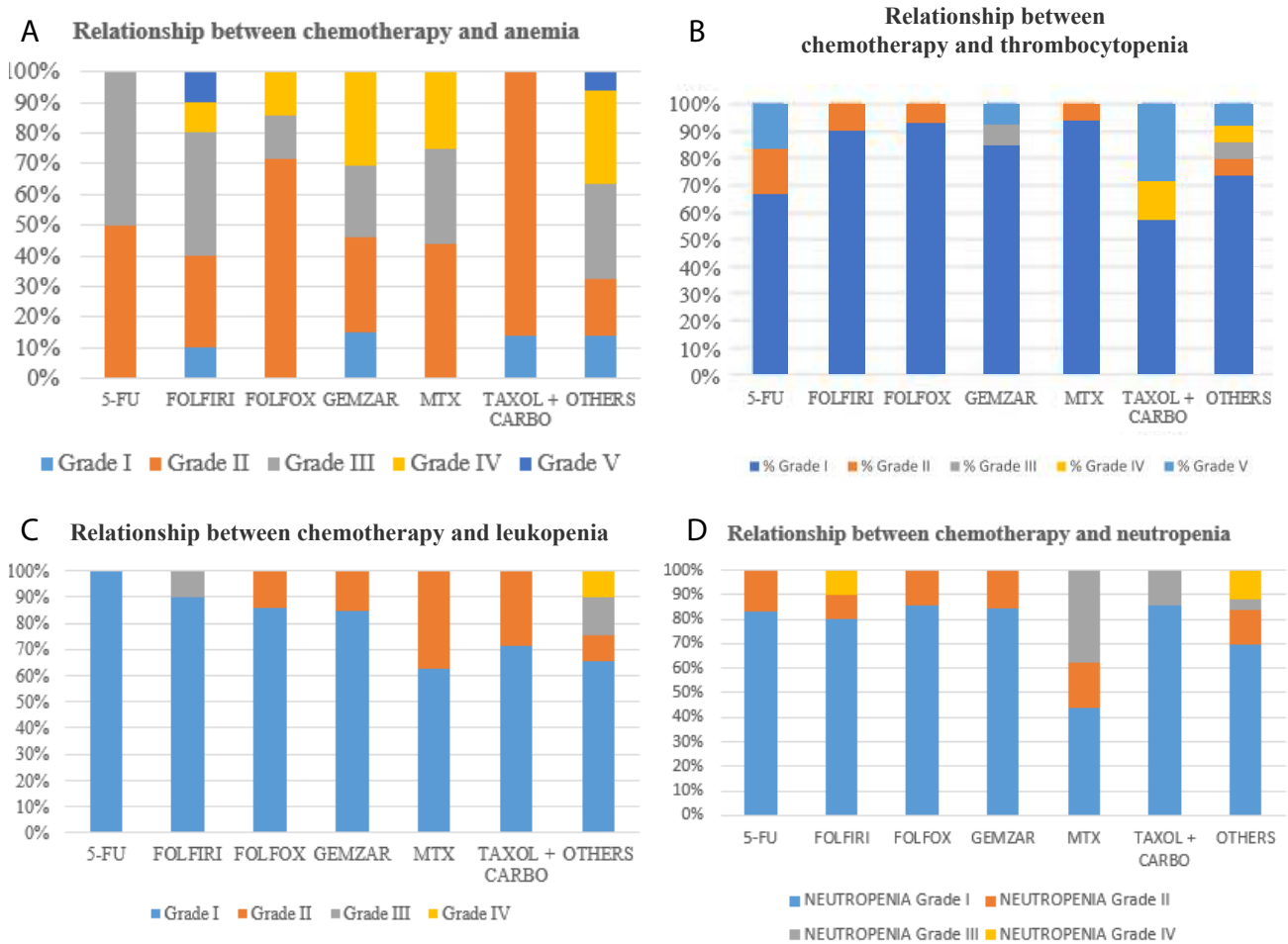
OM-WHO grade 3-4. That incidence rate was similar to the result from our study (16.7%), but the severity differed according to the scale: OM-WHO scale, grade 2, versus mOM-WHO scale, grade 4.[19]

Table 6. Prevalence of myelosuppression (n = 115)

Anemia	n (%)	Thrombocytopenia	n (%)
Grade 0	11 (9.56%)	Grade 0	92 (80.0%)
Grade 1	42 (36.52%)	Grade 1	7 (6.09%)
Grade 2	32 (27.83%)	Grade 2	4 (3.48%)
Grade 3	26 (22.61%)	Grade 3	4 (3.48%)
Grade 4	4 (3.48%)	Grade 4	8 (6.96%)
Leukopenia		**Neutropenia**	
Grade 0	85 (73.91%)	Grade 0	83 (72.17%)
Grade 1	17 (14.78%)	Grade 1	16 (13.91%)
Grade 2	8 (6.96%)	Grade 2	9 (7.83%)
Grade 3	5 (4.35%)	Grade 3	7 (6.09%)

The use of 5-FU worsens oral health, especially in the lips, tongue and gums, considering that these are the mouth regions most affected. When 5-FU was used, the risk of developing severe OM-WHO was found to be 15% higher, consequently worsening the patients' swallowing capacity.[20] The oral health of patients under 5-FU treatment can become worse because, aside from the oral pain caused by OM, these individuals also experience constant nausea and vomiting.[21] In addition, hyposalivation in individuals under 5-FU treatment increases the incidence of mucositis, which suggests that this is a risk factor for OM.[22-25]

Another important symptom, which was also observed in this study, was oral pain. This is a fundamental issue that interferes with the quality of life of individuals with cancer, and it is directly related to severe OM.[16] It has been observed in other studies that patients on AnT for solid tumors who develop OM have worse quality of



OM-WHO = oral mucositis according to the World Health Organization; mOM-WHO = oral mucositis according to the modified World Health Organization classification; 5-FU = fluorouracil; FOLFIRI = folinic acid, fluorouracil and irinotecan; FOLFOX = oxaliplatin + calcium folinate + fluorouracil; MTX = methotrexate; Taxol + Carbo = carboplatin + paclitaxel; Others = vinorelbine, ifosfamide, etoposide, cisplatin, capecitabin, bicalutamide, vincristine, vinblastine, irinotecan, cyclophosphamide and doxorubicin

Figure 3. Relationship between chemotherapy protocols and transient myelosuppression.

life than those without OM, and that this manifestation predisposes them to other side effects such as pain and poor physical and emotional wellbeing, which negatively impacts their quality of life.[17]

Understanding the risk factors relating to OM and the oral conditions that can compromise quality of life and interrupt AnT is necessary. Oral condition is directly related to the severity and repair of OM.[15,26] In previous studies, worse oral condition was related to greater severity of OM. However, those studies did not find any significant relationship between dental and prosthetic conditions and the severity of OM, as found in our study. One possible explanation for this is that although the visible plaque index and gingival plaque index are directly related to the incidence of OM, the ratio of lost, decayed or restored teeth was not determined by those authors.[26]

There is evidence that neutropenic patients are between three and as much as 7.5 times more likely to develop OM than are patients without neutropenia.[27,28] In our study, we analyzed the correlation between the severity of OM and use of certain chemotherapy protocols and transient myelosuppression, but no significant result was found. In a study on oncopediatric patients under hospitalization, a significant relationship was observed, and this was explained by the degree of neutropenia, which was shown to influence the risk of developing OM, and by the difference in the QT protocols applied.[28]

This study brought a lot of relevant information relating to the severity of oral mucositis, with regard to oral pain and chemotherapy protocols for oral health. However, it should be considered that this was a cross-sectional study, consisting of analysis on the medical records of individuals hospitalized under a single cycle, which limited assessment of the cumulative effect of chemotherapy cycles on the severity of oral mucositis. In addition, no data on tumor staging, drug doses used or other drugs used concomitantly that could directly interfere with oral toxicity were collected. Lastly, other limitations of this study that may have confounded the analysis on the results comprised the small sample, wide age range and heterogeneity of the study group.

CONCLUSIONS

Individuals with solid tumors who presented with severe OM had greater severity of oral pain and worse oral health. Use of the FOLFIRI chemotherapy protocol was associated with higher prevalence of severe OM. Individuals who used 5-FU had worse oral condition, mainly with regard to changes to the lips, tongue and gums. Knowledge of chemotherapy protocols helps identify individuals with a greater chance of developing severe OM or with a worse oral condition through use of certain types of chemotherapy during hospitalization. Through screening, it is possible to reduce morbidity and mortality and provide better quality of life for patients with cancer.

REFERENCES

1. Curra M, Soares Junior LAV, Martins MD, Santos PSDS. Chemotherapy protocols and incidence of oral mucositis. An integrative review. Einstein (Sao Paulo). 2018;16(1):eRW4007. PMID: 29694618; https://doi.org/10.1590/s1679-45082018rw4007.
2. Kusial A, Jereczek-Fossa BA, Cichońska D, Alterio D. Oncological-therapy related oral mucositis as an interdisciplinary problem – literature review. Int J Environ Res Public Health. 2020;17(7):2464. PMID: 32260309; https://doi.org/10.3390/ijerph17072464.
3. Villa A, Sonis ST. Mucositis: pathobiology and management. Curr Opin Oncol (Philadelphia). 2015;27(3):159-64. PMID: 25774860; https://doi.org/10.1097/CCO.0000000000000180.
4. Elting LS, Cooksley CD, Chambers MS, Garden AS. Risk, outcomes, and costs of radiation-induced oral mucositis among patients with head-and-neck malignancies. Int J Radiat Oncol Biol Phys (New York). 2007;68(4):1110-20. PMID: 17398022; https://doi.org/10.1016/j.ijrobp.2007.01.053.
5. Lalla RV, Saunders DP, Peterson DE. Chemotherapy or radiation-induced oral mucositis. Dent Clin North Am. 2014;58(2):341-9. PMID: 24655526; https://doi.org/10.1016/j.cden.2013.12.005.
6. Alves FA, Coracin FL, Gasparetto PF, Correa MEP. Oral complications of antineoplastic chemotherapy. JBC J Bras Clin Odontol Integr. 2003;7(40):337-40.
7. Lalla RV, Brennan MT, Gordon SM, et al. Oral Mucositis Due to High-Dose Chemotherapy and/or Head and Neck Radiation Therapy. J Natl Cancer Inst Monogr. 2019;2019(53):lgz011. PMID: 31425601; https://doi.org/10.1093/jncimonographs/lgz011.
8. Barasch A, Peterson DE. Risk factors for ulcerative oral mucositis in cancer patients: unanswered questions. Oral Oncol. 2003;39(2):91-100. PMID: 12509961; https://doi.org/10.1016/s1368-8375(02)00033-7.
9. Damascena LCL, de Lucena NNN, Ribeiro ILA, et al. Severe Oral Mucositis in Pediatric Cancer Patients: Survival Analysis and Predictive Factors. Int J Environ Res Public Health. 2020;17(4):1235. PMID: 32075075; https://doi.org/10.3390/ijerph17041235.
10. Kelly AM. The minimum clinically significant difference in visual analogue scale pain score does not differ with severity of pain. Emerg Med J. 2001;18(3):205-7. PMID: 11354213; https://doi.org/10.1136/emj.18.3.205.
11. World Health Organization. WHO handbook for reporting results of cancer treatment. 48th ed. Geneva: WHO; 1979.
12. Vera-Llonch M, Oster G, Ford CM, Lu J, Sonis S. Oral mucositis and outcomes of autologous hematopoietic stem-cell transplantation following high-dose melphalan conditioning for multiple myeloma. J Support Oncol. 2007;5(5):231-5. PMID: 17564153.
13. Prendergast V, Kleiman C, King M. The Bedside Oral Exam and the Barrow Oral Care Protocol: translating evidence-based oral care into practice. Intensive Crit Care Nurs. 2013;29(5):282-90. PMID: 23702324; https://doi.org/10.1016/j.iccn.2013.04.001.
14. Elting LS, Cooksley C, Chambers M, et al. The burdens of cancer therapy. Clinical and economic outcomes of chemotherapy-induced mucositis. Cancer. 2003;98(7):1531-9. PMID: 14508842; https://doi.org/10.1002/cncr.11671.

15. Santos PS, Coracin FL, Barros JC, et al. Impact of oral care prior to HSCT on the severity and clinical outcomes of oral mucositis. Clin Transplant. 2011;25(2):325-8. PMID: 20482562; https://doi.org/10.1111/j.1399-0012.2010.01283.x.
16. Jehn P, Stier R, Tavassol F, et al. Physical and Psychological Impairments Associated with Mucositis after Oral Cancer Treatment and Their Impact on Quality of Life. Oncol Res Treat. 2019;42(6):342-9. PMID: 30970370; https://doi.org/10.1159/000499720.
17. Kim JW, Cha Y, Kim SJ, et al. Association of oral mucositis with quality of life and symptom clusters in patients with solid tumors receiving chemotherapy. Support Care Cancer. 2012;20(2):395-403. PMID: 21390568; https://doi.org/10.1007/s00520-011-1126-8.
18. Raber-Durlacher JE, Weijl NI, Abu Saris M, et al. Oral mucositis in patients treated with chemotherapy for solid tumors: a retrospective analysis of 150 cases. Support Care Cancer. 2000;8(5):366-71. PMID: 10975685; https://doi.org/10.1007/s005200050004. Erratum in: Support Care Cancer. 2001;9(2):135.
19. Nishimura N, Nakano K, Ueda K, et al. Prospective evaluation of incidence and severity of oral mucositis induced by conventional chemotherapy in solid tumors and malignant lymphomas. Support Care Cancer. 2012;20(9):2053-9. PMID: 22116139; https://doi.org/10.1007/s00520-011-1314-6.
20. Sonis ST, Elting LS, Keefe D, et al. Perspectives on cancer therapy-induced mucosal injury: pathogenesis, measurement, epidemiology, and consequences for patients. Cancer. 2004;100(9 Suppl):1995-2025. PMID: 15108222; https://doi.org/10.1002/cncr.20162.
21. Palappallil DS, Nair BL, Jayakumar KL, Puvathalil RT. Comparative study of the toxicity of 5-fluorouracil-adriamycin-cyclophosphamide versus adriamycin-cyclophosphamide followed by paclitaxel in carcinoma breast. Indian J Cancer. 2011;48(1):68-73. PMID: 21248442; https://doi.org/10.4103/0019-509X.75836.
22. Antuniassi AR. Occurrence and degree of severity of oral mucositis in relation to the salivary flow of patients undergoing chemotherapy [dissertation]. São Paulo: Faculdade de Odontologia da Universidade de São Paulo; 2005.
23. McCarthy GM, Awde JD, Ghandi H, Vincent M, Kocha WI. Risk factors associated with mucositis in cancer patients receiving 5-fluorouracil. Oral Oncol. 1998;34(6):484-90. PMID: 9930359; https://doi.org/10.1016/s1368-8375(98)00068-2.
24. Jensen SB, Vissink A, Limesand KH, Reyland ME. Salivary Gland Hypofunction and Xerostomia in Head and Neck Radiation Patients. J Natl Cancer Inst Monogr. 2019;2019(53):lgz016. PMID: 31425600; https://doi.org/10.1093/jncimonographs/lgz016.
25. Epstein JB, Tsang AH, Warkentin D, Ship JA. The role of salivary function in modulating chemotherapy-induced oropharyngeal mucositis: a review of the literature. Oral Surg Oral Med Oral Pathol Oral Radiol Endod. 2002;94(1):39-44. PMID: 12193891; https://doi.org/10.1067/moe.2002.126018.
26. Coracin FL, Santos PS, Gallottini MH, et al. Oral health as a predictive factor for oral mucositis. Clinics (Sao Paulo). 2013;68(6):792-6. PMID: 23778491; https://doi.org/10.6061/clinics/2013(06)11.
27. Gandhi K, Datta G, Ahuja S, Saxena T, G Datta A. Prevalence of Oral Complications occurring in a Population of Pediatric Cancer Patients receiving Chemotherapy. Int J Clin Pediatr Dent. 2017;10(2):166-71. PMID: 28890617; https://doi.org/10.5005/iD-iournals-10005-1428.
28. Allen G, Logan R, Revesz T, Keefe D, Gue S. The Prevalence and Investigation of Risk Factors of Oral Mucositis in a Pediatric Oncology Inpatient Population; a Prospective Study. J Pediatr Hematol Oncol. 2018;40(1):15-21. PMID: 29045267; https://doi.org/10.1097/MPH.0000000000000970.

Authors' contributions: Laura Costa de Almeida: methodology, project administration, writing-original draft and writing-review and editing; Bernardo da Fonseca Orcina: methodology, project administration, supervision, writing-original draft and writing-review and editing; Aloizio Premoli Maciel: methodology, project administration, supervision, writing-original draft and writing-review and editing; Dayanne dos Santos: visualization, writing-original draft and writing-review and editing; Brena Rodrigues Manzano: methodology, project administration, supervision, writing-original draft and writing review and editing; and Paulo Sérgio da Silva Santos: methodology, project administration, supervision, writing-original draft and writing-review and editing. All authors reviewed and approved the final version for publication

Acknowledgements: Coordenação de Aperfeiçoamento de Pessoal de Nível Superior (CAPES), Brazil
Sources of funding: This study was financed in part by the Coordenação de Aperfeiçoamento de Pessoal de Nível Superior (CAPES), Brazil (Finance Code 001)
Conflict: None

Date of first submission: July 3, 2021
Last received: November 4, 2021
Accepted: November 22, 2021

Address for correspondence:
Paulo Sérgio da Silva Santos
Departamento de Cirurgia, Estomatologia, Patologia e Radiologia, Faculdade de Odontologia de Bauru (FOB), Universidade de São Paulo (USP)
Al. Dr. Octávio Pinheiro Brisolla, 9-75
Bauru (SP) — Brasil
CEP 17012-901
Tel. (+55 14) 99670-0921
E-mail: paulosss@fob.usp.br

Influence of conditional cash transfer program on prenatal care and nutrition during pregnancy: NISAMI cohort study

Jerusa da Mota Santana[I], Marcos Pereira[II], Cinthia Soares Lisboa[III], Djanilson Barbosa Santos[IV], Ana Marlucia Oliveira[V+]

Universidade Federal da Bahia (UFBA), Salvador (BA), Brazil

[I]MSc, PhD. Adjunct Professor, Health Sciences Center, Universidade Federal do Recôncavo da Bahia (UFRB), Cruz das Almas (BA), Brazil.
https://orcid.org/0000-0002-8920-0097

[II]MSc, PhD. Adjunct Professor, Instituto de Saúde Coletiva, Universidade Federal da Bahia (UFBA), Salvador (BA), Brazil.
https://orcid.org/0000-0003-3766-2502

[III]MSc. Doctoral Student, Universidade Estadual de Feira de Santana (UEFS), Feira de Santana (BA), Brazil.
https://orcid.org/0000-0002-9370-0465

[IV]MSc, PhD. Adjunct Professor, Health Sciences Center, Universidade Federal do Recôncavo da Bahia (UFRB), Cruz das Almas (BA), Brazil.
https://orcid.org/0000-0002-6128-1155

[V]MSc, PhD. Full Professor, School of Nutrition, Universidade Federal da Bahia (UFBA), Salvador (BA), Brazil. [+]*In memoriam*.
https://orcid.org/0000-0002-3736-5893

KEY WORDS (MeSH terms):
Feeding behavior.
Public policy.
Pregnancy.
Prenatal care.

AUTHORS' KEY WORDS:
Dietary patterns.
Social protection.
Family health.

ABSTRACT

BACKGROUND: There are few studies on the influence of a cash transfer program on nutritional outcomes from pregnancy.

OBJECTIVES: To analyze how a Brazilian conditional cash transfer program (Bolsa Familia Program, BFP) was associated with changes in body mass index (BMI) and food consumption among pregnant women.

DESIGN AND SETTING: Cohort study on 250 pregnant women (≥ 18 years of age) in Brazilian prenatal services.

METHODS: A food frequency questionnaire was used to evaluate dietary intake. Weight was measured in each gestational trimester. Generalized estimation equations and structural equation modeling were used for statistical analyses. Correlations were analyzed using standardized coefficients (SCs).

RESULTS: Women benefitting from the BFP were of greater age and had lower education. The BFP exerted a direct negative effect on the pregnant women's consumption choices regarding refined grains, regional foods, vegetable oil, sausages, salted meats and snacks (SC = -0.10) and on maternal BMI (SC = -0.12). Among the intermediate variables, we observed that the time elapsed since pregnancy and the month of prenatal onset had direct negative effects; and that the number of visits to doctors, family income and number of years of education had direct positive effects.

CONCLUSIONS: Beneficiaries were less likely to increase their BMI outside of the recommended standards and had a greater tendency to receive prenatal care. Participation in the BFP had a direct negative effect on adherence to unhealthy diets.

INTRODUCTION

Social protection programs for health have grown in popularity around the world, especially for pregnant women within a context of vulnerability to hunger and food insecurity.[1-5] These programs have important effects with regard to improving maternal and child health and nutrition and diminishing child and maternal mortality rates.[6] However, there is an important gap in knowledge regarding interventions through such programs on the diets and gestational weight gains of women living in low and middle-income countries. Thus, epidemiological studies on the repercussions of social protection policies on the health and nutrition of pregnant women are important for evaluating these intervention programs.

There is evidence to suggest that social protection policies such as the Brazilian conditional cash transfer program (Bolsa Familia Program, BFP) attenuate the effects of poverty and ensure the human right to adequate food, thereby promoting food and nutritional security (FNS).[7,8]

In order to remain in the BFP, families must comply with requirements within the areas of education and health. With regard to health, these requirements include prenatal monitoring for pregnant beneficiaries, attendance at scheduled visits to doctors and educational activities relating to breastfeeding and adequate and healthy feeding during pregnancy and early childhood.[9]

The results from some studies have shown that pregnant women in the BFP begin prenatal care earlier and have a greater number of visits to doctors[6,10] than those who are not program beneficiaries. The results indicate that the BFP constitutes a protective factor for the health of the mother-child binomial. This is due to early attention to improvement of health, thus resulting in adequate and healthy nutrition; and to adoption of preventive measures with regard to risk factors that compromise proper development of gestation, especially in the initial cycles of fetal formation.

In addition, beneficiaries of this program have made progress in seeking out nutritional care. In 2012, approximately 165,000 Brazilian pregnant women were monitored by healthcare teams. Among these women, 99% were up-to-date with their prenatal care and 80% had undergone evaluation of their nutritional status.[11]

Regarding the destination of the funds provided by the BFP, the results show that most families used the benefit to purchase foodstuffs. This proportion was higher in the northeastern region and among families in situations of greater food and nutritional insecurity (FNI).[12,13]

An epidemiological survey conducted in Brazil revealed changes to the population's diet after its integration into the BFP. This contributed to greater food and nutritional security among these households through increasing their access to foods such as vegetables, eggs, oils, fruits, beans, meats, grains, milk, biscuits, processed foods and sugars.[14] According to the beneficiaries, the food groups most consumed were rice and grains and milk, with a smaller percentage for vegetables and roots.[14]

In relation to the maternal-infant group, studies have shown that the BFP had positive effects on maternal health conditions, improved children's health and nutritional status,[15,16] reduced the prevalence of low birth weight and reduced the child mortality rate, both in general and due to poverty-associated causes.[6] Information on the influence of the program on pregnant women's food consumption and anthropometric patterns, however, is only just beginning to emerge.

Given the impact of the BFP on pregnant women's health, our key hypothesis was that women who were beneficiaries of the BFP would have greater number of consultations in prenatal services, which would provide these women with a greater amount of nutritional counseling and monitoring from the healthcare teams. Therefore, women who were beneficiaries would achieve a positive impact on their nutrition and the beneficiaries would attain better control of weight gain during pregnancy. In addition, we postulated that the cash transfers would increase pregnant women's food and nutritional security, through their adoption of healthier eating habits during pregnancy.

Thus, the BFP can be considered to be a social protection policy that contributes positively towards ensuring FNS. In addition, it is probable that the BFP can influence these relationships directly or indirectly, or in an intermediary fashion.

OBJECTIVE

The aim of this study was to examine whether the Brazilian conditional cash transfer program was associated with changes to body mass index, food consumption and prenatal care, among pregnant women.

METHODS

Study design and sample

This was a prospective cohort study using a dynamic population of 250 pregnant women living in an urban area who were treated at Family Health Strategy (FHS) units in the city of Santo Antônio de Jesus, Bahia, in the northeastern region of Brazil. These women formed part of the NISAMI Cohort (Mother and Child Health Research Center; in Portuguese: Núcleo de Investigação em Saúde Materno-Infantil). The flowchart for the cohort is presented in **Figure 1**.

Pregnant women were recruited at prenatal services between August 2013 and December 2014. The monitoring lasted for nine months. When a pregnant woman was enrolled in the study after the first trimester of pregnancy, previous weight data were collected from the medical records available at the prenatal health unit. Data on socioeconomic, demographic, health and obstetric status and access to the BFP were collected at the time of the pregnant women's enrollment in the study.

Exclusion and inclusion criteria

The study included women who lived in the municipality's urban area, were aged 18 years or over, had gestational ages of up to 34 weeks at the time of enrollment and were receiving prenatal care through the public healthcare system.

The criteria for exclusion after the baseline consisted of the following: twin/multiple pregnancy; adherence to a vegan diet; and renal, contagious, immunological and/or metabolic and HIV diseases confirmed via medical diagnosis. Absence of confirmation of gestational age through ultrasonography was also a reason for

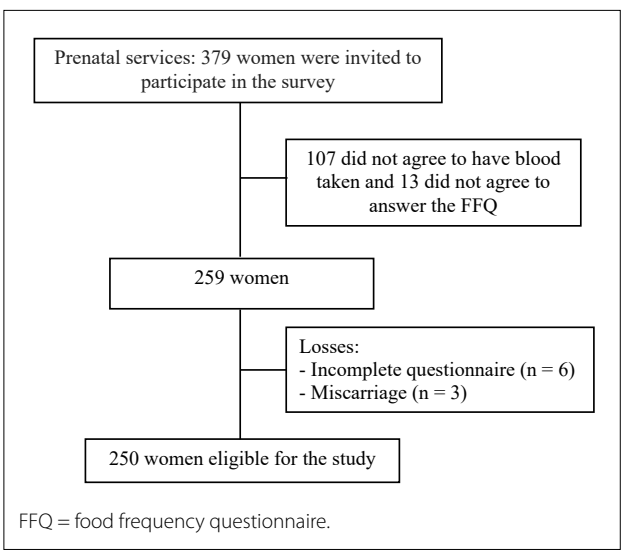


Figure 1. Flowchart of the design of the study conducted on pregnant women receiving prenatal services at a primary care unit in Santo Antônio de Jesus, Bahia, Brazil, 2017.

excluding pregnant women from the study. Gestational age was recorded from the first ultrasound, which was performed by the end of the first trimester and documented in the prenatal services.

Thus, 379 pregnant women met these criteria and were invited to participate in the study. They were invited to answer a closed-end questionnaire and to send blood samples to a clinical laboratory in the city after overnight fasting. Among these women, 107 refused to have blood collected and another 13 women refused to answer the food frequency questionnaire (FFQ). Consequently, a total of 259 pregnant women were eligible to participate. There were nine losses during the follow-up. Among these, six pregnant women did not fully complete the questionnaires and three had miscarriages. After these exclusions, 250 pregnant women were effectively included in the study and monitored for nine months (**Figure 1**).

Bolsa Familia Program assessment

The Bolsa Familia Program (BFP) is a conditional cash transfer program that was created in October 2003 through Provisional Measure No. 132. It was aimed at poor and extremely poor families and used per capita family income as the inclusion criterion.[16] The exposure variable consisted of receipt of BFP benefits.

Outcome assessments

We adopted two continuous response variables: gestational body mass index (BMI) variation during gestation (first, second and third gestational trimesters); and dietary intake pattern relating to fatty acid, at the time of enrollment.

BMI variation during pregnancy

For maternal weight measurements in the first, second and third gestational trimesters, we used a scale with a capacity of 150 kg and sensitivity of 100 g (Filizola, model 31 mechanical, Brazil). To measure height, a stadiometer was used, with a capacity of 2000 cm and sensitivity of 0.1 cm (Sanny, Brazil). Anthropometric measurements were made in duplicate. A maximum variation of 0.5 cm was accepted for length measurement, and a maximum variation of 100 g for weight.[17]

Dietary intake assessments

To evaluate fatty acid consumption, the semi-quantitative FFQ was used.[18] This instrument assesses 89 dietary sources of these lipids, with 13 possible responses for consumption, ranging from rarely/never to ≥ 3 times per day.

A photograph album of food portions and kitchen utensils was used to assist in making estimates of the portion sizes consumed, from the interviewees' memory. Data on frequencies of consumption of foods and the portions consumed were inserted into a spreadsheet and calculated, using an adaptation from Santana et al.[19]

To analyze consumption, we used daily food consumption. Thus, all time intervals relating to polyunsaturated fatty acid consumption were converted into the daily frequency of polyunsaturated fatty acid consumption.[18] In this, daily food intake frequency was assigned a value of one. For the weekly and monthly time intervals, the mean of the interval was divided by the period of fatty acid consumption: when weekly, it was assigned the value of 7, and when monthly, the value was 30.

The daily frequency of consumption of each food was used to form food groups that had the same nutritional characteristics, namely: milk and dairy products, fish, fruits and vegetables, olive oil, oilseeds and whole grains, refined grains, foodstuffs that were part of regional dishes, vegetable oil, sausages, salted meats and foods belonging to the snack and processed foods group.

Statistical analyses

The power of this sample to detect an association between the Bolsa Familia Program and a pregnant woman's nutritional status was 96%. This calculation was based on the prevalence of excess weight gain of 48.1%, among pregnant women in the municipality of the present study.[19]

Descriptive analyses were used to characterize the sample. Mean and standard deviation (SD) were used for the continuous variables (maternal age, number of years of education, family income, number of residents, number of gestational weeks, weight gain, prenatal visits and time when prenatal visits started). The sociodemographic and anthropometric characteristics of the pregnant women according to the BFP exposure variables were compared using Student's t test.

In this study, the BFP was adopted as a categorical dependent variable, dichotomized into (0) beneficiaries of the program and (1) non-beneficiaries of the program. The main exposure variables were the fatty acid consumption pattern and gestational BMI, and these were used in a continuous form. The following covariates were considered in continuous format: maternal age, number of years of education, family income, number of residents, number of gestational weeks, BMI, body weight (BW), birthweight gain, prenatal visits and time when prenatal services started.

The BMI variable was constructed longitudinally, considering weight variation in the first, second and third gestational trimesters using generalized estimation equations. Later on, this variable in its continuous form was exported to the structural equation model (SEM) in order to evaluate the influence of the BFP on BMI variation during gestation. This strategy was adopted because the model in the SEM did not fit when the variable "gestational weight gain variation over time" was included in the confirmatory equation of the factorial analysis.

Dropout analyses were performed to investigate the presence of selection bias, through comparing the mothers who completed the study with those who were lost or excluded during the monitoring.

The following variables were considered: age and consumption of mono and polyunsaturated fatty acids.

The baseline consumption of polyunsaturated fatty acids gave rise to two latent variables. These two variables are here denominated "Pattern 1" (milk and dairy products, fish, fruits and vegetables, olive oil, legumes, oilseeds and tubers and roots) and "Pattern 2" (refined grains, regional foods, vegetable oil, sausages, salted meats and snacks). These patterns were established internally in SEM by using confirmatory factorial analysis and were included in analyses in the continuous form. The composition of the fatty acid consumption pattern and its respective standardized coefficients are presented in **Table 1**.

The direct, indirect and total effects of the relationships studied were evaluated through standardized coefficients (SCs), and these were interpreted as a small effect (SC values close to 0.10 and -0.10), medium effect (SC values of 0.30 and -0.30) or strong effect (SC values > 0.50 and > -0.50).[20] The RMSEA model (root of the mean square error of approximation) was used to evaluate goodness of fit.[21] The statistical analyses were carried out using the Stata software (version 12.0; Stata Corporation, College Station, Texas, United States).

Ethical statement

This study was approved by the Ethics Committee for Research involving Human Beings of the Universidade Federal do Recôncavo da Bahia (UFRB), under the number 241.225, dated April 9, 2013. All study procedures were carried out in accordance with the code of ethics of the World Medical Association (Declaration of Helsinki) for experiments involving humans. Informed consent was obtained for experimentation with human subjects and the privacy rights of human subjects were observed.

Table 1. Sociodemographic and anthropometric characteristics of pregnant women who were beneficiaries and non-beneficiaries of the Bolsa Familia Program (BFP). Santo Antônio Jesus, Bahia, 2013 to 2014 (n = 250).

Characteristics (continuous variables)	BFP beneficiaries				P-value*
	YES		NO		
	Mean	SD	Mean	SD	
Maternal age in years	28.3	5.6	26.1	6.0	< 0.001
Number of years of education	9.9	2.8	10.8	2.9	< 0.001
Family income**	260.48	147.37	420.42	319.07	< 0.001
Number of residents in the home	4.0	1.0	3.0	1.0	0.002
Number of gestational weeks	17.4	7.1	16.3	6.6	0.002
BMI BW	25.8	5.7	23.8	4.2	< 0.001
Birthweight gain (kg)	12.9	4.9	12.8	4.9	0.705
Number of prenatal visits	6.7	2.1	7.3	2.0	0.999
Prenatal visits start (trimester)	2.8	1.6	2.3	1.6	< 0.001

*Student's t test for independent samples; **United States dollars; BMI BW = pre-pregnancy body mass index.

RESULTS

Description of participants

Out of the 259 pregnant women considered for the study, 250 women were included (**Figure 1**), and these participants contributed 750 observations on weight variation during monitoring. This loss of nine participants was recorded over nine months of follow-up and represented a loss rate of 3.47%. The results from the comparative analysis between the selected variables of mean age (P = 0.81), consumption of monounsaturated fatty acids (P = 0.80) and consumption of polyunsaturated fatty acids (P = 0.50) at baseline did not differ significantly between the women who completed the follow-up and the losses.

The sociodemographic and anthropometric characteristics of the pregnant beneficiaries (28.8%) and non-beneficiaries (71.2%) of the BFP are presented in **Table 1**. Women benefitting from the BFP were of greater age (28.3 years; SD = 5.6; P < 0.001), had had lower education (9.9 years; SD = 2.8; P < 0.001) and had lower family income (United States dollars, US$ 260.48; SD = 147.37; P < 0.001).

Information on the daily frequencies of consumption of food groups that were present in the diet of the pregnant beneficiaries and non-beneficiaries of the BFP is set out in **Table 2**. The pregnant beneficiaries of the BFP had basic food groups such as milk and dairy products, grains, legumes and oilseeds

Table 2. Daily frequency of consumption of food groups in the diet of pregnant women who were beneficiaries and non-beneficiaries of the Bolsa Familia Program (BFP). Santo Antônio de Jesus, Bahia, 2013 to 2014 (n =250).

Food groups	BFP beneficiaries		Non-beneficiaries		P-value*
	Median freq	SD	Median freq	SD	
Milk and dairy products	2.0	1.16	2.0	1.29	0.174
Meat and eggs	1.17	0.72	1.17	0.77	0.524
Fish	0.19	0.24	0.16	0.24	0.119
Sausages	0.47	0.66	0.39	0.74	0.067
Salted meats	0.43	0.49	0.34	0.47	0.010
Innards (viscera)	0.14	0.21	0.08	0.24	0.001
Olive oil	0.30	0.41	0.33	0.55	0.183
Oil	1.09	0.38	1.05	0.37	0.095
Fat	1.5	1.13	1.38	1.02	0.055
Snacks	0.34	0.64	0.30	0.39	0.175
Regional foods	0.22	0.32	0.28	0.44	0.033
Grains	2.57	1.72	2.24	1.36	0.002
Whole grains	0.52	0.58	0.49	0.56	0.230
Legumes	1.12	0.75	1.01	0.61	0.016
Oilseeds	1.00	0.17	0.14	0.43	0.062
Fruits, vegetables and legumes	0.59	0.77	0.52	0.82	0.474

*Student's t test for independent samples.

(i.e. components of the healthier pattern 1) in their daily consumption more frequently.

Program influence on fatty acid dietary intake patterns and anthropometric outcomes

The composition of the fatty acid consumption pattern and its respective standardized coefficients are shown in **Table 3**. Pattern 1 consisted of the following food groups: milk and dairy products, fish, fruits and vegetables, olive oil, legumes, oilseeds and whole grains. The root and tuber food groups had the greatest contribution towards formation of this construct and the olive oil and fish groups contributed to a lesser extent. Pattern 2 consisted of refined grains, foodstuffs that were part of regional dishes, vegetable oil, sausages, salted meats and foods belonging to the snack and processed foods group. The food groups that contributed the most notably to this pattern were salted meats, processed foods and those that make up snacks.

The Bolsa Familia Program had a direct negative effect on consumption pattern 2 (SC = -0.10; P = 0.034) and on BMI during pregnancy (SC = -0.12; P = 0.001). This indicated that pregnant women who were beneficiaries of the program had lower adherence to pattern 2 fatty acid dietary intake (refined grains, *caruru*, *vatapá*, vegetable oil, sausages, salted meats and snacks) and presented lower BMI during the gestational cycle (**Table 3**).

Among the other variables evaluated, there were direct negative effects from age (SC = -0.16; P ≤ 0.001) and time when prenatal care started (SC = -0.10; P = 0.004) on the relationship between the BFP and anthropometric status and fatty acid dietary intake conditions throughout gestation, thus indicating that the beneficiaries were younger and began prenatal care earlier. In this relationship, the following variables showed positive effects: number of prenatal consultations (SC = 0.08; P = 0.017), family income (SC = 0.21; P = 0.001) and number of years of schooling (0.08; P = 0.024) showed positive effects. This indicated that the BFP had a positive impact on increased income, greater maternal education and greater number of prenatal consultations (**Table 3**).

DISCUSSION

This study was one of the first in Brazil to investigate the influence of pregnant women's participation in the Bolsa Familia Program on BMI during pregnancy. The results indicate that pregnant beneficiaries of the BFP had lower adherence to food

Table 3. Structural equation modeling on the influence of the Bolsa Familia Program on dietary patterns. Santo Antônio de Jesus, Bahia, 2013 to 2014 (n = 250)

Effects	Standardized coefficient	P-value	95% CI
DIETARY PATTERN 1 →			
Milk and dairy products	0.34	< 0.001	0.26-0.43
Fish	0.23	< 0.001	0.14-0.32
Fruits and vegetables	0.30	< 0.001	0.22-0.59
Olive oil	0.20	< 0.001	0.11-0.29
Legumes	0.47	< 0.001	0.38-0.56
Oilseeds	0.54	< 0.001	0.45-0.66
Tubers and roots	0.67	< 0.001	0.58-0.75
DIETARY PATTERN 2 →			
Refined grains	0.27	< 0.001	0.18-0.36
Regional foods	0.20	< 0.001	0.12-0.29
Vegetable oil	0.23	< 0.001	0.15-0.32
Sausages	0.40	< 0.001	0.33-0.49
Salted meats	0.67	< 0.001	0.58-0.75
Snacks	0.60	< 0.001	0.52-0.68
Pattern 1 ← Bolsa Familia Program	-0.02	0.665	-0.11 – -0.075
Pattern 2 ← Bolsa Familia Program	-0.10	0.034	-0.19 – -0.07
BMI_T ← Bolsa Familia Program	-0.12	0.001	-0.05 – -0.18
Bolsa Familia Program ← age	-0.16	< 0.001	-0.10 – -0.23
Bolsa Familia Program ← number of years of education	0.08	0.024	0.01-0.15
Bolsa Familia Program ← income	0.22	< 0.001	0.14-0.28
Bolsa Familia Program ← number of residents in the home	-0.05	0.097	-0.12 – -0.01
Bolsa Familia Program ← parity	-0.005	0.09	-0.15 – -0.02
Bolsa Familia Program ← prenatal care start	-0.10	0.004	-0.16 – -0.03
Bolsa Familia Program ← number of prenatal care visits	0.08	0.017	0.01-0.14

Goodness-of-fit indicators for the model: root of the mean square error of approximation (RMSEA): 0.0001; n = 250: 750 observations; BMI_T: body mass index (BMI) in the three gestational trimesters.

consumption pattern 2, composed of foods and preparations containing high concentrations of fatty acids, vegetable oil, sausages, salted meats and salty snacks than non-beneficiary pregnant women.

In this context, the results suggest that, as a social policy, the Bolsa Familia Program exerts a protective effect on maternal nutritional health, through increasing access to and consumption of the traditional basic foodstuffs within a healthy diet among Brazilian families, consisting of milk and dairy products, beans, meat, eggs and grains. These food groups have an outstanding physiological function within the development of adequate gestation and maintenance of women's weight throughout pregnancy. It is also worth noting that the results from this study can be interpreted in the light of proposals for social protection programs (PTCRs). These programs focus not only on direct cash transfers to families in order to alleviate poverty over the short term, but also on requirements that encourage beneficiaries to access healthcare and educational services.[6,16]

Population-based studies have shown that PTCRs improve the economic conditions of poor households, which in turn promotes greater access to food and contributes towards ensuring these households' FNS.[15] Accordingly, the results from this study substantiate the direct relationship between the protective aspect of cash transfer programs and the underprivileged population's health and nutrition.

Among the direct effects of these programs are those relating to the gestational cycle, which ensure that pregnant women have access both to food and to prenatal and postpartum consultations, in addition to ensuring their participation in educational interventions relating to nutrition and health within the public healthcare network.[7,8,16]

In a qualitative and quantitative study carried out in municipalities of the state of Bahia, it was found that the Bolsa Familia Program was one of the programs within the National Food and Nutrition Policy that had the greatest coverage in the municipalities evaluated.[22] There was greater monitoring of its requirements, specifically in the area of healthcare, in municipalities where the Family Health Strategy covered more than 70% of the population. This showed that dialogue between these two public health programs favored interaction between positive health and nutritional actions in the population.[22]

Thus, adherence to the population's traditional diet and reduction of consumption of industrialized and processed foods, along with improvement of anthropometric conditions, may reflect the actions of the Bolsa Familia Program. These actions do not mitigate the social determinants but provide guidance that promotes adoption of health and nutritional practices that lead to a healthier lifestyle. The results from the Bolsa Familia Program are consistent with those from other studies conducted elsewhere in the world. In this regard, a randomized, cluster-controlled clinical trial found that both direct income interventions and direct food interventions improved the nutritional consumption and nutritional status of low-income pregnant women in Nepal, Asia. In addition, conditional cash transfers further improved food diversity in family units.[23]

However, a randomized clinical trial that was conducted to evaluate the effectiveness of cash transfers in relation to searching for higher-level infrastructure and equipment services, among low-income African pregnant women in Nairobi, Kenya, did not observe any positive impact on their search for quality services for childbirth delivery.[24]

Nonetheless, the results from a study on Brazilian families who were in situations of poverty corroborated previous results.[23] Those families invested an average of US$ 61.61 more per year for purchasing food than did non-beneficiary families.[25] Reports from beneficiaries have indicated that families increase their purchases of rice, beans,[26] chickenmeat,[27] grains, milk, sugar, cookies, meats, oils, eggs, fruits, roots and processed foods after being included in the Bolsa Familia Program.[14,26,27] It was seen that the food groups most frequently purchased were sugars (78%), rice and cereals (76%) and milk (68%), with lesser acquisition of foods in the vegetable group (40%).

Research results from a region close to that of the present study showed that beneficiary families' diets improved after the program had been established in that region, and that the money received was mainly spent on food (76.4%). There was also an increase in the variety of the foods consumed.[28]

Although the pregnant women of the present study included the Brazilian population's basic healthy food groups in their daily diet (milk and dairy products, beans, meat, eggs and grains), low consumption of fruits and vegetables was registered. These results were similar to those of other investigations carried out among adult Bolsa Familia Program women, and indicated that there was greater access to food after they had been included in the Bolsa Familia Program. Nevertheless, their consumption of vegetables, fruits and legumes remained lower than expected.[29]

The results from the investigations have highlighted social, economic and cultural influences, as well as the geographical region's dietary habits, in constructing the population's dietary patterns. Accordingly, in less favorable socioeconomic contexts such as that of Brazil's northeastern region, families have tended to adapt to subsistence mechanisms and buy the basic and cheaper foodstuffs that are part of the population's diet, while those living in economically more developed regions have adopted greater consumption of processed foods.[26,27]

Thus, we have highlighted the monitoring and follow-up of pregnant Brazilian beneficiaries of the Bolsa Familia Program through the Family Health Strategy program, with regard to

prenatal care actions, with more pronounced insertion in the northeastern region.[10] This result may also be expressing a positive effect from interaction between the Bolsa Familia Program and the FHS program, with greater access to prenatal care for pregnant Bolsa Familia Program beneficiaries and implementation of nutritional and health monitoring interventions throughout the prenatal care period. The net result is a protective impact on maternal and fetal health.

Certainly, the focus of the Bolsa Familia Program has enabled increased family income, which is a major factor in expanding beneficiaries' access to food. Thus, the beneficiaries' average family income was slightly higher than the minimum wage at the time (US$ 260.48; SD = 147.37), although, as expected, below the income of non-beneficiaries (US$ 420.4; SD = 319.07).

The Bolsa Familia Program has also had impacts on the health of the maternal and child populations registered in epidemiological studies, which consisted of reducing the prevalence of low birthweight and the mortality rate among children under five years of age, both in general and due to poverty-related causes such as malnutrition and diarrhea.[6,30] In addition, the program has had a positive influence on children's nutritional status and health, as a result of greater monitoring and mother-child bonding, achieved through actions to prevent risk factors and promote a healthy lifestyle.[30]

Thus, it has been found that the Bolsa Familia Program has had a positive impact on the health of the population served, through contributing to reduction of malnutrition and FNI, increasing monthly family income and allowing access to food, for previously invisible vulnerable population groups.[28] In this light, the Bolsa Familia Program stands out as an intersectoral strategy for social inclusion of vulnerable families, thereby promoting the human right to adequate food (HRAF) through the FNS guarantee.[11,31]

In this way, the decision of the United Nations Food and Agriculture Organization (FAO) to exclude Brazil from the hunger map in 2014, owing to an 82% reduction in the prevalence of malnutrition in the population, can be understood. In the FAO report, the Bolsa Familia Program was highlighted as one of the social interventions that was able to contribute results with social and human importance at a global level, given that it has played an important role in guaranteeing FNS and promoting HRAF among Brazilian families.[32]

Strengths and limitations

This study had some limitations. For instance, information provided by Bolsa Familia Program beneficiaries was used. This may have led to information errors, since these women receiving the benefit may have felt uncomfortable about giving information or may have felt threatened by loss of the benefit if they talked about their condition. Moreover, the pregnant women's level of physical activity was not analyzed.

Another limitation related to non-inclusion of rural pregnant women in the study sample. Inclusion of rural pregnant women in the sample should be considered in the future, since groups may have different access to healthcare services according to where they live. This can also occur with regard to food consumption. In studies in other countries, with different epidemiological contexts, it has been reported that pregnant women have differing health and nutrition vulnerabilities according to their area of residence.[33-35] In our study, however, these differences may not have been significant, given that Family Health Strategy units that serve the population through health monitoring programs, including prenatal care, also exist in rural areas of the municipality. Regarding the losses during the follow-up, we can attest that these were small and were unlikely to have introduced any selection bias in the study.

The robust statistical analysis in our study was a strength. It can thus be concluded that studies that address the Bolsa Familia Program's impact on pregnant women's diet and nutrition are at an early stage. We also noted that there was a lack of study designs with robust methodology for dealing with primary data. From this perspective, the present investigation has contributed to filling the gap, through a longitudinal study on the influence of the Bolsa Familia Program on pregnant women's diets and on maternal weight during pregnancy.

CONCLUSION

This study showed the important role of health conditionalities in expanding access to prenatal services and nutritional guidance during pregnancy, as well as for monitoring and controlling weight gain during pregnancy. Accordingly, the improvement of pregnant women's parameters may have resulted from the Bolsa Familia Program's impact on families' economic conditions, through increasing the population's access to food staples and providing orientation sessions for improving the beneficiary population's health and nutrition.

This study advances the understanding of the positive influence of a social protection policy on the food and nutrition of specific populations, such as the group of pregnant women in urban areas. However, further studies are needed, especially among pregnant women in rural areas, since these women may have different access to healthcare services.

REFERENCES

1. Ickes SB. Supportive Evidence for Program Impact Pathways: Food-Assisted Maternal and Child Health and Nutrition Programs Can Produce Sustained Dietary Improvements. J Nutr. 2020;150(4):661-2. PMID: 32171007; https://doi.org/10.1093/jn/nxaa056.
2. Doocy S, Busingye M, Lyles E, et al. Cash-based assistance and the nutrition status of pregnant and lactating women in the Somalia food crisis: A comparison of two transfer modalities. PloS One. 2020;15(4):e0230989. PMID: 32324761; https://doi.org/10.1371/journal.pone.0230989.

3. Blakeney EL, Herting JR, Zierler BK, Bekemeier B. The effect of women, infant, and children (WIC) services on birth weight before and during the 2007-2009 great recession in Washington state and Florida: a pooled cross-sectional time series analysis. BMC Pregnancy and Childbirth. 2020;20(1):252. PMID: 32345244; https://doi.org/10.1186/s12884-020-02937-5.
4. Leroy JL, Olney DK, Nduwabike N, Ruel MT. Tubaramure, a Food-Assisted Integrated Health and Nutrition Program, Reduces Child Wasting in Burundi: A Cluster-Randomized Controlled Intervention Trial. J Nutr. 2021;151(1):197–205. PMID: 32245129; https://doi.org/10.1093/jn/nxaa330.
5. Nguyen PH, Khương LQ, Pramanik P, et al. Effective coverage of nutrition interventions across the continuum of care in Bangladesh: insights from nationwide cross-sectional household and health facility surveys. BMJ Open. 2021;11(1):e040109. PMID: 33472778; https://doi.org/10.1136/bmjopen-2020-040109.
6. Rasella D, Aquino R, Santos CA, Paes-Sousa R, Barreto ML. Effect of a conditional cash transfer programme on childhood mortality: A nationwide analysis of Brazilian municipalities. Lancet. 2013;382(9886):57-64. PMID: 23683599; https://doi.org/10.1016/S0140-6736(13)60715-1.
7. Segura-Pérez S, Grajeda R, Pérez-Escamilla R. Conditional cash transfer programs and the health and nutrition of Latin American children. Rev Panam Salud Publica. 2016;40(2):124-37. PMID: 27982370.
8. Leroy JL, Ruel M, Verhofstadt E. The impact of conditional cash transfer programmes on child nutrition: a review of evidence using a programme theory framework. Journal of Development Effectiveness. 2009;1(2):103-29. https://doi.org/10.1080/19439340902924043.
9. Magalhães R, Bodstein R, Coelho AV, Nogueira MF, Bocca C. The Bolsa Família (family grant) program in Manguinhos: challenges and lessons learned in a case study: implementation process: development of strategies and evidence. Glob Health Promot. 2011;18(1):13-5. PMID: 21721293; https://doi.org/10.1177/1757975910393164.
10. Castro MC, Massuda A, Almeida G, et al. Brazil's unified health system: the first 30 years and prospects for the future. Lancet. 2019;394(10195):345-56. PMID: 31303318; https://doi.org/10.1016/S0140-6736(19)31243-7.
11. Bolsa Família Program: a decade of social inclusion in Brazil. Executive Summary/Editors: Tereza Campello, Marcelo Côrtes Neri. Brasília: Ipea; 2014. Available from: https://www.ipea.gov.br/portal/images/stories/PDFs/140321_pbf_sumex_ingles.pdf. Accessed in 2021 (Nov 26).
12. Santos EESD, Oliveira MM, Bernardino ÍM, Pedraza DF. Food and nutritional insecurity of families using the family health strategy in two municipalities in Paraíba, Brazil. Cien Saude Colet. 2020;25(5):1607-17. PMID: 32402053; https://doi.org/10.1590/1413-81232020255.33412019.
13. Almeida JA, Santos AS, Nascimento MAO, et al. Factors associated with food insecurity risk and nutrition in rural settlements of families. Cien Saude Colet. 2017;22(2):479-88. https://doi.org/10.1590/1413-81232017222.27102015.
14. Martins AP, Monteiro CA. Impact of the Bolsa Familia program on food availability of low-income Brazilian families: a quasi-experimental study. BMC Public Health. 2016;16(1):827. PMID: 27538516; https://doi.org/10.1186/s12889-016-3486-y.
15. Assis AM, Costa PR, Silva M da C, et al. Effectiveness of the Brazilian Conditional Cash Transfer Program--Bolsa Alimentação--on the variation of linear and ponderal increment in children from northeast of Brazil. Nutr Hosp. 2014;31(2):689-97. PMID: 25617551; https://doi.org/10.3305/nh.2015.31.2.7909. Corrected and republished in: Nutr Hosp. 2015;31(6):2786-94.
16. Valpiani N, Thorne-Lyman AL, Pee S, et al. Proposed strategies for mitigating the impact of high food prices on nutrition and health in Latin America and the Caribbean. CABI Wallingford UK; 2009. Available from: https://doi.org/10.1079/PAVSNNR20083081. Accessed in 2021 (Dec 2).
17. Lohman TG, Roche AF, Martorell R. Anthropometric standardization reference manual. Human Kinetics Books: Michigan; 1988.
18. Queiroz Carvalho G, Pereira M, Santana JM, Louro ID, Santos DB. Relative validation of a food frequency questionnaire to assess dietary fatty acid intake. Rev Chil Nutr. 2020;47(3):396-405. https://dx.doi.org/10.4067/S0717-75182020000300396.
19. Da Mota Santana J, Alves de Oliveira Queiroz V, Monteiro Brito S, Barbosa Dos Santos D, Marlucia Oliveira Assis A. Food consumption patterns during pregnancy: a longitudinal study in a region of the North East of Brazil. Nutr Hosp. 2015;32(1):130-8. PMID: 26262707; https://doi.org/10.3305/nh.2015.32.1.8970.
20. Kline R. Principles and practice of structural equation modeling. 3rd ed. Guilford Press: New York; 2010.
21. Amorim LD, Fiaccone RL, Santos CA, et al. Structural equation modeling in epidemiology. Cad Saude Publica. 2010;26(12):2251-62. PMID: 21243220; https://doi.org/10.1590/s0102-311x2010001200004.
22. Santiago de Souza LM, Chaves dos Santos SM. National Food and Nutrition Policy: Evaluating the implementation of programs in municipalities of the state of Bahia, Brazil. Demetra. 2017;12(1):137-55. https://doi.org/10.12957/demetra.2017.26371.
23. Harris-Fry HA, Paudel P, Harrisson T, et al. Participatory women's groups with cash transfers can increase dietary diversity and micronutrient adequacy during pregnancy, whereas women's groups with food transfers can increase equity in intrahousehold energy allocation. J Nutr. 2018;148(9):1472-83. PMID: 30053188; https://doi.org/10.1093/jn/nxy109.
24. Cohen J, Rothschild C, Golub G, et al. Measuring the impact of cash transfers and behavioral "Nudges" on maternity care in Nairobi, Kenya. Health Aff (Millwood). 2017;36(11):1956-64. PMID: 29137506; https://doi.org/10.1377/hlthaff.2017.0537.
25. Duarte GB, Sampaio B, Sampaio Y. Programa Bolsa Família: impacto das transferências sobre os gastos com alimentos em famílias rurais. Rev Eco Sociol Rural. 2009;47(4):903-18. https://doi.org/10.1590/S0103-20032009000400005.

26. de Bem Lignani J, Sichieri R, Burlandy L, Salles-Costa R. Changes in food consumption among the Programa Bolsa Família participant families in Brazil. Public Health Nutr. 2011;14(05):785-92. PMID: 21129236; https://doi.org/10.1017/S136898001000279X.
27. Sperandio N, Rodrigues CT, Franceschini SDCC, Priore SE. The impact of the bolsa família program on food consumption: a comparative study of the southeast and northeast regions of Brazil. Cien Saude Colet. 2017;22(6):1771-80. PMID: 28614498; https://doi.org/10.1590/1413-81232017226.25852016.
28. Gouvêa VH, Dalt S, Assis AM de O, Monteiro M da C. Survey of the perception of the beneficiaries of the Bolsa program on conditions of food and nutritional security. In: Paes-Sousa R, Vaitsman J, organizers. Cadernos de Estudos Desenvolvimento Social em Debate. Brasília, DF: Ministério do Desenvolvimento Social e Combate à Fome, Secretaria de Avaliação e Gestão da Informação; 2007. Available from: https://aplicacoes.mds.gov.br/sagirmps/ferramentas/docs/caderno%20-%2005.pdf. Accessed in 2021 (Nov 26).
29. Cabral MJ, Vieira KA, Sawaya AL, Florêncio TMMT. Perfil socioeconômico, nutricional e de ingestão alimentar de beneficiários do Programa Bolsa Família. 2013;27(78):71–87. Available from: http://www.scielo.br/pdf/ea/v27n78/06.pdf. Accessed in 2021 (Nov 26).
30. Oliveira F de C, Cotta RM, Sant'Ana LF, Priore SE, Franceschini S do C. Programa Bolsa Família e estado nutricional infantil: desafios estratégicos [Bolsa Família Program and child nutritional status: strategic challenges]. Cien Saude Colet. 2011;16(7):3307-16. PMID: 21808918; https://doi.org/10.1590/s1413-81232011000800030.
31. Cotta RM, Machado JC. Programa Bolsa Família e segurança alimentar e nutricional no Brasil: revisão crítica da literatura [The Bolsa Família cash transfer program and food and nutrition security in Brazil: A critical review of the literature]. Rev Panam Salud Publica. 2013;33(1):54-60. PMID: 23440158; https://doi.org/10.1590/s1020-49892013000100008.
32. Food and Agriculture Organization of the United Nations. The State of Food Insecurity in the World. Strengthening the enabling environment for food security and nutrition. Rome. 2014. Available from: https://www.fao.org/3/i4030e/i4030e.pdf. Accessed in 2021 (Nov 26).
33. Linet MS, Wang L, Wang N, et al. Prospective investigation of folic acid supplements before and during early pregnancy and paediatric and adult cancers in the Chinese children and families cohort: a pilot study in a sample of rural and urban families. BMJ Open. 2018;8(7):e022394. PMID: 30061446; https://doi.org/10.1136/bmjopen-2018-022394.
34. Dwarkanath P, Vasudevan A, Thomas T, et al. Socio-economic, environmental and nutritional characteristics of urban and rural South Indian women in early pregnancy: Findings from the South Asian Birth Cohort (START). Public Health Nutr. 2018;21(8):1554-64. PMID: 29400265; https://doi.org/10.1017/S1368980017004025.
35. Mao L, Ma L, Liu N, et al. Self-reported health problems related to traditional dietary practices in postpartum women from urban, suburban and rural areas of Hubei province, China: The "zuò yuèzi." Asia Pac J Clin Nutr. 2016;25(1):158-64. PMID: 26965775; https://doi.org/10.6133/apjcn.2016.25.2.03.

Authors' contributions: Santana JM: conceptualization (equal), data curation (equal), formal analysis (equal), investigation (equal), methodology (equal), software (equal), supervision (equal), validation (equal), visualization (equal), writing-original draft (equal) and writing-review and editing (equal); Pereira M and Santos DB: data curation (equal), funding acquisition (equal), investigation (equal), methodology (equal), project administration (equal), resources (equal), supervision (equal) and writing-review and editing (equal); Lisboa CS: data curation (equal), investigation (equal) and writing-review and editing (equal); and Oliveira AM: investigation (equal), methodology (equal), supervision (equal), validation (equal), visualization (equal), writing-original draft (equal) and writing-review and editing (equal). All authors reviewed and approved the final version of the manuscript

Sources of funding: This research was funded by the Research Foundation of the State of Bahia, grant numbers 7190/2011 and APP0038/2011; and by the National Council for Scientific and Technological Development, grant number 481509/2012-7
Conflicts of interest: None

Date of first submission: May 25, 2021
Last received: September 5, 2021
Accepted: November 23, 2021

Address for correspondence:
Jerusa da Mota Santana
Centro de Ciências da Saúde, Universidade Federal do Recôncavo da Bahia, Cajueiro
Av. Carlos Amaral, 1.015
Santo Antônio de Jesus (BA) — Brasil
CEP 44574-490
Tel. (+55 75) 3632-1724
E-mail: jerusanutri@ufrb.edu.br

https://doi.org/10.1590/1516-3180.2021.0606.R2.27122021

Augmented reality in interventional radiology education: a systematic review of randomized controlled trials

And Yara Particelli Gelmini[I], Márcio Luís Duarte[II], Mayara Oliveira da Silva[III], Josias Bueno Guimarães Junior[IV], Lucas Ribeiro dos Santos[V]

Evidence-Based Health Department, Universidade Federal de São Paulo (UNIFESP), São Paulo (SP), Brazil

[I]MD. Radiologist, Department of Radiology, WEBIMAGEM Telerradiologia, São Paulo (SP), Brazil.
https://orcid.org/0000-0003-0820-4393

[II]MSc. Musculoskeletal Radiologist, Centro Radiológico e Especialidades Médicas São Gabriel, Praia Grande (SP), Brazil; and Doctoral Student in Evidence-based Health Program, Universidade Federal de São Paulo (UNIFESP), São Paulo (SP), Brazil.
https://orcid.org/0000-0002-7874-9332

[III]BSc. Biomedic, Biomedical imaging, Clínica Mega Imagem, Santos (SP), Brazil.
https://orcid.org/0000-0002-9882-3456

[IV]B.Eng. Engineer, Department of Engineering, MIP Engenharia, Belo Horizonte (MG), Brazil.
https://orcid.org/0000-0002-2963-0730

[V]MSc. Endocrinologist, Department of Physiology and Medical Clinic, and Professor of Physiology and Medical Clinic, Centro Universitário Lusíada (UNILUS), Santos (SP), Brazil; and Doctoral Student in Evidence-based Health Program, Universidade Federal de São Paulo (UNIFESP), São Paulo (SP), Brazil.
https://orcid.org/0000-0001-7897-1198

KEYWORDS (MeSH terms):
Radiology, interventional.
Augmented reality.
Education, medical.
Simulation training.

AUTHORS' KEYWORDS:
Video game.
Perk Tutor.
Google Glass.
Wearable technology.

ABSTRACT

BACKGROUND: Augmented reality (AR) involves digitally overlapping virtual objects onto physical objects in real space so that individuals can interact with both at the same time. AR in medical education seeks to reduce surgical complications through high-quality education. There is uncertainty in the use of AR as a learning tool for interventional radiology procedures.

OBJECTIVE: To compare AR with other learning methods in interventional radiology.

DESIGN AND SETTING: Systematic review of comparative studies on teaching techniques.

METHODS: We searched the Cochrane Library, MEDLINE, Embase, Tripdatabase, ERIC, CINAHL, SciELO and LILACS electronic databases for studies comparing AR simulation with other teaching methods in interventional radiology. This systematic review was performed in accordance with PRISMA and the BEME Collaboration. Eligible studies were evaluated using the quality indicators provided in the BEME Collaboration Guide no. 11, and the Kirkpatrick model.

RESULTS: Four randomized clinical trials were included in this review. The level of educational evidence found among all the papers was 2B, according to the Kirkpatrick model. The Cochrane Collaboration tool was applied to assess the risk of bias for individual studies and across studies. Three studies showed an improvement in teaching of the proposed procedure through AR; one study showed that the participants took longer to perform the procedure through AR.

CONCLUSION: AR, as a complementary teaching tool, can provide learners with additional skills, but there is still a lack of studies with a higher evidence level according to the Kirkpatrick model.

SYSTEMATIC REVIEW REGISTRATION NUMBER: DOI 10.17605/OSF.IO/ACZBM in the Open Science Framework database.

INTRODUCTION

Learning is the process of acquiring new knowledge and skills, and this process has its difficulties and pitfalls.[1,2] In medicine, acquiring new abilities can lead to improvement in outcomes, as in the field of surgery, in which open surgical procedures have been replaced by minimally invasive procedures, and fresh devices are created to refine surgical abilities, and teaching processes as well.[3,4]

The "learning before doing" concept is rapidly replacing the conventional "see one, do one, teach one" technique, in order to avoid potential mistakes.[5,6] According to British National Health Service data, preventable injuries and deficient medical training are responsible for 10% of hospitalizations.[7] In consonance, "warm-up" can be applied to students and experienced professionals, thus boosting performance and self-confidence.[8] This could form another application for augmented reality (AR).

AR involves digitally overlapping virtual objects onto physical objects in real space so that individuals can interact with both at the same time. Virtual reality produces immersion of the user in a given environment, which may or may not be controlled, by depriving the perception of the local environment through use of a computerized scenario or one previously captured on video, and experiencing an environment as if it existed.[9-15] With AR, users visualize the real situation in which they are immersed along with a virtual projection of a 3D image. This immersion can be enhanced with sound, touch and smell through integrated external components.[10,11,13,16-18] Increasingly, use of mobile AR (mAR) makes time and location flexible and expands training time.[10,19,20]

Interventional radiology consists of imaging-guided minimally invasive procedures that enable lower morbidity and shorter hospitalization time.[7] Spatial and cognitive proprioception are the main difficulties identified during training.[21,22] Acquisition of skills to use new devices is also a common issue, which can cause tragic outcomes, especially at the start of a career.[21,22] Therefore, AR may improve medical teaching and enhance skills relating to given procedures.[23,24] Preliminary studies comparing use of AR with traditional teaching methods have produced promising results.[3,4,25]

There is no systematic review about augmented reality in interventional radiology.

OBJECTIVE

The aim of this study was to identify, systematically analyze and summarize the best available evidence comparing AR teaching techniques with various other methods in interventional radiology.

METHODS

The PICO technique (Population, Intervention, Comparison, Outcome) was used to define the study, as follows:

P = Undergraduate healthcare students; postgraduate trainees; continuous professional development training – independent of the specialties.

I = Augmented reality to teach interventional radiology.

C = Traditional methodology versus AR.

O = Improve ultrasound skills to achieve an accurate diagnosis

Study model

This systematic review was executed in accordance with the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) and Best Evidence Medical Education (https://www.bemecollaboration.org/), and was registered in the Open Science Framework (https://osf.io/wn762). This study was exempted from institutional review as no live subjects were studied.

Inclusion criteria

We included studies that compared the AR method with several other teaching methods – phantom, cadavers, porcine method and didactic teaching (books, articles, lectures without the use of AR) – in interventional radiology. No restrictions concerning the language, publication status of the study or population were imposed.

Selection of studies and data extraction

Eligible studies were identified using a two-stage method by two independent reviewers (AYPG, MLD). Disagreements were settled by reaching a consensus. First, after eliminating duplicates, titles and abstracts retrieved through the search strategy were evaluated, thus yielding potentially eligible studies. Second, full-text evaluation of the pre-selected studies was performed to confirm eligibility; this process was carried out through the Rayyan platform (https://rayyan.qcri.org).[26]

Evaluation of methodological quality

The Cochrane Collaboration tool was applied to assess the risk of bias in individual studies and across studies.[27] Eligible randomized controlled trials (RCTs) were analyzed using the quality indicators from Best Evidence Medical Education (BEME) Collaboration Guide no. 11[28] (**Annex 1**) and the Kirkpatrick model (BEME Guide no. 8) (**Table 1**).[29,30] According to BEME Guide no. 11, higher quality studies meet a minimum of seven out of eleven indicators. The tools are well established and cover a wide spectrum of methodological issues.

Articles that did not compare teaching methods, along with those with a population dropout rate ≥ 50% (as prescribed in BEME Collaboration Guide no. 11) and those analyzing factors other than medical teaching, were excluded.

Search methods for choosing studies

Electronic searches were performed in the PubMed, Cochrane Library, Embase, ERIC, CINAHL, Tripdatabase and SciELO

Table 1. Kirkpatrick's hierarchy[30]

Level	Feature	Evaluation
1	Reaction	Participants' opinions about the learning experience, its organization, presentation, content, teaching methods and quality of instruction
2A	Learning - Change in attitude	Changes in attitudes or perceptions among participating groups concerning teaching and learning
2B	Learning - Modification of knowledge or skills	For knowledge, this refers to acquisition of concepts, procedures and principles For skills, this refers to acquisition of thinking/problem-solving, psychomotor and social skills
3	Behavior - Behavioral change	Documents transfer learning to the workplace or students' willingness to apply new knowledge and skills
4A	Results - Change in the organizational system/ practice	Refers to broader changes in the organization, attributable to the educational program
4B	Results - Change between participants, students, residents or colleagues	Refers to the improvement in learning/performance of students or residents as a direct result of educational intervention

databases, using the following MeSH terms: Interventional Radiology; Virtual Reality; Augmented Reality; Video Games; Computer Simulation; Education, Medical; Teaching; and Simulation Training.

References from the studies included and from the main reviews on the subject were also analyzed. The search strategies were carried out on July 29, 2020, for each database, and are shown in **Table 2**.

RESULTS

The search yielded 5189 articles; 50 of these were duplicates and were excluded. Through analysis on the titles and abstracts, 56 articles were selected for full-text evaluation, out of which four were included (**Figure 1**). Among these 56 articles, Grasso et al.[31] did not evaluate the learning that resulted from the teaching methods and was excluded from the analysis.

Two of the four studies were from Canada[15,17] and used a pre-experience questionnaire; the other two were from the United States[14,18] and used both a pre-experience and a post-experience questionnaire. We found that heterogeneity was present among both the participants and the procedures analyzed. All of these studies were RCTs in which, differently from the intervention group, the control group did not have access to an AR device; while the remaining instructions and other materials (books and didactic lessons) were equal for the two groups.

All of these four studies reported that changes in perspective or judgment occurred in the groups of participants, concerning teaching and learning (Kirkpatrick evidence level 2B).

Regarding procedures, two studies analyzed central venous catheter placement,[14,18] one study evaluated the lumbar puncture procedure[15] and one investigated injection into the interfacetal joint.[17] Although a diversity of issues were analyzed among these trials, the performance achieved through the technique was the main outcome in all of them. Regarding the populations investigated, the participants comprised respiratory therapists, sleep technicians, pre-medical and medical undergraduate students, emergency medicine and surgery residents and anesthesiologists. In three of the studies analyzed,[14,15,17] it was concluded that AR could increase students' skills in interventional radiology.

AR is used in a variety of areas of medicine and no systematic review or clinical trial has been carried out using a homogenous population. Because of the heterogeneous nature of the populations studied, different AR devices analyzed and different medical procedures used in these four RCTs, we did not perform any meta-analysis. **Table 3** shows the quality assessment and risk of bias analysis conducted using the Cochrane Collaboration tool.

Huang et al.[14] enrolled 32 adult novice central line operators (physicians, respiratory therapists and sleep technicians) with no visual or auditory impairments. Comparisons were made between simulations using AR reality glasses and conventional instruction; the AR glasses used were Brother AiRScouter WD-200B AR glasses (Brother International Corp., Bridgewater, New Jersey, United States). The authors did not comment on the cost of the teaching techniques. The AR simulation group undertook a five to ten-minute hands-on instructional course on the AR device; the mean time taken for AR head placement was 71 seconds. No significant difference in the median time taken for internal jugular cannulation or in the median total duration of the procedure was found between the groups. Most participants (71%; n = 23) were successful in cannulating the internal jugular upon the first attempt (12 in the AR group versus 11 in the non-AR group). A significant difference in adherence level between the two groups (22.9 ± 4.1 in the AR group versus 18.1 ± 6.3 in the non-AR group; $\eta^2 = 0.90$; $P = 0.003$) was detected. In the post-exercise questionnaire for the AR group, more than 80% of the participants stated that the instrument did not cause any fatigue and was not too heavy to be uncomfortable. Nonetheless, 30% admitted that the equipment affected their action skills and that it was not easy to regulate. On the other hand, 94% reported that the hand, head and foot interactions were undemanding and 80% stated that the information presented on-screen was suitable and reacted fast enough.

In the study by Wu et al.,[18] 20 medical students and 20 emergency medicine residents were compared with regard to learning central venous catheter positioning. All the participants watched a video explaining how to use Google Glass and how to place an internal jugular central venous access catheter under ultrasound guidance in a simulation task trainer. The participants were randomized into two groups: with and without Google Glass. The ultrasound machine setup was the same between the groups; the intervention group participants were asked to execute the procedure by viewing ultrasound images displayed on their Google Glass screen, while the control group executed the procedure by viewing ultrasound images shown on the ultrasound screen. The Google Glass group took longer to perform the procedure, with longer times spent looking at the patient and monitor and greater numbers of needle redirections, at both training levels (medical students and emergency medicine residents). This may have been due to unfamiliarity with Google Glass, thus requiring more attention throughout the procedure. The responses to the post-exercise questionnaire showed that the majority of the participants were not previously familiar with AR or with wearable computing technology (75% and 60%, respectively); however, 73% reported having some degree of knowledge about Google Glass. Nonetheless, 87% of the participants randomized to Google Glass reported that the instrument was comfortable to use for the procedure.

Keri et al.[15] evaluated the effectiveness of Perk Tutor (GPS extension, Ultrasonix, Canada) in relation to a phantom, as a teaching method among anesthesiology and surgery residents for lumbar puncture procedures. Perk Tutor is a training

Table 2. Search strategy according to the corresponding database

Database	Search strategy
Cochrane Library	#1: MeSH descriptor: [Radiology, Interventional] explode all trees #2: MeSH descriptor: [Virtual Reality] explode all trees #3: MeSH descriptor: [Augmented Reality] explode all #4: MeSH descriptor: [Video Games] explode all trees #5: MeSH descriptor: [Computer Simulation] explode all trees #6: MeSH descriptor: [Education, Medical] explode all trees #7: MeSH descriptor: [Teaching] explode all trees #8: MeSH descriptor: [Simulation Training] explode all trees #9: #1 AND #2 OR #3 OR #4 OR #5 AND #6 OR #7 OR #8
MEDLINE	#1: "Radiology, Interventional"[MeSH] OR (Interventional Radiology) #2: "Virtual Reality" [MeSH] OR (Reality, Virtual) OR (Virtual Reality, Educational) OR (Educational Virtual Realities) OR (Educational Virtual Reality) OR (Reality, Educational Virtual) OR (Virtual Realities, Educational) OR (Virtual Reality, Instructional) OR (Instructional Virtual Realities) OR (Instructional Virtual Reality) OR (Realities, Instructional Virtual) OR (Reality, Instructional Virtual) OR (Virtual Realities, Instructional) OR "Augmented Reality"[MeSH] OR (Augmented Realities) OR (Realities, Augmented) OR (Reality, Augmented) OR (Mixed Reality) OR (Mixed Realities) OR (Realities, Mixed) OR (Reality, Mixed) OR "Video Games"[MeSH] OR (Game, Video) OR (Games, Video) OR (Video Game) OR (Computer Games) OR (Computer Game) OR (Game, Computer) OR (Games, Computer) OR "Computer Simulation"[MeSH] OR (Computer Simulations) OR (Simulation, Computer) OR (Simulations, Computer) OR (Computerized Models) OR (Computerized Model) OR (Model, Computerized) OR (Models, Computerized) OR (Models, Computer) OR (Computer Models) OR (Computer Model) OR (Model, Computer) OR (In Silico) OR (In Silicos) OR (Silico, In) OR (Silicos, In) #3: "Education, Medical"[MeSH] OR (Medical Education) OR "Teaching"[MeSH] OR (Training Techniques) OR (Technique, Training) OR (Techniques, Training) OR (Training Technique) OR (Training Technics) OR (Technic, Training) OR (Technics, Training) OR (Training Technic) OR (Pedagogy) OR (Pedagogies) OR (Teaching Methods) OR (Method, Teaching) OR (Methods, Teaching) OR (Teaching Method) OR (Academic Training) OR (Training, Academic) OR (Training Activities) OR (Activities, Training) OR (Training Activity) OR (Techniques, Educational) OR (Technics, Educational) OR (Educational Technics) OR (Educational Technic) OR (Technic, Educational) OR (Educational Techniques) OR (Educational Technique) OR (Technique, Educational) OR "Simulation Training"[MeSH] OR (Training, Simulation) OR (Interactive Learning) OR (Learning, Interactive) #4: #1 AND #2 AND #3
EMBASE	#1: interventional radiology/exp #2: virtual reality/exp #3: augmented reality/exp #4: video game/exp #5: computer simulation/exp #6: medical education/exp #7: simulation training/exp #8: teaching/exp #9: #1 OR #2 AND #3 OR #4 OR #5 OR #6 AND #7 OR #8
LILACS	#1: mh: "Radiologia Intervencionista" OR (Radiología Intervencional) OR (Radiology, Interventional) OR (H02.403.740.675) #2: mh: "Realidade Virtual" OR (Realidad Virtual) OR (Virtual Reality) OR (Educational Virtual Realities) OR (Educational Virtual Reality) OR (Instructional Virtual Realities) OR (Instructional Virtual Reality) OR (Realities, Instructional Virtual) OR (Reality, Educational Virtual) OR (Reality, Instructional Virtual) OR (Reality, Virtual) OR (Virtual Realities, Educational) OR (Virtual Realities, Instructional) OR (Virtual Reality, Educational) OR (Virtual Reality, Instructional) OR (L01.224.160.875) OR (L01.296.555) OR (SP4.011.127.428.806.030) #3: mh: "Realidade Aumentada" OR (Realidad Aumentada) OR (Augmented Reality) OR (Augmented Reality for Health) OR (Augmented Reality in Clinical Simulations) OR (Augmented Reality in Health Care Education) OR (Augmented Reality in Health) OR (Augmented Reality in Healthcare Education) OR (SP4.011.127.428.806.020) #4: mh: "Jogos de Vídeo" OR (Juegos de Video) OR (Video Games) OR (Computer Game) OR (Computer Games) OR (Game, Computer) OR (Game, Video) OR (Games, Computer) OR (Games, Video) OR (Video Game) OR (I03.450.642.693.930) OR (L01.224.900.930) #5: mh: "Educação de Graduação em Medicina" OR (Educación de Pregrado en Medicina) OR (Education, Medical, Undergraduate) OR (Education, Undergraduate Medical) OR (Medical Education, Undergraduate) OR (Undergraduate Medical Education) OR (I02.358.399.450) #6: mh: "Treinamento por Simulação" OR (Entrenamiento Simulado) OR (Simulation Training) OR (Interactive Learning) OR (Learning, Interactive) OR (Training, Simulation) OR (I02.903.847) #7: #1 AND #2 OR #3 OR #4 AND #5 OR #6

Continue...

Table 2. Continuation

Database	Search strategy
Tripdatabase	(Interventional radiology)(Virtual reality OR Augmented reality OR Video game OR Computer simulation) (Medical education OR Simulation training OR Teaching)
ERIC	#1: Interventional radiology #2: Virtual reality #3: Augmented reality #4: Video game #5: Computer simulation #6: Medical education #7: Simulation training #8: Teaching #9: #1 OR #2 AND #3 OR #4 OR #5 OR #6 AND #7 OR #8
CINAHL	#1: Interventional radiology #2: Virtual reality OR vr OR augmented reality OR video games OR computer simulation #3: Medical education OR simulation training or simulation education or simulation learning OR teaching #4: #1 AND #@ AND #3
SciELO	#1: Interventional radiology #2: Virtual reality #3: Augmented reality #4: Video game #5: Computer simulation #6: Medical education #7: Simulation training #8: Teaching #9: #1 OR #2 AND #3 OR #4 OR #5 OR #6 AND #7 OR #8

platform that was designed to display ultrasound images along with real-time three-dimensional images, using wearable technology. The authors did not comment on the participants' experience levels regarding AR. There were 24 participants, who were divided into two groups (ten anesthesiologists and two surgeons): Perk Tutor with phantom and phantom alone. All the participants received a short presentation on spinal anatomy, ultrasound basics and how to use the device. They were also trained to perform ultrasound-guided procedures on three different lumbar spine models. The participants were then tested using conventional ultrasound guidance on an abnormal spinal model that they had not previously seen, for ten minutes at most or until positive fluid backflow ws observed at the needle hub. The potential tissue damage, needle path in tissue, total duration of the procedure and time taken to insert the needle were measured. Eleven participants in the phantom group and all participants in the Perk Tutor with phantom group performed the task successfully. The potential for tissue lesion was significantly lower in the Perk Tutor with phantom group (39.7 [range 21.3-42.7] square centimeters (cm^2) versus 128.3 [50.3-208.2] cm^2). Moreover, the needle tissue path was shorter (426.0 [range 164.9-571.6] millimeters (mm) versus 629.7 [306.4-2,879.1] mm), as also was the time taken to insert the needle (30.3 [14.0-51.0] seconds (sec) versus 59.1 [26.0-136.2] sec). The total duration of the procedure was similar (203.8 [range 135.1-274.9] sec versus 266.9 [221.6-416.2] sec).

Moult et al.[17] compared the performances of 26 pre-medical undergraduate students (with no prior needle insertion experience) in a task of injection into the interfacetal joint. Participants were divided equally into two groups: Perk Tutor with phantom and phantom only. The authors did not comment on the cost of the teaching techniques. Both groups received a ten-minute introductory class on anatomy, procedure, ultrasound image interpretation and needle handling techniques. Afterwards, both groups had a ten-minute practice session on ultrasound-guided facet joint injections on the phantom; the Perk Tutor group had access to ultrasound and Perk Tutor, while the phantom group only had access to the ultrasound machine. The Perk Tutor and phantom group had a mean success rate of 61.5%, while this rate was 38.5% in the phantom only group; the total duration of the procedure was longer in the phantom only group (73 ± 8 versus 66 ± 6 seconds). The total needle distance travel (inside and outside of the phantom body) was greater in the phantom only group (1803 ± 290 versus 1366 ± 185 mm), but the inside distance traveled was shorter (25 ± 3 versus 42 ± 16 mm) in this group. Moreover, within the phantom body, the needle tip time was greater in the Perk Tutor and phantom group (296 ± 45 seconds versus 243 ± 28 seconds).

All of these results are summarized in **Table 4**.[14,15,17,18]

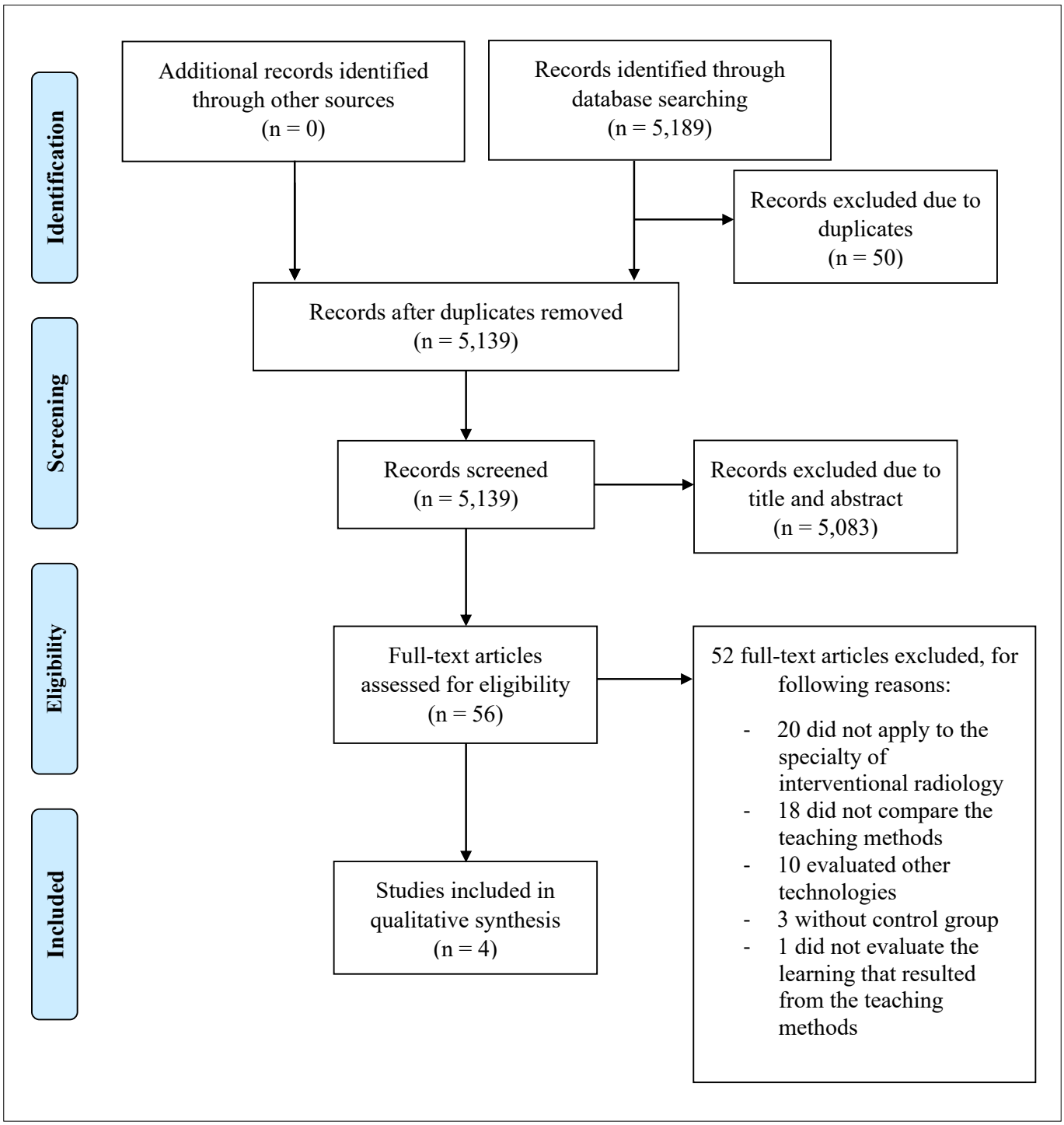


Figure 1. PRISMA flow diagram of study selection.

Table 3. Quality assessment/risk of bias analysis using the Cochrane Collaboration tool

	Underlying bias	Resource bias	Setting bias	Educational bias	Content bias
Huang et al.[14]	+	-	+	+	+
Keri et al.[15]	+	+	-	+	+
Moult et al.[17]	+	-	+	+	+
Wu et al.[18]	-	-	+	+	+

+ Low risk of bias. - Unclear risk of bias.

Table 4. Summary of studies' findings.

Study	Country	Design	Participants	Procedure	Intervention	Comparison	Results	Kirkpatrick
Huang et al.[14]	United States	Randomized clinical trial with pre and post-experience questionnaire	32 novice central line operators including physicians, respiratory therapists and sleep technicians	Positioning of the central venous catheter	- Augmented reality glasses - Brother AiRScouter WD-200B AR glasses - 17 participants	- No augmented reality glasses - 15 participants	Participants who trained in AR needed fewer attempts to perform the procedure.	2B
Keri et al.[15]	Canada	Randomized clinical trial with pre-experience questionnaire	24 anesthesiology and surgery residents	Lumbar puncture	- Perk Tutor + phantom - 12 participants	- Phantom only - 12 participants	Participants who trained in AR injured less tissue and were quicker to insert the needle	2B
Moult et al.[17]	Canada	Randomized clinical trial with pre-experience questionnaire	26 pre-medical undergraduate students	Injection into interfacetal joint	- Perk Tutor + phantom - 13 participants	- Phantom only - 13 participants	Participants who trained in AR obtained much better results, especially regarding the total duration of the procedure.	2B
Wu et al.[18]	United States	Randomized clinical trial with pre and post-experience questionnaire	10 1st and 10 4th year medical students; 10 1st year emergency residents and 10 3rd year residents	Positioning of a central venous catheter	- Google Glass - 5 participants	- Without Google Glass - 5 participants	Glass users took longer to complete the procedure.	2B

DISCUSSION

The objective of our study was to examine the current evidence on training using AR in interventional radiology and its performance, along with the impact of AR on educational outcomes and skills, and its main advantages, disadvantages and challenges during the teaching-learning process.

New teaching techniques such as virtual reality (VR), AR or mixed reality (MR) are being introduced in medical education.[5,32] AR combines virtual and real-world through use of wearable technology that provides a live feed from computer workstations (i.e. from an ultrasound device).[18] Images and information are shown in the user's line of sight through the device.[18]

Everyday use of mobile devices facilitates implementation of this instructional tool in teaching processes, which permits access to learning at any moment.[33,34] However there is still a lack of research regarding the competence of this technology.[33]

AR methods have stood out in the surgical environment over recent years, through providing educational simulation practice free from potential ethical/hygiene concerns.[35] Furthermore, the pressure imposed on healthcare systems during the COVID-19 pandemic has hastened implementation of new technologies, thereby accelerating the learning of healthcare professionals.[36]

Students are now used to dealing with technologies such as the internet, 3D video games, cell phones and others.[19,20,37-40] Teachers can avail themselves of this familiarity to upgrade teaching methods and aids, so as to encourage students.[19,37,41] Kotcherlakota et al. evaluated the utility of clinical simulation through applying AR technology to education outcomes for nurse practitioners in pediatric asthma management.[42] The students showed high motivation, satisfaction and confidence scores.[42] A systematic review by Barteit et al., on AR, VR and MR in several medical specialties, showed similar outcomes that revealed that these techniques were at least not inferior to traditional teaching methods.[43] Moreover, these technologies offer opportunities for scalability and repetition without risk to patients.[43]

A systematic review by Rad et al. demonstrated that, in thoracic surgery, AR-enhanced intraoperative knowledge of anatomy decreased preoperative preparation time and workload.[35] However, with regard to anatomy education, Bölek et al. concluded from a meta-analysis on five studies with a total of 508 participants that AR did not have any meaningful advantages or disadvantages for students' education, compared with several traditional educational tools.[44]

AR could form a viable tool within traditional anatomy teaching in more technological environments.[44] Küçük et al. found that neuroanatomy learning using AR with a smartphone provided support for students, through reducing cognitive effort and increasing educational pleasure.[19] According to our systematic review, the results regarding AR are similar in several medical specialties.

The main purpose of AR involves the concept of "practice makes perfection", given that efficient performance in procedures requires experience.[45] AR simulation provides the possibility of repetition to boost self-confidence, within a safe method.[46]

Over five million central venous catheters are fitted each year in the United States. The complication rates are 5%-8% higher per procedure when these are handled by novice professionals.[14] Teaching with AR aids could result in lower morbidity, hospitalization time and costs.

Comparison of learning between novice physicians and experienced interventional radiologists could enable evaluation of whether AR has the capacity to accelerate learning. Studies comparing different kinds of AR in one specified procedure need to be performed in order to determine which technology is better for that particular procedure. From the current information available, AR is a useful additional tool for teaching interventional radiology, but not a substitute for the traditional methodology.

From the students' perspective, AR can contribute to mastery and confidence in a new procedure, through enabling students to memorize details, thus decreasing the tension in real-life situations. Regarding classroom ambience, AR may enable a shift from the monotonous routine of expository classes, thus providing evolution of the learning experience. Assembling education with technology would engage young people, thereby transforming learning into a pleasant experience and improving learning, as well as clinical practice.

One limitation of this systematic review was that only two studies analyzed the same procedure.[14,18] Numerous procedures are involved in interventional radiology, but in the four studies evaluated, only three different procedures were investigated: central venous catheter placement, lumbar punctures and interfacetal joint injection. Two different types of AR devices were tested: Perk Tutor and AR glasses. Different AR devices could be compared in the future. Moreover, the small samples used in the studies represented another limitation, thus hampering generalization.

Another limitation was the lack of evaluation among experienced professionals. The participants included in these studies were novice physicians or non-physicians; none of these studies investigated radiology residents.

The level of evidence of the studies was also a limitation: all of them were classified as 2B in the Kirkpatrick model.[29] Our searches did not retrieve any studies with educational evidence at level 3 (behavioral change), 4A (change in the organizational system/practice) or 4B (change among participants, students, residents or colleagues). Despite the current interest[22] in using simulators, it remains to be delineated which types of simulation and simulator should be used, and what population this teaching method will be applied to. Hence, a higher level of evidence is needed.

Hardware needs are also a concern, considering that running the application produced intense energy usage as well as device heating.[34] These technical difficulties could be resolved by the smartphone industry. Use of faster networks enables a shared environment through cloud services and shared real-time information. Introduction of artificial intelligence to AR-based learning programs can also provide more positive learning.

The costs of AR devices are expected to decrease along with the evolution of production and increased market competition, thus bringing these technologies to low-income countries. Moreover, AR-based medical training could facilitate teaching for people with reading limitations and could also facilitate remote teaching.

CONCLUSION

It was demonstrated through this study that AR, as a complementary tool, can add skills to learners and thus can improve the teaching-learning process. It needs to be noted that only level 2B studies were found in this systematic review and, thus, that a higher level of evidence is required. Moreover, comparison of beginner physicians and expert interventional radiologists could enable appraisal of the hastening of the learning curve through AR, as well as investigation of which set of AR tools is most adequate for each procedure.

REFERENCES

1. Silva AB, de Amorim AC. A Brazilian educational experiment: teleradiology on web TV. J Telemed Telecare. 2009;15(7):373-6. PMID: 19815908; https://doi.org/10.1258/jtt.2009.090204.
2. Duarte ML, Santos LR, Guimarães Júnior JB, Peccin MS. Learning anatomy by virtual reality and augmented reality. A scope review. Morphologie. 2020;104(347):254-66. PMID: 32972816; https://doi.org/10.1016/j.morpho.2020.08.004.
3. Cates CU, Lönn L, Gallagher AG. Prospective, randomised and blinded comparison of proficiency-based progression full-physics virtual reality simulator training versus invasive vascular experience for learning carotid artery angiography by very experienced operators. BMJ Stel. 2016;2:1-5. https://doi.org/10.1136/bmjstel-2015-000090.
4. Kreiser K, Gehling K, Zimmer C. Simulation in Angiography - Experiences from 5 Years Teaching, Training, and Research. Rofo. 2019;191(6):547-52. PMID: 30754054; https://doi.org/10.1055/a-0759-2248.
5. Chaer RA, Derubertis BG, Lin SC, et al. Simulation improves resident performance in catheter-based intervention: results of a randomized, controlled study. Ann Surg. 2006;244(3):343–52. PMID: 16926560; https://doi.org/10.1097/01.sla.0000234932.88487.75.
6. Mirza S, Athreya S. Review of Simulation Training in Interventional Radiology. Acad Radiol. 2018;25(4):529-39. PMID: 29221857; doi: https://doi.org/10.1016/j.acra.2017.10.009.
7. Johnson SJ, Guediri SM, Kilkenny C, Clough PJ. Development and validation of a virtual reality simulator: human factors input to interventional radiology training. Hum Factors. 2011;53(6):612-25. PMID: 22235524; https://doi.org/10.1177/0018720811425042.

8. Willaert WI, Aggarwal R, Daruwalla F, et al. European Virtual Reality Endovascular Research Team EVEResT. Simulated procedure rehearsal is more effective than a preoperative generic warm-up for endovascular procedures. Ann Surg. 2012;255(6):1184-9. PMID: 22566016; https://doi.org/10.1097/SLA.0b013e31824f9dbf.
9. Chytas D, Johnson EO, Piagkou M, et al. The role of augmented reality in anatomical education: An overview. Ann Anat. 2020;229:151463. PMID: 31978568; https://doi.org/10.1016/j.aanat.2020.151463.
10. Aebersold M, Voepel-Lewis T, Cherara L, et al. Interactive Anatomy-Augmented Virtual Simulation Training. Clin Simul Nurs. 2018;15:34-41. PMID: 29861797; https://doi.org/10.1016/j.ecns.2017.09.008.
11. Mahmood F, Mahmood E, Dorfman RG, et al. Augmented Reality and Ultrasound Education: Initial Experience. J Cardiothorac Vasc Anesth. 2018;32(3):1363-7. PMID: 29452879; https://doi.org/10.1053/j.jvca.2017.12.006.
12. Dhar P, Rocks T, Samarasinghe RM, Stephenson G, Smith C. Augmented reality in medical education: students' experiences and learning outcomes. Med Educ Online. 2021 Dec;26(1):1953953. PMID: 34259122; https://doi.org/10.1080/10872981.2021.1953953.
13. Sandrone S, Carlson CE. Future of Neurology & Technology: Virtual and Augmented Reality in Neurology and Neuroscience Education: Applications and Curricular Strategies. Neurology. 2021:10.1212/WNL.0000000000012413. PMID: 34187858; https://doi.org/10.1212/WNL.0000000000012413.
14. Huang CY, Thomas JB, Alismail A, et al. The use of augmented reality glasses in central line simulation: "see one, simulate many, do one competently, and teach everyone". Adv Med Educ Pract. 2018;9:357-63. PMID: 29785148; https://doi.org/10.2147/AMEP.S160704.
15. Keri Z, Sydor D, Ungi T, et al. Computerized training system for ultrasound-guided lumbar puncture on abnormal spine models: a randomized controlled trial. Can J Anaesth. 2015;62(7):777-84. PMID: 25804431; https://doi.org/10.1007/s12630-015-0367-2.
16. Ebner F, De Gregorio A, Schochter F, et al. Effect of an Augmented Reality Ultrasound Trainer App on the Motor Skills Needed for a Kidney Ultrasound: Prospective Trial. JMIR Serious Games. 2019;7(2):e12713. PMID: 31042155; https://doi.org/10.2196/12713.
17. Moult E, Ungi T, Welch M, et al. Ultrasound-guided facet joint injection training using Perk Tutor. Int J Comput Assist Radiol Surg. 2013;8(5):831-6. PMID: 23329279; https://doi.org/10.1007/s11548-012-0811-5.
18. Wu TS, Dameff CJ, Tully JL. Ultrasound-guided central venous access using Google Glass. J Emerg Med. 2014;47(6):668-75. PMID: 25281180; https://doi.org/10.1016/j.jemermed.2014.07.045.
19. Küçük S, Kapakin S, Göktaş Y. Learning anatomy via mobile augmented reality: Effects on achievement and cognitive load. Anat Sci Educ. 2016;9(5):411-21. PMID: 26950521; https://doi.org/10.1002/ase.1603.
20. Jamali SS, Shiratuddin MF, Wong KW, Oskam CL. Utilising Mobile-Augmented Reality for Learning Human Anatomy. Procedia - Social and Behavioral Sciences 2015;197:659-68. https://doi.org/10.1016/j.sbspro.2015.07.054.
21. Gallagher AG, Smith CD. From the operating room of the present to the operating room of the future. Human-factors lessons learned from the minimally invasive surgery revolution. Semin Laparosc Surg. 2003;10(3):127-39. PMID: 14551655; https://doi.org/10.1177/107155170301000306.
22. Aeckersberg G, Gkremoutis A, Schmitz-Rixen T, Kaiser E. The relevance of low-fidelity virtual reality simulators compared with other learning methods in basic endovascular skills training. J Vasc Surg. 2019;69(1):227-35. PMID: 30579447; https://doi.org/10.1016/j.jvs.2018.10.047.
23. Markovic J, Peyser C, Cavoores T, et al. Impact of endovascular simulator training on vascular surgery as a career choice in medical students. J Vasc Surg. 2012;55(5):1515-21. PMID: 22464708; https://doi.org/10.1016/j.jvs.2011.11.060.
24. Stromberga Z, Phelps C, Smith J, Moro C. Teaching with Disruptive Technology: The Use of Augmented, Virtual, and Mixed Reality (HoloLens) for Disease Education. Adv Exp Med Biol. 2021;1317:147-62. PMID: 33945136.25; https://doi.org/10.1007/978-3-030-61125-5_8.
25. Berry M, Reznick R, Lystig T, Lönn L. The use of virtual reality for training in carotid artery stenting: a construct validation study. Acta Radiol. 2008;49(7):801-5. PMID: 18608009; https://doi.org/10.1080/02841850802108438.
26. Ouzzani M, Hammady H, Fedorowicz Z, Elmagarmid A. Rayyan - a web and mobile app for systematic reviews. Syst Rev. 2016;5(1):210. PMID: 27919275; https://doi.org/10.1186/s13643-016-0384-4.
27. Sterne JAC, Hernan MA, McAleenan A, Reeves BC, Higgins JPT. Chapter 25: assessing risk of bias in a non-randomized study. In: Higgins JPT, Thomas J, Chandler J, Cumpston M, Li T, Page MJ, et al., editors. Cochrane handbook for systematic reviews of interventions version 6.0. Hoboken: John Wiley & Sons; 2019.
28. Buckley S, Coleman J, Davison I, et al. The educational effects of portfolios on undergraduate student learning: a Best Evidence Medical Education (BEME) systematic review. BEME Guide No. 11. Med Teach. 2009;31(4):282-98. PMID: 19404891; https://doi.org/10.1080/01421590902889897.
29. Steinert Y, Mann K, Centeno A, et al. A systematic review of faculty development initiatives designed to improve teaching effectiveness in medical education: BEME Guide No. 8. Med Teach. 2006;28(6):497-526. PMID: 17074699; https://doi.org/10.1080/01421590600902976.
30. Kirkpatrick D, Kirkpatrick J. Evaluating training programs: The four levels. 3rd ed. San Francisco, CA: Berrett-Koehler; 2006.
31. Grasso RF, Faiella E, Luppi G, et al. Percutaneous lung biopsy: comparison between an augmented reality CT navigation system and standard CT-guided technique. Int J Comput Assist Radiol Surg. 2013;8(5):837-48. PMID: 23377707; https://doi.org/10.1007/s11548-013-0816-8.
32. Gelmini AYP, Duarte ML, de Assis AM, Guimarães Junior JB, Carnevale FC. Virtual reality in interventional radiology education: a systematic review. Radiol Bras. 2021;54(4):254-60. PMID: 34393293; https://doi.org/10.1590/0100-3984.2020.0162.

33. Rodríguez-Abad C, Fernández-de-la-Iglesia JD, Martínez-Santos AE, Rodríguez-González R. A Systematic Review of Augmented Reality in Health Sciences: A Guide to Decision-Making in Higher Education. Int J Environ Res Public Health. 2021;18(8):4262. PMID: 33920528; https://doi.org/10.3390/ijerph18084262.
34. Mladenovic R, Matvijenko V, Subaric L, Mladenovic K. Augmented reality as e-learning tool for intraoral examination and dental charting during COVID-19 era. J Dent Educ. 2021. PMID: 34420217; https://doi.org/10.1002/jdd.12780. Epub ahead of print.
35. Arjomandi Rad A, Vardanyan R, Thavarajasingam SG, et al. Extended, virtual and augmented reality in thoracic surgery: a systematic review. Interact Cardiovasc Thorac Surg. 2021:ivab241. PMID: 34542639; https://doi.org/10.1093/icvts/ivab241.
36. Ha J, Parekh P, Gamble D, et al. Opportunities and challenges of using augmented reality and heads-up display in orthopaedic surgery: A narrative review. J Clin Orthop Trauma. 2021;18:209-15. PMID: 34026489; https://doi.org/10.1016/j.jcot.2021.04.031.
37. Ferrer-Torregrosa J, Jiménez-Rodríguez MÁ, Torralba-Estelles J, et al. Distance learning ects and flipped classroom in the anatomy learning: comparative study of the use of augmented reality, video and notes. BMC Med Educ. 2016;16(1):230. PMID: 27581521; https://doi.org/10.1186/s12909-016-0757-3.
38. Moro C, Štromberga Z, Raikos A, Stirling A. The effectiveness of virtual and augmented reality in health sciences and medical anatomy. Anat Sci Educ. 2017;10(6):549-59. PMID: 28419750; https://doi.org/10.1002/ase.1696.
39. McNulty JA, Sonntag B, Sinacore JM. Evaluation of computer-aided instruction in a gross anatomy course: a six-year study. Anat Sci Educ. 2009;2(1):2-8. PMID: 19217066; https://doi.org/10.1002/ase.66.
40. McNulty JA, Halama J, Espiritu B. Evaluation of computer-aided instruction in the medical gross anatomy curriculum. Clin Anat. 2004;17(1):73-8. PMID: 14695594; https://doi.org/10.1002/ca.10188.
41. Lynch TG, Steele DJ, Johnson Palensky JE, Lacy NL, Duffy SW. Learning preferences, computer attitudes, and test performance with computer-aided instruction. Am J Surg. 2001;181(4):368-71. PMID: 11438276; https://doi.org/10.1016/s0002-9610(01)00575-x.
42. Kotcherlakota S, Pelish P, Hoffman K, Kupzyk K, Rejda P. Augmented Reality Technology as a Teaching Strategy for Learning Pediatric Asthma Management: Mixed Methods Study. JMIR Nurs. 2020;3(1):e23963. PMID: 34406970; https://doi.org/10.2196/23963.
43. Barteit S, Lanfermann L, Bärnighausen T, Neuhann F, Beiersmann C. Augmented, Mixed, and Virtual Reality-Based Head-Mounted Devices for Medical Education: Systematic Review. JMIR Serious Games. 2021;9(3):e29080. PMID: 34255668; https://doi.org/10.2196/29080.
44. Bölek KA, De Jong G, Henssen D. The effectiveness of the use of augmented reality in anatomy education: a systematic review and meta-analysis. Sci Rep. 2021 Jul 27;11(1):15292. PMID: 34315955; https://doi.org/10.1038/s41598-021-94721-4.
45. Patel R, Dennick R. Simulation based teaching in interventional radiology training: is it effective? Clin Radiol. 2017;72(3):266.e7-.e14. PMID: 27986263; https://doi.org/10.1016/j.crad.2016.10.014.
46. Aggarwal R, Black SA, Hance JR, Darzi A, Cheshire NJ. Virtual reality simulation training can improve inexperienced surgeons' endovascular skills. Eur J Vasc Endovasc Surg. 2006;31(6):588-93. PMID: 16387517; https://doi.org/10.1016/j.ejvs.2005.11.009.

Authors' contributions: Gelmini AYP: formal analysis (equal), funding acquisition (equal), resources (equal), software (equal) and writing-review and editing (equal); Duarte ML: conceptualization (equal), data curation (equal), formal analysis (equal), investigation (equal), methodology (equal), project administration (equal), validation (equal), visualization (equal), writing-original draft (equal) and writing-review and editing (equal); Silva MO: data curation (equal), formal analysis (equal), resources (equal), software (equal), supervision (equal), writing-original draft (equal) and writing-review and editing (equal); Guimarães Júnior JB: investigation (equal), methodology (equal), project administration (equal), software (equal), supervision (equal), validation (equal), visualization (equal), writing-original draft (equal) and writing-review and editing (equal); and Santos LR: data curation (equal), formal analysis (equal), funding acquisition (equal), investigation (equal), methodology (equal), validation (equal), visualization (equal), writing-original draft (equal) and writing-review and editing (equal)

Sources of funding: No funding was received for this study
Conflicts of interests: The authors declare that they did not have any conflict of interest

Date of first submission: July 11, 2021
Last received: November 24, 2021
Accepted: December 27, 2021

Address for correspondence:
Márcio Luís Duarte
Programa de Pós-graduação: Saúde Baseada em Evidências,
Universidade Federal de São Paulo (UNIFESP)
R. Napoleão de Barros, 865
Vila Clementino — São Paulo (SP) — Brasil
CEP 04024-002
Tel. (+55 11) 5576-4848
E-mail: marcioluisduarte@gmail.com

Annex 1. The 11 questions in BEME GUIDE no. 11 are as follows:

1. Are the research question(s) or hypothesis clearly defined?
2. Is the group of participants appropriate for the study being carried out (number, characteristics, selection and homogeneity)?
3. Are the methods used (qualitative or quantitative) reliable and valid for the research question and context?
4. Did the participants drop out? Is the dropout rate below 50%? For questionnaire-based studies, is the response rate acceptable (60% or more)?
5. Have several factors/variables been removed or accounted for whenever possible?
6. Are the statistical methods or other methods of analyzing the results used appropriately?
7. Is it clear that the data justify the conclusions drawn?
8. Could the study be repeated by other researchers?
9. Does the study look forward in time (prospective) and not backward (retrospective)?
10. Have all relevant ethical issues been addressed?
11. Were the results supported by data from more than one source?

Common mental disorders among medical students: systematic review and meta-analysis of Brazilian studies

Silvio José Batista Soares[I], Cláudia Fernanda Garcez Fernandes[II], Renata Tabalipa[III], Felipe Kogima[IV], Marcelo Augusto Moreira Jubini[V], Isabella Martins Vieira Dias[VI], Victor Emanuel Miranda Soares[VII], Severina Silva Amaral[VIII], Michele Santos da Cruz[IX], Paulo Henrique Guerra[X]

Universidade Federal da Fronteira Sul (UFFS), Chapecó (SC), Brazil

[I]Undergraduate Medicine Student, Department of Medicine, Universidade Federal da Fronteira Sul (UFFS), Chapecó (SC), Brazil.
https://orcid.org/0000-0001-8286-2154

[II]Undergraduate Medicine Student, Department of Medicine, Universidade Federal da Fronteira Sul (UFFS), Chapecó (SC), Brazil.
https://orcid.org/0000-0002-7926-2366

[III]Undergraduate Medicine Student, Department of Medicine, Universidade Federal da Fronteira Sul (UFFS), Chapecó (SC), Brazil.
https://orcid.org/0000-0003-3280-6925

[IV]Undergraduate Medicine Student, Department of Medicine, Universidade Federal da Fronteira Sul (UFFS), Chapecó (SC), Brazil.
https://orcid.org/0000-0002-8755-8474

[V]Undergraduate Medicine Student, Department of Medicine, Universidade Federal da Fronteira Sul (UFFS), Chapecó (SC), Brazil.
https://orcid.org/0000-0002-0770-8584

[VI]Undergraduate Medicine Student, Department of Medicine, Universidade Federal da Fronteira Sul (UFFS), Chapecó (SC), Brazil.
https://orcid.org/0000-0001-7775-0481

[VII]Undergraduate Medicine Student, Department of Medicine, Universidade Federal da Fronteira Sul (UFFS), Chapecó (SC), Brazil.
https://orcid.org/0000-0003-4080-7602

[VIII]Undergraduate Medicine Student, Department of Medicine, Universidade Federal da Fronteira Sul (UFFS), Chapecó (SC), Brazil.
https://orcid.org/0000-0001-6052-3821

[IX]MSc. Doctoral Student, Postgraduate Program on Nutrition, Universidade de São Paulo (USP), São Paulo (SP), Brazil.
https://orcid.org/0000-0002-5324-1233

[X]DSc. Associate Professor, Department of Medicine, Universidade Federal da Fronteira Sul (UFFS), Chapecó (SC), Brazil.
https://orcid.org/0000-0003-4239-0716

KEY WORDS (MeSH terms):
Mental health.
Education, medical, undergraduate.
Review [publication type].
Brazil.

AUTHORS' KEY WORDS:
Common mental disorders.
Prevalence.
Medical students.

ABSTRACT

BACKGROUND: Common mental disorders (CMDs) have been correlated with consequences in different domains of life.

OBJECTIVE: To summarize the prevalence rates of CMDs and factors associated with them among students at Brazilian medical schools.

DESIGN AND SETTING: Systematic review and meta-analysis of studies developed in Brazilian medical schools.

METHODS: In October 2021, searches were carried out in seven electronic databases, in Google Scholar and in reference lists. Observational studies reporting prevalence rates of CMDs among students at Brazilian medical schools were sought. Variables associated with CMDs arising from multivariate regression models were included in the synthesis. A meta-analysis was developed using a random-effects model and the risk of bias was assessed using an instrument developed from previous references.

RESULTS: Fourteen original studies were included. The pooled prevalence rate of CMDs among undergraduate students at Brazilian medical schools was 43.3% (95% confidence interval = 38.9% to 47.6%; I^2 = 87%; n = 3,927). Among the nine studies in which multivariate analyses were conducted, five showed risk associations between CMDs and medical school-related dissatisfactions, among which the desire to abandon the medical course can be highlighted (n = 3). In three studies, CMDs were associated with sleep indicators.

CONCLUSION: Considering that the prevalence of CMDs among medical students is higher than in the general population, we recommend that Brazilian medical schools should give greater attention to this topic, and should enable expansion of care offerings relating to mental health.

SYSTEMATIC REVIEW REGISTRATION: Prospective Register of Systematic Reviews (PROSPERO) database (CRD42020142184).

INTRODUCTION

Medical courses are, as a rule, characterized by an integral routine of theoretical and practical activities, early insertion in a *praxis* that has little margin for errors and permanent contact with illness and death. In the Brazilian context, it is recognized that these demands are associated with different health risk behaviors, such deprivation of sleep[1] and leisure,[2] which, in turn, are determinants of mental health.[3,4]

Since the mental health indicators observed among Brazilian medical students are generally poorer than those observed in the general population,[5] the mental health of medical undergraduate students is an emerging agenda in Brazilian research, enhanced by recognition of the most drastic outcomes associated with it.[3] For example, common mental disorders (CMDs) are one of the mental health indicators that have been studied in these populations.[5]

CMDs present as a mixture of somatic, anxiety-related and depressive symptoms, such as insomnia, irritability, forgetfulness and difficulty in concentrating, among others.[6] However, these symptoms do not meet sufficient formal criteria to be diagnosed as depression or anxiety, according to the classifications of the DSM-V (Diagnostic and Statistical Manual of Mental Disorders, 5th edition) and the International Classification of Diseases, 11th revision (ICD-11).[7]

Nonetheless, the literature available suggests that CMD symptoms among Brazilian medical students are already observed in the early stages of the medical course.[8] In this sense, it can be understood that early recognition of CMD prevalence rates, as well as the factors associated with

these disorders, can provide support for efforts to address them at different levels. These can range from the strategies available for mental healthcare in medical schools to a broader view of the curricula of Brazilian medical schools.

Considering the distinct biopsychosocial impairments associated with CMDs, identifying the prevalence rates of CMDs and factors associated with them can support development of preventive strategies involving these populations.

OBJECTIVE

Thus, the aim of this study was to identify and statistically summarize CMD prevalence rates and factors associated with these disorders among students at Brazilian medical schools.

METHODS

We developed a systematic review of the literature, with meta-analysis. Its protocol was previously registered in the International Prospective Register of Systematic Reviews (PROSPERO) database (CRD42020142184) and its design and report were developed from the items of the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) checklist.[9]

Our inclusion criteria were formulated from the possible items of the "PICOS" structure, considering the following: (I) Population: students at Brazilian medical schools, without restrictions regarding the stage of the course and the profile of the university (i.e. public or private); (II) Outcome: "common mental disorders", not considering studies that addressed other terminologies and other specific psychiatric disorders/diseases, such as anxiety, stress and depression; and (III) Study design: observational studies (e.g. cross-sectional or cohort studies), without restriction as to their representativeness (i.e. whether local, regional or national), reported in English, Portuguese or Spanish. It is worth mentioning that, in accordance with the study designs of interest, the PICOS items "Intervention" and "Control" were not applicable.

On the other hand, dissertations, theses, abstracts and preprints were not considered for the synthesis. Nor was research involving students on healthcare courses in which no stratified analysis of CMD prevalence rates among medical students was presented.

As our secondary outcome, we sought to identify the variables associated with CMDs in studies in which multivariate regression model-based analyses were conducted (i.e. independent of the regression type and effect measurements presented). This was done while considering their robustness in adjustment of confounders.

Potential studies were screened up to the cutoff date of October 4, 2021, using three strategies: (I) application of search strategies in seven electronic databases (Embase, Lilacs, PsycINFO, PubMed, SciELO, Scopus and Web of Science), based on the syntaxis developed for PubMed: ((((common mental disorder [Text Word]) or (common mental disorder [Text Word])) and (((medicine [Text Word]) or (medical school [Text Word])) or (medical schools [Text Word])))) and ((Brazil [Text Word]) or (Brazilian [Text Word])); (II) searches through the first 200 records of Google Scholar, using the terms "common mental disorder(s)", "medicine", "medical" and "Brazil"; and (III) manual searches in the reference lists of articles that were evaluated through their full texts. In the Lilacs and SciELO databases and in Google Scholar, the terms were also searched in Portuguese. There were no restrictions regarding the year of publication of the articles.

The operational process, which involved analysis of titles, abstracts and full texts, was conducted by four independent researchers, with collaboration from two other researchers to resolve doubts and establish consensus. Searches in Google Scholar were conducted by two researchers, also independently. Data extraction, performed in an electronic spreadsheet, was divided into descriptive information, methods and results, and was also conducted by two researchers, independently, with subsequent verification of the data conducted by another six members, organized in pairs. The descriptive synthesis was elaborated from the main topics of the data extraction worksheet.

The risk of bias of the studies included was assessed considering our primary outcome (i.e. summarized CMD prevalence rates). For this, an adapted version of the quality assessment tool for quantitative studies of the Effective Public Health Practice Project (EPHPP)[10] was used. This covers the following five methodological domains: (I) Selection bias (i.e. information about the sample, such that studies involving all phases of the medical course were considered to present "low risk of bias"); (II) Study design (i.e. methods used in sampling); (III) CMD assessment tool (e.g. which tool was used, a report on its previous validation and information that enables replication of the measurement, in the case of questionnaires developed specifically for the study); (IV) Losses and dropouts (i.e. information on losses and dropouts, along with the percentage of students whose data were analyzed, compared with the initially proposed number); and (V) Analysis protocol (e.g. analysis plan and adequacy of the method used to identify the prevalence of CMDs in the sample). This instrument may be requested from the corresponding author.

A random-effects meta-analysis was conducted, based on the original prevalence rate data from each individual study and the respective 95% confidence interval (CI). Given that variability data is not reported with the 95% CI in many studies, these data were manually calculated from the sample size and the prevalence of identified CMDs and subsequently checked in the statistical software.

To conduct the analysis, the Review Manager software was used (version 5.4; Cochrane Collaboration, 2020). Thus, the summarized effect was constructed from the random model, considering the differences between the samples (e.g. phase/year of the course

and type of institution). The I^2 statistic was used to assess heterogeneity between studies: this was classified as "moderate heterogeneity" when the summarized effects using I^2 were between 50% and 74%, or as "high heterogeneity" when $I^2 \geq 75\%$, as suggested in the study by Higgins et al.[11]

RESULTS

Overall, the searches retrieved 325 potential studies (**Figure 1**). After identification and removal of duplicates (n = 71), 254 studies remained for assessment using their titles and abstracts. At the end of this stage, 20 studies were considered eligible for evaluation using their full texts. Six of these were subsequently excluded, for the following reasons: study design (n = 3); no use of the term "common mental disorders" (n = 2); and lack of presentation of stratified data from undergraduate medical students (n = 1). Thus, the synthesis was developed based on the data from 14 original studies.[8,12-24]

Regarding geographical location, the studies were conducted in ten cities (Aracajú, Blumenau, Botucatu, Jequié, Montes Claros, Ponta Grossa, Salvador, São José do Rio Preto, Vila Velha and Vitória), located in seven Brazilian states (Bahia, Espírito Santo, Minas Gerais, Paraná, Santa Catarina, Sergipe and São Paulo). Regarding study design, twelve studies were cross-sectional[11-15,17-24] and two were longitudinal.[8,16] The samples ranged from 40[16] to 477[20] undergraduate medical students, with a higher frequency of women in nine of these studies (64.3%). Eight studies involved

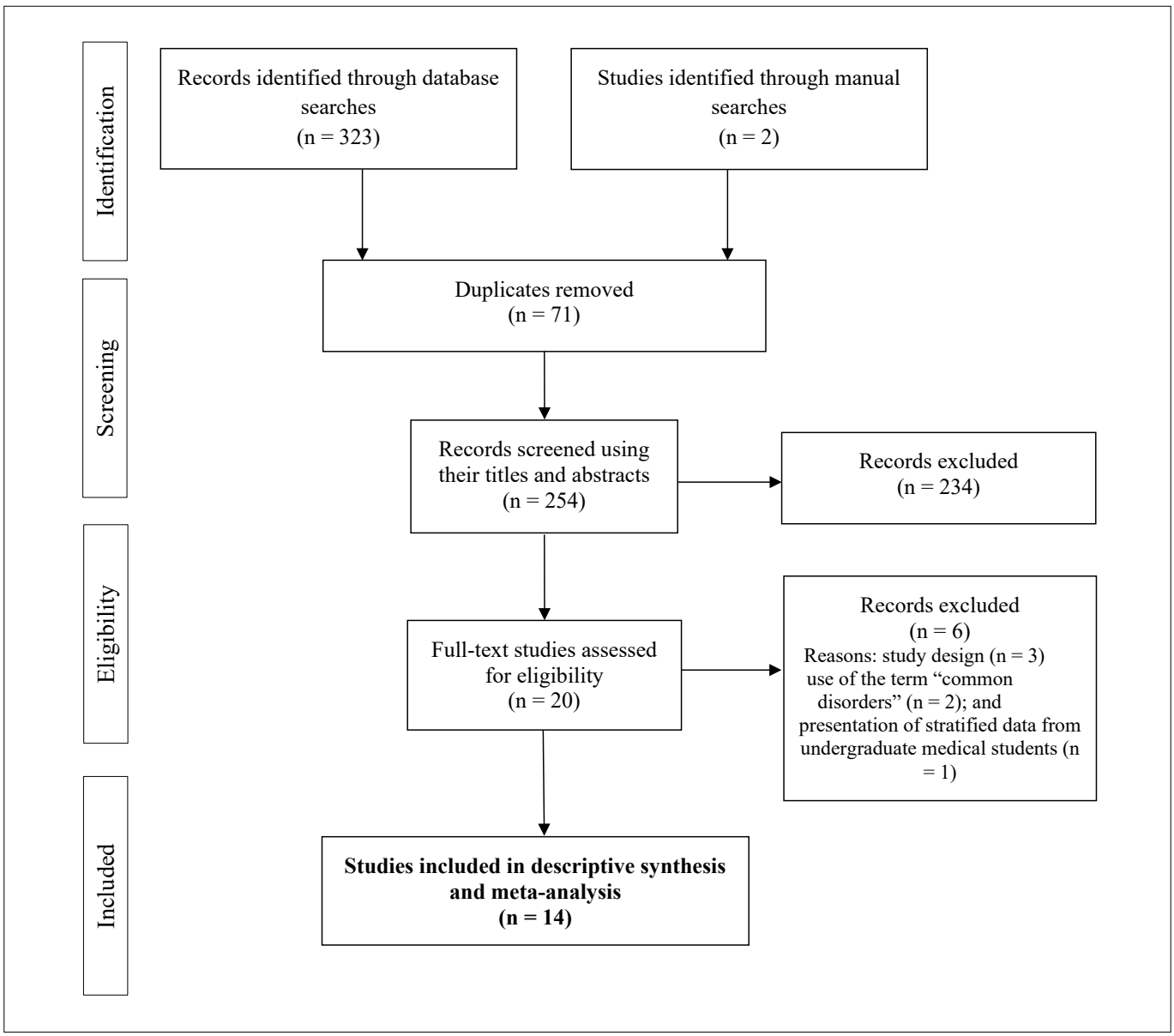


Figure 1. Flowchart of systematic review and meta-analysis.

students enrolled in all stages of the medicine course (57.1%) (**Table 1**).[13,16,17-20,22,24]

Two questionnaires for CMD assessment were identified: the Self Reporting Questionnaire (SRQ-20), in 12 studies (80%);[8,12,14-20,22-24] and the General Health Questionnaire (GHQ-12), in the other two studies.[13,21] The risk-of-bias ratings were low in the majority of the methodological domains assessed. Specifically regarding the "statistical analysis" and the "CMD assessment tool", all the studies included were assessed as presenting low risk of bias. On the other hand, due to limitations in the sampling processes (i.e. convenience-based samples), the "study design" domain was the one most impacted by studies classified as having high risk of bias (n = 6) (**Table 1**).[12,17-19,21,23]

The pooled prevalence rate for CMDs was 43.3% (95% CI = 38.9% to 47.6%; I^2 = 87%; n = 3,927) among the undergraduate medical students at Brazilian medical schools (**Figure 2**). The highest and lowest CMD prevalence rates were found in the studies by Costa et al. (25.9%) and Grether et al. (50.9%), respectively. In view of the high heterogeneity in the primary analysis, a subgroup analysis on the studies that covered undergraduate students from all medicine course stages was conducted. The pooled prevalence was 45.7% (95% CI = 40.8% to 50.7%; I^2 = 85%) (data not shown).

A funnel plot for the overall pooled prevalence rate of CMDs is presented in **Figure 3**. From the funnel shape, it was assessed that there was no significant publication bias in this meta-analysis.

Multivariate regression models to identify factors associated with CMDs were developed in nine studies (64.3%). Despite the differences relating to the types of regression and variables used for adjustment, the results suggest that CMDs were frequently associated with dissatisfaction relating to the medicine course.[12,15,19,22,24] The factors of "desire to quit the course"[19,22,24] and "feeling uncomfortable with the course"[12,15] can be highlighted. Furthermore, risk associations between CMDs and sleep indicators[8,12,22] were also shown (**Table 2**).

DISCUSSION

Based on the data from 14 original studies, the pooled prevalence rate of CMDs was 43.3% among undergraduate students at Brazilian medical schools. Compared with a previous study,[5] which reported a pooled prevalence of 31%, our study had two specificities: inclusion of studies that specifically used the 'common mental disorders' terminology and inclusion of studies that assessed CMDs through questionnaires other than the SRQ-20.

Specifically regarding CMD assessment, it is important to highlight that the GHQ-12 is classified by the Brazilian Federal Council of Psychology as an "unfavorable psychological test" and, therefore, is not indicated for psychologists' professional activities.[25] However, these studies using the GHQ-12 were kept in our synthesis,[13,21] for two reasons: our recognition of a Brazilian validation study on the GHQ-12 in which the SRQ-20 was used as

Table 1. Descriptive characteristics of the studies included (n = 15)

References	Study location (year of data collection)	Number of participants (% of women in the sample)	Stages of medical course covered	Tool used for CMD assessment	Risk-of-bias domains				
					Selection bias	Study design	CMD assessment tool	Losses and dropouts	Statistical analysis protocol
Almeida et al.[12]	Salvador-BA (2005)	223 (48)	2, 4, 6 and 8	SRQ-20	Moderate	Weak	Strong	Strong	Strong
Aragão et al.[13]	nd (nd)	428 (66)	1-12	GHQ-12	Strong	Moderate	Strong	Moderate	Strong
Bellinati et al.[14]	São José do Rio Preto-SP (nd)	118 (77)	1, 5 and 8	SRQ-20	Moderate	Strong	Strong	Strong	Strong
Costa et al.[15]	Aracajú-SE (2006)	473 (50)	2-12	SRQ-20	Strong	Strong	Strong	Strong	Strong
Costa et al.[16]	Aracajú-SE (2006)[a]	40 (58)	1-12[b]	SRQ-20	Strong	Strong	Strong	Strong	Strong
Ferreira et al.[8]	Ponta Grossa-PR (2013)[a]	134 (48)	1-8	SRQ-20	Moderate	Strong	Strong	Strong	Strong
Fiorotti et al.[17]	Vitória-ES (2007)	229 (50)	1-12	SRQ-20	Strong	Weak	Strong	Strong	Strong
Grether et al.[18]	Blumenau-SC (2017)	340 (67)	1-12	SRQ-20	Strong	Weak	Strong	Moderate	Strong
Lima et al.[19]	Botucatu-SP (2002)	455 (61)	1-12	SRQ-20	Strong	Strong	Strong	Strong	Strong
Lima et al.[20]	Botucatu-SP (2011)	477 (59)	1-12	SRQ-20	Strong	Weak	Strong	nd	Strong
Medeiros et al.[21]	Montes Claros-MG (2015)	101 (64)	1	GHQ-12	Weak	Weak	Strong	Moderate	Strong
Melado et al.[22]	Vila Velha-ES (2018)	360 (60)	1-12	SRQ-20	Strong	Strong	Strong	Strong	Strong
Santos et al.[23]	Jequié-BA (2016)	115 (47)	nd	SRQ-20	nd	Weak	Strong	Weak	Strong
Silva et al.[24]	Botucatu-SP (nd)	434 (58)	1-12	SRQ-20	Strong	Strong	Strong	Strong	Strong

[a]Study with repeated measurements in the same sample; [b]A group of students who were followed throughout the six years of their medical course; BA = Bahia; ES = Espírito Santo; GHQ-12 = General Health Questionnaire; MG = Minas Gerais; nd = not described; PR = Paraná; SC = Santa Catarina; SE = Sergipe; SP = São Paulo; SRQ-20 = Self Reporting Questionnaire.

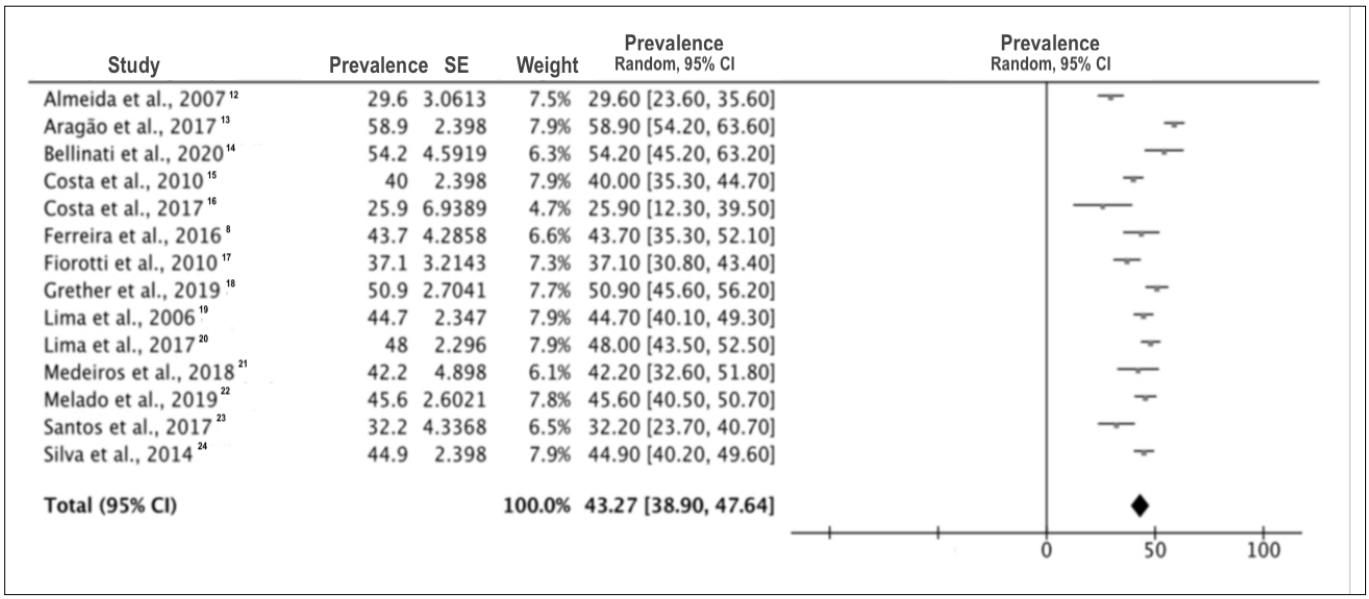
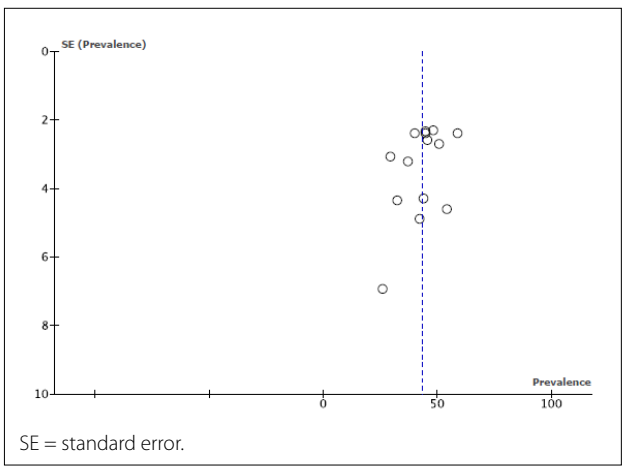


Figure 2. Meta-analysis on the prevalence of common mental disorders among Brazilian medical school students.



SE = standard error.

Figure 3. Funnel plot from the meta-analysis on the prevalence of common mental disorders among Brazilian medical school students

a comparison;[26] and our recognition that the GHQ-12 has been used in other population-based studies.[27,28]

Even though no nationwide survey exists, our findings corroborate the understanding that the prevalence of CMDs observed among Brazilian undergraduate medical students is higher than that of the general adult population.[7,29] We believe that this result is important and can contribute to efforts relating to the debate about the structure of medical courses offered in Brazil, through highlighting the need for provision of specialized mental healthcare for undergraduate students.

From this perspective, one of the actions can consist of monitoring of mental health indicators (e.g. CMDs, burnout syndrome, stress and anxiety) from the outset of the medical course. Previous research has suggested that high levels of stress are observed in pre-university preparatory courses,[30] and absence of care may lead to maintenance and/or worsening of risk indicators as the undergraduate course progresses. Among the studies included in the synthesis, only one specifically involved a sample of freshmen.[21] In that study, in addition to the high prevalence of CMDs (i.e. 42.2%), presence of other negative health indicators was suggested, such as pathological levels of daytime sleepiness, depressive symptoms of varying degrees, emotional exhaustion and depersonalization.[21]

Identifying these indicators in the early phases of the medicine course can be of interest, in order to avoid chronicity among them, along with the more deleterious outcomes mentioned above.[3] Another suggestion is to investigate whether there are phases, course cycles (i.e. basic, clinical or internship) or even moments in each semester when the risk of developing CMDs is higher. It is worth mentioning that in the longitudinal studies by Ferreira et al.[8] and Costa et al.,[16] it was suggested that the prevalence of CMDs increases over the semester[8] and over the years,[16] respectively.

As our secondary result, we also showed that course-related dissatisfaction[12,15,19,22,24] and sleep indicators[19,22,24] were associated with CMDs. Even though three studies pointed out that CMDs were associated with the desire to drop out of medical school, it has been recognized in the literature available that medicine courses have lower dropout rates than nursing, pharmacy and dentistry courses.[31] This finding can largely be explained by different perspectives,

Table 2. Factors associated with common mental disorders that were identified in studies in which multivariate regression analyses were conducted (n = 9)

References	Variables associated with common mental disorders
Almeida et al.[12]	Sleep pattern changes (OR = 6.7; 95% CI = 3.2 to 13.8) Not having own transportation (OR = 3.9; 95% CI = 1.9 to 8.0) Did not have a job (OR = 3.5; 95% CI = 1.0 to 12.4) Not exercising (OR = 2.2; 95% CI = 1.0 to 4.5)
Costa et al.[15]	Not believing in acquiring skills to become a good doctor (OR = 2.8) Being uncomfortable with course activities (OR = 3.8) Considering oneself emotionally tense (OR = 2.1) Not considering oneself happy (OR = 2.9) Finding that the course was less than expected (OR = 1.6) Having a previous diagnosis of mental disorder made by a psychiatrist (OR = 3.8)
Costa et al.[16]	Factors associated in analysis carried out in the 5th year of the course: Female (PR = 1.4) Being from state capital (PR = 1.9) Finding that the course was less than expected (PR = 3.2) Being uncomfortable with course activities (PR = 2.1) Being dissatisfied with teaching strategies (PR = 1.4) Feeling that the course was not a source of pleasure (PR = 2.1)
Ferreira et al.[8]	At beginning of the semester: Monthly family income per capita ≤ R$ 2,000.00 (OR = 3.2; 95% CI = 1.3 to 8.0) Poor sleep quality (OR = 3.3; 95% CI = 1.1 to 9.5) At end of the semester: Poor sleep quality (OR = 3.3; 95% CI = 1.2 to 7.9)
Fiorotti et al.[17]	Not receiving the emotional support needed (OR = 7.4; 95% CI = 3.1 to 17.9) Report of "difficulty in answering questions in the classroom due to shyness" during childhood or adolescence (OR = 2.5; 95% CI = 1.0 to 6.1)
Lima et al.,[19]	Difficulty in making friends (OR = 2.0; 95% CI = 1.2 to 3.3) Poor evaluation of school performance (OR = 1.7; 95% CI = 1.1 to 2.7) Thinking about quitting the course (OR = 5.0; 95% CI = 1.1 to 2.7) Not receiving the emotional support needed (OR = 4.6; 95% CI = 2.0-9.9)
Melado et al.[22]	Mental disorder in the family (RR = 1.2; 95% CI = 1.0 to 1.5) Poor sleep quality (RR = 1.5; 95% CI = 1.2 to 1.9) Fear that affected school performance (RR = 1.3; 95% CI = 1.0 to 1.8) Feeling rejected by friends (RR = 1.5; 95% CI = 1.1 to 1.9) Thinking about quitting the course (RR = 1.7; 95% CI = 1.3 to 2.2) Physical discomfort during the test (RR = 1.6; 95% CI = 1.2 to 2.2)
Santos et al.[23]	Physical domain (adjusted β = 0.9; 95% CI = 0.89 to 0.97) Psychological domain (adjusted β = 0.9; 95% CI = 0.91 to 0.99)
Silva et al.[24]	Feeling rejected in the last year (OR = 2.5; 95% CI = 1.5 to 4.2) Having thought about or thinking about quitting the course (OR = 6.9; 95% CI = 2.4 to 19.4) Interaction (OR = 2.4; 95% CI = 1.4 to 4.2)

CI = confidence interval; OR = odds ratio; PR = prevalence ratio; RR = relative risk; β = beta; R$ = Real, the national currency of Brazil, also known as Brazilian Real (BRL).

such as remuneration, job expectations and social recognition.[32] Nonetheless, apart from the social role of medical doctors and the social constructs that permeate the profession, these associations relating to dissatisfaction and frustration with the course suggest that there is a need for periodic assessment of course workloads. Adoption of innovative strategies that go beyond purely technicist and poorly humanized approaches can also be highlighted.[33]

Regarding sleep indicators, it has been recognized that sleep disorders are associated with other mental health indicators, such as anxiety and depression.[34] The routines required by different curricular components and the pressure for better performance in tasks can lead to constant sleep deprivation. In addition, there is also high and recurrent consumption of psychostimulant substances (e.g. energy drinks and caffeine) among medical students, to prolong their state of alertness.[35] Thus, beyond guidance about the harm of sleep deprivation, better care in the internal organization of courses is suggested, so that overlapping of activities, tests and/or important tasks on specific dates or in specific weeks can be avoided.

In addition, since most of the studies included here had cross-sectional designs, we would recommend that longitudinal studies should be conducted. These would not only investigate whether there are phases/cycles of higher risk of CMDs during the medical course, but also provide understanding of the possible causal relationships between the variables. Therefore, we would emphasize that caution is required in interpreting the findings from this study, since most of the studies included were cross-sectional. This formed a limitation on deeper discussion of temporality and causality, i.e. whether CMDs are the cause or the consequence of sleep disorders.

CONCLUSION

Our study showed that the pooled prevalence rate of CMDs was 43.3% among the undergraduate medical students. It also showed that risk associations existed between CMDs and course-related dissatisfaction and sleep indicators. Considering that the prevalence of CMDs among medical students is higher than in the general population, we recommend that Brazilian medical schools should give greater attention to this topic and should enable expansion of care provision relating to mental health.

REFERENCES

1. Purim KS, Guimarães AT, Titski AC, Leite N. Sleep deprivation and drowsiness of medical residents and medical students. Rev Col Bras Cir. 2016;43(6):438-44. PMID: 28273216; https://doi.org/10.1590/0100-69912016006005.
2. Vieira JL, Romera LA, Lima MCP. Lazer entre universitários da área da saúde: revisão de literatura [Leisure among university students in the healthcare area: a review of the literature]. Cien Saude Colet. 2018;23(12):4221-9. PMID: 30540005; https://doi.org/10.1590/1413-812320182312.31012016.

3. Santa ND, Cantilino A. Suicídio entre médicos e estudantes de medicina: revisão de literatura [A Review of Literature on Suicide among Doctors and Medical Students]. Rev Bras Educ Med. 2016;40(4):772-80. https://doi.org/10.1590/1981-52712015v40n4e00262015.
4. Lessa RT, Fonseca LANS, Silva VL, et al. A privação do sono e suas implicações na saúde humana: uma revisão sistemática da literatura. Rev Eletr Acervo Saude. 2020;56:e3846. https://doi.org/10.25248/reas.e3845.2020.
5. Pacheco JP, Giacomin HT, Tam WW, et al. Mental health problems among medical students in Brazil: a systematic review and meta-analysis. Braz Psychiatry. 2017;39(4):369-78. PMID: 28876408; https://doi.org/10.1590/1516-4446-2017-2223.
6. Goldberg D, Huxley P. Common mental disorders: a bio-social model. Acta Psychiatr Scand Suppl. 1994;385:66-70. PMID: 7740974; https://doi.org/10.1111/j.1600-0447.1994.tb05916.x.
7. Santos GBVD, Alves MCGP, Goldbaum M, Cesar CLG, Gianini RJ. Prevalência de transtornos mentais comuns e fatores associados em moradores da área urbana de São Paulo, Brasil [Prevalence of common mental disorders and associated factors in urban residents of São Paulo, Brazil]. Cad Saude Publica. 2019 Oct 31;35(11):e00236318. PMID: 31691788; https://doi.org/10.1590/0102-311X00236318.
8. Ferreira CMG, Kluthcovsky, ACGC, Cordeiro TMG. Prevalence of Common Mental Disorders and associated factors among Medical students: a Comparative Study. Rev Bras Educ Med. 2016;40(2):268-77. https://doi.org/10.1590/1981-52712015v40n2e02812014.
9. Page MJ, McKenzie JE, Bossuyt PM, et al. The PRISMA 2020 statement: an updated guideline for reporting systematic reviews. Syst Rev. 2021;10(1):89. PMID: 33781348; https://doi.org/10.1186/s13643-021-01626-4.
10. Thomas BH, Ciliska D, Dobbins M, Micucci S. A process for systematically reviewing the literature: providing the research evidence for public health nursing interventions. Worldviews Evid Based Nurs. 2004;1:176-84. PMID: 17163895; https://doi.org/10.1111/j.1524-475X.2004.04006.x.
11. Higgins JP, Thompson SG, Deeks JJ, Altman DG. Measuring inconsistency in meta-analyses. BMJ. 2003;327(7414):557-60. PMID: 12958120; https://doi.org/10.1136/bmj.327.7414.557.
12. Almeida ADM, Godinho TM, Bitencourt AGV, et al. Common Mental Disorders among Medical students. Rev Bras Psiquiatr. 2007;56(4):245-251. https://doi.org/10.1590/S0047-20852007000400002.
13. Aragão JCS, Casiraghi B, Mota EM, et al. Saúde mental em estudantes de Medicina [Mental health in medical students]. Rev Estud Investig Psicol Educ. 2014;14:38-41. https://doi.org/10.17979/reipe.2017.0.14.2267.
14. Bellinati YCG, Campos GAL. Avaliação da prevalência de transtornos mentais comuns nos estudantes de medicina em uma faculdade do interior de São Paulo. Rev Corp Hippoc 2020;1(1). Available from: http://revistas.unilago.edu.br/index.php/revista-medicina/article/view/235. Accessed in 2022 (May 24).
15. Costa, EFO, Andrade TM; Silvany Neto, AM, et al. Common Mental Disorders among medical students at Universidade Federal de Sergipe: a cross-sectional study. Rev Bras Psiquiatr. 2010;32(1):11-9. PMID: 20339730; https://doi.org/10.1590/S1516-44462010000100005.
16. Costa EFO, Mendes CMC, Andrade TM. Common Mental Disorders in Medical students: A repeated cross-sectional study over six years. Rev Assoc Med Bras. 2017;63(9):771-8. https://doi.org/10.1590/1806-9282.63.09.771.
17. Fiorotti KP, Rossoni RR, Borges LH, Miranda AE. Transtornos mentais comuns entre os estudantes do curso de medicina: prevalência e fatores associados [Common mental disorders in medical students: prevalence and associated factors]. J Bras Psiquiatr. 2010;59(1):17-23. https://doi.org/10.1590/S0047-20852010000100003.
18. Grether EO, Becker MC, Menezes HM, Nunes CRDO. Prevalência de Transtornos Mentais Comuns entre estudantes de Medicina da Universidade Regional de Blumenau (SC) [Prevalence of Common Mental Disorders in Medical Students from Universidade Regional de Blumenau – SC]. Rev Bras Educ Med. 2019;43(suppl.1):276-85. https://doi.org/10.1590/1981-5271v43suplemento1-20180260.
19. Lima MCP, Domingues MS, Cerqueira ATAR. Prevalência e fatores de risco para transtornos mentais comuns entre estudantes de medicina [Prevalence and risk factors of common mental disorders among medical students]. Rev Saúde Pública. 2006;40(6):1035-41. PMID: 17173160; https://doi.org/10.1590/S0034-89102006000700011.
20. Lima MCP, Cerqueira AT, Dantas CL, et al. O trote e a saúde mental de estudantes de Medicina [Hazing and the Mental Health of Medical Students]. Rev Bras Educ Med. 2017;41(2):110-20. https://doi.org/10.1590/1981-52712015v41n2rb20160025.
21. Medeiros MRB, Camargo JF, Barbosa LAR, Caldeira AP. Saúde mental de ingressantes no curso médico: uma abordagem segundo o sexo [Mental health of first-year academics in the Medical school: a gender approach]. Rev Bras Educ Med. 2018;42(3):214-21. https://doi.org/10.1590/1981-52712015v42n3rb20170008.
22. Melado ASSG, Vitorino FAC, Szpilman ARM, Poton WL. Prevalence and risk factors associated with Common Mental Disorders among Medical students. Rev Bras Med Fam Comunidade. 2019;14(41):1911. https://doi.org/10.5712/rbmfc14(41)1911.
23. Santos LS, Ribeiro IJS, Boery EM, Boery RNSO. Quality of life and common mental disorders among Medical students. Cogitare Enferm. 2017;22(4):e52126. http://dx.doi.org/10.5380/ce.v22i4.52126.
24. Silva AG, Cerqueira ATAR, Lima MCP. Social support and common mental disorder among medical students. Rev Bras Epidemiol. 2014;17:229-42. PMID: 24896795; https://doi.org/10.1590/1415-790X201400010018ENG.
25. Conselho Federal de Psicologia. Testes Desfavoráveis [Unfavorable tests]. Available from: https://satepsi.cfp.org.br/testesDesfavoraveis.cfm. Accessed in 2022 (Jan 14).
26. Mari JJ, Williams P. A comparison of the validity of two psychiatric screening questionnaires (GHQ-12 and SRQ-20) in Brazil, using Relative Operating Characteristic (ROC) analysis. Psychol Med 1985;15(3):651-9. PMID: 4048323; https://doi.org/10.1017/s0033291700031500.

27. Soares PSM, Meucci RD. Epidemiologia dos Transtornos Mentais Comuns entre mulheres na zona rural de Rio Grande, RS, Brasil [Epidemiology of Common Mental Disorders among women in the rural zones of Rio Grande, RS, Brazil]. Cien Saúde Coletiva. 2020;25(8):3087-3095. PMID: 32785544; https://doi.org/10.1590/1413-81232020258.31582018.
28. Moehlecke M, Blume CA, Cureau FV, Kieling C, Schaan BD. Self-perceived body image, dissatisfaction with body weight and nutritional status of Brazilian adolescents: a nationwide study. J Pediatr (Rio J). 2020;96(1):76-83. PMID: 30098939; https://doi.org/10.1016/j.jped.2018.07.006.
29. Quadros LCM, Quevedo LA, Gonçalves DH, et al. Common Mental Disorders and Contemporary Factors: 1982 Birth Cohort. Rev Bras Enferm. 2020;73(1): e20180162. https://doi.org/10.1590/0034-7167-2018-0162.
30. Santos FS, Maia CRC, Faedo FC, et al. Estresse em Estudantes de Cursos Preparatórios e de Graduação em Medicina [Stress among pre-university and undergraduate Medical students]. Rev Educ Med Bras. 2017;41(2):194-200. https://doi.org/10.1590/1981-52712015v41n2RB20150047.
31. Gomes MJ, Monteiro M, Damasceno AM, Almeida TJS. Evasão acadêmica no ensino superior: estudo na área da saúde [Academic evasion in superior education – study in the area of the health]. Rev Bras Pesq Saúde. 2010;12(1):6-13. Available from: https://periodicos.ufes.br/rbps/article/view/278. Accessed in 2022 (Jan 14).
32. Ramos-Cerqueira ATA, Lima MCP. A formação da identidade do médico: implicações para o ensino de graduação em Medicina [The establishment of the physician's identity: implications for undergraduate medical teaching]. Interface. 2002;6(11):107-16. https://doi.org/10.1590/S1414-32832002000200008.
33. Benedetto MAC, Gallian DMC. Narrativas de estudantes de Medicina e Enfermagem: currículo oculto e desumanização em saúde [The narratives of medicine and nursing students: the concealed curriculum and the dehumanization of health care]. Interface. 2018;22(67):1197-1207. https://doi.org/10.1590/1807-57622017.0218.
34. Barnes CM, Drake CL. Prioritizing sleep health: public health policy recommendations. Perspect Psychol Sci. 2015;10(6):733-7. PMID: 26581727; https://doi.org/10.1177/1745691615598509.
35. Morgan HL, Petry AF, Licks PAK, et al. Consumo de estimulantes cerebrais por estudantes de Medicina de uma universidade do extremo sul do Brasil: prevalência, motivação e efeitos percebidos [The consumption of brain stimulants by Medical students at a university in Southern Brazil: prevalence, motivation, and perceived effects]. Rev Bras Educ Med. 2017;41(1):102-9. https://doi.org/10.1590/1981-52712015v41n1rb20160035.

Authors' contributions: Soares SJB: conceptualization (equal), formal analysis (equal), investigation (equal), methodology (equal), visualization (equal), writing-original draft (equal) and writing-review and editing (equal); Fernandes CFG: formal analysis (equal), investigation (equal), methodology (equal), visualization (equal), writing-original draft (equal) and writing-review and editing (equal); Tabalipa R: formal analysis (equal), investigation (equal), visualization (equal) and writing-review and editing (equal); Kogima F: formal analysis (equal), investigation (equal), visualization (equal) and writing-review and editing (equal); Jubini MAM: formal analysis (equal), investigation (equal), visualization (equal) and writing-review and editing (equal); Dias IMV: formal analysis (equal), investigation (equal), visualization (equal) and writing-review and editing (equal); Soares VEM: formal analysis (equal), investigation (equal), visualization (equal) and writing-review and editing (equal); Amaral SS: formal analysis (equal), investigation (equal), visualization (equal) and writing-review and editing (equal); Cruz MS: formal analysis (equal), investigation (equal), methodology (equal), validation (equal), visualization (equal) and writing-review and editing (equal); and Guerra PH: conceptualization (equal), data curation (equal), formal analysis (equal), investigation (equal), methodology (equal), project administration (equal), supervision (lead), validation (equal), visualization (equal), writing-original draft (equal) and writing-review and editing (equal)

Sources of funding: The present study did not receive funding for its execution

Conflicts of interest: All authors declare that there were no conflicts of interest

Date of first submission: October 22, 2021
Last received: December 27, 2021
Accepted: January 27, 2022

Address for correspondence
Paulo Henrique Guerra
Departamento de Medicina, Universidade Federal da Fronteira Sul (UFFS)
Rodovia SC 484, Km 02 — Sala 110 — Bloco dos Professores
Fronteira Sul — Chapecó (SC) — Brasil
CEP 89815-899
Tel. (+55 49) 2049-6542
E-mail: paulo.guerra@uffs.edu.br

In the manuscript titled "Could serum total cortisol level at admission predict mortality due to coronavirus disease 2019 in the intensive care unit? A prospective study", DOI number 10.1590/1516-3180.2020.0722.R1.2302021, published in the Sao Paulo Medical Journal, volume 139, issue number 4, pages 398-404, on page 399:

Where it read:

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

It should read:

"The study protocol was approved by the Clinical Research Ethics Committee of the Health Sciences University Gazi Yaşargil Training and Research Hospital (Diyarbakır, Turkey) (March 11, 2020; number: 38)."

INSTRUCTIONS FOR AUTHORS

Scope and indexing

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

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

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

Editorial policy

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

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

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

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

São Paulo Medical Journal applies a publication fee in the form of an article processing charge (APC) for all studies conducted outside of Brazil. This rate will be charged to the corresponding author when the study has been accepted on the grounds of its scientific merit. This fee is US$ 500.00 and is independent of the length of the text. The corresponding author should wait to receive the journal's invoice before making the payment. The article will only be published after presentation of the proof of payment. Submission is free for all. Associação Paulista de Medicina provides financial support for the Journal.

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

Transparency and integrity: guidelines for writing

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

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

Conflicts of interest

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

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

Acknowledgements and funding

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

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

Authorship

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

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

The corresponding author is the primary guarantor of all ethical issues relating to the manuscript, before, during and after its

publication. However, *São Paulo Medical Journal* and ICMJE consider that all authors are held fully responsible for the study, regarding the accuracy or integrity of data and data interpretation in the text. Contributions such as data collection only do not constitute authorship.

The addition or deletion of authors' names in the manuscript byline is possible only if the corresponding author provides the reason for the rearrangement and a written signed agreement from all authors. Modifications to the order of the authors are possible, but also need to be justified. Authors whose names are removed or inserted must agree with this in writing. Publication of the article cannot proceed without a declaration of authorship contributions signed by all authors.

São Paulo Medical Journal supports the ORCID initiative. All authors should create an ORCID identification (ID) record (in www.orcid.org) before submitting their article and should link the submission to their existing ORCID ID in the electronic submission system. ORCID identifications help to distinguish researchers with similar names, give credit to contributors and link authors to their professional affiliations. In addition, this may increase the ability of search engines to retrieve articles.

São Paulo Medical Journal supports Open Science practices. Authors must therefore complete an open science compliance form, which is available from: https://wp.scielo.org/wp-content/uploads/Open-Science-Compliance-Form_en.docx.

Redundant or duplicate publication

São Paulo Medical Journal will avoid publishing redundant or duplicate articles. The Journal agrees with the ICMJE definition of redundant publication,[11] i.e. an attempt to report or publish the same results from a study twice. This includes but is not limited to publication of patient cohort data that has already been published, without clear reference to the previous publication. In situations in which authors are making a secondary analysis on data that has already published elsewhere, they must state this clearly. Moreover, the outcomes assessed in each analysis should be clearly differentiated.

The Journal's peer review policy and procedures

After receipt of the article through the electronic submission system, it will be read by the editorial team, who will check whether the text complies with the Journal's Instructions for Authors regarding format. The Journal has adopted the *CrossRef Similarity Check* system for identifying plagiarism and any text that has been plagiarized, in whole or in part, will be promptly rejected. Self-plagiarism will also be monitored.

When the general format of the manuscript is deemed acceptable and fully compliant with these Instructions for Authors, and only then, the editorial team will submit the article to the Editor-in-Chief, who will firstly evaluate its scope. If the editor finds that the topic is of interest for publication, he will assign at least two reviewers/referees with expertise in the theme, to evaluate the quality of the study. After a period varying from one to several weeks, the authors will then receive the reviewers' evaluations and will be required to provide all further information requested and the corrections that may be necessary for publication. These reviewers, as well as the Editorial Team and the Editor-in-Chief, may also deem the article to be unsuitable for publication by *São Paulo Medical Journal* at this point.

At the time of manuscript submission, the authors will be asked to indicate the names of three to five referees. All of them should be from outside the institution where the authors work and at least two should preferably be from outside Brazil. The Editor-in-Chief is free to choose them to review the paper or to rely on the *São Paulo Medical Journal's* Editorial Board alone.

Articles will be rejected without peer review if:

- they do not present Ethics Committee approval (or a justification for the absence of this);
- they fail to adhere to the format for text and figures described here.

After peer review

Peer reviewers, associated editors and the Editor-in-Chief may ask for clarifications or changes to be made to the manuscript. The authors should then send their article back to the Journal, with the modifications made as requested. Changes to the text should be highlighted (in a different color or using a text editor tool to track changes). Failure to show the changes clearly might result in the paper being returned to the authors.

The modified article must be accompanied by a letter answering the referees' comments, point by point. The modified article and the response letter are presented to the editorial team and reviewers, who will verify whether the problems have been resolved adequately. The text and the reviewers' final evaluations, along with the response letter, will then be sent to the Editor-in-Chief for a decision.

Manuscripts that are found to be suitable for publication through their scientific merit will be considered "provisionally accepted". However, all articles will subsequently be scrutinized to check for any problems regarding the reporting, i.e. sentence construction, spelling, grammar, numerical/statistical problems, bibliographical references and other matters that may arise, especially in the Methods section. The adherence to reporting guidelines will be checked at this point, and the staff will point out any information regarding methodology or results that the authors should provide. This is done in order to ensure transparency and integrity of publication, and to allow reproducibility.

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

Submission

Articles should be submitted only after they have been formatted as described below. Texts must be submitted exclusively through the Internet, using the Journal's electronic submission system, which is available at http://mc04.manuscriptcentral.com/spmj-scielo. Submissions sent by e-mail or through the post will not be accepted.

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

To format these documents, use Times New Roman font, font size 12, line spacing 1.5, justified text and numbered pages.

The corresponding author is responsible for the submission. However, all authors should approve the final version of the manuscript that is to be submitted and should be aware of and approve any changes that might be made after peer review.

Covering letter

All manuscripts must be submitted with a covering letter signed at least by the corresponding author. The letter must contain the following five essential items relating to the manuscript:

1. a declaration that the manuscript is original and that the text is not under consideration by any other journal;
2. a statement that the manuscript has been approved by all authors, who agree to cede the copyrights to the Journal, disclose all sources of funding and declare all potential conflicts of interest;
3. a statement that the study protocol was endorsed by an Internal Review Board (Ethics Committee), including the date and number of the approval (in the case of original articles). This is required for absolutely all studies involving human subjects or patient data (such as medical records), in accordance with the Committee on Publication Ethics (COPE) guidelines, and even for case reports. A copy of the approval document must be submitted to the Journal;
4. each author should indicate a valid, up-to-date email address for contact;
5. a list of a minimum of five potential referees outside of the authors' institutions, who could be invited, at the Editor-in-Chief's discretion, to evaluate the manuscript.

General guidelines for original articles

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

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

Trial and systematic review registration policy

São Paulo Medical Journal supports the clinical trial registration policies of the World Health Organization (WHO) and the International Committee of Medical Journal Editors (ICMJE) and recognizes the importance of these initiatives for registration and international dissemination of information on randomized clinical trials, with open access. Thus, since 2008, manuscripts on clinical trials are accepted for publication if they have received an identification number from one of the public clinical trial registration database (such as ClinicalTrials.gov and/or REBEC and/or the World Health Organization; the options are stated at http://www.icmje.org). The identification number should be declared at the end of the abstract. Articles describing systematic reviews must provide the protocol registration number from a reliable database, such as PROSPERO, Open Science Framework, Cochrane, Joanna Briggs and others. Articles presenting clinical trials or systematic reviews without registration protocols will be promptly rejected without peer review.

Results from cases with DNA sequences must be deposited in appropriate public databases. The protocol number or URL can be requested at any time during the editorial review. Publication of other research data in public repositories is also recommended, since it contributes towards replicability of research, increases article visibility and possibly improves access to health information.

Sample size

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

- power (usually 80% or more);
- level of significance (usually 0.05 or lower);
- clinically meaningful difference (effect size targeted), according to the main outcome measurement.

Regardless of study results (if "positive" or "negative"), the journal will probably reject articles of trials using underpowered samples, when sample size has not been properly calculated or the calculation has not been fully described as indicated above.

Abbreviations, acronyms and products

Abbreviations and acronyms must not be used, even those in everyday use, unless they are defined when first used in the text. However, authors should avoid them for clarity whenever possible. Drugs or medications must be referred to using their generic names (without capital letters), with avoidance of casual mention of commercial or brand names.

Interventions

All drugs, including anesthetics, should be followed by the dosage and posology used.

Any product cited in the Methods section, such as diagnostic or therapeutic equipment, tests, reagents, instruments, utensils, prostheses, orthoses and intraoperative devices, must be described together with the manufacturer's name and place (city and country) of manufacture in parentheses. The version of the software used should be mentioned.

Any other interventions, such as exercises, psychological assessments or educational sessions, should be described in enough details to allow reproducibility. The Journal recommends that the TIDieR reporting guidelines should be used to describe interventions, both in clinical trials and in observational studies.[13]

Supplementary material

Because supplementary material comprises documents that do not form part of the text of the manuscript, São Paulo Medical Journal will not publish it. The authors should cite an access link that allows readers to view the supplementary material.

Short communications

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

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

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

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

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

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

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

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

FORMAT: FOR ALL TYPES OF ARTICLES

Title page

The title page must contain the following items:

1. Type of paper (original article, review or updating article, short communication or letter to the editor);
2. Title of the paper in English, which should be brief but informative, and should mention the study design.[14] Clinical trial, cohort, cross-sectional or case-control study, and systematic review are the most common study designs. Note: the study design declared in the title should be the same in the methods and in the abstract;
3. Full name of each author. The editorial policy of the *São Paulo Medical Journal* is that abbreviations of authors' names must not be used; therefore, we ask that names be stated in full, without using abbreviations;
4. Place or institution where the work was developed, city and country;
5. Each author should indicate the way his/her name should be used in indexing. For example: for "João Costa Andrade", the indexed name could be "Costa-Andrade J." or "Andrade JC", as preferred;
6. The author's professional background (Physician, Pharmacist, Nurse, Dietitian or another professional description, or Undergraduate Student); and his/her position currently held (for example, Master's or Doctoral Student, Assistant Professor, Associate Professor or Professor), in the department and institution where he/she works, and the city and country (affiliations);

7. Each author should present his/her ORCID identification number (as obtained from HYPERLINK "http://www.orcid.org/" www.orcid.org);
8. Each author must inform his contribution, preferably following the CRediT system (see above in Authorship);
9. Date and venue of the event at which the paper was presented, if applicable, such as congresses, seminars or dissertation or thesis presentations.
10. Sources of financial support for the study, bursaries or funding for purchasing or donation of equipment or drugs. The protocol number for the funding must be presented with the name of the issuing institution. For Brazilian authors, all grants that can be considered to be related to production of the study must be declared, such as fellowships for undergraduate, master's and doctoral students; along with possible support for postgraduate programs (such as CAPES) and for the authors individually, such as awards for established investigators (productivity; CNPq), accompanied by the respective grant numbers.
11. Description of any conflicts of interest held by the authors (see above).
12. Complete postal address, e-mail address and telephone number of the author to be contacted about the publication process in the Journal (the "corresponding author"). This author should also indicate a postal address, e-mail address and telephone number that can be published together with the article. *São Paulo Medical Journal* recommends that an office address (rather than a residential address) should be informed for publication.

Second page: abstract and keywords

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

The following headings must be used in the structured abstract:

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

References

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

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

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

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

At the end of each reference, please insert the "PMID" number (for papers indexed in PubMed) and the link to the "DOI" number if available.

Authors are responsible for providing a complete and accurate list of references. All references cited in the text must appear in the reference list, and every item in the reference list must be cited in the text. Also, citations must be in the correct sequence.

Manuscripts that do not follow these guidelines for references will be returned to the authors for adjustments.

The reference list should be inserted after the conclusions and before the tables and figures.

Figures and tables

Images must be submitted at a minimum size that is reproducible in the printed edition. Figures should be sent at a resolution of 300 DPI and minimum size of 2,500 pixels (width) and be recorded in ".jpg" or ".tif" format. Images submitted in inadequate formats will not be accepted.

Images must not be embedded inside Microsoft PowerPoint or Microsoft Word documents, because this reduces the image size. Authors must send the images separately, outside of .doc or .ppt documents. Failure to send the original images at appropriate sizes leads to paper rejection before peer review.

Flowcharts are an exception: these must be drawn in an editable document (such as Microsoft Word or PowerPoint), and should not be sent as an image that can't be changed.

Figures such as bars of line graphs should be accompanied by the tables of data from which they have been generated (for example, sending them in the Microsoft Excel spreadsheets, and not as image files). This allows the Journal to correct legends and titles if necessary, and to format the graphs according to the Journal's style. Graphs generated from software such as SPSS or RevMan must be generated at the appropriate size, so that they can be printed (see above). Authors must provide internal legends/captions in correct English.

All the figures and tables should be cited in the text. All figures and tables must contain legends or titles that precisely describe their content and the context or sample from which the information was obtained (i.e. what the results presented are and what the kind of sample or setting was). The reader should be able to understand the content of the figures and tables simply by reading the titles (without the need to consult the text), i.e. titles should be complete. Acronyms or abbreviations in figure and table titles are not acceptable. If it is necessary to use acronyms or abbreviations inside a table or figure (for better formatting), they must be spelled out in a legend below the table or figure.

For figures relating to microscopic findings (i.e. histopathological results), a scale must be embedded in the image to indicate the magnification used (just like in a map scale). The staining agents (in histology or immunohistochemistry evaluations) should be specified in the figure legend.

DOCUMENTS CITED

1. Internal Committee of Medical Journal Editors. Recommendations for the Conduct, Reporting, Editing, and Publication of Scholarly Work in Medical Journals. Available from: http://www.icmje.org/recommendations/. Accessed in 2019 (March 11).
2. The CONSORT Statement. Available from: http://www.consort-statement.org/. Accessed in 2018 (May 3).
3. Moher D, Cook DJ, Eastwood S, et al. Improving the quality of reports of meta-analyses of randomised controlled trials: the QUOROM statement. Br J Surg 2002. Available at: https://onlinelibrary.wiley.com/doi/abs/10.1046/j.1365-2168.2000.01610.x. Accessed in 2019 (April 4).
4. PRISMA. Transparent Reporting of Systematic Reviews and Meta-Analyses. Available from: www.prisma-statement.org. Accessed in 2019 (April 4).
5. STROBE Statement. Strengthening the reporting of observational studies in epidemiology. What is strobe? Available from: http://www.strobe-statement.org/. Accessed in 2018 (May 3).
6. von Elm E, Altman DG, Egger M, et al. The Strengthening the Reporting of Observational Studies in Epidemiology (STROBE) statement: guidelines for reporting observational studies. J Clin Epidemiol. 2008;61(4):344-9. PMID: 18313558. doi: 10.1016/j.jclinepi.2007.11.008.
7. The CARE Guidelines: Consensus-based Clinical Case Reporting Guideline Development. Enhancing the QUAlity and Transparency Of health Research. Available from: https://www.equator-network.org/reporting-guidelines/care/. Accessed in 2018 (May 3).
8. STARD Statement. STAndards for the Reporting of Diagnostic accuracy studies. Available from: http://www.equator-network.org/reporting-guidelines/stard/. Accessed in 2018 (May 3).
9. Rennie D. Improving reports of studies of diagnostic tests: the STARD initiative. JAMA. 2003;289(1):89-90. doi:10.1001/jama.289.1.89.
10. International Committee of Medical Journal Editors (ICMJE). Defining the Role of Authors and Contributors. Available from: http://www.icmje.org/recommendations/browse/roles-and-responsibilities/defining-the-role-of-authors-and-contributors.html. Accessed in 2019 (March 11).
11. International Committee of Medical Journal Editors. Overlapping Publications. Available from: http://www.icmje.org/recommendations/browse/publishing-and-editorial-issues/overlapping-publications.html. Accessed in 2018 (Feb 18).
12. Phillips B, Ball C, Sackett D, et al. Oxford Centre for Evidence-based Medicine Levels of Evidence (March 2009). Available from: https://www.cebm.net/2009/06/oxford-centre-evidence-based-medicine-levels-evidence-march-2009/. Accessed in 2018 (May 3).
13. Hoffmann TC, Glasziou PP, Boutron I, et al. Better reporting of interventions: template for intervention description and replication (TIDieR) checklist and guide. BMJ. 2014;348:g1687. PMID: 24609605; doi: 10.1136/bmj.g1687.
14. Non-randomised controlled study (NRS) designs. Available from: http://childhoodcancer.cochrane.org/non-randomised-controlled-study-nrs-designs. Accessed in 2018 (May 3).

X Congresso Brasileiro de MEDICINA AEROESPACIAL

21 e 22 de outubro de 2022 APM

O congresso será realizado em comemoração ao Centenário da Travessia Aérea do Atlântico Sul, com o objetivo de promover uma experiência científica única, unindo os mais renomados cientistas do continente.

Atualize-se com profissionais especializados e participe de construções enriquecedoras.

Dra. Rozania Sobreira
- Médica Credenciada pela ANAC para certificação médica aeronáutica
- Médica otorrinolaringologista
- Médica do Trabalho

Dr. Marco Canteiro
- Médico Especialista em Medicina do Trabalho, Ginecologia e Pós-graduado em Medicina Aeroespacial
- Coordenador Científico do Departamento de Medicina Aeroespacial da APM

Dra. Rosirene Gessinger
- Especialista em Otorrinolaringologia e Medicina do Trabalho
- Doutoranda do PPRG-CR UFCSPA
- Pós-graduação em Medicina Aeroespacial
- Médica credenciada pela Anac

Dra. Ana Oshiro
- Médica Anestesiologista
- Pós-graduada em Medicina do Tráfego pela FMUSP e Medicina Aeroespacial pela Universidade Estácio de Sá

Dra. Daniela Rancan
- Formada em Medicina e Ortopedia na Santa Casa de São Paulo
- Pós-graduação em Medicina aeroespacial pela FPCS

Temas: Fisiologia de voo nas diversas especialidades médicas | Fadiga de voo | Acidentes aeronáuticos | Medicina espacial e a relação com as viagens espaciais | Legislação e regulamentação da aviação civil | Passageiros enfermos e transporte aeromédico | Pandemia: o que aprendemos com as viagens aéreas | Medicina do viajante

Local do Evento
Sede da APM: Av. Brigadeiro Luís Antônio, 278 -Bela Vista- São Paulo/SP

Realização: Sociedade Brasileira de Medicina Aeroespacial

Organização: APM Associação Paulista de Medicina

INSCREVA-SE

Lançamento

Programa
Agentes APM

Sabemos que estar próximo é fazer parte, por isso criamos um programa feito para você, acadêmico de medicina.

O programa agentes é destinado exclusivamente para acadêmicos do curso de medicina e tem como objetivo criar uma rede de conexão entre os estudantes, visando:

- Promover eventos de interesse dos estudantes de medicina;
- Criar fóruns de debates;
- Trazer conteúdos mais atuais sobre carreiras e especialidades;
- Apoiar os acadêmicos nas necessidades relacionadas a questões tributárias e legais.

Seja um **Agente APM** e tenha inúmeras vantagens, veja quais são:

- Cursos de extensão IESAPM
- Eventos científicos
- Webinars
- Espaços e ações culturais
- Hotel Fazenda
- Clube de benefícios
- Plano de saúde
- Consultas à defesa
- Previdência privada
- Assessoria de investimentos
- Revista científica São Paulo Medical Journal
- Revista científica Tratamento & Diagnóstico
- Locação de apartamentos

Entre outros benefícios do programa agente, estão:

Kit Médico Acadêmico para o melhor agente

Bonificações

Cursos / Workshops e treinamentos de aprimoramento, e muito mais!

Saiba mais. Acesse: apm.org.br/agentesapm **ou Escaneie o Qr Code**

E faça parte do programa agora mesmo!

Contato

Central de Relacionamento APM
Telefone/WhatsApp (11) 3188-4200
central.relacionamento@apm.org.br

apm.org.br

IESAPM
Instituto de Ensino Superior da Associação Paulista de Medicina

Novidade

IESAPM

Curso Modular de Telemedicina

O objetivo deste curso é capacitar os médicos para a prática da Telemedicina. Buscando prover um conjunto de conhecimentos que permitam o uso adequado deste método de cuidados à saúde.

CARGA HORÁRIA
24h

DURAÇÃO
180 dias
após a inscrição do curso

FORMATO
Curso
ON-LINE

INVESTIMENTO
R$ 495,00
Ex-Alunos

INVESTIMENTO
R$ 550,00
Associado APM

INVESTIMENTO
R$ 800,00
Não associado APM

Programa

Módulo 01 — Introdução à Telemedicina e Telessaúde

Módulo 02 — Bioética Digital

Módulo 03 — LGPD e Saúde Digital

Módulo 04 — Telemedicina: Legislação, Evidências e Experiências

Módulo 05 — Características das Plataformas de Telemedicina

Módulo 06 — Certificação Digital e Prescrição Eletrônica

Módulo 07 — A Prática da Teleconsulta

Módulo 08 — Telepropedêutica

Módulo 09 — Telemedicina na Cadeia de Saúde

Coordenador do Curso

Prof. Dr. Jefferson G. Fernandes

Matricule-se já
bit.ly/36d4j7u

Mais informações
11 3188 4313 (Whatsapp)
contato@iesapm.org.br

Mantenedora
APM ASSOCIAÇÃO PAULISTA DE MEDICINA

iesapm.org.br

SANTOS-SP

XXXVI CONGRESSO BRASILEIRO DE CEFALEIA

XVII CONGRESSO DE DOR OROFACIAL

28 E 29 DE OUTUBRO DE 2022

27 DE OUTUBRO DE 2022 – PRÉ-CONGRESSO

ESTÁ ABERTO O EDITAL PARA A **SUBMISSÃO DE TRABALHOS** DO **XXXVI CONGRESSO BRASILEIRO DE CEFALEIA** E **XVII CONGRESSO DE DOR OROFACIAL**

PRAZO LIMITE PARA ENVIO DO TRABALHO:

10 DE AGOSTO 2022

RESULTADO DOS TRABALHOS APROVADOS:

20 DE AGOSTO 2022

PREMIAÇÃO AO VIVO !!

Lembramos que os autores dos pôsteres escolhidos para apresentação oral terão que enviar um texto com 1.000 palavras sobre o estudo, contendo no máximo 4 tabelas e figuras e até 15 referências. Prazo: 02 de setembro de 2022

ESCANEIE E CONFIRA

LOCAL / INFORMAÇÃO / INSCRIÇÃO:

apm.org.br/cefaleia2022

Sheraton Santos Hotel - Rua Guaiaó, 70 - Aparecida – Santos – SP

Tel.: (11) 3188-4281

inscricoes@apm.org.br

Realização

Sociedade Brasileira de Cefaleia
Filiada à Sociedade Internacional de Cefaleia

Organização e promoção

APM ASSOCIAÇÃO PAULISTA DE MEDICINA

CNA

Apoio Institucional

ABMFR

CBO CONSELHO BRASILEIRO DE OFTALMOLOGIA

VISITE SANTOS 20


Médicos,
quem busca
o melhor
pra saúde
escolhe a Quali.
amil
bradesco saúde
SulAmérica Saúde
Central Nacional Unimed
*ANSs e condições no site.
Simule seu plano:
APM ASSOCIAÇÃO PAULISTA DE MEDICINA
quali corp