ISSN 1516-3180

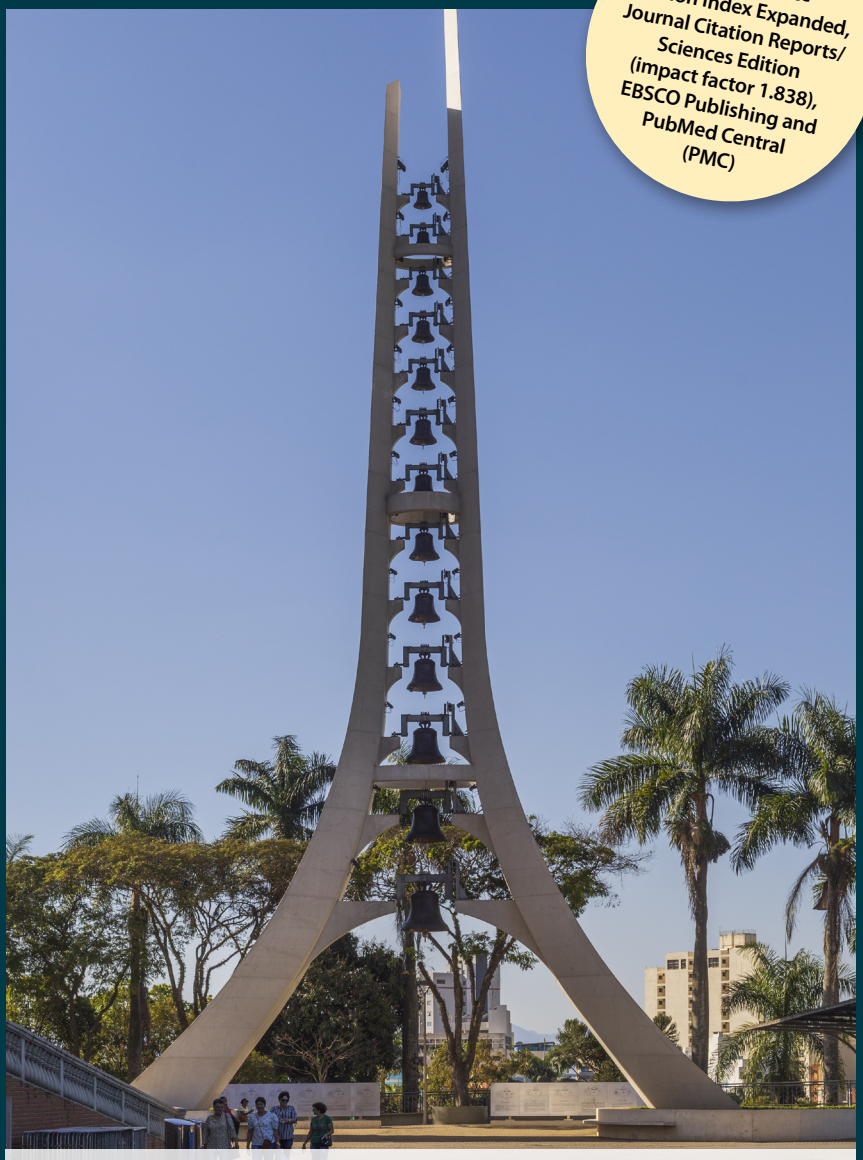
São Paulo Medical Journal/Evidence for Health Care, 2024 November 7

São Paulo Medical Journal

EVIDENCE FOR HEALTH CARE

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

November 7 - Volume 142 - Number 6



The tower of bells outside the Basilica of the National Shrine of Our Lady of Aparecida, Brazil, Sao Paulo state, Brazil
Photo: Alessandro Pires De Souza - Dreamstime.com

São Paulo Medical Journal does not charge authors for publication.

APM ASSOCIAÇÃO PAULISTA DE MEDICINA

Federada da AMB Associação Médica Brasileira

XV Congresso Paulista de NEUROLOGIA

4 A 7 DE JUNHO DE 2025 | BLUEMED CONVENTION CENTER - SANTOS/SP

Prepare-se para uma **grande experiência** em um dos maiores congressos do país!

Ambiente imersivo com conteúdo de alto nível

Discussões de práticas, tratamentos e diagnósticos **inovadores na Neurologia**

Acesse o site e não perca nada do **#CPN25**

congressopaulistadeneurologia.com

Escaneie o QR code e não deixe de acompanhar o #CPN25

Presidente:
Ana Marli Nucci

Comissão Científica:
Rubens Gagliardi
Acary Bulle
Marcel Simis
José Luiz Pedroso
Wilson Marques Jr.

Realização:

APAN
Associação Paulista de Neurologia

Organização, Promoção e Comercialização:

APM
ASSOCIAÇÃO PAULISTA DE MEDICINA

São Paulo Medical Journal
EVIDENCE FOR HEALTH CARE

INDEX

APM ASSOCIAÇÃO PAULISTA DE MEDICINA

Correspondence to:

ASSOCIAÇÃO PAULISTA DE MEDICINA
Publicações Científicas
Av. Brig. Luís Antônio, 278 - 7ª 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

ORGANIZATION

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

Editors: Paulo Manuel Pêgo Fernandes, Marianne Yumi Nakai and Álvaro Nagib Atallah.
Editorial assistants: Thiago Silva and Stefane Silva.
Associate editors: Adriana Seber, 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: Editage.
Desktop publishing: Zeppelini Publishers (www.zeppelini.com.br).
Listed in: Medline, Lilacs, SciELO, Science Citation Index Expanded and Journal Citation Reports/Sciences Edition, EBSCO publishing and PubMed Central.
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 2023-2026)

Challenges and perspectives in preventing and treating obesity

Denis Pajecki[I], Paulo Manuel Pêgo Fernandes[II]

Hospital das Clínicas, Faculdade de Medicina, Universidade de São Paulo, São Paulo, Brazil.

[I]MD, PhD, Department of Gastroenterology, Hospital das Clínicas, Faculdade de Medicina, Universidade de São Paulo, São Paulo, Brazil.
https://orcid.org/0000-0002-0898-9285

[II]MD, PhD, Vice-Director, School of Medicine, University of São Paulo, São Paulo, Brazil; Full Professor, Department of Cardiopulmonary Diseases, Faculdade de Medicina, Universidade de São Paulo, São Paulo, Brazil; Director of the Scientific Department, Associação Paulista de Medicina, São Paulo, Brazil
https://orcid.org/0000-0001-7243-5343

The American Medical Association recognized obesity as a chronic disease in 2013, followed by the World Health Organization. At that time, the global incidence and prevalence of obesity had already been progressively increasing for at least three decades. This scenario has not changed; recent data estimate that 1 billion people worldwide will be obese by 2030. The Brazilian Institute of Geography and Statistics has reported that 25% of the adult Brazilian population lives with the disease, a percentage that has quadrupled in children and adolescents since the 1990s.[1]

The etiology of obesity is mostly related to a combination of genetic and environmental factors, such as diet and lifestyle that influence people at different levels, resulting in heterogeneous presentations. Genome-wide association studies have identified hundreds of single nucleotide polymorphisms associated with body mass index (BMI), fat distribution, body composition, and other phenotypic differences. The pathophysiology of obesity involves dysfunctional energy balance, which is regulated by several complex metabolic pathways that interfere with appetite control and energy expenditure, leading to body fat accumulation. Metabolic adaptation phenomena such as increased orexigenic hormone secretion and decreased energy expenditure justify a tendency to regain weight when treatment is interrupted.[2]

However, both the general population and health professionals continue to view the disease as a behavioral disorder. This bias, or stigma, affects the search for and prescription of treatment blurs the distinction between prevention and treatment, and hinders investment in public policies aimed at disease control. Consequently, the incidence of severe obesity—defined by a higher BMI or the presence of comorbidities—rises exponentially, resulting in higher mortality rates from cardiovascular disease and cancer in affected people, deterioration in quality of life, and greater healthcare costs. Recent data indicate that the Brazilian Unified Health System has annual direct costs of BRL 1.5 billion and indirect costs, related to treating associated comorbidities, of up to BRL 190 billion. In the supplementary health sector, direct and indirect spending on obesity will account for an estimated 46% of claims by 2030.[3]

Improving eating habits and lifestyle forms the basis of *prevention* and public policies to control obesity. Recent taxation of sugary beverages under the Selective Tax (PEC 45/2019) represents significant progress; however, excluding ultra-processed foods from the proposal was a missed opportunity. For decades, the United States has attempted to change the habits of children and adolescents through tax policies and projects to reduce the incidence of obesity, without success.[4]

However, the belief that diet and physical activity are the most effective *treatment* measures still prevails. Although these measures are necessary and may be sufficient for a few patients, especially those with milder disease, they have poor mean long-term effectiveness in patients with established and more severe disease. More than a weight loss method, patients with obesity require long-term strategies to maintain treatment results.[2]

Thus, medications acting on different aspects of appetite may be necessary. In the past, obesity was treated with nonselective anorectic medications that had many adverse effects, reinforcing the stigma associated with the disease and its treatment. Modern medications are more selective and have a good safety profile, opening new perspectives for long-term disease control. These medications include glucagon-like peptide-1 agonists and their combination with other gastrointestinal hormone agonists, which have shown mean weight losses of more than 15% in controlled studies, delivering unprecedented results. Evidence that effective obesity treatment

with these medications leads to fewer cardiovascular events and better control of other comorbidities has encouraged physicians from several specialties to prescribe this type of treatment to their patients. Facilitating access to these medications remains challenging due to their high cost; encouraging patients to engage in prolonged treatment associated with lifestyle changes is as challenging.[5]

Treatment with bariatric and metabolic surgery is reserved for severe forms of obesity. Historically, the concept of severe obesity was closely related to a patient's BMI, with a basis for surgical indication criteria established more than three decades ago (i.e., BMI above 40 kg/m^2 or above 35 kg/m^2 with comorbidities). More recently, severity scoring systems such as the Edmonton Obesity Scoring System have shown that the presence and severity of comorbidities are more sensitive factors for predicting cardiovascular risk and mortality. In this context, surgery may be indicated for patients with a BMI of between 30 and 35 kg/m^2 with poorly controlled comorbidities.[2]

Over the last 30 years, the field of surgical treatment has progressed considerably with the advent of minimally invasive access (i.e., laparoscopic surgery) and improved treatment safety. Surgical morbidity and mortality have significantly reduced and are now comparable to common surgical procedures such as hysterectomy, hernia correction, or orthopedic procedures. Controlled and observational studies involving thousands of patients have demonstrated the long-term effectiveness of the treatment, with 1-year weight loss of 30% to 40% and long-term weight loss of 20% to 30% reported, depending on the technique used. These studies have reported the control of comorbidities such as type 2 diabetes and high blood pressure, with operated patients presenting an increased life expectancy of 6 years.[2]

However, patient referrals for surgery by physicians from other disciplines remain low, with most patients seeking treatment on their own and often struggling with difficult access, especially in the Brazilian Unified Health System.[3] The stigma surrounding surgery is high, with this treatment often viewed as futile or as representing patient failure.[4] Therapeutic options for controlling obesity have progressed in several fields. However, understanding that treatments do not compete, but rather that their incorporation into a treatment strategy depends on the individual condition of each patient, is vital. Surgical treatment associated with multidisciplinary care is a safe and effective option for more severely obese patients and should be used when other alternatives fail.[5]

REFERENCES

1. GBD 2021 Diseases and Injuries Collaborators. Global incidence, prevalence, years lived with disability (YLDs), disability-adjusted life-years (DALYs), and healthy life expectancy (HALE) for 371 diseases and injuries in 204 countries and territories and 811 subnational locations, 1990-2021: a systematic analysis for the Global Burden of Disease Study 2021. Lancet. 2024;403(1040):2133-61. PMID: 38642570; https://doi.org/10.1016/s0140-6736(24)00757-8.
2. Syn NL, Cummings DE, Wang LZ, et al. Association of metabolic-bariatric surgery with long-term survival in adults with and without diabetes: a one-stage meta-analysis of matched cohort and prospective controlled studies with 174 772 participants. Lancet. 2021;397(10287):1830-41. PMID: 33965067; https://doi.org/10.1016/s0140-6736(21)00591-2.
3. Instituto de Estudos de Saúde Suplementar. Como o aumento da prevalência da obesidade entre beneficiários pode impactar a sustentabilidade da saúde suplementar. São Paulo: IESS; 2022. Available from: https://www.iess.org.br/sites/default/files/2022-06/Obesidade_Cen%C3%A1rios%20para%20o%20Futuro.pdf. Accessed in 2024 (Jun. 14).
4. Sharma AM, Kushner RF. A proposed clinical staging system for obesity. Int J Obes. 2009;33(3):289-95. PMID: 19188927; https://doi.org/10.1038/ijo.2009.2.
5. Eisenberg D, Shikora SA, Aarts E, et al. 2022 American Society of Metabolic and Bariatric Surgery (ASMBS) and International Federation for the Surgery of Obesity and Metabolic Disorders (IFSO) Indications for Metabolic and Bariatric Surgery. Obes Surg. 2023;33(1):3-14. PMID: 36336720; https://doi.org/10.1007/s11695-022-06332-1.

Postorotracheal intubation dysphagia in patients with COVID-19: A retrospective study

Mariana Saconato[I], Jean Henri Maselli-Schoueri[II], Ceila Maria Sant'Ana Malaque[III], Rosa Maria Marcusso[IV], Augusto César Penalva de Oliveira[V], Lucio Antonio Nascimento Batista[VI], Graziela Ultramari[VII], José Angelo Lauletta Lindoso[VIII], Maria Inês Rebelo Gonçalves[IX], Jaques Sztajnbok[X]

This study was performed in Intensive Care Unit, Instituto de Infectologia Emílio Ribas (IIER), São Paulo, SP, Brazil

[I]PhD. Speech therapist, Technical manager of the Speech Therapy team, Instituto de Infectologia Emílio Ribas (IIER), São Paulo (SP), Brazil.
http://orcid.org/0000-0001-9816-7041

[II]MD. Physician , Centro Universitário Faculdade de Medicina do ABC (FMABC), Santo André (SP), Brazil.
http://orcid.org/0000-0003-2509-3592

[III]PhD. Physician, Intensive Care Unit Physician, Instituto de Infectologia Emílio Ribas (IIER), São Paulo (SP), Brazil.
http://orcid.org/0000-0001-9328-7925

[IV]MSc. Statistician, Instituto de Infectologia Emílio Ribas (IIER), São Paulo (SP), Brazil.
http://orcid.org/0000-0002-8396-0263

[V]PhD. Neurologist, Instituto de Infectologia Emílio Ribas (IIER), São Paulo (SP), Brazil.
http://orcid.org/0000-0002-0488-8188

[VI]Speech Therapist, Instituto de Infectologia Emílio Ribas (IIER), São Paulo (SP), Brazil.
https://orcid.org/0000-0001-9519-1484

[VII]MSc. Physiotherapist, Head of the Diagnostic and Therapeutic Support Department, Instituto de Infectologia Emílio Ribas (IIER), São Paulo (SP), Brazil.
https://orcid.org/0000-0003-0025-7001

[VIII]PhD. Physician, Director of the Diagnostic and Therapeutic Support Department, Instituto de Infectologia Emílio Ribas (IIER), São Paulo (SP), Brazil.
http://orcid.org/0000-0002-4405-4401

[IX]PhD. Speech therapist and Professor, Department of Speech Therapy, Universidade Federal de São Paulo (UNIFESP), São Paulo (SP), Brazil
http://orcid.org/0000-0002-3050-5849

[X]MD. Physician, Head of the Intensive Care Unit, Instituto de Infectologia Emílio Ribas (IIER), São Paulo (SP), Brazil.
http://orcid.org/0000-0002-3188-8044

KEYWORDS (MeSH terms):
Deglutition.
Intubation.
COVID-19.
Deglutition disorders.
Rehabilitation.

AUTHOR'S KEYWORDS:
Post orotracheal intubation.
Dysphagia.
Swallowing.
Tracheostomy.

ABSTRACT

BACKGROUND: The cause of oropharyngeal dysphagia in patients with coronavirus disease (COVID-19) can be multifactorial and may underly limitations in swallowing rehabilitation.

OBJECTIVE: Analyze the factors related to dysphagia in patients with COVID-19 immediately after orotracheal extubation and the factors that influence swallowing rehabilitation.

DESIGN AND SETTING: A retrospective study.

METHODS: The presence of dysphagia was evaluated using the American Speech-Language Hearing Association National Outcome Measurement System (ASHA NOMS) scale and variables that influenced swallowing rehabilitation in 140 adult patients who required invasive mechanical ventilation for >48 h.

RESULTS: In total, 46.43% of the patients scored 1 or 2 on the ASHA NOMS (severe dysphagia) and 39.29% scored 4 (single consistency delivered orally) or 5 (exclusive oral diet with adaptations). Both the length of mechanical ventilation and the presence of neurological disorders were associated with lower ASHA NOMS scores (odds ratio [OR]: 0.80, 95% confidence interval [CI]: 0.74–0.87 $P < 0.05$; and OR: 0.13, 95% CI: 0.61–0.29; $P < 0.05$, respectively). Age and the presence of tracheostomy were negatively associated with speech rehabilitation (OR: 0.92; 95% CI: 0.87−−0.96; OR: 0.24; 95% CI: 0.80−−0.75), and acute post-COVID-19 kidney injury requiring dialysis and lower scores on the ASHA NOMS were associated with longer time for speech therapy outcomes (β: 1.62, 95% CI, 0.70–3.17, $P < 0.001$; β: −1.24, 95% CI: −1.55−−0.92; $P < 0.001$).

CONCLUSION: Prolonged orotracheal intubation and post-COVID-19 neurological alterations increase the probability of dysphagia immediately after extubation. Increased age and tracheostomy limited rehabilitation.

INTRODUCTION

The most common and severe complication in patients with coronavirus disease 2019 (COVID-19) is the acute respiratory distress syndrome (ARDS), with acute respiratory failure as the main cause of hospitalization and orotracheal intubation (OTI) in intensive care units (ICU).[1-4] Consequently, several studies have shown an OTI rate ranging from 12% to 33% of hospitalized patients while the time they remained intubated also varied but deserves attention with >50% of those patients needed mechanical ventilation for up to 14 days.[5-8] Thus, the longer the time under OTI, the greater the chances of mechanical and sensitive sequelae.[9-16]

Therefore, the longer the length of mechanical ventilation, the greater the chances that the patient will present lesions in the oropharyngolarynx region, vocal fold paresis or paralysis, supraglottic edema, arytenoid dislocation, granulomas, and infraglottic strictures in addition to weakness in the base of the tongue and pharynx muscles and desensitization of sensory receptors in the tongue, pharynx, and larynx,[12-19] all of which could contribute to or even cause dysphagia.

OBJECTIVE

Thus, considering the high prevalence of dysphagia, the present study analyzed the risk factors associated with dysphagia onset in patients with severe COVID-19 who were administered OTI for >48 h in the ICU.

METHODS

Study design and inclusion/exclusion criteria

This was a retrospective cohort study conducted in the ICU of a reference center for the care of infectious diseases, which has exclusively received suspected and confirmed cases of COVID-19 since March 2020.

Initially, 161 patients who underwent invasive mechanical ventilation for >48 h were considered for this study. However, 15 patients with previous neurological diseases and six patients with a diagnosis of and treatment for head and neck cancer were excluded because these patients could already present pre-existing alterations in swallowing biomechanics. In total, 140 patients were included in the final sample.

All patients included in this study required OTI for >48 h and were evaluated by speech therapists according to the institutional protocol.

Therefore, 140 adult patients who were admitted to the ICU between March and June 2020 and who had positive reverse transcription PCR (RT-PCR) results for severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) were considered eligible for the study.

Variables

In addition to the time of OTI, complications developed by the patients were observed and categorized as: neurological, defined as persistent delirium, ischemic and/or hemorrhagic strokes, encephalitis, and encephalopathies; cardiac, confirmed by clinical criteria, imaging, and laboratory tests, such as increased levels of troponin, myoglobin, C-reactive protein, serum ferritin, and interleukin-6;[20,21] or renal, defined as the need for hemodialysis in individuals without a history of chronic kidney disease. All alterations were diagnosed and confirmed by critical care physicians. The prone position, a ventilatory support strategy to increase oxygenation levels by reducing the ventilation/perfusion ratio, was considered in this study only when invasive mechanical ventilation was required.

Speech therapy assessment

Speech therapy assessment of swallowing is routinely performed in the ICU of the Instituto de Infectologia Emílio Ribas (IIER). Before the pandemic, all patients undergoing prolonged OTI were evaluated 24 h after extubation. However, this changed for patients with SARS-CoV-2 and for 48 h afterwards. Thus, all 140 patients included in this study were evaluated by a speech therapy team 48 h after extubation.

This change was justified by the severity of the pulmonary condition associated with possible extubation failures, which can occur within 72 h after orotracheal extubation and is more common in patients diagnosed with pulmonary diseases.[14] Another factor that determined the postponement of the evaluation was the presence of residual sedation that could interfere with the evaluation findings[12] since many patients with COVID-19 require high doses of analgesia and neuromuscular blockers to maintain respiratory synchrony during mechanical ventilation.

After analyzing the electronic medical records for a survey of demographic, clinical, and laboratory information, a speech-language evaluation of swallowing was initiated.

Swallowing assessment procedures

The oral sensory-motor system was evaluated, which included the assessment of the strength and mobility of the lips and tongue, contraction of the masseter muscles during mastication, soft palate and mandible mobility, hyolaryngeal complex elevation and support, and vocal quality before food offering.

The functional evaluation of swallowing consisted initially of the offer of pasty food, followed by a thickened liquid with honey and nectar consistencies, liquids without thickeners, and finally, semi-solid and dry solids.

Food volumes ranged from 3 to 100 mL for the pasty food, offered by a spoon; 3 to 180 mL for thin and thickened liquids offered in 3 and 5 mL scoops, controlled and free sips; a portion of soft solid (small roll) and dry solid (cream cracker).

The volume and consistency provided during the evaluation progressed according to the findings of the oral and pharyngeal phases of swallowing. Important changes in the preparatory and oral phases of swallowing homogeneous pasty and thickened liquids make it impossible to offer liquids without thickeners or semi-solids and solid foods.

The significant drop in peripheral oxygen saturation due to the removal of the nonrebreather mask also caused the interruption of the functional assessment of swallowing, as well as the need to remove the speech valve and reinflate the cuff in tracheostomized patients who had respiratory distress.

The American Speech-Language Hearing Association National Outcome Measurement System (ASHA NOMS)[22] was used to determine the level of swallowing function after bedside assessments. the patients were divided into three groups according to the ASHA scale score for tube feeding, moderate dysphagia, and minimal dysphagia (ASHA-NOMS scores of 1–3, 4–5, and 6, respectively).

The IIER ICU beds have a negative-pressure system. Despite this, all speech therapists performed speech therapy evaluations using personal protective equipment: private clothing, disposable aprons, caps, goggles, N95 masks, face shields, and gloves. All recommendations for dressing and undressing steps provided by the Hospital Infection Control Commission were followed.

Swallowing assessment procedures in tracheostomized patients

Due to the inaccessibility of RT-PCR tests to confirm the negative status of the patients, the speech-language evaluation was performed even in tracheostomized patients. For this population, it

was initially stipulated that the assessment with cuff deflation and adaptation of the Passy–Muir phonatory valve or occlusion of the tracheostomy should be performed at least 25 days after the positive RT-PCR result. Until May 2020, no scientific evidence was available for the virus transmission time.

From May 2020 onwards, the evaluation protocol for tracheostomized patients was modified once again as one study showed that a sharp drop occurred in infecting viral particles and antibody growth after 20 days. Thus, tracheostomized patients were evaluated 20 days after positive RT-PCR results were obtained.[2]

Statistical analysis and ethical aspects

The prespecified outcome variables were the time to discharge from speech therapy, time spent under OTI, ASHA scale score 48 h after extubation, successful rehabilitation (yes or no), and oral diet onset time.

For cases where time was considered a dependent variable, multiple linear regression was used; thus, three models were created: 1) time to discharge from speech therapy, 2) oral diet onset time, and 3) time spent intubated. Logistic regression was used for both situations in which the outcome variable was either binary (simple logistic regression for successful rehabilitation) or ordinal (ordinal logistic regression for the ASHA NOMS scale after 48 h of extubation). A stepwise backward strategy with the withdrawal of variables at 0.05 was used for all five models.

The confidence interval (CI) was 95% and the statistical program used was Stata (Stata Corp., College Station, United States) 12.0. This study was approved by the IIER Ethics Committee (protocol number 4.168.189).

RESULTS

Initially, 161 patients were eligible for inclusion. However, 21 patients were excluded from the sample because they presented with alterations in swallowing before the OTI (**Figure 1**).

Table 1 shows that the average age of patients evaluated after orotracheal extubation was 55.58 years with a predominance of

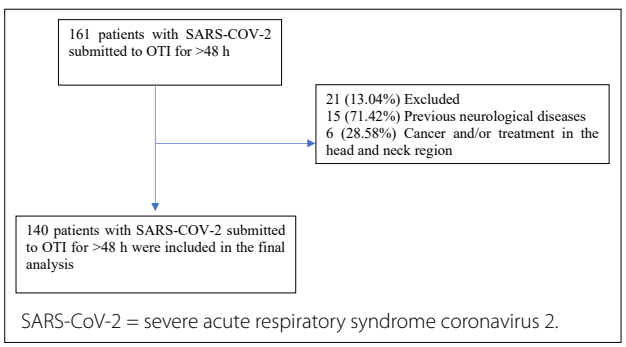


Figure 1. Sample selection according to inclusion and exclusion criteria.

Table 1. Population, clinical characteristics and American Speech-Language Hearing Association National Outcome Measurement System scale and its outcomes after assessment and speech therapy discharge

Demographic and clinical variables	Total (n = 140)	(%)
Age		
Minimum–maximum	18–85	-
Median	57.5	-
Average ± standard deviation	55.58 ± 14.32	-
Gender		
Female	71	50.71
Male	69	49.29
Previous comorbidities		
Systemic arterial hypertension	65	46.43
Obesity	60	42.86
Diabetes mellitus	49	35.00
Heart disease	24	17.14
Chronic kidney injury	13	9.29
Human immunodeficiency virus	4	2.86
Smoking	28	20.00
Orotracheal intubation and complications		
Length of mechanical ventilation		
Minimum–maximum	2.0–33.0	-
Median	11	-
Average ± standard deviation	12.05 ± 6.07	-
Reintubation	30	21.43
Tracheostomy	23	16.43
Prone position	68	48.57
Acute complications of COVID-19		
Acute kidney injury requiring dialysis	37	26.43
Cardiomyopathies	17	12.14
Neurological disorders	58	41.43
ASHA NOMS scale after speech therapy assessment		
Tube feeding		
ASHA 1, ASHA 2	65	46.43
Moderate dysphagia		
ASHA 4, ASHA 5	55	39.29
Minimal dysphagia		
ASHA 6	20	14.29
Speech-language therapy outcome		
Rehabilitated	93	66.43
Not rehabilitated	47	33.57
Time of onset for oral diet		
Minimum–maximum	1.0–15.0	-
Median	3.0	-
Average ± SD	4.4 ± 2.81	-
Average time for speech therapy discharge (days)		
Tube feeding (ASHA 1, ASHA 2, and ASHA 3)		
Minimum–maximum	2.0–26.0	-
Median	7.0	-
Average ± SD	8.55 ± 5.26	-
Moderate dysphagia (ASHA 4 and ASHA 5)		
Minimum–maximum	1.0–3.0	-
Median	1.0	-
Average ± SD	1.03 ± 0.27	-

COVID-19 = coronavirus disease 2019, SD = standard deviation; ASHA NOMS = American Speech-Language Hearing Association National Outcome Measurement System

females (50.71%). Systemic arterial hypertension was the most frequent comorbidity (46.43%), followed by obesity (42.86%) and diabetes mellitus (35%). As IIER is a reference in the care of infectious or contagious diseases, 2.86% of patients presented with the human immunodeficiency virus.

The patients remained under OTI for an average time of 12.05 days with a standard deviation ranging from 2 to 33 days. Of the 140 patients, 30 patients (21.43%) required reintubation within 72 h after extubation while tracheostomy was performed in 23 patients (16.43%). In addition, a prone position maneuver was required for 68 patients (48.57%) while they were still intubated. During the ICU stay, 27 patients (26.43%) developed acute kidney injury and required hemodialysis while 58 (41.43%) had neurological disorders. Cardiac abnormalities after COVID-19 were observed in 17 (12.14%) patients.

The number of patients with severe or moderate dysphagia reached 46.43%, and the nasogastric tube was maintained as the exclusive feeding route for these patients; 39.29% of patients needed significant adaptations, such as the ingestion of homogeneous pasty foods and thickened hydration.

Speech therapy evaluation was performed 48 h after extubation, and 65 patients (46.43%) presented with severe dysphagia and needed to maintain the nasoenteral tube as an exclusive alternative to feeding, with ASHA scores of 1 and 2. In addition to clinical signs of penetration/aspiration, such as coughing, gagging, and changes in vocal quality shortly after swallowing, these patients showed significant fatigue when the nonbreathing mask was removed, further increasing the risk of bronchoaspiration during and after swallowing owing to a lack of coordination between swallowing and breathing.

No patient was rated on the ASHA NOMS level 3 scale; 55 patients (39.29%) had an exclusive oral diet with restrictions on consistency and the use of compensatory strategies, and 20 (14.29%) had minimal changes or normal swallowing, without the need for modifications and/or compensatory strategies during feeding.

Among the patients with dysphagia in whom the ASHA NOMS scale ranged from 1 to 5, 93 (66.43%) were rehabilitated while 47 (33.57%) were not. The average time for reintroduction of the oral diet in patients who needed to remain on an exclusive nasoenteral tube after the evaluation was 3 days.

Speech therapy discharge, with complete swallowing recovery, was achieved with an average of 8.55 days in patients with an initial ASHA NOMS score of 1–3, and 1.03 days in patients with an initial ASHA NOMS score of 4–5.

In the ordinal logistic regression, considering the values of the ASHA NOMS scale as the dependent variable, we found that both intubation time and the presence of neurological disorders were associated with lower scores on the ASHA NOMS scale (odds ratio, [OR]: 0.80, 95% CI: 0.74–0.87 $P < 0.05$; and OR: 0.13, 95% CI: 0.61–0.29 $P < 0.05$, respectively). Conversely, an inverse association was present for those patients who had been pronated (OR: 3.24; 95% CI: 1.51–6.94, $P < 0.005$) (**Table 2**).

We found that both age and the presence of tracheostomy were negatively associated with speech rehabilitation (OR, 0.92: 95% CI: 0.87–0.96; OR, 0.24, 95% CI: 0.80–0.75), respectively. Finally, higher ASHA NOMS scores were negatively associated with the time needed for speech therapy discharge (β: −1.24; 95% CI: −1.55–−0.92; $P < 0.001$) (**Table 2**).

Table 2. Multivariate models for variable analysis: ASHA NOMS scale, rehabilitation and average time for speech therapy discharge

Model 1: Ordinal logistic regression	**ASHA NOMS scale**			**P value**
	Z	**OR**	**95% CI**	
Length of mechanical ventilation	-5.36	0.80	0.74–0.87	< 0.001
Prone position	3.04	3.24	1.51–6.94	0.002
Acute complications of COVID-19				
Neurological disorders	-4.99	0.13	0.06–0.29	< 0.001
Model 2: Logistic regression	**Rehabilitation**			**P value**
	Z	**OR**	**95% CI**	
Age	-3.48	0.92	0.87 - 0.96	0.001
Tracheostomy	-2.45	0.24	0.80 - 0.75	0.014
Model 3: Multivariate linear regression	**Average time for speech therapy discharge (days)**			**P value**
	β	**R^2**	**95% CI**	
Acute complications of COVID-19				
Acute kidney injury requiring dialysis	1.62	0.38	0.70–3.17	0.001
ASHANOMS scale	-1.24	0.38	(-1.55)–(-0.92)	0.001

ASHA NOMS = American Speech–Language–Hearing Association's National Outcome Measurement System; OR = odds ratio; CI = confidence interval; COVID-19 = coronavirus disease 2019.

DISCUSSION

Dysphagia after orotracheal intubation is multifactorial but is strongly related to the length of invasive mechanical ventilation. The presence of dysphagia can increase the time to reintroduction of an oral diet and the total hospital stay.

Herein, 46.43% of patients had severe dysphagia when assessed 48 h after extubation by the speech therapy team. The mean time to oral diet reintroduction was 4.4 days.

The prolonged duration of orotracheal intubation, which was an average of 11 days in this study, and the presence of acute complications of COVID-19 were related to severe dysphagia in the study population. Additionally, older patients and those who required tracheostomy had the greatest therapeutic limitations.

Some patients with severe COVID-19 can rapidly progress to ARDS, necessitating OTI and intensive care. In this sense, studies have shown that these patients could remain intubated between 7 and 14 days,[23] which could be extended to >20 days in unfavorable cases.[24-26] Thus, our study showed that for the 140 patients who were intubated, the average time spent under OTI was 12.05 days and the reintubation rate was 21.43%, which is slightly higher than that reported in specialized literature.[5]

One of the risk factors for dysphagia is the time spent under OTI, which is considered long if it exceeds 48 h.[22-24] However, in addition to prolonged OTI, other conditions may justify the presence of changes in the swallowing biodynamics in ICU patients; these conditions include previous comorbidities and poor scores on disease severity scales, namely the Acute Physiology and Chronic Health Evaluation IV and the Simplified Acute Physiology Score II.[27-29] Similarly, we found that many of our patients not only presented long periods under OTI but also had comorbidities before ICU admission.

No consensus is present in the literature regarding the ideal time to evaluate patients after orotracheal extubation. Although the average time for evaluation was 24 h;[27-31] for the present study, all patients were evaluated 48 h after extubation.

Even after 48 h of extubation, 46.43% of patients in the present study had severe dysphagia, with lower scores on the ASHA NOMS scale (OR: 0.80; 95% CI: 0.74–0.87 $P < 0.05$) and prolonged orotracheal intubation time was directly related to these findings (Table 2).

Studies that evaluated swallowing after extubation in patients with COVID-19 showed dysphagia rates of 20%–90%, and dysphagia was attributed to prolonged mechanical ventilation time, age >60 years, duration of analgesia and neuromuscular blocker use, and the presence of tracheostomy.[32-34]

Information regarding the incidence of dysphagia in extubated patients without COVID-19 varies. This is mainly because of the different diagnostic methods and inconsistent evaluation intervals after extubation. In patients intubated for >48 h, the prevalence of dysphagia increases by 56%.[35] According to other studies, dysphagia occurs in 3%–62% of patients recovering after critical illness[35] and one-third of patients intubated after ARDS have dysphagia upon discharge from the hospital.[36]

Prolonged intubation contributes to the reduction of strength and mobility in both the lips and tongue and may contribute to the reduction of sensitivity of the tongue, pharynx, and larynx. Patients may present with increased oral transit time, delay in starting pharyngeal swallowing, reduced elevation of the hyolaryngeal complex during swallowing, and stasis in the oral cavity and hypopharynx after swallowing.[11,12,37,38] In addition to motor and sensory failures, these patients may present with supraglottic edema, dislocation of the arytenoid cartilages, and paralysis or paresis of the vocal folds.[39,40] Nevertheless, most of our patients still presented ASHA NOMS scores <6, thus requiring dietary alternatives, whether through feeding restrictions or supplementary feeding routes.

In addition to the extended period under OTI and the rate of reintubation, almost half of the patients included in this study were pronated. This is a ventilatory support strategy for increasing oxygenation levels through a reduction in the ventilation/perfusion ratio that has become more frequent during the COVID-19 pandemic.[41]

We previously hypothesized that prone positioning would decrease ASHA NOMS scores because of possible laryngeal lesions. However, we later found that the prone position was positively associated with ASHA NOMS scores. We also found no meaningful association between OTI time and maneuver, despite their tendency to be positively associated. Thus, these findings may be justified by the possible absence of laryngeal lesions in these patients given that several of these patients benefited from prone positioning, which may have reduced the total time spent on OTI.

Tracheostomy was performed in 16.43% of patients who were difficult to wean from mechanical ventilation. Following the speech therapy protocol, the speech therapist was recommended to assess these patients after at least 25 days elapsed since a positive RT-PCR result. However, as many patients remained on pressure-controlled mechanical ventilation for a long time, most started to meet the criteria for speech therapy 30 days after a positive RT-PCR result.

Tracheostomized patients did not tolerate the Passy–Muir speech valve for a prolonged period and presented with respiratory discomfort and decreased peripheral oxygen saturation. Severe dysphagia was present mainly in tracheostomized patients who developed ischemic and hemorrhagic stroke, both of which were defined as neurological complications herein. The strength, mobility, and sensitivity of the oral cavity and oropharyngeal structures was reduced, which contributed to the classification of these patients as having a score of 1 on the ASHA NOMS scale.

The difficulty in maintaining the Passy–Muir phonatory valve and the cannula occlusion for prolonged periods also contributed

negatively to the rehabilitation of these patients as shown in the multivariate analysis in Table 2 (OR: 0.24; 95% CI: 0.80–0.75). This was because the reduction of subglottic pressure in tracheostomized patients can affect the time of lower airway closure and reduce the efficiency of cough.

In our sample, many patients had hypoactive delirium, whereas others had other neurological and cardiac disorders as well as renal disorders requiring hemodialysis. This combination of factors could have played a role in the number of nonrehabilitated patients (33.7%) and the average time (8.55 days) found for speech therapy discharge in patients with scores of 1 or 2 on the ASHA NOMS scale.

Regarding COVID-19 sequelae and other disorders, the virus exhibits neurotropic behavior with the capacity to invade the central nervous system. In addition, studies have shown that patients with acute kidney damage secondary to COVID-19 can present with important changes in fluid balance, with hemodynamic changes being common in this population. In our study, the presence of neurological disorders (stroke or delirium) was negatively associated with the ASHA NOMS scores. In addition, patients with acute kidney injury requiring dialysis spent more time on OTI.

Age is another factor contributing to the rehabilitation of patients with dysphagia. The results in Table 2 show that increasing age was negatively associated with rehabilitation success. This finding is also supported by current literature, which shows that disorders in swallowing biodynamics due to increasing age may be related to sarcopenia, sensory changes, and muscle weakness.[13,18]

Finally, although 46.43% of the patients had a score of 1 or 2 on the ASHA NOMS scale after the speech-language evaluation, the average time of onset of oral diet was 4.4 days. However, this does not mean that these patients were completely rehabilitated during this period as the average time to speech therapy discharge was 8.55 days.

Recent research has shown that patients with COVID-19 who require mechanical ventilation have the heaviest impact on quality within one year after discharge, with an increase in cardiovascular events, dyspnea, and rehospitalizations.[42] Sarcopenic dysphagia resulting from the considerable loss of muscle mass during the ICU stay may be present in this group, as well as respiratory and vocal complaints related to possible late tracheal stenosis secondary to prolonged orotracheal intubation.

The present study had several limitations. Prolonged orotracheal intubation, reintubation, tracheostomy, and neurological, cardiac, and renal complications in individuals who develop severe forms of COVID-19 are factors that reinforce the multifactorial causes of dysphagia in these patients. However, other important variables were not analyzed in this study but also deserve attention, such as the period in which the patient remains sedated and pronated and the evaluation of sedoanalgesia (both drug and dose needed to achieve the desired effect), which might cause possible glottic lesions compromising speech and swallowing safety and causing persistent delirium, respectively. Notably, that the severity of COVID-19 at hospital or ICU admission was not considered in this study because of a lack of data.

CONCLUSION

Prolonged orotracheal intubation and neurological alterations acquired after COVID-19 infection increase the probability of dysphagia immediately after extubation. Increasing age and the need for tracheostomies have limited the rehabilitation of these patients.

REFERENCES

1. Worldometer. COVID-19 coronavirus pandemic. 2020, April 2. Available from: https://www.worldometers.info/coronavirus/. Accessed in 2022 (Ap 02).
2. McGrath BA, Brenner MJ, Warrillow SJ, et al. Tracheostomy in the COVID-19 era: global and multidisciplinary guidance. Lancet Respir Med. 2020;8(7):717-25. PMID: 32422180; https://doi.org/10.1016/s2213-2600(20)30230-7.
3. Berlin DA, Gulick RM, Martinez FJ. Severe Covid-19. N Engl J Med. 2020;383(25):2451-60. PMID: 32412710; https://doi.org/10.1056/nejmcp2009575.
4. COVID-ICU Group on behalf of the REVA Network and the COVID-ICU Investigators. Clinical characteristics and day-90 outcomes of 4244 critically ill adults with COVID-19: a prospective cohort study. Intensive Care Med. 2021;47(1):60-73. PMID: 33211135; https://doi.org/10.1007/s00134-020-06294-x.
5. Hur K, Price CPE, Gray EL, et al. Factors associated with intubation and prolonged intubation in hospitalized patients with COVID-19. Otolaryngol Head Neck Surg. 2020;163(1):170-8. PMID: 32423368; https://doi.org/10.1177/0194599820929640.
6. Goyal P, Choi JJ, Pinheiro LC, et al. Clinical characteristics of COVID-19 in New York City. N Engl J Med. 2020;382(24):2372-4. PMID: 32302078; https://doi.org/10.1056/nejmc2010419.
7. Richardson S, Hirsch JS, Narasimhan M, et al. Presenting characteristics, comorbidities, and outcomes among 5700 patients hospitalized with COVID-19 in the New York City area. JAMA. 2020;323(20):2052-2059. PMID: 32320003; https://doi.org/10.1001/jama.2020.6775.
8. Wang D, Hu B, Hu C, et al. Clinical characteristics of 138 hospitalized patients with 2019 novel coronavirus-infected pneumonia in Wuhan, China. JAMA. 2020;323(11):1061-9. PMID: 32031570; https://doi.org/10.1001/jama.2020.1585.
9. Murry T, Carrau R. The abnormal swallow: conditions and diseases. In: Murry T, Carrau RL, Chan KMK, editors. Clinical management of swallowing disorders. Vol. 2. San Diego: Plural Publishing; 2006. P. 17-32.
10. François B, Bellissant E, Gissot V, et al. 12-h pretreatment with methylprednisolone versus placebo for prevention of postextubation laryngeal oedema: a randomized double-blind trial. Lancet.

2007;369(9567):1083-9. PMID: 17398307; https://doi.org/10.1016/s0140-6736(07)60526-1.

11. Macht M, Wimbish T, Clark BJ, et al. Diagnosis and treatment of post-extubation dysphagia: results from a national survey. J Crit Care. 2012;27(6):578-86. PMID: 23084136; https://doi.org/10.1016/j.jcrc.2012.07.016.
12. Macht M, Wimbish T, Bodine C, Moss M. ICU-acquired swallowing disorders. Crit Care Med. 2013;41(10):2396-405. PMID: 23939361; https://doi.org/10.1097/ccm.0b013e31829caf33.
13. Kim MJ, Park YH, Park YS, Song YH. Associations between prolonged intubation and developing post-extubation dysphagia and aspiration pneumonia in non-neurologic critically Ill patients. Ann Rehabil Med. 2015;39(5):763-71. PMID: 26605174; https://doi.org/10.5535/arm.2015.39.5.763.
14. Cork G, Camporota L, Osman L, Shannon H. Physiotherapist prediction of extubation outcome in the adult intensive care unit. Physiother Res Int. 2019;24(4):e1793. PMID: 31237395; https://doi.org/10.1002/pri.1793.
15. Macht M, White SD, Moss M. Swallowing dysfunction after critical illness. Chest. 2014;146(6):1681-9. PMID: 25451355; https://doi.org/10.1378/chest.14-1133.
16. Macht M, Wimbish T, Clark BJ, et al. Diagnosis and treatment of post-extubation dysphagia: Results from a national survey. J Crit Care. 2012;27(6):578-86. PMID: 23084136; https://doi.org/10.1016/j.jcrc.2012.07.016.
17. Macht M, Wimbish T, Clark BJ, et al. Postextubation dysphagia is persistent and associated with poor outcomes in survivors of critical illness. Crit Care. 2011;15(5):R231. PMID: 21958475; https://doi.org/10.1186/cc10472.
18. Skoretz SA, Flowers HL, Martino R. The incidence of dysphagia following endotracheal intubation: a systematic review. Chest. 2010;137(3):665-73. PMID: 20202948; https://doi.org/10.1378/chest.09-1823.
19. Barker J, Martino R, Reichardt B, Hickey EJ, Ralph-Edwards A. Incidence and impact of dysphagia in patients receiving prolonged endotracheal intubation after cardiac surgery. Can J Surg. 2009;52(2):119-24. PMID: 19399206.
20. Spiezia L, Boscolo A, Poletto F, et al. COVID-19-related severe hypercoagulability in patients admitted to intensive care unit for acute respiratory failure. Thromb Haemost. 2020;120(06):998-1000. PMID: 32316063; https://doi.org/10.1055/s-0040-1710018.
21. Ruan Q, Yang K, Wang W, Jiang L, Song J. Correction to: clinical predictors of mortality due to COVID-19 based on an analysis of data of 150 patients from Wuhan, China. Intensive Care Med. 2020;46(6):1294-7. PMID: 32253449; https://doi.org/10.1007/s00134-020-06028-z.
22. American Speech-Language-Hearing Association National Outcome Measurement System (NOMS). Adult Speech-Language Pathology training manual. Rockville: ASHA; 1998.
23. Hur K, Price CPE, Gray EL, et al. Factors Associated With Intubation and Prolonged Intubation in Hospitalized Patients With COVID-19. Otolaryngol Head Neck Surg. 2020;163(1):170-8. PMID: 32423368; https://doi.org/10.1177/0194599820929640.
24. Hernandez-Romieu AC, Adelman MW, Hockstein MA, et al. Timing of intubation and mortality among critically ill coronavirus disease 2019 patients: a single-center cohort study. Crit Care Med. 2020;48(11):e1045-e1053. PMID: 32804790; https://doi.org/10.1097/ccm.0000000000004600.
25. Helms J, Tacquard C, Severac F, et al. High risk of thrombosis in patients with severe SARS-CoV-2 infection: a multicenter prospective cohort study. Intensive Care Med 2020; 46: 1089-98. PMID: 32367170; https://doi.org/10.1007/s00134-020-06062-x.
26. Moore JB, June CH. Cytokine release syndrome in severe COVID-19. Science. 2020;368(6490):473-4. PMID: 32303591; https://doi.org/10.1126/science.abb8925.
27. Marvin S, Thibeault S, Ehlenbach WJ. Post-extubation Dysphagia: Does Timing of Evaluation Matter? Dysphagia. 2019;34(2):210-9. PMID: 30043081; https://doi.org/10.1007/s00455-018-9926-3.
28. Schefold JC, Berger D, Zürcher P, et al. Dysphagia in mechanically ventilated ICU patients (DYnAMICS): a prospective observational trial. Crit Care Med. 2017;45(12):2061-9. PMID: 29023260; https://doi.org/10.1097/ccm.0000000000002765.
29. Leder SB, Warner HL, Suiter DM, et al. Evaluation of swallow function post-extubation: is it necessary to wait 24 hours? Ann Otol Rhinol Laryngol. 2019;128(7):619-24. PMID: 30841709; https://doi.org/10.1177/0003489419836115.
30. Borders JC, Fink D, Levitt JE, et al. Relationship between laryngeal sensation, length of intubation, and aspiration in patients with acute respiratory failure. Dysphagia. 2019;34(4):521-8. PMID: 30694412; https://doi.org/10.1007/s00455-019-09980-1.
31. Barquist E, Brown M, Cohn S, Lundy D, Jackowski J. Postextubation fiberoptic endoscopic evaluation of swallowing after prolonged endotracheal intubation: a randomized, prospective trial. Crit Care Med. 2001;29(9):1710-3. PMID: 11546969; https://doi.org/10.1097/00003246-200109000-00009.
32. Lima MS, Sassi FC, Medeiros GC, Ritto AP, Andrade CRF. Functional development of swallowing in ICU patients with COVID-19. Codas. 2020;32(4):e20200222. PMID: 33053075; https://doi.org/10.1590/2317-1782/20192020222.
33. Archer SK, Iezzi CM, Gilpin L. Swallowing and Voice Outcomes in Patients Hospitalized With COVID-19: An Observational Cohort Study. Arch Phys Med Rehabil. 2021;102(6):1084-90. PMID: 33529610; https://doi.org/10.1016/j.apmr.2021.01.063.
34. Mallart R, Rossignol C, Poppe JB, et al. Prevalence and evaluation of oropharyngeal dysphagia in patients with severe acute respiratory syndrome coronavirus 2 infection in the intensive care unit. J Laryngol Otol. 2022;136(7):649-53. PMID: 35000623; https://doi.org/10.1017/S0022215121004710.
35. Skoretz SA, Flowers HL, Martino R. The incidence of dysphagia following endotracheal intubation: a systematic review. Chest. 2010;137(3):665-73. PMID: 20202948; https://doi.org/10.1378/chest.09-1823.
36. Brodsky MB, Huang M, Shanholtz C, et al. Recovery from dysphagia symptoms after oral endotracheal intubation in acute respiratory distress syndrome survivors. A 5-year longitudinal study. Ann Am

Thorac Soc. 2017;14(3):376-83. PMID: 27983872; https://doi.org/10.1513/AnnalsATS.201606-455OC.

37. Bradley RM. Sensory receptors of the larynx. Am J Med. 2000;108(Suppl 4a):47S-50S. PMID: 10718452; https://doi.org/10.1016/s0002-9343(99)00339-3.
38. Linden P, Siebens AA. Dysphagia: predicting laryngeal penetration. Arch Phys Med Rehabil. 1983;64(6):281-4. PMID: 6860100.
39. Goldsmith T. Evaluation and treatment of swallowing disorders following endotracheal intubation and tracheostomy. Int Anesthesiol Clin. 2000;38(3):219-42. PMID: 10984854; https://doi.org/10.1097/00004311-200007000-00013.
40. Combes X, Schauvliege F, Peyrouset O, et al. Intracuff pressure and tracheal morbidity: influence of filling with saline during nitrous oxide anesthesia. Anesthesiology. 2001;95(5):1120-4. PMID: 11684980; https://doi.org/10.1097/00000542-200111000-00015.
41. Sztajnbok J, Maselli-Schoueri JH, Cunha de Resende Brasil LM, et al. Prone positioning to improve oxygenation and relieve respiratory symptoms in awake, spontaneously breathing nonintubated patients with COVID-19 pneumonia. Respir Med Case Rep. 2020;30:101096. PMID: 32455107; https://doi.org/10.1016/j.rmcr.2020.101096.
42. Rosa RG, Cavalcanti AB, Azevedo LCP, et al. Association between acute disease severity and one-year quality of life among post-hospitalisation COVID-19 patients: Coalition VII prospective cohort study. Intensive Care Med. 2023;49(2):166-77. PMID: 36594987; https://doi.org/10.1007/s00134-022-06953-1.

Authors contributions: Saconato M: conceptualization (lead), data curation (lead), formal analysis (lead), investigation (lead), methodology (lead), project administration (lead), visualization (lead), writing – original draft (lead), writing – review and editing (lead); Maselli-Schoueri JH: data curation (supporting), formal analysis (lead), visualization (supporting), writing – original draft (supporting), writing – review and editing (supporting); Malaque CMS: data curation (supporting); Marcusso RM: data curation (supporting), formal analysis (supporting), methodology (supporting); Oliveira ACP: methodology (supporting), supervision (supporting), visualization (supporting), writing – original draft (supporting), writing – review and editing (supporting); Batista LAN: data curation (supporting); Ultramari G: supervision (supporting); Lindoso JAL: conceptualization (supporting), methodology (supporting), supervision (supporting), visualization (supporting); Gonçalves MIR: formal analysis (supporting), supervision (supporting), visualization (supporting), writing – review and editing (supporting); Sztajnbok J: conceptualization (lead), data curation (supporting), formal analysis (supporting), investigation (supporting), methodology (supporting), visualization (supporting), writing – original draft (supporting), writing – review and editing (supporting). All authors have reviewed and approved the final version of the manuscript submitted for publication

Acknowledgements:
We thank Paulo Luis Fodra and Fabio Correia Leite for their contributions to the translation and statistical analyses of this study.

Date of first submission: December 11, 2022
Last received: December 09, 2023}
Accepted: March 14, 2024

Source of funding: None
Conflict of interest: None

Address for correspondence:
Mariana Saconato
Instituto de Infectologia Emílio Ribas
Av. Dr. Arnaldo, 165
Pacaembu — São Paulo (SP), Brasil
CEP 01246-900
Tel. (+55 11) 3896-1379
E-mail: marisac35@yahoo.com.br

Editor responsible for the evaluation process:
Paulo Manuel Pêgo-Fernandes, MD, PhD

Combined association of insufficient physical activity and sleep problems with healthcare costs: a longitudinal study

Kelly Akemi Kikuti-Koyama[I], Ítalo Ribeiro Lemes[II], Luana Carolina de Morais[III], Henrique Luiz Monteiro[IV], Bruna Camilo Turi-Lynch[V], Rômulo Araújo Fernandes[VI], Jamile Sanches Codogno[VII]

Universidade Estadual Paulista (UNESP), SP, Brazil

[I]MSc. Student, Department of Physical Education, Laboratory of InVestigation in Exercise (LIVE), Universidade Estadual Paulista (UNESP), Presidente Prudente (SP), Brazil.
https://orcid.org/0000-0003-2313-993X

[II]PhD. Assistant Professor, Physiotherapy Department, Universidade Estadual Paulista (UNESP), Presidente Prudente (SP), Brazil; Assistant Professor, Physiotherapy Department, Faculdade Israelita de Ciências da Saúde Albert Einstein (FICSAE), São Paulo (SP), Brazil.
https://orcid.org/0000-0001-9245-287X

[III]PhD. Student, Laboratory of InVestigation in Exercise (LIVE), Department of Physical Education, Universidade Estadual Paulista (UNESP), Presidente Prudente (SP), Brazil.
https://orcid.org/0000-0003-0960-4954

[IV]PhD. Assistant Professor, Department of Physical Education, Universidade Estadual Paulista (UNESP), Bauru (SP), Brazil.
https://orcid.org/0000-0001-6639-1532

[V]PhD. Assistant Professor, Physical Education and Exercise Science Department, Lander University, Greenwood, United States.
https://orcid.org/0000-0002-1314-6258

[VI]PhD. Associate Professor, Laboratory of InVestigation in Exercise – LIVE, Department of Physical Education, Universidade Estadual Paulista (UNESP), Presidente Prudente (SP), Brazil.
https://orcid.org/0000-0003-1576-8090

[VII]PhD. Assistant Professor, Laboratory of InVestigation in Exercise – LIVE, Department of Physical Education, Universidade Estadual Paulista (UNESP), Presidente Prudente (SP), Brazil.
https://orcid.org/0000-0003-4273-9375

KEYWORDS (MeSH terms):
Exercise.
Health care cost.
Sleep.

AUTHOR KEYWORDS:
Public health.
Lifestyle.
Observational.

ABSTRACT

BACKGROUND: The magnitude of economic losses attributed to sleep problems and insufficient physical activity (PA) remains unclear. This study aimed to investigate the association between insufficient PA, sleep problems, and direct healthcare costs.

OBJECTIVE: To investigate the association between insufficient physical activity (PA), sleep problems, and direct healthcare costs among adults.

DESIGN AND SETTING: Adults aged ≥ 50 years attended by the Brazilian National Health Service were tracked from 2010 to 2014.

METHODS: Direct healthcare costs were assessed using medical records and expressed in US$. Insufficient PA and sleep problems were assessed through face-to-face interviews. Differences were identified using the analysis of covariance and variance for repeated measures.

RESULTS: In total, 454 women and 166 men were enrolled. Sleep problems were reported by 28.9% (95%CI: 25.2% to 32.4%) of the sample, while insufficient PA was reported by 84.8% (95%CI: 82.1% to 87.6%). The combination of sleep problems and insufficient PA explained 2.3% of all healthcare costs spent on these patients from 2010 to 2014, which directly accounts for approximately US$ 4,765.01.

CONCLUSION: The combination of sleep problems and insufficient PA plays an important role in increasing direct healthcare costs in adults. Public health stakeholders, policymakers, and health professionals can use these results to reinforce the need for strategies to improve sleep quality and increase PA, especially in nations that finance their National Health Systems.

INTRODUCTION

The prevalence of sleep problems (e.g., obstructive sleep apnea, insomnia, and snoring) in adults is high worldwide,[1-3] which is concerning due to its association with the development of many diseases.[4] The epidemiological background, which is characterized by a high prevalence of the outcome and an association with diseases, supports a relevant economic burden attributed to sleep problems.[5] In fact, primary care costs for medicines are 75% higher in Brazilian adults who report severe sleep difficulties than in those who report normal sleep,[6] while the total healthcare costs related to sleep problems and attributed conditions in Australia reached US$ 655.5 million in 2019–2020.[5]

Similar to sleep problems, insufficient physical activity (PA) is also a common outcome among adults and is associated with the development of many diseases and increased healthcare costs.[7,8] Figures indicate that insufficiently active adults spend 40% more on healthcare costs than sufficiently active adults, while potential savings on direct healthcare costs attributed to sufficient PA range from US$ 500 million to US$ 1.6 billion per year in Australia and Canada, respectively.[7,9] The association between PA and health outcomes varies depending on context. While overall and leisure-time PA generally have positive effects on health outcomes, PA during work may have less favorable effects, a phenomenon known as the PA paradox.

Although have substantial impacts on healthcare costs among adults, it is not yet clear whether the combination of both boosts economic losses. We hypothesize that the coexistence of sleep problems and insufficient PA may have an additive effect on healthcare costs in adults. This effect would suggest that the simultaneous presence of both risk factors—poor sleep and low PA—could result in healthcare costs that exceed the sum of their individual impacts. This potential

synergistic effect is particularly relevant considering the association between sleep problems and insufficient PA.[10,11]

OBJECTIVE

The present study sought to investigate the association of combined insufficient PA and sleep problems with direct healthcare costs in adults during a four-year follow-up.

METHODS

Sample

This longitudinal study is part of an ongoing cohort study that began in 2010, and included adults from the Brazilian National Health Service, in the city of Bauru, state of São Paulo, Brazil. The study was approved by the Ethics Committee of the Universidade Estadual Paulista (UNESP) (process number 1046/46/01/10 date 08/24/2010).

In terms of sampling, the city of Bauru is a middle-sized city (~ 410,000 inhabitants in 2018 and human development index of 0.801) located in the most industrialized Brazilian state. In Brazil, the Brazilian National Health Service offers free-of-charge health services at all levels (primary, secondary, and tertiary) to all citizens (even foreign citizens legally living in Brazil have full access to these services). All primary care services are offered in small-to-medium-sized medical facilities, called Basic Health Units, which cover all residents living in the surrounding neighborhood. In 2010, Bauru had 17 Basic Health Units spread out in the metropolitan region of the city (only 5% of all citizens live in rural areas). The largest (number of patients) Basic Health Unit in each geographical region of the city (west, east, north, south, and center) was selected to participate in the cohort study.

Random selection was carried out in each selected Basic Health Unit according to the following inclusion criteria: i) registered for at least one year in the Basic Health Unit, ii) ≥ 50 years old, iii) an active registry (at least one consultation in the previous 6 months), and iv) signing the consent form to participate in the study. Participants who fulfilled all inclusion criteria were contacted by phone and invited to participate (face-to-face interviews and physical evaluations were scheduled for those who accepted the invitation). The minimum sample size to start this longitudinal study required 958 participants, which considered the following: i) 60% of all Brazilians exclusively used the Brazilian National Health Service, ii) error of 3.8%, iii) alpha error of 5%, and iv) sample increased by 50% due to cluster sampling. During the sampling process, 4,209 participants had at least one consultation in the last 6 months (west [n = 796], east [n = 402], north [n = 1,212], south [n = 718], and center [n = 1,081]), 1,915 (double the minimum required to protect against losses) were randomly selected/contacted (west [n = 395], east [n = 287], north [n = 416], south [n = 404], and center [n = 413]), and the final sample was composed of 963 participants (west [n = 195], east [n = 193], north [n = 193], south [n = 189], and center [n = 193]), which represents 50.2% of all contacted potential participants (**Figure 1**).

The minimum sample size was calculated considering expected differences in healthcare costs according to the presence of sleep problems (US$ 10.00 higher in adults with sleep problems)[6] and insufficient PA (US$ 13.00 higher in insufficiently active adults).[12] In all simulations for the minimum sample size, the statistical power (80%) and significance (Z = 1.95 [5%]) were standardized. Considering sleep problems, the minimum sample size required was 279 participants (93 in each group), whereas for insufficient PA, the minimum sample size was 366 participants (122 in each group). Additionally, the minimum calculated sample size was increased by 50% as a result of the inclusion of covariates in the multivariate models, and reached n = 418 and n = 549 participants for sleep problems and insufficient PA, respectively. Thus, the minimum sample size estimated for the present study was 549.

Direct healthcare costs

Direct healthcare costs from 2010 to 2014 were assessed using medical records. The Brazilian National Health Service recommends that health professionals register all procedures performed during consultations, including but not limited to blood tests, vaccines, and drug prescriptions. Drugs prescribed during medical consultations are collected from the pharmacy in the Basic Health Unit. All healthcare services are free of charge to the patient. Each patient authorized access to the medical records

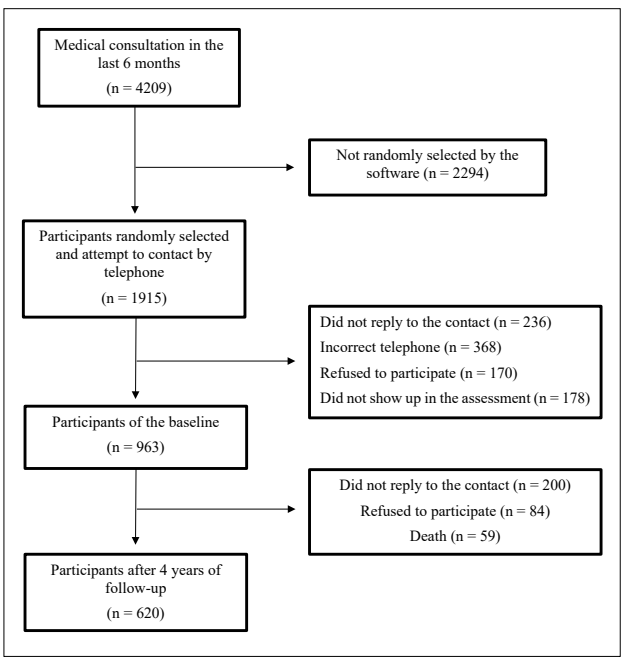


Figure 1. Flow diagram of participants.

and the Department of Health of Bauru provided the direct cost of each service (e.g., medical consultation, medicine taken by the patient, exams, vaccines). Total direct healthcare costs from 2010 to 2014 were calculated in the Brazilian currency (Real [R$]) and then converted to American Dollars (US$) using the official average exchange rate (adjusted for the inflation rate of the period).[8,13]

Sleep problems

The Brazilian Portuguese version of the Mini-sleep Questionnaire was used to assess sleep problems.[14] This questionnaire was inserted in the cohort in 2014 and comprises 10 questions assessed on a 7-point Likert scale (never-1, almost never-2, rarely-3, sometimes-4, often-5, very often-6, always-7) to evaluate different sleep aspects (sleepiness, insomnia, snoring, difficulty getting to sleep, and waking up during the night). Although the Mini-Sleep Questionnaire is a short questionnaire, it consists of two sub-scales that investigate sleep problems and daytime sleepiness. The questionnaire generates a numerical score ranging from 10 to 70 (10–24 for good sleep, 25–27 for mild sleep difficulties, 28–30 for moderate, > 30 for severe). In the present study, sleep problems were defined as a score ≥ 25.

Insufficient PA

The Brazilian Portuguese version of the Baecke questionnaire was administered during interviews in 2010, 2012, and 2014.[15] This questionnaire comprises 16 questions with responses rated on a 5-point Likert scale (never, seldom, sometimes, very often, and always) and addresses PA in three domains: occupational, sports participation in leisure-time, and active commuting. Only data from sports participation in leisure-time were considered for this study. We specifically selected the leisure-time domain due to its strong and well-documented association with health outcomes. This domain has been recognized as a reliable proxy for general PA levels and exhibits a direct correlation with the lifestyle factors under investigation. First, the section considers one yes/no question regarding sports participation. Participants who answer "yes" are then asked additional questions (intensity [light, moderate or vigorous], weekly volume [< 1h/week; 1–2h/week; 2–3h/week; 3–4h/week; > 4h/week], and previous time of engagement [< 1 month; 1–3 months; 4–6 months; 7–9 months; > 9 months]). In line with previous publications,[16] sufficiently active participants were those who reported a minimum of 180 minutes per week (either 3–4 h/week or > 4h/week) of moderate-to-vigorous PA over the previous four months (either 4–6 months, 7–9 months, or > 9 months) in 2014.

Combination of sleep problems and insufficient PA

Finally, seeking a combined variable that includes sleep problems and insufficient PA, the sample was divided into three groups: i) None (Sufficient PA + No sleep problems [n = 82]), ii) Only one (either Sufficient PA + Sleep problems [n = 12] or Insufficient PA + No sleep problems [n = 361], [n = 373]), and iii) Both (Insufficient PA + Sleep problems [n = 165]).

Covariates

For all covariates, the baseline values were adopted. Sex, age, diagnosis of Type 2 diabetes mellitus, arterial hypertension, and any dyslipidemia were assessed during the face-to-face interview. Body mass index (BMI, kg/m^2) was calculated using body weight (kg) and height (cm) and classified as normal (< 25 kg/m^2), overweight (≥ 25 – < 30 kg/m^2), and obese (≥ 30 kg/m^2). A score for economic condition was generated using a standardized Brazilian questionnaire.[17] Smoking status (never, former, and current smoker) was assessed during the face-to-face interview.

Statistical analysis

Descriptive statistics included mean, median, standard deviation (SD), and 95% confidence interval (95%CI). The chi-square test was used to analyze the association between categorical data, and partial correlations were performed to analyze the relationships between variables. Analysis of covariance (ANCOVA) was used to compare healthcare costs among the three groups created by combining sleep problems and insufficient PA (models were adjusted for all covariates). The measures of effect size were expressed as eta-squared (ES-r) values. For the ANCOVA, Levene's test was used to assess the assumption of homogeneity of variances, which was considered satisfactory ($P > 0.05$). Repeated-measures analysis of variance (ANOVA) was used to assess changes in healthcare costs over the four years of follow-up according to the three groups. The assumption of sphericity was tested using Mauchly's test, and the Greenhouse-Geisser approach was used as a correction factor and was considered satisfactory. Interaction analysis was conducted to identify the joint effect of sleep problems and insufficient PA on healthcare costs. To this end, healthcare costs were categorized considering the 90th percentile as the main outcome (an outcome of 10% was selected because odds ratio [OR] and relative risk are similar when the prevalence of the outcome is ≤ 10%) and its association with the combination of sleep problems and insufficient PA tested ($P = 0.001$). The OR for each category was estimated (None [OR_{00}], OR = 1.0; Sufficient PA + Sleep problems [OR_{01}], OR = 1.750; Insufficient PA + No sleep problems [OR_{10}], OR = 1.842; Insufficient PA + Sleep problems [OR_{11}], OR = 3.277). Sinergy index ($[OR_{11} - 1] / \{[OR_{10} - 1] + [OR_{01} - 1]\}$) and the proportion of the joint effects of both exposures (sleep problems and insufficient PA) attributed to interaction on healthcare costs were calculated ($[OR_{11} - OR_{10} - OR_{01} + OR_{00}] / OR_{11}$-1).[18] A synergy index > 1.0 denotes positive additive interaction.[18]

The level of significance was set at $P < 0.05$ and the Stata software (StataCorp LLC., College Station, Texas, United States, version 16.0) was used to perform all analyses.

RESULTS

A total of 963 participants were initially evaluated. After four years, 343 dropouts were recorded (due to deaths, impossible to contact the participant, desire to quit the study). Therefore, 620 participants were included in the present analysis (73.2% women; *n* = 454). Sleep problems were reported by 28.9% (95%CI: 25.2% to 32.4%) of the sample, while insufficient PA was reported by 84.8% (95%CI: 82.1% to 87.6%). From 2010 to 2014, the overall healthcare costs spent by the government on these patients reached US$ 207,174.60 (median of US$ 212.14 per patient). Participants with both sleep problems and insufficient PA presented lower economic conditions (P = 0.006), whereas the coexistence of both was associated with the female sex (P = 0.001) and obesity (P = 0.009) (**Table 1**).

Specific questions in the Mini-Sleep Questionnaire revealed that the use of hypnotic medications (r = 0.116), falling asleep during the day (r = 0.114), snoring (r = 0.093), excessive daytime sleepiness (r = 0.085), and excessive movement during sleep (r = 0.114) were associated with higher healthcare costs (**Table 2**). By contrast, higher intensity, weekly volume, and previous time of engagement in PA were related to lower healthcare costs.

The combination of sleep problems and insufficient PA explained 2.3% of all healthcare costs spent on these patients from 2010 to 2014, which directly account for approximately US$ 4,765.01. Adults who are insufficiently active and with sleep problems had the highest healthcare costs, whereas adults with either insufficient PA or sleep problems and those with neither outcome had similar costs (**Figure 2**, **Panel A**). In this multivariate model, the diagnosis of diabetes mellitus increased healthcare costs by approximately 2.5%.

When compared to those with no sleep problems and sufficient PA, adults with both sleep problems and insufficient PA presented higher healthcare costs throughout the follow-up period (P = 0.001) (**Figure 2**, **Panel B**).

Interaction analysis identified a synergy index of 1.8 (> 1.0, denoting positive additive interaction), while the proportion of the joint effects of sleep problems and insufficient PA attributed to interaction on healthcare costs reached 30.1%.

DISCUSSION

This four-year longitudinal study established that the coexistence of sleep problems and insufficient PA increased direct healthcare costs in adults.

Table 1. General information according to the presence of sleep problems and insufficient physical activity (Bauru, Brazil; n = 620)

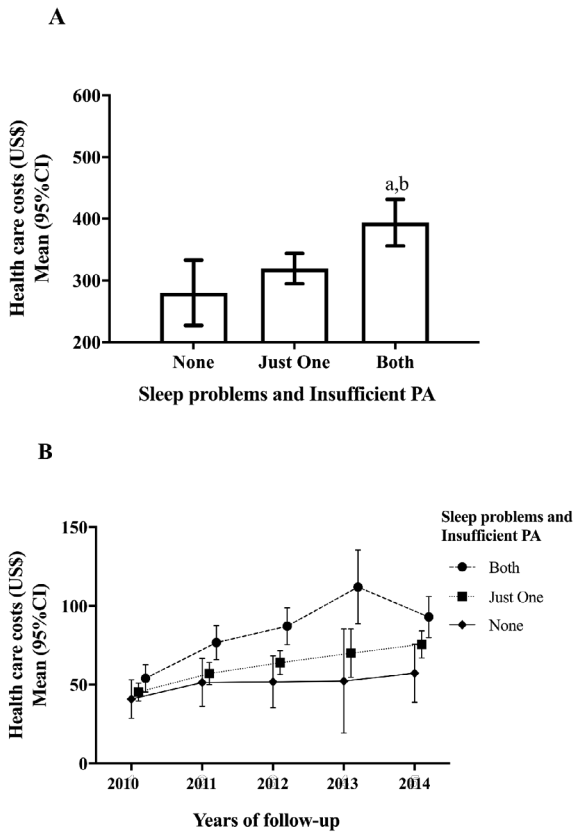
	Sleep problems and Insufficient physical activity			
	None (n = 82)	Only one (n = 373)	Both (n = 165)	
Continuous	**Mean (SD)**	**Mean (SD)**	**Mean (SD)**	**P value**
Age (years)	63.9 (7.2)	65.1 (9.1)	64.2 (8.5)	0.405
Body weight (kg)	70.8 (16.1)	73.2 (14.9)	75.8 (17.3)	0.050
Height (cm)	157.9 (20.1)	157.4 (11.8)	155.7 (7.8)	0.294
EC (score)	20.1 (6.4)	18.4 (5.5)[a]	17.7 (5.5)[a]	**0.006**
Categorical (n [%])				
Sex				**0.001**
Male	31 (37.8%)	110 (29.5%)	25 (15.2%)	
Female	51 (62.2%)	263 (70.5%)	140 (84.8%)	
Smoking				0.448
Never	37 (45.1%)	210 (56.3%)	98 (59.4%)	
Former	39 (47.6%)	124 (33.2%)	43 (26.1%)	
Current	6 (7.3%)	39 (10.5%)	24 (14.5%)	
BMI				**0.009**
< 25 kg/m²	19 (23.2%)	66 (17.7%)	23 (13.9%)	
25.0 – 29.9 kg/m²	37 (45.1%)	150 (40.2%)	62 (37.6%)	
≥ 30.0 kg/m²	26 (31.7%)	157 (42.1%)	80 (48.5%)	
Diseases				
DM (yes)	22 (26.8%)	98 (26.3%)	55 (33.3%)	0.284
AH (yes)	61 (74.4%)	295 (79.1%)	136 (82.4%)	0.142
DLP (yes)	27 (32.9%)	125 (33.5%)	67 (40.6%)	0.234

SD = standard deviation; BMI = body mass index; EC = economic condition; DM = diabetes mellitus; AH = arterial hypertension; DLP = dyslipidemia; a = denotes significant difference (P < 5%) compared to "None."

Table 2. Relationship between healthcare costs and questions regarding sleep and physical activity among adults (Bauru, Brazil; n = 620)

	Dependent variable: Healthcare costs 2010-2014	
Independent variables	**Partial Correlation (*r*)***	**P value**
Mini-sleep Questionnaire		
Difficulty falling asleep	0.033	0.422
Waking up too early	0.024	0.550
Hypnotic medication use	0.116	**0.004**
Falling asleep during the day	0.114	**0.005**
Feeling tired upon waking up in the morning	0.058	0.150
Snoring	0.093	**0.022**
Mid-sleep awakenings	0.011	0.791
Headaches on awakening	0.043	0.294
Excessive daytime sleepiness	0.085	**0.036**
Excessive movement during sleep	0.114	**0.005**
Baecke questionnaire		
Intensity	-0.100	**0.013**
Weekly volume	-0.109	**0.007**
Previous time of engagement	-0.106	**0.009**

* Correlation adjusted by sex, chronological age, economic condition, body mass index, arterial hypertension, diabetes mellitus, and dyslipidemia.



[a] P < 0.05 compared to None. [b] P < 0.05 compared to Just One. PANEL A: Analysis of covariance: Insufficient PA and Sleep problems (P = 0.001; Eta-squared 0.023 [2.3%]). Covariates (P value [eta-squared in %]): Sex (P = 0.677 [<0.1%]), BMI (P = 0.278 [0.2%]), Economic condition (P = 0.871 [<0.1%]), Smoking (P = 0.377 [0.1%]), Health care Costs in 2010 (P = 0.001 [48.7%]), Arterial hypertension (P = 0.479 [0.1%]), Diabetes mellitus (P = 0.001 [2.5%]), Dyslipidemia (P = 0.066 [0.6%]). PANEL B: Analysis of variance for repeated measures (P value): Time (P = 0.051), Group (P = 0.001), Time x Group (P = 0.077).

Figure 2. Amount of health care costs from 2010 to 2014 according to the combination of sleep problems and insufficient physical activity (Bauru, Brazil; n = 620).

Sleep problems and insufficient PA were frequently identified outcomes in our participants, which is similar to previous studies[1,2,19] and highlights the relevant problem that both outcomes present in modern society. Obesity and female were variables associated with the coexistence of sleep problems and insufficient PA. In the case of obesity, this finding is not surprising, especially because obesity is frequently associated with lower PA and a higher occurrence of sleep problems.[19,20] Regarding sex, menopause tends to have a detrimental impact on women's body composition,[21] while aging is related to reductions in PA in women.[9] Thus, women over 50 years of age present a group that is potentially exposed to the harmful combination of insufficient PA and sleep problems, and thus, actions should be focused on preventing these behaviors among them.

Regarding PA, all the components assessed using the Baecke questionnaire were similarly related to healthcare costs in terms of direction and magnitude. In terms of direction, previous studies have documented the potential of PA in the mitigation of direct healthcare costs in primary care.[7,8] Regarding magnitude, the mitigation role attributed to PA seems to be of small magnitude, below 3%.[7,8] The low effect size attributed to the relationship between PA and healthcare costs may be explained, at least in part, by the fact that it is not a direct relationship but is mediated by the impact of PA on other variables that affect healthcare costs, such as obesity, mental health, and chronic diseases. Although the relationship between PA and healthcare costs is not large in terms of magnitude, it has been proven to be economically relevant, especially when considered at the population level.[7-9]

Regarding sleep problems, an additional analysis considering all the questions covered by the Mini-Sleep Questionnaire revealed that the most relevant questions related to healthcare costs were those that assess snoring, excessive daytime sleepiness, and the use of hypnotic medicine. The burden of hypnotic medicines on healthcare costs is not a surprise given the increased popularity of this kind of medicine among adults with sleep problems.[22] Even so, the identification of snoring and symptoms of excessive sleepiness as determinants of healthcare costs was an interesting finding. Snoring and excessive sleepiness are frequently diagnosed symptoms in adults with obstructive sleep apnea,[20] which is the most common sleep problem diagnosed in adults and is responsible for substantial economic losses.[5] In fact, our study did not assess obstructive sleep apnea (which is a limitation); however, it is reasonable to believe that the observed relationships may be explained by this condition, at least in part.

Our findings revealed that the coexistence of sleep problems and insufficient PA was associated with increased healthcare costs in adults, while this impact was more tangible than that observed on the isolated manifestation of either variable (interaction analysis identified that healthcare costs were impacted in 30% due to the combination of both variables), thereby denoting both variables are potentially harmful to economic maintenance of Brazilian National Health Service. Sleep problems and insufficient PA accounted for 2.3% of all variances in healthcare costs. This figure initially seems small, but is similar to the burden of obesity on healthcare costs in Canada[7] and of hospitalizations in Brazil, for example.[23] Moreover, at the population level (with 36,894,000 adults ≥ 50 years old in Brazil who exclusively use the Brazilian National Health Service for health assistance[24] and a median healthcare cost of US$ 212.14 from 2010 to 2014), and assuming there is a causal relationship in our analyses, a mitigation of 2.3% on direct healthcare costs would represent a saving

of US$ 180 million in primary care services from 2010 to 2014 among adults aged ≥ 50 years.

Public health stakeholders, policymakers, and health professionals can use these results to reinforce the need for strategies to improve sleep quality and increase PA levels, especially in nations financing National Health Systems similar to Brazil (e.g., Australia, Canada, and the United Kingdom). Future clinical trials should investigate whether changes in these behaviors would mitigate healthcare costs at secondary/tertiary levels, as well as indirect costs, especially in a post-pandemic scenario during which both variables were severely affected.[25]

The study has the following limitations. Although the questionnaires used to assess both insufficient PA and sleep problems in our sample have been previously validated, widely used in epidemiological studies, and applied by trained researchers, the non-objective measures of PA and sleep may be considered relevant limitations. This aspect seems relevant because both the relationships between PA and sleep and between PA and costs seem to be affected by intensity and sleep patterns,[10,26] which are easier to measure using objective methods. Physiological pathways linking diet and sleep problems exist, such as synthesis of serotonin and melatonin, and thus, the absence of diet control constitutes a limitation of our study. Our economic figures are probably underestimated because only primary healthcare costs were assessed, while indirect costs (e.g., absenteeism) and healthcare costs at secondary and tertiary levels (e.g., hospitalizations, surgeries) are also affected by PA and sleep problems but were not included in our analyses. Owing to the small sample size of patients with sleep problems and sufficient PA (n = 12), we were unable to split the "Only one" group. Consequently, the results should be interpreted with caution as they may not be generalizable to the broader population. Finally, although this is a longitudinal study, we are not able to infer causality for healthcare costs, mainly because sleep problems were not assessed at all time-points of data collection.

CONCLUSION

In summary, our findings suggest that the combination of sleep problems and insufficient PA plays an important role in increasing direct healthcare costs among adults.

REFERENCES

1. Foley D, Ancoli-Israel S, Britz P, Walsh J. Sleep disturbances and chronic disease in older adults: Results of the 2003 National Sleep Foundation Sleep in America Survey. J Psychosom Res. 2004;56(5):497-502. PMID: 15172205; https://doi.org/10.1016/j.jpsychores.2004.02.010.
2. Kim JK, In KH, Kim JH, et al. Prevalence of sleep-disordered breathing in middle-aged Korean men and women. Am J Respir Crit Care Med. 2004;170(10):1108-13. PMID: 15347562; https://doi.org/10.1164/rccm.200404-519oc.
3. Barros MB de A, Lima MG, Ceolim MF, Zancanella E, Cardoso TAMO. Quality of sleep, health and well-being in a population-based study. Rev Saude Publica. 2019;53:82. PMID: 31576942; https://doi.org/10.11606/s1518-8787.2019053001067.
4. St-Onge MP, Grandner MA, Brown D, et al. Sleep Duration and Quality: Impact on Lifestyle Behaviors and Cardiometabolic Health: A Scientific Statement from the American Heart Association. Circulation. 2016;134(18):e367-86. PMID: 27647451; https://doi.org/10.1161/cir.0000000000000444.
5. Streatfeild J, Smith J, Mansfield D, Pezzullo L, Hillman D. The social and economic cost of sleep disorders. Sleep. 2021;44(11):zsab132. PMID: 34015136; https://doi.org/10.1093/sleep/zsab132.
6. da Silva EP, Rocha APR, Araujo MYC, et al. Sleep pattern, obesity and healthcare expenditures in Brazilian adults. Ciencia e Saude Coletiva. 2019;24(11):4103-10. PMID: 31664383; https://doi.org/10.1590/1413-812320182411.26972017.
7. Katzmarzyk PT, Janssen I. The economic costs associated with physical inactivity and obesity in Canada: an update. Can J Appl Physiol. 2004;29(1):90-115. PMID: 15001807; https://doi.org/10.1139/h04-008.
8. Codogno JS, Turi BC, Kemper HCG, et al. Physical inactivity of adults and 1-year health care expenditures in Brazil. Int J Public Health. 2015;60(3):309-16. PMID: 25680327; https://doi.org/10.1007/s00038-015-0657-z.
9. Gomes GAO, Brown WJ, Codogno JS, Mielke GI. Twelve year trajectories of physical activity and health costs in mid-age Australian women. Int J Behav Nutr Phys Act. 2020;17(1):101. PMID: 32778110; https://doi.org/10.1186/s12966-020-01006-6.
10. Seol J, Lee J, Park I, et al. Bidirectional associations between physical activity and sleep in older adults: a multilevel analysis using polysomnography. Sci Rep 2022;12(1):15399. PMID: 36100642; https://doi.org/10.1038/s41598-022-19841-x.
11. Alhainen M, Myllyntausta S, Pentti J, Vahtera J, Stenholm S. Concurrent changes in sleep and physical activity during the transition to retirement: a prospective cohort study. Sleep Med. 2020;68:35-41. PMID: 32028224; https://doi.org/10.1016/j.sleep.2019.09.009.
12. Turi BC, Codogno JS, Sarti FM, et al. Determinants of outpatient expenditure within primary care in the Brazilian National Health System. Sao Paulo Med J. 2017;135(3):205-212. PMID: 28380203; https://doi.org/10.1590/1516-3180.2016.0224141116.
13. Codogno JS, Fernandes RA, Sarti FM, Freitas Júnior IF, Monteiro HL. The burden of physical activity on type 2 diabetes public healthcare expenditures among adults: a retrospective study. BMC Public Health. 2011;11(1):275. PMID: 21542924; https://doi.org/10.1186/1471-2458-11-275.
14. Falavigna A, De Souza Bezerra ML, Teles AR, et al. Consistency and reliability of the Brazilian Portuguese version of the Mini-Sleep Questionnaire in undergraduate students. Sleep and Breathing. 2011;15(3):351-5. PMID: 20652835; https://doi.org/10.1007/s11325-010-0392-x.

15. Baecke JA, Burema J, Frijters JE. A short questionnaire for the measurement of habitual physical activity in epidemiological studies. Am J Clin Nutr 1982:36(5):936–42. PMID: 7137077; https://doi.org/10.1093/ajcn/36.5.936.
16. Fernandes RA, Zanesco A. Early physical activity promotes lower prevalence of chronic diseases in adulthood. Hypertens Res. 2010;33(9):926-31. PMID: 20574424; https://doi.org/10.1038/hr.2010.106.
17. Associação Brasileira de Empresas de Pesquisa - Critério de Classificação Econômica Brasil. Available from: www.abep.org. Accessed in 2023 (Oct. 4).
18. VanderWeele TJ, Knol MJ. A Tutorial on Interaction. Epidemiol Methods. 2014;3(1):33-72; https://doi.org/10.1515/em-2013-0005.
19. Zanuto EAC, De Limai CSM, De Araújo GR, et al. Sleep disturbances in adults in a city of Sao Paulo state. Rev Bras Epidemiol. 2015;18(1):42-53. PMID: 25651010; https://doi.org/10.1590/1980-5497201500010004.
20. Verbraecken J. More than sleepiness: prevalence and relevance of nonclassical symptoms of obstructive sleep apnea. Curr Opin Pulm Med. 2022;28(6):552-8. PMID: 36101923; https://doi.org/10.1097/mcp.0000000000000915.
21. Pegington M, Harvie M, Harkness EF, et al. Obesity at age 20 and weight gain during adulthood increase risk of total and premature all-cause mortality: findings from women attending breast screening in Manchester. BMC Womens Health. 2023;23(1):17. PMID: 36635680; https://doi.org/10.1186/s12905-023-02162-0.
22. Wesselhoeft R, Rasmussen L, Jensen PB, et al. Use of hypnotic drugs among children, adolescents, and young adults in Scandinavia. Acta Psychiatr Scand. 2021;144(2):100-12. PMID: 34021908; https://doi.org/10.1111/acps.13329.
23. Sichieri R, Do Nascimento S, Coutinho W. The burden of hospitalization due to overweight and obesity in Brazil. Cad Saude Publica. 2007;23(7):1721-7. PMID: 17572823; https://doi.org/10.1590/s0102-311x2007000700025.
24. Malta DC, Bernal RTI, Prates EJS, et al. Self-reported arterial hypertension, use of health services and guidelines for care in Brazilian population: National Health Survey, 2019. Epidemiol Serv Saude. 2022;8;31(spe1):e2021369. PMID: 35946670; https://doi.org/10.1590/ss2237-9622202200012.especial.
25. Dokkedal-Silva V, Morelhão PK, Moreira GA, Tufik S, Andersen ML. The next step: how sleep and physical activity can act together in the post-COVID-19 scenario. Sleep and Breathing. 2023;27(2):689-690. PMID: 35713758; https://doi.org/10.1007/s11325-022-02657-4.
26. Torres W, de Moraes Chagas LG, Fernandes RA, et al. Relationship between vigorous physical activity and health care costs among adolescents: ABCD Growth Study. BMC Pediatr. 2022;22(1):141. PMID: 35300655; https://doi.org/10.1186/s12887-022-03201-9.

Author's contributions: Koyama KAK,: curation (equal), investigation, (equal) methodology (equal),writing – original draft (equal), writing – review and editing (equal); Lemes IR: formal analysis (equal), investigation (equal), methodology (equal), project administration (equal), writing – original draft (equal), writing – review and editing (equal); Morais LC: data curation (equal), investigation (equal), methodology (equal), writing – original draft (equal), writing – review and editing (equal); Monteiro HL: conceptualization (equal), data curation, formal analysis, investigation, methodology, project administration, resources (equal), supervision (equal), writing – original draft, writing – review and editing; Turi-Lynch BC: conceptualization (equal), formal analysis, investigation, methodology, project administration, writing – original draft, writing – review and editing; Fernandes RA: conceptualization (equal), formal analysis, investigation, methodology, validation (equal), project administration, writing – original draft ,writing – review and editing; Codogno JS: conceptualization (equal), investigation, methodology, project administration, supervision (equal), writing – original draft writing – review and editing. All authors reviewed and approved the final version submitted for publication

Acknowledgments: The authors acknowledge the Health Secretary of Bauru and the health professionals of primary care units

Sources of funding: This article was supported by Coordenação de Aperfeiçoamento de Pessoal de Nível Superior (CAPES) and Fundação de Amparo à Pesquisa do Estado de São Paulo (FAPESP) (2015/17777-3 2016/11140-6)

Conflicts of interests: None

Date of first submission: July 10, 2023
Last received: February 26, 2023
Accepted: March 25, 2024

Address for correspondence:
Ítalo Ribeiro Lemes
Departamento de Fisioterapia, Faculdade de Ciências e Tecnologia, Universidade Estadual Paulista (UNESP)
Rua Roberto Simonsen, 305 — Centro Educacional
CEP 19060-900 — Presidente Prudente (SP), Brasil.
Tel.: (18) 3229-5388 – Ramal 5555
E-mail: itolemes@hotmail.com

Editor responsible for the evaluation process:
Paulo Manuel Pêgo-Fernandes, MD, PhD

Prevalence of Congenital Anomalies of the Upper Limbs in Brazil: a descriptive cross-sectional study

Samuel Ricardo Batista Moura[I], Luis Renato Nakachima[II], João Baptista Gomes dos Santos[III], João Carlos Belloti[IV], Carlos Henrique Fernandes[V], Flavio Faloppa[VI], Vinicius Ynoe de Moraes[VII], Rodrigo Guerra Sabongi[VIII]

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

[I]MD. Hand Surgeon, Department of Orthopedics and Traumatology, Escola Paulista de Medicina - Universidade Federal de São Paulo (EPM-UNIFESP), São Paulo (SP), Brazil
https://orcid.org/0000-0001-9248-1136

[II]MD, MSc, PhD. Adjunct Professor, Department of Orthopedics and Traumatology. Discipline of Hand and Upper Limb Surgery, Escola Paulista de Medicina - Universidade Federal de São Paulo (EPM-UNIFESP), São Paulo (SP), Brazil
https://orcid.org/0000-0003-1901-9820

[III]MD, MSc, PhD. Adjunct Professor, Department of Orthopedics and Traumatology, Escola Paulista de Medicina - Universidade Federal de São Paulo (EPM-UNIFESP), São Paulo (SP), Brazil
https://orcid.org/0000-0003-0199-6578

[IV]MD, PhD. Adjunct Professor, Department of Orthopedics and Traumatology, Escola Paulista de Medicina - Universidade Federal de São Paulo (EPM-UNIFESP), São Paulo (SP), Brazil.
https://orcid.org/0000-0003-3396-479

[V]MD, PhD. Adjunct Professor, Department of Orthopedics and Traumatology, Escola Paulista de Medicina - Universidade Federal de São Paulo (EPM-UNIFESP), São Paulo (SP), Brazil.
https://orcid.org/0000-0003-0146-6091

[VI]MD, MSc, PhD. Full Professor, Department of Orthopedics and Traumatology, Escola Paulista de Medicina - Universidade Federal de São Paulo (EPM-UNIFESP), São Paulo (SP), Brazil
https://orcid.org/0000-0003-3688-8729

[VII] MD, PhD. Orthopedic Surgeon, Department of Orthopedics and Traumatology, Escola Paulista de Medicina - Universidade Federal de São Paulo (EPM-UNIFESP), São Paulo (SP), Brazil.
https://orcid.org/0000-0002-4933-4007

[VIII]MD. Hand Surgeon, Department of Orthopedics and Traumatology, Escola Paulista de Medicina - Universidade Federal de São Paulo (EPM-UNIFESP), São Paulo (SP), Brazil.
https://orcid.org/0000-0003-0164-3596

KEY WORDS (MeSH terms):
Epidemiology.
Upper extremity.
Congenital abnormalities.
Hand deformities.

AUTHOR'S KEYWORDS:
Upper Limb.
Prevalence.
Congenital upper limb anomaly.

ABSTRACT

BACKGROUND: Congenital Anomalies of the Upper Limb (CAUL) are a group of structural or functional abnormalities that develop during intrauterine life and can lead to limb dysfunction.

OBJECTIVES: To analyze the prevalence of congenital anomalies of the upper limbs in Brazil and assess maternal and neonatal variables.

DESIGN AND SETTING: A cross-sectional, descriptive study was conducted on congenital upper limb malformations among live births across Brazil.

METHODS: The study spanned from 2010 to 2019. Data were sourced from the Department of Informatics of the Unified Health System (DATASUS) and the Live Birth Information System (SINASC) portal. Analyses focused on the information reported in field 41 of the Live Birth Declaration Form entered into the computerized system.

RESULTS: The most common anomaly in Brazil was supernumerary fingers, classified as ICD-Q69.0, affecting 11,708 children, with a prevalence of 4.02 per 10,000 live births. Mothers aged over 40 years had a 36% higher prevalence of having children with CAUL than mothers under 40 years old (OR = 1.36; 95% CI 1.19-1.56). Newborns weighing ≤ 2,499 g were 2.64 times more likely to have CAUL compared to those weighing ≥ 2,500 g (OR = 2.64; 95% CI 2.55-2.73).

CONCLUSION: There was an observed increase in the reporting of CAUL cases over the decade studied. This trend serves as an alert for health agencies, as understanding the prevalence of CAUL and its associated factors is crucial for preventive medicine.

INTRODUCTION

Congenital anomalies (CAs) are structural or functional alterations in embryos or fetuses that result from factors occurring before birth.[1] These developmental changes can be genetic, environmental, unknown, or multifactorial in origin.[2] CAs affect 1% to 3% of newborns, with approximately 10% of these cases involving congenital anomalies of the upper limb (CAUL).[3,4]

CAUL varies from minor isolated alterations with minimal impact on limb function to significant changes affecting vital organs. Monitoring these anomalies can help reduce morbidity and mortality in affected patients.[5]

Prevalence studies are essential in epidemiology for planning preventive public health measures. Currently, there are no studies on the prevalence of congenital upper limb anomalies in Brazil. This study aims to fill that gap using data from a Brazilian database. Worldwide, several databases monitor these anomalies, including the "Latin American Collaborative Study of Congenital Malformations," a universal database in Latin America that supports clinical and epidemiological research.[6]

In Brazil, the Department of Informatics of the Unified Health System (DATASUS) under the Ministry of Health developed the "Live Birth Information System" (SINASC) in 1990 to collect epidemiological data on births nationwide. The standard document utilized is the "Live Birth Certificate" (DNV), which is mandatory for all live births regardless of delivery circumstances.[7]

Understanding the causes of CAs, especially those that are preventable, is crucial. Specific strategies in health policies can elucidate the increase in the proportion of deaths caused by CAs. The chronic nature of CAUL incurs significant socioeconomic costs and necessitates long-term multidisciplinary care. Increased investment in support strategies for patients with CAs is necessary, and further studies are needed to identify primary causes and associated factors.[2]

Epidemiological data on CAUL are vital for the development, planning, and monitoring of public health strategies. Studies on etiology and prevention depend on high-quality epidemiological data.[8] The accuracy of an epidemiological study hinges on understanding the studied population and the authenticity of the collected data.[9] This study hypothesizes that the national prevalence data for CAUL are consistent with those collected globally.

OBJECTIVE

The objective of this study was to analyze the prevalence of CAUL in Brazil from 2010 to 2019, utilizing the DATASUS database, and to evaluate the associated maternal and neonatal variables.

METHODS

Research design

This descriptive cross-sectional study examined cases of CAUL in newborns in Brazil from 2010 to 2019, adhering to the Strengthening the Reporting of Observational Studies in Epidemiology (STROBE) guidelines.

Data-gathering period

Data were collected from September to October 2021 and extracted from the Department of Informatics of the Unified Health System - DATASUS (available at http://www2.datasus.gov.br).[10] This database compiles information from the mandatory Live Birth Certificate (DNV) for all live births in Brazil, maintained in the SINASC system.

Selection criteria

The study variables included demographic details, types of upper limb congenital anomalies, and maternal and newborn variables as recorded in DATASUS. The data from the live birth certificates, which contain 41 fields divided into seven blocks, were utilized. Field 41 specifies congenital anomalies as noted by the delivery personnel or a neonatologist. Following Chapter XVII, titled "Congenital Malformations, Deformities, and Chromosomal Abnormalit" all anomalies were recorded non-hierarchically, with a detailed description of the codes from the International Classification of Diseases (ICD-10).

Data-gathering

The Swanson classification was employed to categorize CAUL,[11] grouping similar deficiency patterns based on specific embryological faults. The categories included: (I) failure of formation, (II) failure of differentiation, (III) duplication, (IV) overgrowth, (V) undergrowth, (VI) congenital constriction band syndrome, and (VII) generalized skeletal abnormalities. Anomalies were grouped according to their corresponding ICD-10 codes.

All ICD-10 codes corresponding to CAUL diagnosed at birth were selected. Diagnoses were grouped to categorize anomalies according to related pathologies (**Table 1**).

The variables of interest selected for analysis pertained to the period and place of birth, maternal data (age, education, gestational duration, type of delivery, type of pregnancy, and prenatal visits), and newborn variables (Apgar scores at 1 and 5 min, sex, birth weight, and race/ethnicity).

Table 1. ICD-10 grouping in relation to the type of CAUL Brazil, 2010-2019

* CAUL	** ICD-10
Training Deficiency	Q71.0 - Complete congenital absence of the upper limb(s) Q71.1 - Congenital absence of the arm and forearm, with hand presente Q71.2 - Congenital absence of the forearm and hand Q71.3- Congenital absence of the hand and finger(s) Q71.4 - Radius longitudinal reduction defect Club hand (congenital) / Radial hand Q71.5 - Longitudinal reduction defect of the ulna [ulna] Q71.6 - Lobster claw hand Q71.8 - Other upper limb reduction defects Congenital shortening of the upper limb(s) Q71.9 Defect due to reduction of the upper limb, unspecified
Differentiation Deficiency	Q70.0- Coalescence of the fingers (fused fingers)/Complex syndactyly of the fingers with synostosis Q70.1 - Webbed fingers / Simple syndactyly of the fingers without synostosis Q70.4- Polysyndactyly
Duplication Deficiency	Q69.0- Supernumerary finger(s) Q69.1 - Supernumerary thumb(s)
Widespread anomalies	Q68.1 - Other congenital musculoskeletal deformities - Congenital hand deformity Q74.0 - Other congenital malformations of the upper limb(s), including the shoulder girdle Q74.3 - Multiple arthrogryposis congenita

Data processing and analysis

Data were collected between February and June 2022. Based on these data, the total prevalence of CAUL in DATASUS from 2010 to 2019, as well as the specific prevalence according to maternal and newborn variables, were calculated using the following formula:

$$\frac{\text{Number of malformed live births in the period } 2010-2019 \times 10.000}{\text{Number of live births in the in the period } 2010-2019}$$

Data were extracted, organized, and encoded in a spreadsheet using Microsoft Excel, version 16.0, developed by Microsoft (Redmond, Washington, United States), and then processed using the Statistical Package for the Social Sciences (SPSS) software, version 23.0, developed by International Business Machines Corporation (IBM) (New York, United States).

Due to the limitations of individualized data, a linear trend model was applied. The three-point moving average (MM (3)) smoothing method was utilized to enhance the visualization of the linear trend. Simple univariate linear regression analysis was conducted for predictive modeling and to estimate future values. No discernible patterns of cyclic or irregular components were identified during the subjective analysis of the graph; therefore, no cyclical analysis was performed. As the source data were annual, it was impossible to identify a seasonal component throughout the year. Each year of occurrence was used as the independent variable, and the ratio of live births with upper limb malformations to the total number of live births per year was used as the dependent variable. An overall analysis was conducted for Brazil, and a regional analysis was performed for the country (North, South, East, and West). For statistical inference, a statistically significant difference was considered at a type I error rate of $P < 0.05$.

This study was submitted to and approved by the Research Ethics Committee of the Federal University of São Paulo (UNIFESP) with the approval number 5.036.478.

RESULTS

Between 2010 and 2019, Brazil registered 29,157,184 live births, of which 238,571 had general CAs. The Southeast region recorded the highest number of live births, while the Central-West had the fewest during this period.

In total, 216,801 congenital anomalies were identified, including 21,770 cases of CAUL. The anomalies were categorized into four types based on related pathologies: formation defects, with 3,938 cases (18%); differentiation, with the fewest cases at 1,572 (7.2%); duplication, encompassing the majority with 12,012 cases (55.0%); and generalized anomalies, with 4,248 cases (19.5%).

The number of newborns with CAUL was analyzed separately by ICD codes and country. The national prevalence of CAUL was 7.5 per 10,000 LBs. The most prevalent anomaly was supernumerary fingers, represented by ICD-Q69.0, affecting 11,708 children (a prevalence of 4.02 per 10,000 live births). In contrast, the anomaly with the lowest national prevalence was the longitudinal reduction defect of the ulna, represented by ICD-Q71.5, with a prevalence of 0.01 per 10,000 live births (**Table 2**).

Regional prevalence of CAUL per 10,000 LBs by ICD-10 code from 2010 to 2019, showed the Southeast having the highest rate of 9.15. The Northeast had the second-highest prevalence (**Table 2**).

The anomaly of supernumerary fingers (ICD-Q69.0) had the highest regional prevalence in the Southeast, at 5.34 per 10,000 LBs. The congenital hand deformity (ICD-Q68.1), the second most prevalent anomaly nationwide, had its highest prevalence in the Southern region, at 1.14 per 10,000 live births (**Table 3**).

Duplication defects, representing a group of CAUL, had the highest prevalence in all studied years, increasing from 3.6 cases per 10,000 LBs in 2010 to 4.8 in 2019.

Maternal and newborn variables were analyzed and are detailed in **Tables 4** and **5**. Concerning maternal age at the time of delivery, the majority of cases did not specify the age; however, children born to mothers over 40 years old exhibited a prevalence 1.36 times (or 36%) higher than those born to mothers under 40 years of age (OR = 1.36; 95% CI 1.19-1.56).

In terms of delivery type, Cesarean sections accounted for 12,418 cases of CAUL, with a prevalence of 7.6 per 10,000 LBs. In these cases, the prevalence of children born with CAUL was 1.07 times (or 7%) higher than in those born via spontaneous delivery (OR = 1.07; 95% CI 1.04-1.10). The number of prenatal visits was often unknown. Mothers who had three or fewer prenatal visits showed a 1.37 times (or 37%) higher prevalence of having children with CAUL compared to mothers who had four or more prenatal visits (OR = 1.37; 95% CI 1.27-1.48). Mothers with 11 years of education or less had a 1.22 times (or 22%) higher prevalence of having children with CAUL compared to those with 12 or more years of education (OR = 1.22; 95% CI 1.18-1.27).

Mothers with a gestational duration of 36 weeks or less were 1.89 times (or 89%) more likely to have children with CAUL than those with a gestational duration of 37 weeks or more (OR = 1.89; 95% CI 1.82-1.96). In cases of multiple pregnancies, such as twins or triplets, the prevalence of children born with CAUL was 1.29 times (or 29%) higher than in single pregnancies (OR = 1.37; 95% CI 1.27-1.48) (**Table 4**).

When analyzing newborn variables related to birth weight, the highest prevalence of CAUL was observed in children weighing ≤ 2,499 g. Newborns in this weight range had a prevalence 2.64 times (or 64%) higher for CAUL compared to newborns with a birth weight ≥ 2,500 g (OR = 2.64; 95% CI 2.55-2.73).

Male newborns exhibited a 23% higher prevalence of CAUL than female newborns (OR = 1.23; 95% CI 1.17-1.30). Black newborns

Table 2. Prevalence of congenital malformations of the upper limbs by regions of Brazil for every 10 thousand LB (2010-2019)

ICD – CAUL	Regiões do Brasil						
	North	Northeast	West Central	Southeast	South	Total	
	LB*						
	3.127.884	8.286.407	2.371.666	11.482.289	3.888.938	29.157.184	
	CAUL (**)	CAUL (**)	CAUL (**)	CAUL (**)	CAUL (**)	CAUL (**)	Prevalence
Q69.0- Supernumerary finger(s);	441	3.435	731	6.137	964	11.708	4,02
Q68.1 - Congenital hand deformity;	215	682	212	1.104	443	2.656	0,91
Q71.3 - Congenital absence of the hand and finger(s);	147	392	169	724	280	1.712	0,59
Q74.0- Other Congenital Malformations of the Upper Limbs	136	283	72	583	149	1.223	0,42
Q71.8- Other upper limb reduction defects. Congenital shortening of the upper limb(s);	67	157	51	331	110	716	0,25
Q70.4- Polysyndactyly	44	143	40	271	109	607	0,21
Q70.0- Coalescence of the fingers - Complex syndactyly of the fingers with synostosis	43	152	51	245	99	590	0,20
Q719-Defect of upper limb reduction, unspecified.	55	123	37	246	75	536	0,18
Q71.2- Congenital absence of the forearm and hand	31	92	30	159	72	384	0,13
Q70.1- Webbed fingers Simple syndactyly of the fingers without synostosis	24	124	39	146	42	375	0,13
074.3- Multiple Congenital Arthrogryposis	20	123	15	161	50	369	0,13
Q69.1- Supernumerary thumb(s)	20	59	32	150	43	304	0,10
Q71.6- Lobster claw hand	28	63	16	91	30	228	0,08
Q71.0- Complete congenital absence of the upper limb(s)	19	47	20	67	22	175	0,06
Q71.4- Radius longitudinal reduction defect | Club hand (congenital) | Radial hand	09	18	06	50	10	93	0,03
Q71.1- Congenital absence of the arm and forearm, with hand present	05	16	08	24	07	60	0,02
Q71.5- Longitudinal reduction defect of the ulna [ulna];	02	06	04	18	04	34	0,01
Total	1.306	5.915	1.533	10.507	2.509	21.770	7,5

(*) LB= live births; (*) CAUL=congenital anomaly of the upper limbs

Table 3. Prevalence de CAUL by region (per 10,000 LB) by ICD-10 code between 2010 and 2019

CAUL*	N	NE	WC	SE	S
Q69.0- Supernumerary finger(s);	1,41	4,15	3,08	5,34	2,48
Q68.1 - Congenital hand deformity;	0,69	0,82	0,89	0,96	1,14
Q71.3 - Congenital absence of the hand and finger(s);	0,47	0,47	0,71	0,63	0,72
Q74.0- Other Congenital Malformations of the Upper Limbs	0,43	0,34	0,30	0,51	0,38
Q71.8- Other upper limb reduction defects. Congenital shortening of the upper limb(s);	0,21	0,19	0,22	0,29	0,28
Q70.4- Polysyndactyly	0,14	0,17	0,17	0,24	0,28
Q70.0- Coalescence of the fingers - Complex syndactyly of the fingers with synostosis	0,14	0,18	0,22	0,21	0,25
Q719-Defect of upper limb reduction, unspecified.	0,18	0,15	0,16	0,21	0,19
Q71.2- Congenital absence of the forearm and hand	0,10	0,11	0,13	0,14	0,19
Q70.1- Webbed fingers Simple syndactyly of the fingers without synostosis	0,08	0,15	0,16	0,13	0,11
074.3- Multiple Congenital Arthrogryposis	0,06	0,15	0,06	0,14	0,13
Q69.1- Supernumerary thumb(s)	0,06	0,07	0,13	0,13	0,11
Q71.6- Lobster claw hand	0,09	0,08	0,07	0,08	0,08
Q71.0- Complete congenital absence of the upper limb(s)	0,06	0,06	0,08	0,06	0,06
Q71.4- Radius longitudinal reduction defect | Club hand (congenital) | Radial hand	0,03	0,02	0,03	0,04	0,03
Q71.1- Congenital absence of the arm and forearm, with hand present	002	0,02	0,03	0,02	0,02
Q71.5- Longitudinal reduction defect of the ulna [ulna];	0,01	0,01	0,02	0,02	0,01

Regions of Brazil N- North; NE- northeast; CO- west center; SE- Southeast; S – South

Tabela 4. Prevalence of CAUL according to maternal variables in Brazil for every 10,000 LB - 2010-2019

Variables	Prevalence	IC* 95%	
		Inferior limit	Upper limit
Mother's Age			
20-34	2	2	2,13
35-49	2	1,87	2,2
40-44	2,7	2,4	3,18
45-50	4,2	2,31	6,23
Type of birth			
Cesarean section	7,6	7,55	7,82
Vaginal	7,1	7,03	7,32
Consultations/prenatal care			
1 to 3	3	2,77	3,27
4 to 6	2,3	2,26	2,49
≥ 7	1,9	1,88	2,01
Mother's Education			
1 to 3 years	6,9	6,46	7,53
4 to 7 years	7,5	7,34	7,8
8 to 11 years old	7,9	7,77	8,04
≥ 12 years	6,3	6,15	6,59
Length of Pregnancy			
< 37 weeks	12,9	12,57	13,38
37 to 41 weeks	6	6,77	6,98
≥ to 42 weeks	6,9	6,38	7,56
Type of Pregnancy			
Only	7,4	7,32	7,52
Multiple	9,5	8,77	10,36

(*) CI – Confidence interval

Tabela 5. Prevalence of CAUL according to newborn variables in Brazil per 10,000 LB (2010-2019)

Variables	Prevalence	IC 95%	
		Inferior limit	Upper limit
Birth weight			
≤ 2499 g	17,6	17,08	18,15
2500 a 3999 g	6,5	6,42	6,62
≥ 4000 g	6	6,2	7,05
Sex			
Male	2,3	2,27	2,43
Female	1,9	1,83	1,98
Race			
White	6	6,66	6,97
Black	12	12,18	13,37
brown	7,5	7,37	7,56
Yellow	6	4,84	7,9
Indigenous	4	3,94	5,8
Apgar 1st minute			
≤ 7	14	13,95	14,74
> 7	6	6,47	6,67
Apgar 5th minute			
≤ 7	30	28,76	31,43
> 7	7	6,92	7,12

(*) IC- Confidence interval

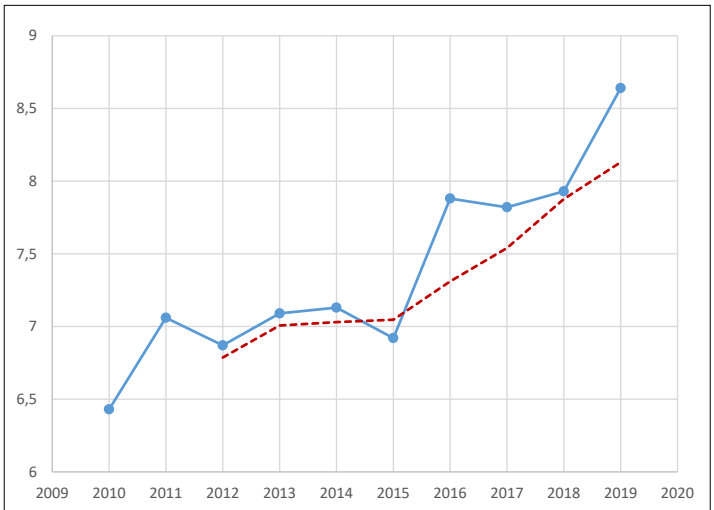
had an 88% higher prevalence of CAUL compared to newborns of other races (OR = 2.88; 95% CI 2.74-3.03). Regarding the Apgar score, the highest prevalence of CAUL was noted when the score was ≤ 7 at both the first (OR = 2.19; 95% CI 2.12-2.26) and fifth minutes (OR = 4.30; 95% CI 4.10-4.50) (**Table 5**).

Through linear trend and moving average (MA) analysis of cases, an increase in prevalence was observed during the study period, with approximately 2.2 CAUL cases per 10,000 LBs when comparing 2010 and 2019. Linear regression analysis of the adjusted data for prevalence per 10,000 LBs showed an increase of 0.185 per year, with a standard error of 0.021. Thus, there was a linear trend of an increase in the prevalence of 0.206 (95% CI 0.133–0.237) CAUL per 10,000 LBs per year (P < 0.001). Notably, graph visualization demonstrated a linear trend component of increased CAUL prevalence when analyzing raw data over the years and smoothed moving averages (**Figure 1**). Remarkably, the graph visualization showed a linear trend component of increased CAUL prevalence when analyzing raw data over the years and the smoothed moving average (**Figure 2**).

DISCUSSION

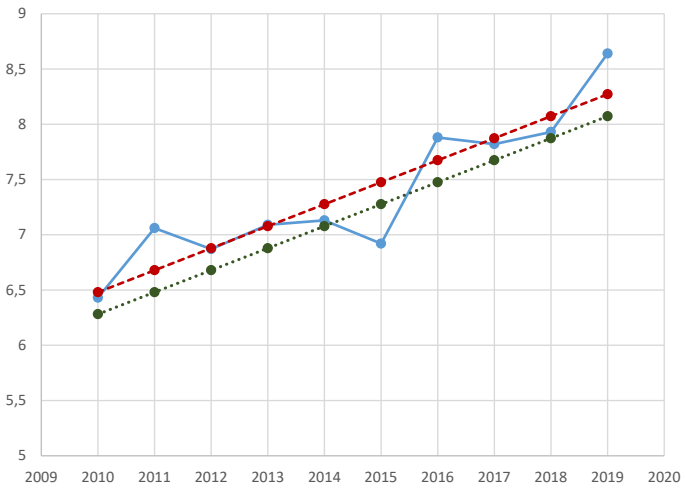
This study represents the first prevalence analysis of CAUL in Brazil, utilizing a national database to identify associated factors in newborns (NBs) and mothers. The national prevalence of upper limb anomalies between 2010 and 2019 was 7.5 per 10,000 LBs.

Several studies have examined the prevalence of CA in large populations. For instance, an assessment in New York, United States, based on state data, evaluated 4,883,072 children from 1992



Source: DATASUS, SINASC 2010-2019
Legend: Blue Line – annual prevalence; Red dashed line – moving average

Figure 1. Linear trend based on the moving average – prevalence of CAUL for every 10,000 LB (2010-2019)



Source: DATASUS, SINASC 2010-2019
Legend: Blue Line – annual prevalence; Green Line – Model; Red line – Adjusted model

Figure 2. Linear trend - prevalence of CAUL for every 10,000 live births (2010-2019)

to 2010, finding a CAUL prevalence of 27.2 cases per 10,000 births.[12] Another study on the epidemiology of congenital limb anomalies in Japan estimated a prevalence of 4.15 per 10,000 LBs.[13] In Finland, the national incidence of CAUL was observed at 5.25 per 10,000 LBs between 1993 and 2005, with these anomalies often associated with other congenital disabilities in up to two-thirds of cases.[14]

The data presented in this study are consistent with global findings on CAUL prevalence. In our analysis, the ICD code for supernumerary fingers (Q69.0) had the highest absolute number of cases with 11,708 and the highest prevalence at 4.02 cases per 10,000 LBs, comparable to findings in New York, where polydactyly was the most common CAUL, totaling 12,418 cases at a rate of 23.4 per 10,000 LB.[12]

Our study also analyzed maternal and newborn factors and their associations with CAUL. The findings indicate higher rates of CAUL in mothers over 40 years old, in preterm births (before 37 weeks), during multiple pregnancies, and among women who had fewer than seven prenatal visits.

In Tangará da Serra, Brazil, between 2006 and 2016, a study demonstrated a higher prevalence of CAs in newborns of mothers over 35 years old, an expected finding as maternal age is a primary risk factor for chromosomal anomalies.[15]

From 2010 to 2014, São Paulo reported 819,018 live births, 14,657 (1.6%) of which had CAs, predominantly osteoarticular and circulatory. An association was observed between congenital anomalies and maternal age over 40 years, multiple pregnancies, and newborns with low birth weight[16], which aligns with our own results.

Examining factors associated with newborns, we found higher prevalence rates in those with low birth weight (< 2,500 g), male gender, Black race, and Apgar scores at both the 1st and 5th minute of ≤ 7. A study in Peru from 2009 to 2019 analyzed predictors of low Apgar scores and found that 65.3% of neonates with persistently low scores at 5 minutes had congenital anomalies, indicating a significant risk factor for low scores (OR = 5.81; P < 0.01). Notably, higher percentages of congenital anomalies were observed in newborns with birth weights < 1499 g (32.7% vs. 2.7%) and 1500–2499 g (11.9% vs. 7.2%) compared to controls, showing that birth weights < 1499 g (OR = 18.77; P < 0.01) and 1500–2499 g (OR = 2.51; P < 0.01) are significant risk factors for low Apgar scores.[25]

Between 2005 and 2014, 1,386,803 births occurred in Rio Grande do Sul, with diagnosed CA cases corresponding to an average overall rate of 9.2 per thousand. Higher rates of CAs were noted in mothers of newborns with Apgar scores less than 7, birth weights ≤ 1,500 g, and gestational ages ≤ 31 weeks. CAs were most frequently found in the intermuscular, nervous, and circulatory systems.[17]

In a study conducted in Rio de Janeiro between 1990 and 2002, the incidence of CAs in male newborns was higher, particularly in those born before 37 weeks with a birth weight of less than 2,500g[19]. Another study in Vale Paraíba Paulista identified a statistically significant association between gestational duration (< 37 weeks), lower Apgar scores (< 7), low birth weight (< 2,500 g), and CAs (P < 0.001).[18]

Several instruments are available for collecting epidemiological data to integrate and unify information on notifications of congenital anomalies. Established in 1974, the "International Clearinghouse for Birth Defects Surveillance and Research" (ICBDSR) aims to prevent congenital disabilities and currently includes 42 member programs worldwide.[21] EUROCAT, a European network for epidemiological surveillance founded in 1979, now has 21 participating countries.[23] This system has developed and matured over the past two decades through the standardization of definitions, diagnoses, and terminology.[24]

In Latin America, the Collaborative Latin American Study of Congenital Malformations, founded in 1967, covers South America, Costa Rica, and the Dominican Republic, employing a case-control methodology.[20] However, a significant limitation in Brazil is the low participation of national maternity hospitals in this program, with only four of the 35 registered hospitals located in Brazil.[22]

We utilized data from DATASUS via the SINASC portal, a nationwide computerized data collection system where all birth-related data in Brazil are recorded. Given the country's vast size, this method offers rapid and convenient data collection and integration for public health, facilitating better analysis.

This study has limitations that should be considered when interpreting the results. Despite its nationwide scope and mandatory reporting, the SINASC database may contain inconsistencies,

such as possible duplications, and does not allow for the individualization of cases, which would enable a more detailed statistical analysis of variables.

The cross-sectional nature of the study and the lack of individual case details regarding the exposure factor and disease at a specific time prevent establishing any cause-and-effect relationship between congenital anomalies and the analyzed variables.

The results underscore the significance of this research by providing a representative overview of the burden of CAUL among live births in Brazil. Multiple analyses facilitated an understanding of the variables associated with congenital anomalies. Enhancing the diagnosis of CAUL and ensuring the accurate completion of the Live Birth Certificate (DNV) through the ongoing education of health professionals responsible for record-keeping is a strategy that should be implemented by the Health Departments of Brazilian states to minimize the incidence of missing or inaccurate data, thereby reducing underreporting.

This nationwide study was conducted in a country with a continental span. Nearly 30 million cases over ten years were analyzed. A national computerized reporting system that allows for the rapid and precise exchange of information across distant states and municipalities is invaluable.

CONCLUSION

The prevalence of CAUL in Brazil between 2010 and 2019 was 7.5 per 10,000 LBs. ICD Q69.0, representing supernumerary fingers, is the most common CAUL in our population. The maternal factors associated with CAUL included being under 40 years of age, undergoing cesarean delivery, having fewer than three prenatal consultations, having less than 11 years of education, a gestational age of 36 weeks or less, and experiencing multiple pregnancies. For newborns, associated factors included a birth weight of 2,500 grams or less, male gender, Black race, and Apgar scores of 7 or less at both the 1st and 5th minutes.

A consistent upward trend in CAUL case reports has been observed over the past decade. This study can inform more effective public health policy strategies. However, further research is essential to enhance our understanding of the underlying causes of the increase in CAUL cases, particularly concerning supernumerary fingers and their implications.

REFERENCES

1. World Health Organization, Centers for Disease Control and Prevention (U.S.) & International Clearinghouse for Birth Defects Monitoring Systems. 2014. Birth defects surveillance: atlas of selected congenital anomalies. World Health Organization. Available From: https://apps.who.int/iris/handle/10665/1279417. Accessed in 2023 (Nov 22).
2. Mendes IC, Jesuino RSA, Pinheiro D da S, Rebelo ACS. Anomalias congênitas e suas principais causas evitáveis: uma revisão. Rev Med Minas Gerais. 2018;28:e-1977. http://www.dx.doi.org/10.5935/2238-3182.20180011
3. Flatt AE. Care of Congenital Hand Anomalies. St. Louis: Quality Medical Publishing; 1994.
4. Parker SE, Mai CT, Canfield MA, et al. Updated National Birth Prevalence estimates for selected birth defects in the United States, 2004-2006. Birth Defects Res A Clin Mol Teratol. 2010;88(12):1008-16. PMID: 20878909. https://doi.org/10.1002/bdra.20735.
5. Kozin, Scott; Embryology of the Upper Extremity; in WOLFE, Scott; et. Al. MD, Green's Operative Hand Surgery, 8th Edition, Philadelphia, Editora Elsevier. 2021;1370-72.
6. Pinto HB, Pais AP, Vitorio SC, et al. CASE STUDY OF CONGENITAL ANOMALIES OF THE UPPER LIMB IN REFERENCE AMBULATORY CARE FACILITY. Acta Ortop Bras. 2018;26(5):325-327. PMID: 30464714; https://doi.org/10.1590/1413-785220182605197649.
7. Departamento de Informática do SUS (DATASUS) (BR). Available from: https://datasus.saude.gov.br/. Accessed in 2023 (Nov 22).
8. Giele H, Giele C, Bower C, Allison M. The incidence and epidemiology of congenital upper limb anomalies: a total population study. J Hand Surg Am. 2001;26(4):628-34. PMID: 11466636. https://doi.org/10.1053/jhsu.2001.26121.
9. Ekblom AG, Laurell T, Arner M. Epidemiology of congenital upper limb anomalies in 562 children born in 1997 to 2007: a total population study from stockholm, sweden. J Hand Surg Am. 2010;35(11):1742-54. PMID: 20961708. https://doi.org/10.1016/j.jhsa.2010.07.007.
10. Departamento de Informática do SUS (DATASUS) (BR). Available from: https://datasus.saude.gov.br/. Accessed in 2023 (Nov 22).
11. Swanson AB. A classification for congenital limb malformations. J Hand Surg Am. 1976;1(1):8-22. PMID: 1021591. https://doi.org/10.1016/s0363-5023(76)80021-4.
12. Goldfarb CA, Shaw N, Steffen JA, Wall LB. The Prevalence of Congenital Hand and Upper Extremity Anomalies Based Upon the New York Congenital Malformations Registry. J Pediatr Orthop. 2017;37(2):144-148. PMID: 27078227; https://doi.org/10.1097/bpo.0000000000000748.
13. Mano, H., Fujiwara, S., Takamura, K, et al. Congenital limb deficiency in Japan: a cross-sectional nationwide survey on its epidemiology. BMC Musculoskelet Disord. 2018;19(1):262. PMID: 30053842; https://doi.org/10.1186/s12891-018-2195-3.
14. Koskimies E, Lindfors N, Gissler M, Peltonen J, Nietosvaara Y. Congenital upper limb deficiencies and associated malformations in Finland: a population-based study. J Hand Surg Am. 2011;36(6):1058-65. PMID: 21601997. https://doi.org/10.1016/j.jhsa.2011.03.015.
15. Silva JHD, Terças ACP, Pinheiro LCB, et al. Profile of congenital anomalies among live births in the municipality of Tangará da Serra, Mato Grosso, Brazil, 2006-2016. Epidemiol Serv Saude. 2018;27(3):e2018008. PMID: 30365695. https://doi.org/10.5123/s1679-49742018000300017.
16. Cosme HW, Lima LS, Barbosa LG. PREVALENCE OF CONGENITAL ANOMALIES AND THEIR ASSOCIATED FACTORS IN NEWBORNS IN THE CITY OF SÃO PAULO FROM 2010 TO 2014. Rev Paul Pediatr. 2017;35(1):33-38. PMID: 28977314. https://doi.org/10.1590/1984-0462/;2017;35;1;00002.

17. Luz GDS, Karam SM, Dumith SC. Congenital anomalies in Rio Grande do Sul State: a time series analysis. Rev Bras Epidemiol. 2019;22:e190040. PMID: 31038573. https://doi.org/10.1590/1980-549720190040.
18. Pinto CO, Nascimento LF. Prevalence study of birth defects in Vale do Paraíba, São Paulo, Brazil. Rev Paul Pediatr. 2007; 25(3): 233-9. https://doi.org/10.1590/S0103-05822007000300007
19. Guerra FAR, Llerena Jr. JC, Gama SGN, Cunha CB, Theme Filha MM. Birth defects in Rio de Janeiro, Brazil: an evaluation through birth certificates (2000- 2004). Cad Saúde Pública. 2008;24(1):140-9. PMID: 18209842. https://doi.org/10.1590/S0102-311X2008000100014
20. Castilla EE, Orioli IM. ECLAMC: the Latin-American collaborative study of congenital malformations. Community Genet. 2004;7(2-3):76-94. PMID:15539822. https://doi.org/10.1159/000080776
21. International Clearinghouse for Birth Defects Surveillance and Research. Available from: www.icbdsr.org. Accessed in 2023 (Nov 22).
22. ECLAMC:O Estudo Colaborativo Latino-Americano de Malformações Congênitas. Available from: http://www.eclamc.org/port/index.php#. Accessed in 2023 (Nov 22).
23. European Surveillance of Congenital Anomalies. Available from: www.eurocat-network.eu. Accessed in 2023 (Nov 22).
24. Tucker FD; Morris JK; Neville A; Garne E; Kinsner-Ovaskainen A; Lanzoni M; et al. EUROCAT: an update on its functions and activities. J Community Genet. 2018;9(4):407-410. PMID: 29736796; https://doi.org/10.1007/s12687-018-0367-3
25. Chilipio-Chiclla MA; Atencio-Castillo KE; Santillán-Árias JP. Preditores perinatais de APGAR persistentemente baixos em 5 minutos em um hospital peruano, Rev. Fac. Med. Hum. Enero 2021;21(1):40-49. https://doi.org/10.25176/RFMH.v21i1.3345.

Authors' contributions: Moura SRB: conceptualization (equal), data curation (equal), formal analysis (equal), methodology (equal), resources (equal), and writing original draft (equal); Nakachima LR: conceptualization (equal), data curation (equal), formal analysis (equal), methodolog (equal), and writing original draft (equal); Santos JBG: conceptualization (equal), data curation (equal), formal analysis (equal), methodology (equal), resources (equal), software (equal), and writing original draft (equal); Belotti JC: conceptualization (equal), data curation (equal), investigation (equal), methodology (equal), resources (equal), visualization (equal) and writing original draft (equal); Sabongi RG and Moraes VY: conceptualization (equal), data curation (supporting), formal analysis (equal), methodology (supporting), resources (equal), and writing review and editing (equal); Fernandes CH: conceptualization (supporting), data curation (equal), formal analysis (equal), methodology (equal), resources (equal), writing original draft (supporting) and writing-review and editing (supporting); Faloppa F: conceptualization (equal), formal analysis (equal), project administration (lead), resources (lead), supervision (lead) and writing review and editing (equal). All the authors have read and approved the final version of the manuscript for publication

Sources of funding: Coordination for the Improvement of Higher Education Personnel
Conflicts of interest: None

Date of first submission: September 30, 2023
Last received: February 21, 2024
Accepted: April 08, 2024

Address for correspondence
Samuel Ricardo Batista Moura
Universidade Federal de São Paulo, São Paulo, SP, Brasil
R. Prof. Francisco de Castro, 101 - Vila Mariana, São Paulo - SP, Brasil
CEP 04020-050
Tel.: (+55 86) 99930-7174
E-mail: srbmoura@outlook.com

Editor responsible for the evaluation process:
Paulo Manuel Pêgo-Fernandes, MD, PhD

Burden of metabolic syndrome on primary healthcare costs among older adults: A cross-sectional study

Suelen Jane Ricardo[I], Monique Yndawe Castanho Araujo[II], Lionai Lima dos Santos[III], Marcelo Romanzini[IV], Rômulo Araújo Fernandes[V], Bruna C. Turi-Lynch[VI], Jamile Sanches Codogno[VII]

Presidente Prudente, SP, Brazil

[I]MSc. Student, Laboratory of Investigation in Exercise (LIVE), Department of Physical Education, Universidade Estadual Paulista (UNESP), Presidente Prudente (SP), Brazil. https://orcid.org/0000-0002-8933-6250

[II]PhD. Postdoctoral student, Laboratory of Investigation in Exercise (LIVE), Department of Physical Education, Universidade Estadual Paulista (UNESP), Presidente Prudente (SP), Brazil. https://orcid.org/0000-0001-8131-8202

[III]MSc. Student, Laboratory of Investigation in Exercise (LIVE), Department of Physical Education, Universidade Estadual Paulista (UNESP), Presidente Prudente (SP), Brazil. https://orcid.org/0000-0002-9892-9787

[IV]PhD. Assistant Professor, Department of Physical Education, Universidade Estadual de Londrina (UEL), Londrina (PR), Brazil. https://orcid.org/0000-0003-1355-331X

[V]PhD. Assistant Professor, Laboratory of Investigation in Exercise (LIVE), Department of Physical Education, Universidade Estadual Paulista (UNESP), Presidente Prudente, (SP), Brazil. https://orcid.org/0000-0003-1576-8090

[VI]PhD. Assistant Professor, Department of Physical Education & Exercise Science, Lander University, Greenwood, USA. https://orcid.org/0000-0002-1314-6258

[VII]PhD. Assistant Professor, Laboratory of Investigation in Exercise (LIVE), Department of Physical Education, Universidade Estadual Paulista (UNESP), Presidente Prudente (SP), Brazil. https://orcid.org/0000-0003-4273-9375

KEYWORDS (MeSH terms):
Hypertension.
Health services research.
Diabetes mellitus.
Obesity.
Exercise.

AUTHOR KEYWORDS:
National Health Service.
Health economics.
Physical activity.

ABSTRACT

BACKGROUND: The impact of metabolic syndrome (MetS) on healthcare costs remains unclear in the literature.

OBJECTIVES: To determine the impact of MetS on primary healthcare costs of adults, as well as to identify the impact of physical activity and other covariates on this phenomenon.

DESIGN AND SETTING: This cross-sectional study was conducted in the city of Presidente Prudente, State of São Paulo/Brazil, in 2016.

METHODS: The sample comprised 159 older adults (> 50 years) of both sexes (110 women) who were identified from their medical records in the Brazilian National Health Service. Healthcare costs (US$) were assessed through medical records and divided into medical consultations, medications, laboratory tests, and total costs. MetS was assessed using medical records.

RESULTS: The Brazilian National Health Service spent more on consultations (US$ 22.75 versus US$ 19.39; + 17.3%) and medication (US$ 19.65 versus US$ 8.32; + 136.1%) among adults with MetS than among those without MetS, but the costs for laboratory tests were similar (P = 0.343). Total costs were 53.9% higher in adults with MetS than in those without the diagnosis of the disease (P = 0.001). Regarding total costs, there was an increase of US$ 38.97 when five components of MetS were present (P = 0.015), representing an increase of approximately 700%, even after adjusting for sex, age, and physical activity.

CONCLUSION: In conclusion, the presence of the MetS is responsible for increasing primary care costs among older adults, especially in those related to medicines.

INTRODUCTION

Metabolic syndrome (MetS) is a complex disorder characterized by a set of cardiovascular risk factors.[1-4] According to the National Cholesterol Education Program's Adult Treatment Panel III,[1] the diagnosis of MetS is made by altering at least three of these components: abdominal obesity, high triglycerides (TG), low high-density lipoprotein (HDL), high blood pressure (BP), and high fasting blood glucose levels.[1]

Diabetes mellitus (DM), arterial hypertension (AH), and cardiovascular diseases (CVDs), in isolation, are known as public health problems responsible for high mortality rates worldwide.[1-5] There are indications that MetS, in most cases, foreshadows some CVDs,[6-8] which are responsible for the highest mortality rate (31% worldwide) according to the World Health Organization.[4] People with MetS are more likely to have CVD than those without MetS (45.6% versus 8.6%, P < 0.0001) and show increased mortality risk of CVD.[7] Another concern related to MetS is its increasing prevalence worldwide,[9-11] which is a concerning phenomenon observed in both developed (Korea and United States)[9,10] and developing nations (Brazil and India).[3,11]

In fact, the components of MetS contribute negatively to the economy.[11,12] In the United States, patients with hypertension have generated an annual expenditure of approximately US$ 2,000 higher than people without the disease.[13] In Brazil, a follow-up study identified that patients with DM spend approximately 41% more on health services when compared with individuals without DM.[12] In contrast, the economic burden of MetS has been less investigated, mainly in developing nations.

Moreover, the literature confirms the positive impact of physical activity on the control of the different components of MetS[14] and the mitigation of healthcare costs attributed to the treatment of diseases related to MetS,[15] but its impact on the relationship between MetS and healthcare costs is not clear.

OBJECTIVE

This study aimed to determine the impact of MetS on the primary healthcare costs of older adults from the Brazilian National Health System and to identify the impact of physical activity and other covariates on this phenomenon.

METHODS

Study Population

This cross-sectional study, conducted in March 2016, is the sixth data collection of a cohort study performed in the city of Presidente Prudente, Western State of São Paulo, Brazil (population estimated at ~ 200,000 inhabitants and human development index of 0.806).[16] Data collection was conducted in two Basic Healthcare Units (BHUs) designated by the Municipality Administration (Municipal Health Department). BHUs are health facilities spread out in different areas of the city, offering primary health services (e.g., vaccination, consultations, medicine delivery) and representing the most distal arm of the Brazilian National Health System (maintained by the Federal Government, offering free of charge primary [BHU], secondary [hospital], and tertiary services [hospital] for more than 200 million citizens). This study was approved by the Research Ethics Committee of the Faculty of Science and Technology of the Universidade Estadual Paulista (UNESP) and Presidente Prudente Campus (CAAE: 13750313.2.0000.5402; date: 04/05/2013).

The sample size was based on the study by Boudreau et al.,[17] which compared primary care costs according to the presence (US$ 813.00/year) and absence (US$ 625.00/year) of MetS (US$ 88.00 difference between groups). Thus, with an expected difference of US$ 88.00, statistical power of 80%, alpha error of 5%, and standard deviations (presence MetS US$ 197.00 and absence MetS US$ 171.00), the minimum sample size estimated for each group was 69 participants (138 total).

The inclusion criteria were: i) active registration at the BHU for at least 1 year, ii) age > 50 years, iii) participation in the previous five data collections, and iv) signing a written consent form.

Dependent Variable

Direct costs with health services

The treatment costs for each patient in the BHUs were verified through medical records in a time horizon of 12 months prior to data collection.[18,19]

Information regarding the number and types of consultations, laboratory tests, and medications was obtained. Additionally, to calculate the consultation costs used at the BHU, costs of other services (e.g., attendance services, utility bills, and dispensed medication) were added.

Monetary values were estimated from the perspective of the SUS based on the sum of resources used directly in the treatment of the patient, and micro-costing (bottom up) approaches were used to estimate costs.[20]

The cost calculation for each health service was based on the methodology described below:[18,19,21,22]

I. Medical consultations: Costs were retrieved from the SUS System Management Procedures Table (SIGTAP), provided by the Ministry of Health.
II. Attendance services (e.g., scheduling, medication dispensing, and management): Costs were calculated using the daily salary rate of the professionals involved in the services provided (monthly salary divided by 30 d) and the average number of patients visiting daily (daily salary rate divided by the number of daily visits).
III. Utility bills of the healthcare unit (electricity, water, and telephone): Costs were calculated using the average of the last 3 months for each utility bill divided by 30 d. The utility bill value was divided by the number of patients visiting daily.
IV. Medications dispensed, specific consumables, and diagnostic services (laboratory tests and others): Costs were calculated by multiplying the specific cost of each standard procedure by the number of procedures performed.
V. Medication and laboratory test costs were calculated as the specific cost of each standard procedure multiplied by the number of procedures performed.

Information regarding salaries, costs of laboratory tests, medications, and utility bills was provided by the Municipal Secretary of Health. To convert this information into current values (R$), values referring to the year of the purchase were informed by the Municipal Health Department. Monetary values were updated in accordance with the official Brazilian inflation index (IPCA) and converted into US dollars (US$) using the official exchange rate on July 10, 2020, published by the Central Bank of Brazil.[23]

Independent Variables

MetS Components

To check for the presence of MetS, we considered the following criteria:[1] Levels of glucose, HDL, and TG were analyzed through blood collection after 12 h of fasting (performed and analyzed by a licensed laboratory that follows clinical standard guidelines, located in the city of Presidente Prudente). Cutoff point was established as glucose ≥ 110 mg/dL; TG ≥ 150 mg/dL; and HDL < 40 mg/dL for men or < 50 mg/dL for women. For central obesity, waist circumference (WC) was measured following the protocol of Lohman, Roche, Martorell (1988),[24] with cutoff points of 102 cm for men and 88 cm for women.[1] Systolic (SBP) and

diastolic (DBP) blood pressure was assessed with the individual at rest, following the recommendations of the 7th Brazilian Guideline for Arterial Hypertension.[25] The cutoff point was established as SBP ≥ 130 mmHg/DBP ≥ 85 mmHg.

Patients were classified into two groups: i) "presence of MetS" when three or more altered components were observed, and ii) "absence of MetS" when two or fewer altered components were observed.

Covariates

Patients reported their age and sex. For statistical analyses, individuals were classified as under or over 65 years old. WC, SBP, and DBP were assessed by the research team. Nutritional status was assessed using the body mass index (BMI), calculated by dividing the weight (kg) by the square of the height (m). Overweight was considered when the BMI showed values between 25 and 29.9 kg/m² and obesity when BMI was ≥30 kg/m².[26]

Habitual physical activity (HPA) was verified through a questionnaire validated for Brazilian Portuguese,[27] involving three components and 16 questions: occupational physical activity (questions 1 to 8), physical exercise practiced during leisure time (questions 9 to 12), and physical activity during leisure time and locomotion (questions 13 to 16). The answers were reported on a Likert scale, and the sum of the points was transformed into a score corresponding to the participants' HPA.[27] The possible HPA score ranged from 3 to 15. The higher the total score obtained with the sum of the three domains, the greater was the HPA level.

Statistical analysis

Descriptive analyses included numerical and categorical data presented as median values and interquartile ranges. The Kolmogorov–Smirnov normality test was applied, and the Kruskal–Wallis and Mann–Whitney tests were used to detect differences between the two groups. Quantile regression was used to compare healthcare costs according to the number of MetS components, adjusting for covariates (differences are expressed as coefficients and their 95% confidence intervals [95% CI]). In this study, the independent variable (components of MetS) was composed of six groups (sum varied from 0 to 5, regardless of which component) to verify how each group of the independent variable affected the dependent variable (healthcare costs) in comparison with a reference group (0 components). The values of the dependent variables represent the 50th percentile. Statistical significance (P value) was pre-fixed at values below 5%, and software used was Stata 16.0 statistical software (StataCorp LLC, Texas, United States).

RESULTS

The sample consisted of 159 patients, 110 women (69.2%) and 49 men (30.8%), with a mean age of 64.06 (8.65) years (74 participants met the criteria for "presence of MetS" [48%]).

Adults with MetS were older and heavier than those without the diagnosis of the disease (**Table 1**). Moreover, markers of obesity, abdominal obesity, and AH were poorly controlled in adults with MetS. Physical activity was similar across the groups (P = 0.638).

The overall costs of these adults were US$ 32,401.58, being 28% higher in adults with MetS (US$ 14,156.84 versus US$ 18,244.74). Brazilian National Health System spent more with consultations (US$ 22.75 versus US$ 19.39; + 17.3%) and medication (US$ 19.65 versus US$ 8.32; + 136.1%) among adults with MetS than among those without MetS; however, the costs for laboratory tests were similar (P = 0.343). Average total costs were 53.9% higher in adults with MetS than in those without the diagnosis of the disease (P = 0.001) (**Table 2**).

When the difference between costs was considered, in addition to the presence of MetS and sex, it was found that women with

Table 1. Sample characteristics according to presence and absence of MetS (Presidente Prudente, 2018)

	Metabolic Syndrome		P value*
	Absence (n = 85)	Presence (n = 74)	
	Median (IR)	Median (IR)	
Numerical Variables			
Age (Years)	61.28 (11.34)	65.38 (11.89)	**0.036**
Weight (Kg)	67.10 (19.30)	74.60 (17.40)	**0.001**
BMI (Kg/m²)	26.53 (5.50)	30.75 (7.00)	**0.001**
WC (cm)	92.00 (15.10)	101.50 (14.30)	**0.001**
SBP (mm/Hg)	123.00 (21.00)	134.50 (26.00)	**0.001**
DBP (mm/Hg)	74.00 (16.00)	78.00 (12.00)	**0.031**
HPA (score)	6.37 (1.80)	6.37 (1.90)	0.638
Categorical Variables	% (n)	% (n)	P value**
AH	41.0 (32)	59.0 (46)	**0.003**
Low HDL-c	30.7 (31)	69.3 (70)	**0.001**
High TG	10.8 (7)	89.2 (58)	**0.001**
High Glucose	19.5 (8)	80.5 (33)	**0.001**
WC (abdominal obesity)	34.4 (33)	65.6 (63)	**0.001**

*Mann–Whitney test; **Chi-square test; IR = interquartile range; BMI = body mass index; WC = waist circumference; SBP = systolic blood pressure; DBP = diastolic blood pressure; AH = arterial hypertension; HPA = habitual physical activity; HDL-c = high density lipoprotein cholesterol; TG = triglycerides.

Table 2. Healthcare costs based on presence of metabolic syndrome (Presidente Prudente, 2018)

Health expenditures	Metabolic Syndrome		P value*
	Absence (n = 85)	Presence (n = 74)	
	Median (IR)	Median (IR)	
Consultation	19.39 (13.26)	22.75 (15.37)	**0.014**
Laboratory tests	0.0 (13.53)	0.0 (14.46)	0.343
Medication	8.32 (17.35)	19.65 (26.67)	**0.001**
Total	35.15 (31.91)	54.13 (48.25)	**0.001**

*Mann–Whitney's test; IR = interquartile range; MetS = metabolic syndrome.

MetS spent more on the Brazilian National Health System with consultations (+ 34.6% than men and + 24.6% than other women without MetS), medications (+ 49.3% than men and + 67.6% than other women without MetS), and total (+ 249.8% than men and + 175.2% than other women without MetS) (**Table 3**). When the age of the individuals was considered, it was found that, in the presence of MetS, those aged < 65 and > 65 years spent more on healthcare than those aged < 65 years without MetS (best scenario) (**Table 4**).

In the quantile regression analysis (**Table 5**), when three or more components of MetS were present, there was a significant increase in medication costs. In detail, there was an increase of US$ 14.74 when three components of the MetS were present (71%; P = 0.040), US$ 14.88 when four components were present (72%; P = 0.047), and US$ 28.25 when five components were present (220%; P = 0.02).

Regarding total costs, there was an increase of US$ 38.97 when five components of MetS were present (P = 0.015; compared to the presence of one component), representing an increase of approximately 700%, even after adjustments for sex, age, and HPA. However, when analyzing the effect of individual covariates on costs, there was no significant difference.

Table 3. Healthcare costs according to sex and the presence of metabolic syndrome (Presidente Prudente, 2018)

Health expenditures	Metabolic Syndrome				P value*
	Absence		Presence		
	Men (n = 29)	Women (n = 56)	Men (n = 20)	Women (n = 54)	
	Median (IR)	Median (IR)	Median (IR)	Median (IR)	
Consultation	16.44 (12.71)	17.76 (10.87)	15.50 (12.23)	22.13 (13.85)[a,b,c]	**0.005**
Laboratory tests	0.0 (14.67)	0.0 (10.37)	0.0 (12.30)	0.0 (12.74)	0.441
Medication	6.04 (13.16)	7.68 (17.07)	12.30 (17.85)	21.13 (24.57)[a,b]	**0.001**
Total	34.27 (35.05)	30.53 (23.86)	36.02 (28.79)	51.17 (40.13)[a,b]	**0.001**

*Kruskal–Wallis's test; IR = interquartile range; MetS = metabolic syndrome; a = different from the group Absence and Men; b = different from the group Absence and Women; c = different from the group Presence and Men.

Table 4. Healthcare costs according to age and presence of metabolic syndrome (Presidente Prudente, 2018)

Health expenditures	Metabolic Syndrome				P value*
	Absence		Presence		
	< 65 years (n = 54)	> 65 years (n = 31)	< 65 years (n = 36)	> 65 years (n = 38)	
	Median (IR)	Median (IR)	Median (IR)	Median (IR)	
Consultation	15.93 (13.01)	18.66 (9.12)	21.46 (15.06)[a]	19.31 (13.13)[a]	**0.044**
Laboratory tests	0.0 (9.58)	0.0 (15.32)	0.0 (14.87)	0.0 (0.0)	0.087
Medication	5.84 (12.84)	12.01 (18.64)	18.39 (22.32)[a,b]	17.24 (26.55)[a]	**0.001**
Total	29.12 (21.95)	40.56 (27.56)[a]	48.93 (39.93)[a]	40.48 (38.06)[a]	**0.001**

*Kruskal–Wallis test; IR = interquartile range; MetS = metabolic syndrome; a = different from the group Absence and < 65 years; b = different from the group Absence and > 65 years.

Table 5. Quantile regression for the association between the number of metabolic syndrome components and costs (Presidente Prudente, 2018)

	Medication (US$)		Consultation (US$)		Total (US$)	
	β ($\beta_{95\%CI}$)	P value	β ($\beta_{95\%CI}$)	P value	β ($\beta_{95\%CI}$)	P value
MetS $_{components}$						
0	Reference	---	Reference	---	Reference	---
1	8.62 (-5.31; 22.55)	0.223	-3.39 (-15.58; 8.80)	0.584	4.88 (-19.77; 29.53)	0.696
2	2.63 (-11.45;16.72)	0.712	-4.64 (-16.96 ;7.69)	0.458	-4.24 (-29.16; 20.69)	0.737
3	14.74 (0.66; 28.82)	**0.040**	-0.41 (-12.73;11.92)	0.948	18.24 (-.68; 43.16)	0.150
4	14.88 (0.18; 29.57)	**0.047**	-4.85 (-17.72; 8.01)	0.457	10.27 (-15.74; 36.28)	0.436
5	28.25 (10.60; 45.90)	**0.002**	9.38 (-6.06; 24.83)	0.232	38.97 (7.74; 70.20)	**0.015**
Covariates						
Sex	2.08 (-5.33; 9.49)	0.580	4.32 (-2.17; 10.81)	0.190	6.91 (-6.21; 20.03)	0.300
Age	0.24 (-0.15; 0.64)	0.221	0.07 (-0.27; 0.42)	0.680	0.51 (-0.18;1.21)	0.148
HPA	0.69 (-1.27; 2.65)	0.489	0.50 (-1.21; 2.22)	0.564	-0.16 (-3.63; 3.31)	0.929

MetS = Metabolic Syndrome; 95% CI = 95% confidence interval; US$ = USA dollar; HPA = habitual physical activity.

DISCUSSION

This cross-sectional study explored the contributions of MetS components to primary healthcare costs among adults. Our findings suggest that three or more components of MetS, especially medications, have a significant impact on healthcare costs.

The presence of various components of MetS represents a concern to health systems due to its impact on patients' health and economic burden.[3,13,18] This concern is well-founded, as it is possible to observe an increase in the prevalence of MetS and its isolated components in some countries.[8,9,28] In Brazil, MetS has shown high prevalence, as reported by Ramires et al. (2018).[11] In our study, the prevalence of MetS was 48%, which is similar to another Brazilian study carried out in 2011 that estimated a prevalence of 53.7% in the population aged over 40 years.[29] In fact, the prevalence of MetS seems to be a relevant public health concern, mainly because it represents the combination of other relevant cardiovascular and metabolic outcomes.

Our main finding was that individuals with MetS had higher costs of medication, consultation, and total costs than those without MetS, which corroborates the literature.[30] Given that MetS is the sum of three or more components, and each component contributes individually and differently to the use of health services,[5,12,30] it was expected that treatment for MetS would lead to significantly higher costs.[28]

There is strong evidence that type 2 DM, one of the components of MetS, even when isolated, leads to higher costs for health services (R$ 317.19 versus R$ 225.09) than in individuals without the disease.[12] The same happens with AH, which was responsible for US$ 2,000.00 higher costs than non-hypertensive people,[13] and obesity, showing twice as many costs (R$ 3,141.84 versus R$ 1,349.60) with hospitalization when compared to individuals with normal weight.[30]

Understanding the contribution of MetS components to universal health systems is of high importance Although our study did not find significant contributions of physical activity levels between the two MetS groups (presence/absence), Ramires et al.[11] found that physical inactivity was present in 98.1% of Brazilian individuals diagnosed with MetS. Moreover, the beneficial impact of other manifestations of physical activity and exercise, such as yoga on MetS (and its costs), needs to be investigated in deep, such as yoga.[31]

Another important point is that our results, when stratified by sex and age, showed that female sex can be a potential factor in the increase in health spending and the presence of MetS. As shown in **Table 4**, the health spending in those aged < 65 and > 65 years were more expensive in the presence of MetS than in those without MetS. In contrast, **Table 3** shows that in the presence of MetS, only women showed significant differences from those without MetS. Turi et al.[32] aimed to evaluate the determinants of healthcare costs for patients receiving primary health care in the Brazilian National Health System and found that several factors influence increases in healthcare costs, such as physical inactivity and obesity. Among other factors, gender stands out for its association with different cost indicators, with women having higher healthcare costs for exams, medical consultations, and total expenses than men. A possible explanation for men's lower demand for primary health services could be related to differences in gender roles, which, according to social imagination, attributes care to the female sphere, requiring men to be associated with invulnerability, strength, and virility.[33]

This study has some limitations. First, our sample was selected in a BHU because of their medical records (not randomly), which may cause bias in costs due to high chances of being treated for other diseases not detected in this study. Furthermore, it was impossible to transform the scores provided by the HPA questionnaire into measures/units that could be used for exercise prescription. In addition, the cross-sectional design did not allow for cause-effect assumptions between costs and MetS. Moreover, our economic analysis focused on the primary level, and costs from the secondary and tertiary levels were not considered.

However, it is worth highlighting that this is one of the few studies conducted in developing nations to investigate the burden of MetS on primary care costs. Furthermore, the present findings are of great value, not only for public policy strategies, but also for health professionals involved in the prevention, control, and treatment of MetS components and, with the monetary information provided by the results of the present study, decision makers can estimate, in local contexts, the impact of the studied comorbidities on healthcare costs on primary care.

CONCLUSION

In summary, MetS is responsible for increasing primary care costs among adults, particularly those related to medication. Our findings are particularly relevant for developing nations where the economic impact of MetS is an additional burden for the NHS in large populations, such as Brazil, India, and China.

REFERENCES

1. Expert Panel on Detection, Evaluation, and Treatment of High Blood Cholesterol in Adults. Executive Summary of The Third Report of The National Cholesterol Education Program (NCEP) Expert Panel on Detection, Evaluation, And Treatment of High Blood Cholesterol In Adults (Adult Treatment Panel III). JAMA. 2001;285(19)2486-97. PMID: 11368702; https://doi.org/10.1001/jama.285.19.2486.
2. World Health Organization. Global action plan for the prevention and control of noncommunicable diseases 2013–2020. Geneva: WHO; 2013. Available from: https://www.who.int/publications/i/item/9789241506236. Accessed in 2018 (Sep. 12).

3. Misra A, Misra R, Wijesuriya M, Banerjee D. The metabolic syndrome in South Asians: continuing escalation & possible solutions. Indian J Med Res. 2007;125(3):345-54. PMID: 17496360.
4. World Health Organization. Cardiovascular Diseases. WHO. Available from: https://www.who.int/news-room/fact-sheets/detail/cardiovascular-diseases-(cvds). Accessed in 2018 (May 20).
5. American Diabetes Association. 2. Classification and Diagnosis of Diabetes: Standards of Medical Care in Diabetes-2019. Diabetes Care. 2019;42(suppl 1):s13-28. PMID: 30559228; https://doi.org/10.2337/dc19-s002.
6. Yen YF, Hu HY, Lin IF, et al. Associations of metabolic syndrome and its components with mortality in the elderly: a cohort study of 73,547 Taiwanese adults. Medicine. 2015;94(23):e956. PMID: 26061328; https://doi.org/10.1097/md.0000000000000956.
7. Mazloomzadeh S, Karami Zarandi F, Shoghli A, Dinmohammadi H. Metabolic syndrome, its components and mortality: a population-based study. Med J Islam Repub Iran. 2019;33:11. PMID: 31086790; https://doi.org/10.34171/mjiri.33.11.
8. Georgiopoulos G, Tsioufis C, Tsiachris D, et al. Metabolic syndrome, independent of its components, affects adversely cardiovascular morbidity in essential hypertensives. Atherosclerosis. 2016;244:66-72. PMID: 26584141; https://doi.org/10.1016/j.atherosclerosis.2015.10.099.
9. Lee SE, Han K, Kang YM, et al. Trends in the prevalence of metabolic syndrome and its components in South Korea: findings from the Korean National Health Insurance Service Database (2009-2013). PLoS One. 2018;13(3):e0194490. PMID: 29566051; https://doi.org/10.1371/journal.pone.0194490.
10. Mahabaleshwarkar R, Taylor YJ, Spencer MD, Mohanan S. Prevalence of metabolic syndrome in a large integrated health care system in North Carolina. NC Med J. 2016;77(3):168-74. PMID: 27154881; https://doi.org/10.18043/ncm.77.3.168.
11. Ramires EKNM, Menezes RCE, Longo-Silva G, et al. Prevalence and factors associated with metabolic syndrome among Brazilian adult population: National Health Survey – 2013. Arq Bras Cardiol. 2018;110(5):455-466. PMID: 29898045; https://doi.org/10.5935/abc.20180072.
12. Araujo MYC, Turi BC, Queiroz DC, et al. Type 2 diabetes, healthcare expenditures and its correlation with anthropometric factors and physical activity: 18-month follow-up in a Brazilian city. Motriz Rev Educ Fis. 2018;24(1):e101867. https://doi.org/10.1590/S1980-6574201800010006.
13. Kirkland EB, Heincelman M, Bishu KG, et al. Trends in healthcare expenditures among US adults with hypertension: national estimates, 2003-2014. J Am Heart Assoc. 2018;7(11):e008731. PMID: 29848493; https://doi.org/10.1161/jaha.118.008731.
14. Kusuayi Mabele G, Nkiama Ekisawa C, Delecluse C, Lepira Bompeka F, Nkodila Matuhoyila A. Effects of a structured exercise program on cardiovascular risk factors linked to metabolic syndrome in obese workers in Kinshasa, Democratic Republic of Congo. Sci Sports. 2018;33(3):e115-22. https://doi.org/10.1016/j.scispo.2018.01.006.
15. Bielemann RM, Silva BG, Coll CV, Xavier MO, Silva SG. Burden of physical inactivity and hospitalization costs due to chronic diseases. Rev Saúde Pública. 2015;49:75. PMID: 26487291; https://doi.org/10.1590/s0034-8910.2015049005650.
16. Instituto Brasileiro de Geografia e Estatística. Demographic census: preliminary results. São Paulo: IBGE; 2017. Available from: https://cidades.ibge.gov.br/brasil/sp/presidente-prudente/panorama. Accessed in 2018 (May 20).
17. Boudreau DM, Malone DC, Raebel MA, et al. Health care utilization and costs by metabolic syndrome risk factors. Metab Syndr Relat Disord. 2009;7(4):305-14. PMID: 19558267; https://doi.org/10.1089/met.2008.0070.
18. Codogno JS, Fernandes RA, Sarti FM, Freitas Júnior IF, Monteiro HL. The burden of physical activity on type 2 diabetes public healthcare expenditures among adults: a retrospective study. BMC Public Health. 2011;11:275. PMID: 21542924; https://doi.org/10.1186/1471-2458-11-275.
19. Codogno JS. Influence of physical activity on spending on outpatient treatment of patients from public system in Bauru, São Paulo. (thesis). Rio Claro: Universidade Estadual Paulista (UNESP); 2012. Available from: http://hdl.handle.net/11449/100403. Accessed in 2020 (May 20).
20. Brasil. Diretrizes metodológicas: Diretriz de Avaliação Econômica. 2 ed. Brasília: Ministério da Saúde; 2014. Available from: https://bvsms.saude.gov.br/bvs/publicacoes/diretrizes_metodologicas_diretriz_avaliacao_economica.pdf. Accessed in 2024 (May 13).
21. Araujo MYC, Kokubun E, Norberto MCCS, et al. Habitual physical activity minimizes healthcare costs resulting from comorbidities among adults with cardiovascular diseases. Braz J Phys Ther. 2023;27(5):100551. PMID: 37827018; https://doi.org/10.1016/j.bjpt.2023.100551.
22. Araujo MYC, da Guarda FRB, Nakamura PM, et al. Comorbidities do not mitigate the effect of habitual physical activity on the reduction of healthcare costs among adults with cardiovascular diseases: a mediation analysis. Obes Res Clin Pract. 2023;17(3):257-63. PMID: 37202240; https://doi.org/10.1016/j.orcp.2023.05.005.
23. Banco Central do Brasil. Exchange and international capital. Available from: http://www4.bcb.gov.br/pec/taxas/port/ptaxnpesq.asp?id=txcotacao. Accessed in 2018 (Sep 10).
24. Lohman, TG, Roche AF, Martorell R. Anthropometric Standardization Reference Manual. Ann Arbor: Braun-Brumfield; 1988.
25. Malachias MVB, Gomes MAM, Nobre F, et al. 7th Brazilian Guideline of Arterial Hypertension: Chapter 2 – Diagnosis and Classification. Arq Bras Cardiol. 2016;107(3):7-13. PMID: 27819381; https://doi.org/10.5935/abc.20160152.
26. World Health Organization. Obesity: preventing and managing the global epidemic: report of a WHO Consultation on Obesity, Geneva, 3-5 June 1997. Geneva: WHO; 1998. Available from: https://apps.who.int/iris/handle/10665/63854. Accessed in 2018 (March 15).
27. Florindo AA, Latorre MR, Jaime PC, Tanaka T, Zerbini CA. Methodology to evaluation the habitual physical activity in men aged 50 years or more. Rev Saúde Pública. 2004;38(2):307-14. PMID: 15122389; https://doi.org/10.1590/s0034-89102004000200022.

28. Xu T, Liu J, Liu J, Zhu G, Han S. Relation between metabolic syndrome and body compositions among Chinese adolescents and adults from a large-scale population survey. BMC Public Health. 2017;17(1):337. PMID: 28427375; https://doi.org/10.1186/s12889-017-4238-3.
29. Lemes IR, Fernandes RA, Turi-Lynch BC, et al. Metabolic syndrome, physical activity, and medication-related expenditures: a longitudinal analysis. J Phys Act Health. 2019;16(10):830-5. PMID: 31365903; https://doi.org/10.1123/jpah.2018-0609.
30. Kudel I, Alves JS, de Menezes Goncalves T, Kull K, Nørtoft E. The association between body mass index and health and economic outcomes in Brazil. Diabetol Metab Syndr. 2018;10:20. PMID: 29568332; https://doi.org/10.1186/s13098-018-0322-9.
31. Naik D, Thomas N. Yoga- a potential solution for diabetes & metabolic syndrome. Indian J Med Res. 2015;141(6):753-6. PMID: 26205017; https://doi.org/10.4103/0971-5916.160689.
32. Turi BC, Codogno JS, Sarti FM, et al. Determinants of outpatient expenditure within primary care in the Brazilian National Health System. Sao Paulo Med J. 2017;135(3):205-12. PMID: 28380203; https://doi.org/10.1590/1516-3180.2016.0224141116.
33. Gomes R, Nascimento EF, Araújo FC. Why do men use health services less than women? Explanations by men with low versus higher education. Cad Saude Publica. 2007;23(3):565-74. PMID: 17334571; https://doi.org/10.1590/s0102-311x2007000300015.

Authors' contributions: Ricardo SJ: conceptualization (equal), data curation (equal), investigation (equal), writing – original draft (equal), writing – review and editing (equal); Araujo MYC: data curation (equal), formal analysis (equal); Santos LL: data curation (equal), funding acquisition (equal); Romanzini M: formal analysis (equal); Fernandes RA: conceptualization (equal); Turi-Lynch BC: formal analysis (equal); Codogno JS: conceptualization (equal), data curation (equal), formal analysis (equal). All authors reviewed and approved the final version submitted for publication

Sources of funding: Conselho Nacional de Desenvolvimento Científico e Tecnológico (CNPq), process: 401178/2013-7 and the Coordenação de Aperfeiçoamento de Pessoal de Nível Superior – Brazil (CAPES) – Financing Code 001
Conflicts of interest: None

Date of first submission: September 11, 2023
Last received: March 4, 2024
Accepted: May 13, 2024

Address for correspondence:
Monique Yndawe Castanho Araujo
Department of Physical Education, Universidade Estadual Paulista (UNESP)
Rua Roberto Simonsen, 305
Presidente Prudente (SP), Brazil.
CEP 19060-900
Tel.: +55 18 32295712
E-mail: mo_castanho@hotmail.com

Editor responsible for the evaluation process:
Paulo Manuel Pêgo-Fernandes MD., PhD

Impact of the improvement of living conditions on tuberculosis mortality in Brazil: an ecological study

Marcio Natividade[I], Marcos Pereira[II], Christine Stauber[III], Samilly Miranda[IV], Maria Glória Teixeira[V], Ramon Andrade de Souza[VI], Marilia Santos dos Anjos[VII], Rafael Barros[VIII], Daniela Gonçalves Morato[IX], Erika Aragão[X], Susan Martins Pereira[XI], Maria da Conceição Nascimento Costa[XII]

Instituto de Saúde Coletiva (ISC), Universidade Federal da Bahia (UFBA), Salvador (BA), Brazil

[I]MSc, PhD. Adjunct Professor, Department of Public Health, Institute of Collective Health, Universidade Federal da Bahia (UFBA), Salvador (BA), Brazil.
https://orcid.org/0000-0002-3986-5656

[II]MSc, PhD. Adjunct Professor, Department of Public Health, Institute of Collective Health, Universidade Federal da Bahia (UFBA), Salvador (BA), Brazil.
https://orcid.org/0000-0003-3766-2502

[III]MSc, PhD. Professor, Department of Population Health Sciences, School of Public Health, Georgia State University, Atlanta, Georgia, United States.
https://orcid.org/0000-0002-2226-0976

[IV]MSc, PhD. Adjunct Professor, Department of Public Health, Institute of Collective Health, Universidade Federal da Bahia (UFBA), Salvador (BA), Brazil.
https://orcid.org/0000-0002-1488-1246

[V]MD, PhD. Department of Public Health, Institute of Collective Health, Universidade Federal da Bahia (UFBA), Salvador (BA), Brazil.
https://orcid.org/0000-0003-3318-3408

[VI]MSc, PhD. Nurse, Postgraduate Program in Collective Health, Institute of Collective Health, Universidade Federal da Bahia (UFBA), Salvador (BA), Brazil.
https://orcid.org/0000-0003-1814-745X

[VII]MSc. Nurse, Postgraduate Program in Collective Health, Institute of Collective Health, Universidade Federal da Bahia (UFBA), Salvador (BA), Brazil.
https://orcid.org/0000-0002-9942-7869

[VIII]MSc, PhD. Adjunct Professor in Nursing School, Universidade Federal da Bahia (UFBA), Salvador (BA), Brazil.
https://orcid. org/0000-0002-1782-7253

[IX]MSc. Bachelor of Science in Biological Sciences, Institute of Collective Health, Universidade Federal da Bahia (UFBA), Salvador (BA), Brazil.
https://orcid.org/0000-0002-7686-939X

[X]MSc, PhD. Associate Professor, Department of Public Health, Institute of Collective Health, Universidade Federal da Bahia (UFBA), Salvador (BA), Brazil.
https://orcid.org/0000-0002-4903-0556

[XI]MD, PhD. Associate Professor, Department of Public Health, Institute of Collective Health, Universidade Federal da Bahia (UFBA), Salvador (BA), Brazil.
https://orcid.org/0000-0001-5291-454X

[XII]MD, PhD. Associate Professor, Department of Public Health, Institute of Collective Health, Universidade Federal da Bahia (UFBA), Salvador (BA), Brazil.
https://orcid.org/0000-0001-7275-4280

KEYWORDS (MeSH terms):
Tuberculosis.
Social Conditions.
Spatio-Temporal Analysis.

AUTHORS' KEYWORDS:
Living Conditions.
Tuberculosis Mortality Rate.
Mortality.

ABSTRACT

BACKGROUND: The risk of death due to tuberculosis (TB) in Brazil is high and strongly related to living conditions (LC). However, epidemiological studies investigating changes in LC and their impact on TB are lacking.

OBJECTIVES: To evaluate the impact of LC on TB mortality in Brazil.

DESIGN AND SETTING: This ecological study, using panel data on spatial and temporal aggregates, was conducted in 1,614 municipalities between 2002 and 2015.

METHODS: Data were collected from the Mortality Information System and the Brazilian Institute of Geography and Statistics. The proxy variable used for LC was the Urban Health Index (UHI). Negative binomial regression models were used to estimate the effect of the UHI on TB mortality rate. Attributable risk (AR) was used as an impact measure.

RESULTS: From 2002 to 2015, TB mortality rate decreased by 23.5%, and LC improved. The continuous model analysis resulted in an RR = 0.89 (95%CI = 0.82–0.96), so the AR was -12.3%. The categorized model showed an effect of 0.92 (95%CI = 0.83–0.95) in municipalities with intermediate LC and of 0.83 (95%CI = 0.82–0.91) in those with low LC, representing an AR for TB mortality of -8.7% and -20.5%, respectively.

CONCLUSIONS: Improved LC impacted TB mortality, even when adjusted for other determinants. This impact was greater in the strata of low-LC municipalities.

INTRODUCTION

Tuberculosis (TB) is associated with poverty and poor living conditions (LC), especially in low- and middle-income countries.[1] This neglected disease requires strategies that consider humanitarian, economic, and public health aspects for its control.[2,3]

Globally, the incidence of TB has fallen by approximately 2% annually between 2015 and 2020, with a cumulative reduction of 11%.[4] However, the COVID-19 pandemic has contributed to an increase in the number of cases and increasing TB mortality in some countries. In 2022, an estimated d 10.6 million people developed active TB compared to 10,1 million in 2020.[4] The incidence rate of TB increased by 3.9% between 2020 and 2022, suggesting a reversal from the trend of nearly 2% decrease per year during the past two decades. In addition, 1.6 million deaths from the disease, compared with 1.5 million in 2020,[4] and TB is the third leading cause of death due to infectious diseases and the first among patients diagnosed with human immunodeficiency virus (HIV).[5]

Brazil has the highest number of reported TB cases in the Americas.[6] In 2019, tuberculosis incidence and mortality in Brazil were estimated as 46 and 3.3 per 100,000 population, respectively.[7] From 2011 to 2015, this coefficient had an annual percentage change of –1.9%, followed by an increase of 2.4% until 2019.[8] In 2022, Brazil recorded 81,000 new TB cases, corresponding to an incidence rate of 32.0 cases per 100,000 population.[9]

Most TB deaths primarily occur in low-income countries, and their incidence is associated with precarious living conditions, especially precarious living and work conditions, including overcrowding and inadequate ventilation. These results highlight TB as a serious public health problem, characterizing it as one of the infectious diseases with the highest mortality rates in the world.[1,10]

According to the United Nations Sustainable Development Goals (2016-2030), the 90-90-90 targets for TB involve monitoring 90% of vulnerable populations, diagnosing and starting

treatment in 90% of cases, curing at least 90% of these, reducing the number of families affected by TB to zero, and facing catastrophic costs due to the disease.[11]

Social protection interventions aimed at reducing social inequalities and improving the LC of vulnerable populations can contribute to controlling TB and containing the epidemic.[12,13] This is because social protection interventions synergistically affect treatment results owing to improvements in nutritional conditions, psychosocial health, and access to health services.[13,14]

Epidemiological studies have reported that the implementation of public social policies in the last 15 years, focusing on the poorest population in Brazil, has improved the LC of the population, which has produced favorable effects on some health problems.[15,16] Despite this evidence, no studies have been conducted on the impact of LC on TB mortality, considering Brazil as a whole.

OBJECTIVE

This study aimed to verify the impact of LC on TB mortality in Brazil between 2002 and 2015.

METHODS

Data, population, and sources

A longitudinal ecological study was conducted with panel data on multiple spatial and temporal aggregates, using Brazilian municipalities and calendar year as units of analysis between 2002 and 2015.

Of the 5,570 municipalities in Brazil, 1,614 (28.9%) were selected, whose vital records (death and birth information) presented satisfactory quality, according to the criteria adopted by Andrade and Szwarcwald[17] and Rasella et al.,[15] as follows: average relative deviation of the general mortality coefficient ≤ 20.0 for municipalities with < 50 thousand inhabitants; ≤ 6.1 for municipalities with ≥ 50 thousand inhabitants; proportion of live births reported and estimated ≥ 0.9 for municipalities with < 50 thousand inhabitants; ≥ 0.7 for municipalities with ≥ 50 thousand inhabitants; mean deviation relative to birth rate ≤ 17.1 for municipalities with < 50 thousand inhabitants; ≤ 8.1 for municipalities with ≥ 50 thousand inhabitants; and proportion of deaths without definition of the basic cause ≤ 20.7 for municipalities with < 50 thousand inhabitants; ≤ 16.2 for municipalities with ≥ 50 thousand inhabitants.[15,17]

Variables of the study and measurement

The number of deaths from all forms of TB (codes A15 – A19 in the International Classification of Diseases, 10th revision) was obtained from the Mortality Information System, and the population of the municipalities was extracted from the databases (including interpolation and extrapolation estimates) made available by the Brazilian Institute of Geography and Statistics.[18] The annual TB mortality rate was calculated from the ratio between the total number of TB deaths and the population of the municipality multiplied by 100,000 inhabitants.

Variables known as potential determinants of TB mortality were selected based on their availability and relevance. They were used in the statistical analysis, continuously and categorically, as follows: TB-HIV coinfection rate ("0" < 5.0% and "1" ≥ 5.0%); TB treatment dropout rate ("0" < 5.0% and "1" ≥ 5.0%); coverage of the Family Health Strategy (FHS) ("0" ≥ 30.0% and "1" < 30.0%); TB cure rate ("0" < 10.0% and "1" ≥ 10.0%); rate of hospitalization for TB/100 thousand inhabitants ("0" < 10.0% and "1" ≥ 10.0%); proportion of older men – 65 years and over ("0" < 4.0% and "1" ≥ 4.0%). These data were obtained from the Department of Informatics of the Brazilian Unified Health System of the Ministry of Health.[19]

The variable used as a proxy for LC was the "Urban Health Index" (UHI), also used in continuous and categorical modeling, and it was stratified into tertiles: first tertile (< 0.278) high LC; second tertile (≥ 0.278 and < 0.330) intermediate LC; and third tertile (≥ 0.330) low LC. This composite indicator allows for a flexible approach to the selection, compilation, and presentation of data in the health field to graphically and visually show statistical health inequalities.[20–22]

To construct this index, the following indicators were selected for each municipality: population of low-income people (proportion of residents with a monthly household income per capita of up to 1/2 minimum wage); income per capita (monthly household income per person); black population (proportion of black people); illiteracy rate (proportion of people aged 15 and over who are illiterate); schooling rate (proportion of people with 15 and more years of study); piped water (proportion of households connected to a regular water supply network); garbage collection (proportion of households with regular garbage collection); household density (average number of people per household); unemployment rate (proportion of economically active people who are unemployed, per 100 inhabitants); GDP per capita (gross domestic product per 100 inhabitants living in the municipality); and health establishments (proportion of basic healthcare establishments per 100 inhabitants).

After their selection, these indicators were classified in ascending order for those where higher values indicated worse LC and in descending order for those where the higher the value, the worse the situation. Mathematical standardization of the indicators was then performed,[20] followed by their combination and calculation of the geometric mean for each municipality, using the tool to calculate the UHI.[20] The result of which is an adapted score that varies from 0 to 1 for each area, in which the closer to 1 or higher this score is, the worse the LC of the population of that municipality.[22]

Variables of the study and measurement

The evolution of the mean annual TB mortality rates, UHI, and selected covariates is described. The effects of the UHI (crude and adjusted) on the mean mortality rate were estimated using negative (continuous and categorical) binomial regression models for panel data with fixed effects specifications for the covariates mentioned in the selected municipalities through risk ratio (RR) estimates.

The choice between fixed and random effects was based on the Hausman test, which evaluates the differences in the estimates of the two effects.[23,24] For the evaluation of public policies, the fixed-effects model is the most appropriate, as it allows the control of unobserved variables that are constant over time (geographic and sociocultural characteristics of the municipality), which can be correlated with the independent variables, controlling the bias prior to the implementation of the programs. These analyses were performed using the Stata software version 15 (StataCorp LLC., College Station, Texas, United States).

The following equation expresses the panel data regression model, where municipalities are represented by subscript i and years by subscript t.

$$TB_{it} = \beta 1UHI_{it} + \beta X_{it} + \alpha_i + u_{it}$$

TB*it*: Logarithm of the mortality coefficient for tuberculosis in municipality i in year t.
β1UHI*it*: Level of the Urban Health Index in municipality i in year t.
β*Xit*: Value of each covariable included in municipality i in year t;
α*i*: Fixed effect for municipality i that captures all the unobserved characteristics that vary in time;
u*it*: Regression error.

To verify the contribution of the improvement in LC to reducing the relative risk of TB mortality, we used attributable risk (AR).[25]

Ethical approval

This study was approved by the Ethics Committee for Research Involving Human Beings of the Institute of Collective Health of the Universidade Federal da Bahia (No. 1,527,799) on May 3, 2016. All study procedures were performed in accordance with the Code of Ethics of the World Medical Association (Declaration of Helsinki) for experiments involving humans. Informed consent for experimentation with human participants and their privacy rights were not required owing to the use of secondary data.

RESULTS

Mortality due to tuberculosis and other causes in Brazil

Between 2002 and 2015, 65,148 (2.4/100,000 inhabitants) TB deaths were documented in Brazil. In the 1,614 municipalities analyzed, this number was 26,336 (2.8/100,000 inhabitants), corresponding to 40.4% of the total number of TB deaths. There was a decline in the mortality rate from this disease (23.5 %), varying from 3.4/100,000 in 2002 to 2.6/100,000 inhabitants in 2015 (**Table 1**).

Table 1. Tuberculosis,[1] annual number of deaths (n) and mortality rate (MR/1,000 inhabitants) for Brazil and a set of municipalities selected for the study, from 2002 to 2015

Year	Brazil		Selected municipalities[2]		
	n	MR	n	%[3]	MR
2002	5,048	2.8	2,149	42.6	3.4
2003	4,843	2.7	2,007	41.4	3.2
2004	4,838	2.6	2,002	41.4	3.1
2005	4,602	2.5	1,868	40.6	2.9
2006	4,721	2.5	1,882	30.9	2.9
2007	4,612	2.4	1,781	38.6	2.7
2008	4,756	2.5	1,908	40.1	2.8
2009	4,690	2.4	1,877	40.0	2.8
2010	4,568	2.3	1,801	39.4	2.6
2011	4,460	2.3	1,780	39.9	2.6
2012	4,316	2.2	1,758	40.7	2.5
2013	4,617	2.3	1,856	40.2	2.6
2014	4,467	2.2	1,841	41.2	2.6
2015	4,610	2.3	1,826	39.6	2.6
Variation (%)	**-8.7**	**-17.9**	**-15.0**	**--**	**-23.5**
Total	**65,148**	**2.4**	**26,336**	**40.4**	**2.8**

Source: Mortality Information System. SINAN / Datasus / Ministry of Health.
[1]All forms; [2]They refer to 1,614 municipalities that had better information quality; [3]Percentage of the total number of municipalities in Brazil; MR = mortality rate.

The mean UHI value was 0.309 (0.126–0.541). In 2002, this index was 0.323; in 2015, it was 0.296, an average reduction of 8.4% in the selected municipalities. On average, 4.1% of the TB-notified individuals in the municipalities included in the study were HIV-infected, an increase of 17.8% (3.9% in 2002 to 4.6% in 2015). The treatment dropout rate decreased by 51.5% during this period, with an overall average rate of 5.2%. Among the 1,614 municipalities, a 52.6% increase was observed in the average coverage of FHS, with an average coverage ratio of 64.7%. The mean cure rate for this disease is 61.7%. Hospitalizations for TB decreased by 46.7% over the study period, with an average of 4.9/100,000 inhabitants. The proportion of older adults living in these areas was 3.9%, which increased by an average of 39.9% during the study period (**Table 2**).

Living conditions and tuberculosis mortality

In the analysis with the continuous and adjusted modeling for the selected covariates, a statistically significant overall protective effect of UHI on TB mortality was observed, with an RR = 0.89 (95%CI = 0.82–0.96), and the AR was -12.3% (**Table 3**). For the model with categorized variables, **Table 4** shows that UHI was also associated with TB mortality rate. For municipalities with intermediate LC, the effect was 0.92 (95%CI = 0.83–0.95), and in those with low LC, it was 0.83 (95%CI = 0.82–0.91); that is, the AR for TB mortality was -8.7% and -20.5%, respectively.

A statistically significant effect was observed for municipalities with a proportion of TB-HIV coinfection of > 5.0%, where RR = 1.32 (95%CI = 1.24–1.42). The mean risk of dying from TB in municipalities with a proportion of elderly patients > 4.0% was 41.0% (RR = 1.41; 95%CI = 1.30–1.53).

In municipalities where the FHS coverage was below 30.0%, the risk of death from this disease was 1.12 times higher than in those with a mean coverage greater than or equal to 30.0% (95%CI = 1.08–1.14). Municipalities where the cure rates for TB treatment were below 10.0% had an RR = 2.87 (95%CI = 2.65–3.12). In municipalities with a treatment dropout rate of > 5.0%, the RR = 1.33 (95%CI = 1.25–1.42). Areas with hospitalization rates for TB of < 10.0% presented an RR of 1.22 (95%CI = 1.14–1.32).

DISCUSSION

The findings of this longitudinal study of spatial and temporal aggregates revealed that, from 2002 to 2015, the risk of dying from TB in the municipalities analyzed decreased by > 23% and that the improvement in LC in this period produced an overall reduction of 11% in the relative risk of death from TB. This protective effect remained even after adjusting for other important determinants and was higher in the strata of municipalities with low LC than in those with intermediate LC.

These results can be interpreted in light of social determinants and health inequalities.[12,26] The differences observed in the risk of TB mortality between areas, populations, and social groups result from heterogeneity in the level of social development, income distribution, access to health resources, basic sanitation, education, and other LC determinants. From this perspective, TB can be spread unequally, both in the urban space and between subjects,

Table 2. Average annual values of the Urban Health Index (UHI), proportion of demographic indicators and health care variation (%), and average in the period. Brazil[1] 2002–2015

Years/ Indicators	UHI	% TB-HIV coinfection ratio	% TB treatment dropout	% coverage FHS	% cure TB	Rate hospitalization TB[2]	% older men
2002	0.323	3.9	6.2	46.6	61.9	6.4	3.3
2003	0.321	3.0	5.4	51.9	61.3	6.7	3.3
2004	0.318	3.2	6.8	56.2	65.1	6.0	3.4
2005	0.316	3.3	4.8	60.6	60.5	5.4	3.5
2006	0.314	3.5	4.8	64.2	58.6	5.3	3.5
2007	0.312	4.1	4.9	67.0	61.8	4.5	3.6
2008	0.310	4.1	5.4	68.0	61.5	8.9	3.7
2009	0.308	4.8	5.2	68.6	62.3	3.7	3.8
2010	0.306	4.7	5.1	69.9	63.8	3.8	4.0
2011	0.304	5.1	5.5	69.3	60.8	3.8	4.1
2012	0.302	5.2	5.4	70.4	62.2	3.8	4.2
2013	0.300	4.1	5.8	71.1	60.3	3.7	4.4
2014	0.298	4.4	4.5	71.2	63.4	3.4	4.6
2015	0.296	4.6	3.0	71.1	60.1	3.4	4.6
Variation (%)	**-8.4**	**17.8**	**-51.5**	**52.6**	**-3.0**	**-46.7**	**39.9%**
Average	**0.309**	**4.1**	**5.2**	**64.7**	**61.7**	**4.9**	**3.9**

Source: Mortality Information System. SINAN / Datasus / Ministry of Health.

[1]They refer to 1,614 municipalities that had better information quality.

UHI = Urban Health Index; TB = tuberculosis; HIV = human immunodeficiency virus; FHS = Family Health Strategy.

Table 3. Estimated relative risk (RR) for the association between tuberculosis mortality rate[1] and Negative Binomial Regression Urban Health Index.[2] Brazil[3] 2002–2015

Variables	Model			
	Crude		Adjusted	
	RR	95%CI	RR	95%CI
Urban Health Index	0.72	**0.66–0.77**	**0.89**	**0.82–0.96**
TB-HIV coinfection ratio			1.01	1.01–1.05
Proportion of TB treatment dropout			1.00	1.00–1.04
Coverage of the Family Health Strategy			0.97	0.97–0.99
TB cure rate			1.00	1.00–1.01
Rate of hospitalization TB			1.20	1.00–1.33
Proportion of older men – 65 years and over			1.81	1.80–1.83

Source: Mortality Information System. SINAN / Datasus / Ministry of Health.

[1]All forms; [2]Continuous model; [3] They refer to 1,614 municipalities with better information quality.

RR = relative risk; CI = confidence interval.

Table 4. Estimated relative risk (RR) for the association between tuberculosis mortality rate[1] and Urban Health Index obtained through Negative Binomial Regression.[2] Brazil[3] 2002–2015

Variables	Model			
	Crude		Adjusted	
	RR	95%CI	RR	95%CI
Urban Health Index				
1º Tercil (< 0.278) High LC	**1**	**-**	**1**	**-**
2º Tercil (≥ 0.278 e < 0.330) Intermediate LC	**0.95**	**0.87–0.99**	**0.92**	**0.83–0.95**
3º Tercil (≥ 0.330) Low LC	**0.89**	**0.82–0.98**	**0.83**	**0.82–0.91**
TB-HIV coinfection ratio				
< 5.0%	-	-	1	-
≥ 5.0%	-	-	1.32	1.24–1.42
Proportion of TB treatment dropout				
< 5.0%	-	-	1	-
≥ 5.0%	-	-	1.33	1.25–1.42
Coverage of the Family Health Strategy				
≥ 30.0%	-	-	1	-
< 30.0%	-	-	1.12	1.08–1.14
TB cure rate				
> 10.0%	-	-	1	-
≤ 10.0%	-	-	2.87	2.65–3.12
Rate of hospitalization TB				
> 10.0%	-	-	1	-
≤ 10.0%	-	-	1.22	1.14–1.32
Proportion of older men – 65 years and over				
< 4.0%	-	-	1	-
≥ 4.0%	-	-	1.41	1.30–1.53

Source: Mortality Information System. SINAN / Datasus / Ministry of Health.

[1]All forms.

[2]Categorical model.

[3] They refer to 1,614 municipalities that had better information quality.

RR = relative risk; TB = tuberculosis; HIV = human immunodeficiency virus; CI = confidence interval; LC = living conditions.

due to its inclusion in the social reproduction process.[13] Thus, in countries marked by poverty and marginalization, thousands of people are disproportionally and heavily affected by TB due to its strong social determination, particularly regarding the social inequality that predominates, as studies show, in countries with different living and income conditions, such as the Philippines,[27] England,[28] South Korea,[29] and China.[30] These characteristics can be observed in Brazil, given its economic development model is characterized by high inequality, social exclusion, and insufficient political and financial investments.[15,17]

Concomitantly, with the improvement in the population's LC in the municipalities studied, there was a reduction in treatment

dropouts and hospitalizations for TB, which, in the continuous regression model, were not associated with this mortality in 2002–2015. Increased FHS coverage, in turn, had a protective effect.

These results provide evidence of the importance of public policies with multisector coverage, which contribute to improving the population's LC and health to promote health, prevent disease, and reduce mortality. On the other hand, there was an increase in the proportion of TB-HIV co-infection in the older adult population, which are important risk factors for this mortality and were shown to be associated with the outcome studied in the aforementioned regression model.

TB-HIV co-infection is a public health problem with high rates of occurrence worldwide, and it is related to the social determinants of health by systematically affecting more vulnerable populations, thus raising TB mortality indicators.[31,32] Regarding the increased risk of TB death among the elderly, the displacement of the incidence of this disease to the elderly population stands out, highlighting the difficulty of diagnosing the illness in this age group, which may determine its high mortality,[33] TB in the elderly is expressed as the resurgence of long inactive infection, as well as being due to the greater vulnerability of this population to reinfection.[34] This greater vulnerability may be due to aging, relapses, difficult response to treatment, trivialization of symptoms, and immune system deficiency due to advanced age. These findings show the need for the elderly to receive greater attention from health services and professionals, not only for the early identification of TB but also for monitoring to reduce complications and deaths.[35]

Another fundamental point to discuss relates to the significant effect of the FHS, which presented a mean overall impact of 3% in reducing TB mortality, as observed by Souza.[36] This strategy has a high level of decentralization and coverage, facilitating access to the health system and providing higher-quality care to TB patients. Many of these actions, such as early diagnosis of the disease, home treatment and visits, bacillus Calmette–Guéri vaccination, and anti-HIV testing, are performed using FHS units and may have consistently contributed to reducing mortality from this cause in the country.[37]

It is worth mentioning that since the 1980s, there has been a reduction in TB mortality in Brazil.[38] However, its levels are still far from those of developed countries, which record mean values of 0.1/100 thousand inhabitants.[39] Moreover, it is worth highlighting that the pace of this fall slowed after the advent of HIV in the country.

It is important to remember that Brazil has undergone profound political, economic, and social transformations geared toward less favored populations to reduce poverty in the country and promote better LC for these populations especially,[40] which may explain the greater impact on the poorest populations. Studies indicate that the initiatives implemented and the progress achieved by the social programs in the country, as well as by the conditional income transfer programs for families living in poverty, such as the *Bolsa Familia* and Eradication of Child Labor programs, have generally promoted a significant improvement in LC.[41] Income transfer programs play a fundamental role in reducing poverty and improving LC since they enable improvements in income, which can be used for housing, food, and nutritional security.[42,43]

Attention should be drawn to the fact that the use of secondary data may constitute a potential limitation of this study, given that they present restrictions in terms of quality, coverage, completeness, and validity. In addition, the study's 2000–2015 time frame was another limiting factor owing to access to data up to more recent periods. It is also worth noting that variables such as alcoholism, malnutrition, and mental illnesses, among other determinants of TB mortality, were not included in the regression model. However, we sought to minimize this restrictive effect by including in the study only municipalities with better quantity and quality of information. Moreover, the fact that all indicators employed presented a similar evolution to that observed in Brazil strengthens the results of this study.

CONCLUSION

This study suggests that the improvement in the LC of the Brazilian population from 2002 to 2015 contributed to the reduction in TB mortality, especially in the stratum of low-LC municipalities, as the social interventions were primarily directed toward populations living in poverty and extreme poverty. Therefore, we must consider the social determinants of the disease and intersectoral strategies as priorities for a more significant reduction in TB mortality in Brazil. It is also evident that alongside the adoption of measures that provide access to adequate quantity and quality services for the population, the implementation of greater and continuous investments from other sectors seeking to reduce poverty and improve education is imperative, as their effects will be positively reflected in the quality of life and health of human collectivities.

REFERENCES

1. Su Y, Garcia Baena I, Harle AC, et al. Tracking total spending on tuberculosis by source and function in 135 low-income and middle-income countries, 2000-17: a financial modelling study. Lancet Infect Dis. 2020;20(8):929-42. PMID: 32334658; https://doi.org/10.1016/S1473-3099(20)30124-9.
2. Holveck JC, Ehrenberg JP, Ault SK, et al. Prevention, control, and elimination of neglected diseases in the Americas: pathways to integrated, inter-programmatic, inter-sectoral action for health and development. BMC Public Health. 2007;7:6. PMID: 17229324; https://doi.org/10.1186/1471-2458-7-6.
3. Chakaya J, Khan M, Ntoumi F, et al. Global Tuberculosis Report 2020 - Reflections on the Global TB burden, treatment and prevention efforts. Int J Infect Dis. 2021;113(Suppl 1):S7-12. PMID: 33716195; https://doi.org/10.1016/j.ijid.2021.02.107.

4. World Health Organization. World Health Organization Global TB Report: Global Tuberculosis Report 2022. Geneva: WHO; 2023. Available from: https://cdn.who.int/media/docs/default-source/hq-tuberculosis/global-tuberculosis-report-2022/global-tb-report-2022-factsheet.pdf?sfvrsn=88f8d76_8&download=true. Accessed in 2023 (Oct 26).
5. World Health Organization. World Health Organization Global TB Report. Global tuberculosis report 2021. Geneva: WHO; 2021. Available from: https://www.who.int/publications/i/item/9789240037021. Accessed in 2023 (Oct 26).
6. World Health Organization. Tuberculosis in the Americas. Regional Report 2021. Washington: WHO; 2021. Available from: https://iris.paho.org/handle/10665.2/57001. Accessed in 2024 (March 22)
7. Li Y, de Macedo Couto R, Pelissari DM, et al. Excess tuberculosis cases and deaths following an economic recession in Brazil: an analysis of nationally representative disease registry data. Lancet Glob Health. 2022;10(10):e1463-72. PMID: 36049488; https://doi.org/10.1016/s2214-109x(22)00320-5.
8. Silva Júnior JNB, Couto RM, Alves LC, et al. Trends in tuberculosis incidence and mortality coefficients in Brazil, 2011-2019: analysis by inflection points. Rev Panam Salud Publica. 2023;47:e152. PMID: 37937313; https://doi.org/10.26633/rpsp.2023.152.
9. Brasil. Boletim Epidemiológico Tuberculose 2023. Secr Vigilância em Saúde. Brasília: Ministério da Saúde; 2023. Available from: https://www.gov.br/saude/pt-br/centrais-de-conteudo/publicacoes/boletins/epidemiologicos/especiais/2023/boletim-epidemiologico-de-tuberculose-numero-especial-mar.2023/view. Accessed in: 2024 (Jun. 13).
10. Bernal O, López R, Montoro E, et al. Social determinants and the Sustainable Development Goals' tuberculosis target in the Americas. Rev Panam Salud Publica. 2020;44:e153. PMID: 33362288; https://doi.org/10.26633/rpsp.2020.153.
11. Suthar AB, Zachariah R, Harries AD. Ending tuberculosis by 2030: can we do it? Int J Tuberc Lung Dis. 2016;20(9):1148-54. PMID: 27510238; https://doi.org/10.5588/ijtld.16.0142.
12. Hargreaves JR, Boccia D, Evans CA, et al. The social determinants of tuberculosis: from evidence to action. Am J Public Health. 2011;101(4):654–62. PMID: 21330583; https://doi.org/10.2105/AJPH.2010.199505.
13. Barreto ML. Health inequalities: a global perspective. Cien Saude Colet. 2017;22(7):2097-108. PMID: 28723991; https://doi.org/10.1590/1413-81232017227.02742017.
14. Oliosi JGN, Reis-Santos B, Locatelli RL, et al. Effect of the Bolsa Familia Programme on the outcome of tuberculosis treatment: a prospective cohort study. Lancet Glob Health. 2019;7(2):e219-26. PMID: 30584050. https://doi.org/10.1016/s2214-109x(18)30478-9.
15. Rasella D, Aquino R, Barreto ML. Impact of the Family Health Program on the quality of vital information and reduction of child unattended deaths in Brazil: an ecological longitudinal study. BMC Public Health. 2010;10:380. PMID: 20587036; https://doi.org/10.1186/1471-2458-10-380.
16. Hone T, Rasella D, Barreto ML, Majeed A, Millett C. Association between expansion of primary healthcare and racial inequalities in mortality amenable to primary care in Brazil: A national longitudinal analysis. PLoS Med. 2017;14(5):e1002306. PMID: 28557989; https://doi.org/10.1371/journal.pmed.1002306.
17. de Andrade CL, Szwarcwald CL. Socio-spatial inequalities in the adequacy of Ministry of Health data on births and deaths at the municipal level in Brazil, 2000-2002. Cad Saude Publica. 2007;23(5):1207-16. PMID: 17486242; https://doi.org/10.1590/s0102-311x2007000500022.
18. IBGE. Portal do IBGE -IBGE. Available from: https://www.ibge.gov.br/en/home-eng.html. Accessed in 2023 (Oct 26)
19. TabNet Win32 3.0: Sistema de Informação de Atenção Básica - Situação de Saúde – Bahia. Available from: http://tabnet.datasus.gov.br/cgi/deftohtm.exe?siab/cnv/SIABSba.def. Accessed in 2023 (Oct 26)
20. World Health Organization. The Urban Health Index: a handbook for its calculation and use. Kobe: WHO; 2014. Available from: https://www.who.int/publications/i/item/9789241507806. Accessed in 2023 (Oct 26)
21. Rothenberg R, Stauber C, Weaver S, et al. Urban health indicators and indices--current status. BMC Public Health. 2015;15:494. PMID: 25981640; https://doi.org/10.1186/s12889-015-1827-x.
22. Bortz M, Kano M, Ramroth H, Barcellos C, et al. Disaggregating health inequalities within Rio de Janeiro, Brazil, 2002-2010, by applying an urban health inequality index. Cad Saude Publica. 2015;31(Suppl 1):107-19. PMID: 26648367; https://doi.org/10.1590/0102-311x00081214.
23. Frees EW. Longitudinal and Panel Data: Analysis and Applications in the Social Sciences Cambridge: Cambridge University Press; 2004. https://doi.org/10.1017/CBO9780511790928.
24. Wooldridge JM, Calhoun JW, Smart SC, Kunkler M. Introductory econometrics: a modern approach. 3rd ed. Mason: Thomson South-Western; 2006.
25. Mansournia MA, Altman DG. Population attributable fraction. BMJ. 2018;360:k757. PMID: 29472187; https://doi.org/10.1136/bmj.k757.
26. Rasanathan K, Sivasankara Kurup A, Jaramillo E, Lönnroth K. The social determinants of health: key to global tuberculosis control. Int J Tuberc lung Dis. 2011;15(Suppl 2):30–6. PMID: 21740657; https://doi.org/10.5588/ijtld.10.0691.
27. Flores GP, Alberto IRl, Eala MAB, Cañal JPA. The social determinants of tuberculosis in the Philippines. Lancet Glob Heal. 2022;10(1):e38. PMID: 34919852; https://doi.org/10.1016/s2214-109x(21)00516-7.
28. Nguipdop-Djomo P, Rodrigues LC, Abubakar I, Mangtani P. Small-area level socio-economic deprivation and tuberculosis rates in England: An ecological analysis of tuberculosis notifications between 2008 and 2012. PLoS One. 2020;15(10):e0240879. PMID: 33075092; https://doi.org/10.1371/journal.pone.0240879.
29. Choi H, Chung H, Muntaner C. Social selection in historical time: The case of tuberculosis in South Korea after the East Asian financial crisis. PLoS One. 2019;14(5):e0217055. PMID: 31095637; https://doi.org/10.1371/journal.pone.0217055.

30. Zhang QY, Yang DM, Cao LQ, et al. Association between economic development level and tuberculosis registered incidence in Shandong, China. BMC Public Health. 2020;20(1):1557. PMID: 33066742; https://doi.org/10.1186/s12889-020-09627-z.
31. Guimarães RM, Lobo Ade P, Siqueira EA, Borges TF, Melo SC. Tuberculosis, HIV, and poverty: temporal trends in Brazil, the Americas, and worldwide. J Bras Pneumol. 2012;38(4):511-7. PMID: 22964936; https://doi.org/10.1590/s1806-37132012000400014.
32. Zille AI, Werneck GL, Luiz RR, Conde MB. Social determinants of pulmonary tuberculosis in Brazil: an ecological study. BMC Pulm Med. 2019;19(1):87. PMID: 31068155; https://doi.org/10.1186/s12890-019-0855-1.
33. Chaimowicz F. Age transition of tuberculosis incidence and mortality in Brazil. Rev Saude Publica. 2001;35(1):81–7. PMID:11285522; https://doi.org/10.1590/s0034-89102001000100012.
34. Caraux-Paz P, Diamantis S, de Wazières B, Gallien S. Tuberculosis in the Elderly. J Clin Med. 2021;10(24):5888. PMID: 34945187; https://doi.org/10.3390/jcm10245888.
35. Hino P, Cunha TN, Villa TC, Santos CB. Profile of new cases of tuberculosis in Ribeirão Preto, São Paulo State, in the period of 2000 to 2006. Cien Saude Colet. 2011;16(Suppl 1):1295-301. PMID: 21503479; https://doi.org/10.1590/s1413-81232011000700063.
36. de Souza RA, Nery JS, Rasella D, et al. Family health and conditional cash transfer in Brazil and its effect on tuberculosis mortality. Int J Tuberc Lung Dis. 2018;22(11):1300-6. PMID: 30355409; https://doi.org/10.5588/ijtld.17.0907.
37. Marquieviz J, Alves Idos S, Neves EB, Ulbricht L. Family Health Strategy in tuberculosis control in Curitiba, State of Paraná. Cien Saude Colet. 2013;18(1):265-71. PMID: 23338516; https://doi.org/10.1590/s1413-81232013000100027.
38. Bierrenbach AL, Duarte EC, Gomes AB, Souza Mde F. Mortality trends due to tuberculosis in Brazil, 1980-2004. Rev Saude Publica. 2007;41(Suppl 1):15-23. PMID: 18038087. https://doi.org/10.1590/s0034-89102007000800004.
39. Centers for Disease Control and Prevention. Reported Tuberculosis in the United States. Available from: https://www.cdc.gov. Accessed in 2023 (Oct 26).
40. Rocha MA, Fontes RMO, Mattos LB de, Cirino JF. Brazilian social programs and their relashionship with poverty, inequality and development. Rev Bras Políticas Públicas. 2014;4(1):138-53. https://doi.org/10.5102/rbpp.v4i1.2661.
41. Carvalho IMM de. Algumas lições do Programa de Erradicação do Trabalho Infantil. São Paulo Perspec. 2004;18(4):50–61. https://doi.org/10.1590/S0102-88392004000400007.
42. Rasella D, Aquino R, Santos CAT, 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.
43. Cotta RM, Machado JC. 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.

Authors' contributions: Natividade M: conceptualization (equal), data curation (equal), formal analysis (equal), investigation (equal), methodology (equal), validation (equal) and writing-original draft (equal); Pereira M: validation (equal), visualization (equal) and writing-review and editing (equal); Stauber C: visualization (equal) and writing-review and editing (equal); Miranda S: visualization (equal) and writing-review and editing (equal); Teixeira MG: visualization (equal) and writing-review and editing (equal); Souza RA: visualization (equal) and writing-review and editing (equal); Anjos MS: visualization (equal) and writing-review and editing (equal); Barros R: visualizatio (equal) and writing-review and editing (equal); Morato DG: visualization (equal) and writing-review and editing (equal); Aragão E: visualization (equal) and writing-review and editing (equal); Pereira SM: visualization (equal) and writing-review and editing (equal); Costa MCN: conceptualization (equal), formal analysis (equal), investigation (equal), methodology (equal), supervision (equal) and writing-review and editing (equal). All authors actively contributed to the discussion of the study results and reviewed and approved the final version of the manuscript.

Acknowledgements: We thank the Postgraduate Program of the Institute of Collective Health at UFBA for the contributions to Natividade M's thesis

Sources of funding: None
Conflict of interest: None

Date of first submission: November 6, 2023
Last received: March 22, 2024
Accepted: May 13, 2024

Address for correspondence:
Marcio Natividade/Marcos Pereira
Institute of Collective Health, Universidade Federal da Bahia (UFBA)
R. Basílio da Gama, s/n°
Canela — Salvador (BA) — Brasil
CEP: 40110-040
Tel. (+55 71) 3283-7373
E-mail: marcio.natividade@outlook.com; pereira.santosm@yahoo.com

Editor responsible for the evaluation process:
Paulo Manuel Pêgo-Fernandes MD, PhD

Knowledge, attitudes, and beliefs regarding skin cancer among health sciences students in Turkey: A cross-sectional study

Esin Sevgi Dogan[I], Ozden Dedeli Caydam[II]

Manisa Celal Bayar University Faculty of Health Sciences, Manisa, Turkey

[I]PhD. Ress. Assistant, Department of Nursing, Manisa Celal Bayar University, Manisa, Turkey. https://orcid.org/0000-0003-0901-3062

[II]PhD. Associated Professor, Department of Nursing, Manisa Celal Bayar University, Manisa, Turkey. https://orcid.org/0000-0003-0558-9400

KEYWORDS (MeSH terms):
Skin neoplasms.
Attitude of health personnel.
Health belief model.
Students.
Knowledge.
Attitude.

AUTHOR KEYWORDS:
Skin cancer.
Belief.
Prevention.
Sun protection.

ABSTRACT

BACKGROUND: Healthcare professionals' knowledge, attitudes, and beliefs regarding skin cancer are important for reducing the future impact of the disease.

OBJECTIVE: This study evaluated university students' knowledge, attitudes, and beliefs about skin cancer and examined the variables influencing their attitudes and beliefs about the disease.

DESIGN AND SETTING: This descriptive cross-sectional study was conducted at the Faculty of Health Sciences at Manisa Celal Bayar University, Manisa, Turkey.

METHOD: A total of 960 students participated in this study. Data were collected using the Student Introduction Form, Fitzpatrick Skin Type Scale, Skin Cancer and Sun Knowledge Scale (SCSKS), and Health Belief Model Scale for Skin Cancer (HBMSSC).

RESULTS: The mean SCSKS score of the participants was 14.91 ± 4.23. The mean HBSSC scores of the participants were 23.58 ± 7.79 for perceived susceptibility, 14.79 ± 4.59 for perceived severity, 20.64 ± 6.60 for perceived benefits, 15.93 ± 4.09 for perceived barriers, and 21.78 ± 7.14 for self-efficacy. The mean SCSKS total scores of the university students were significantly and positively correlated with the HBMSSC subdimensions. Gender explained 1.58 of the variance in perceived benefits and 1.65 of the variance in self-efficacy, whereas the SCSKS score explained most other variables.

CONCLUSION: The students' knowledge of skin cancer and sun protection was moderate. Their attitudes and beliefs regarding skin cancer were unexpected. This study identified students' knowledge of skin cancer and sun protection as the most important variables for improving their attitudes and beliefs about skin cancer.

INTRODUCTION

Cancer is the leading cause of death worldwide.[1,2] However, certain types of cancer can be prevented by avoiding risk factors and using current evidence-based prevention strategies.[3] Skin cancer is one of the preventable types of cancer.[4] Skin cancer is becoming more common worldwide, particularly in Turkey.[5,6] "Malignant melanoma," the most fatal type of skin cancer, is increasingly common, particularly among young individuals.[7] Skin cancer is the most prevalent type of cancer among individuals aged 25–29 years and the second most common type of cancer in those aged 15–29 years.[8,9] Therefore, skin cancer prevention practices should primarily target young individuals.[10]

Conducting visual education campaigns, particularly among young individuals, is recommended to improve prevention practices and sun protection against skin cancer (e.g., sun protection and self-skin examination).[11,12] Numerous studies have been conducted on skin cancer prevention.[13-15] However, in Turkey, most studies on skin cancer and sun protection have been conducted on primary and secondary school students,[16-20] with only limited studies on university students.[21-23]

To develop skin cancer prevention behaviors, people's knowledge, attitudes, and beliefs about the topic must be evaluated.[13,14] These knowledge, attitudes, and beliefs can lead to the development of specific strategies tailored to the sociocultural contexts of diverse groups. Increased knowledge and positive attitudes and beliefs can influence skin cancer prevention practices.[24]

Healthcare professionals are crucial in providing consumers with health information.[25] Future healthcare professionals will play a significant role in preventing skin cancer.[26] Their knowledge, attitudes, and beliefs regarding this issue are important for reducing the impact of

the disease in the future. Therefore, this study evaluated university students' knowledge, attitudes, and beliefs about skin cancer and examined the variables that predict students' attitudes and beliefs about the disease.

Although there are many studies on this issue in the literature[27-32], these studies have typically focused on health professionals, medical students, and nursing students. To the best of our knowledge, no such study has been conducted on health science, midwifery, nursing, or social work students. The results of this study will be useful for future research, providing valuable insights into the implementation of skin cancer prevention practices aimed at health science students.

OBJECTIVE

This study aimed to evaluate health science students' knowledge, attitudes, and beliefs about skin cancer and to examine the variables influencing their attitudes and beliefs about the disease.

Research questions

1. What do health science students know about skin cancer and sun protection?
2. What are the attitudes and beliefs of university students about skin cancer?
3. What variables influence health science students' attitudes and beliefs about skin cancer?

METHODS

This cross-sectional study included 960 health science students. It was conducted between March and July 2023 at the university's Faculty of Health Sciences in the nursing, midwifery, social work, physical therapy, and rehabilitation departments. No sampling method was used in this study, resulting in a participation rate of 61.34%.

The inclusion criteria were participants aged 18 years or older who agreed to participate. Students who chose to leave the study or did not complete the forms were excluded.

Instruments

Based on the literature, the Information Form for Students included nine questions on demographic data (age and gender), sun exposure, and sunburn history.[18,20-23,33,34]

The Fitzpatrick Skin Type Scale

The Fitzpatrick skin type scale was used as a classification scheme. The scale was divided into six categories according to the skin's susceptibility to sunburn, indicating that the risk of developing skin cancer reduces from skin types 1 to 6. Skin types 1 and 2 have a high risk of developing skin cancer, skin types 3 and 4 have a moderate risk, and skin types 5 and 6 have a low risk.[35]

Skin Cancer and Sun Knowledge Scale

The Skin Cancer and Sun Knowledge Scale (SCSKS) was developed for young adults (aged 18 to 26).[36] The scale comprises 25 items that evaluate skin cancer and sun knowledge. The domains include sun production, tanning, skin cancer risk factors, skin cancer prevention, and skin cancer symptoms. The total score ranges from 0 to 25, with a high score on this scale indicating a high level of knowledge.[34,36] The Turkish validity and reliability of the scale were evaluated among nursing students in a previous study, with an internal consistency reliability coefficient (KR-20) of 0.51.[34] In this study, it was determined to be 0.52.

Health Belief Model Scale in Skin Cancer

The Health Belief Model Scale in Skin Cancer (HBMSSC) was developed by Dogan and Caydam (2021) for university students.[37] The scale comprises 26 items and five subdimensions: perceived susceptibility, perceived benefit, perceived severity, perceived barriers, and self-efficacy. Each item on the scale received was scored as follows: 5 = *strongly agree*, 4 = *agree*, 3 = *neutral*, 2 = *strongly disagree*, or 1 = *disagree*. The subdimension "perceived barriers" is reverse coded, and the HBMSSC does not have a total score. Higher scores on the subdimensions indicate higher perceived susceptibility, perceived benefits, perceived severity, and self-efficacy. The total Cronbach's α coefficient of the HBMSSC is 0.86, while for the subdimensions, it is 0.89, 0.79, 0.77, 0.65, and 0.86, respectively.[37] In this study, Cronbach's α coefficients were 0.97, 0.98, 0.93, 0.94, 0.89, and 0.97, respectively.

Data Collection

The research data were collected online. Data collection forms were distributed to the students' class WhatsApp groups via Google Forms. The participants signed an informed consent form if they wished to participate in the study.

Statistical Analysis

The analysis was performed using Statistical Package for the Social Sciences (SPSS) V15. The suitability of the data for a normal distribution was determined by evaluating the skewness coefficient. The data showed a normal distribution as the coefficient of skewness was between +1 and −1.[38] Quantitative variables are presented as mean, standard deviation, minimum, and maximum, while qualitative variables are presented as numbers and percentages. Differences between groups were evaluated using the t-test for independent groups and analysis of variance. The homogeneity of variance was determined using Levene's test. Tukey's test was used to determine which group caused a difference in three or more groups if the variances followed a homogeneous distribution, whereas Tamhane's T^2 test was used if the variances were not equally distributed. Relationships between variables

were examined using Pearson's correlation analysis. After univariate analysis, multivariate regression analysis was used to identify significant variables. Before using the multiple regression model, the relationships between the independent variables in the model were analyzed, and the variables to be included in the model were selected. Statistical significance was set at $p < 0.05$.

Ethical Considerations

To conduct this study, ethics committee approval (Manisa Celal Bayar University's Health Sciences Ethics Committee: 04/01/2023-1653) and institutional permissions (Manisa Celal Bayar University's Faculty of Health Sciences Deanship-11.01.2023-E-64031256-605.99-465123) required for the conduct of the study were obtained. Students who agreed to participate in the study were informed about its purpose and scope. This study was conducted in accordance with the principles of the Declaration of Helsinki.

RESULTS

Descriptive statistics

The study included 84.2% female students, with 44.9% studying nursing and 27.8% in their third year. Among the students, 46.1% had dark brown hair, 72.1% had brown eyes, 42.2% had light skin, and 25.1% had type II skin (**Table 1**).

Skin cancer and sun knowledge

The mean SCSKS score of the students was 14.91. The SCSKS scores varied significantly depending on gender, class, department, hair color, and skin color (**Table 2**).

Attitudes and beliefs about skin cancer

The attitudes and beliefs about skin cancer are presented in **Table 2**. The mean HBSSC scores were 23.58 ± 7.79 for perceived susceptibility, 14.79 ± 4.59 for perceived severity, 20.64 ± 6.60 for perceived benefits, 15.93 ± 4.09 for perceived barriers, and 21.78 ± 7.14 for self-efficacy.

The mean perceived susceptibility scores were significantly higher in female participants studying in the midwifery department, third grade students, those with dark brown hair, and those living in the Aegean Region with their families.

The mean perceived severity scores were significantly higher among female students in the midwifery department, those with fair hair color, and those living in the Aegean Region with their families.

The mean perceived benefits scores were significantly higher in female participants studying in the midwifery department, those with dark brown hair, and those living in the Aegean Region with their families.

The mean perceived barrier score was significantly higher among those studying in the midwifery department.

The mean self-efficacy scores of female participants studying in the midwifery department, those with light brown hair, and those living in the Aegean Region with their families were significantly higher.

Table 1. Sociodemographic characteristics and skin types of participants (n = 960)

Age (year)	$\bar{x} \pm SD$	Min–Max
	21.28 ± 1.99	**18–35**
Gender	*n*	%
Female	808	84.2
Male	152	15.8
Training department		
Nursing	431	44.9
Midwifery	227	23.6
Physical therapy and rehabilitation	219	22.8
Social work	83	8.6
Class		
First	226	23.5
Second	227	23.6
Third	267	27.8
Fourth	240	25.0
Hair color		
Fair	99	10.3
Light brown	182	19.0
Dark brown	443	46.1
Black	236	24.6
Eye color		
Blue/green	83	8.6
Hazel	115	12.0
Brown	692	72.1
Black	70	7.3
Skin color		
Fair	405	42.2
Auburn/light brown	293	30.5
Brown/brunette	262	27.3
Skin type		
Type I	89	9.3
Type II	241	25.1
Type III	233	24.3
Type IV	206	21.5
Type V	191	19.9
History of sunburn in the last one year		
No	457	47.6
Once	234	24.4
Twice	148	15.4
Three times or more	121	12.6
Region living with family		
Aegean	528	55.0
Mediterranean	107	11.1
Southeastern Anatolian	78	8.1
Eastern Anatolian	54	5.6
Inner Anatolian	66	6.9
Black Sea	28	2.9
Marmara	99	10.3

Max = maximum; min = minimum; SD = standard deviation.

Table 2. Assessment of Skin Cancer and Sun Knowledge Scale scores and Health Belief Model Scale scores among students (n = 960)

Participants (n = 960)	SCSKS	PSus	PSev	PBen	PBar	SE
	14.91 ± 3.02	**23.58 ± 7.79**	**14.79 ± 4.59**	**20.64 ± 6.60**	**15.93 ± 4.09**	**21.78 ± 7.14**
Gender						
Female (n=808)	15.10 ± 2.98	24.12 ± 7.35	15.11 ± 4.35	21.11 ± 6.26	-	22.34 ± 6.83
Male (n = 152)	13.91 ± 3.07	20.66 ± 9.33	13.13 ± 5.47	18.16 ± 7.74	-	18.83 ± 8.02
t/p	**4.528/<0.000**	**5.085/0.000**	**4.951/0.000**	**5.108/0.000**	-	**5.645/0.000**
Training department						
Nursing (*n* = 431)[a]	14.96 ± 3.13	23.34 ± 7.87	14.72 ± 4.62	20.60 ± 6.71	15.32 ± 4.56	21.60 ± 6.98
Midwifery (*n* = 227)[b]	14.55 ± 2.82	25.58 ± 6.29	15.72 ± 3.83	22.51 ± 5.26	16.69 ± 3.69	23.70 ± 6.03
Physical therapy and rehabilitation (*n* = 219)[c]	14.91 ± 2.96	22.02 ± 8.51	13.76 ± 4.97	19.02 ± 6.96	16.11 ± 3.24	20.40 ± 7.91
Social work (*n* = 83)[d]	15.62 ± 2.99	23.39 ± 8.07	15.39 ± 4.91	20.02 ± 7.20	16.54 ± 3.21	21.09 ± 7.65
F/p	**2.636/0.049** a = b = c, d > b*	**8.252/0.000** a = c = d, b = d, b > a, b > c*	**7.356/0.000** a = c = d, b = d, b > a, b > c*	**10.998/0.000** a = d, c = d, b > a > c, b > d*	**6.955/0.000** a = c, b = c = d, b > a, d > a*	**8.740/0.000** a=c=d, b>a, b>c, b>d*
Class						
First (*n* = 226)[a]	14.28 ± 3.04	22.35 ± 8.13	14.37 ± 4.86	19.95 ± 7.08	-	20.71 ± 7.65
Second (*n* = 227)[b]	14.65 ± 2.98	23.49 ± 7.63	14.75 ± 4.59	20.64 ± 6.62	-	21.49 ± 6.85
Third (*n* = 267)[c]	15.22 ± 3.03	24.52 ± 7.74	15.13 ± 4.46	21.18 ± 6.33	-	22.76 ± 7.10
Fourth (*n* = 240)[d]	15.42 ± 2.89	23.75 ± 7.57	14.87 ± 4.49	20.69 ± 6.40	-	21.97 ± 6.84
F/p	**7.204/<0.000** c = d > a = b*	**3.222/0.022** a = b = d, c = d, b = b, c > a**	1.148/0.329	1.436/0.231	-	**3.569/0.014** a = b = d, c = d, c > a**
Hair color						
Fair (*n* = 99)[a]	15.16 ± 2.86	23.95 ± 7.82	15.40 ± 4.66	20.20 ± 6.45	-	21.90 ± 6.97
Light brown (*n* = 182)[b]	15.38 ± 3.34	23.59 ± 7.59	14.77 ± 4.47	20.79 ± 6.51	-	22.39 ± 7.30
Dark brown (*n* = 443)[c]	14.91 ± 2.92	24.19 ± 7.33	15.09 ± 4.29	21.21 ± 6.25	-	22.28 ± 6.73
Black (*n* = 236)[d]	14.46 ± 2.96	22.26 ± 8.63	14.01 ± 5.13	19.65 ± 7.26	-	20.32 ± 7.67
F/p	**3.482/0.015** a = b, a = c, a = d, c = d, b > c, b > d**	**3.234/0.022** a = b = c, a = d, b = d, c > d*	**3.546/0.014** a = b = c, a = d, a = c, b = d, c > d*	**3.076/0.027** a = b = c, a = d, a = c, b = d, c > d*	-	**4.537/0.004** a = b = c, a = d, a = c, b = d, c > d*
Skin color						
Fair (*n* = 405)[a]	15.30 ± 2.98	-	-	-	-	-
Auburn/light brown (*n* = 293)[b]	14.67 ± 2.98	-	-	-	-	-
Brown/brunette (*n* = 262)[c]	14.58 ± 3.05	-	-	-	-	-
F/p	**6.056/0.002** a > b = c**	-	-	-	-	-
Region living with family						
Mediterranean (*n* = 107)[a]	-	23.65 ± 7.58	14.68 ± 4.58	21.10 ± 6.66	-	22.25 ± 7.10
Eastern Anatolian (*n* = 54)[b]	-	19.24 ± 9.58	12.72 ± 5.74	16.62 ± 7.49		17.48 ± 8.27
Aegean (*n* = 528)[c]	-	24.46 ± 7.28	15.28 ± 4.25	21.20 ± 6.30	-	22.54 ± 6.64
Southeastern Anatolian (*n* = 78)[d]	-	22.88 ± 7.89	14.47 ± 4.52	21.07 ± 6.42	-	20.92 ± 7.23
Inner Anatolian (*n* = 66)[e]	-	22.22 ± 8.27	13.78 ± 5.13	19.95 ± 6.56	-	20.42 ± 7.79
Black Sea (*n* = 28)[f]	-	20.42 ± 9.34	12.39 ± 5.23	19.21 ± 7.91	-	19.96 ± 8.71
Marmara (*n* = 99)[g]	-	23.43 ± 7.68	15.06 ± 4.67	19.85 ± 6.62	-	21.61 ± 7.11
F/p	-	**5.275/0.000** a = b = d = e = f = g, a = c = d = e = f = g, c > b*	**4.884/0.000** a = b = d = e = f = g, a = c = d = e = f = g, c > b**	**4.783/0.000** a = b = d = e = f = g, a = c = d = e = f = g, c > b*	-	**5.399/0.000** a = b = d = e = f = g, a = c = d = e = f = g, c > b*

t, independent t-test; F, one-way analysis of variance; SCSKS, Skin Cancer Sun Knowledge Scale; Pbar, perceived barriers; PBen, perceived benefits; PSev, perceived severity; PSus, perceived susceptibility; SE, self-efficacy; Significance, p < 0.05; *Tamhane's T^2 test, **Tukey's test.

Relationship between knowledge about skin cancer and attitudes and beliefs about the disease

A significant positive correlation was observed between the mean SCSKS total score of the students and the HBMSSC sub-dimensions: perceived susceptibility (r = 0.193, $p < 0.001$), perceived severity (r = 0.176, $p < 0.001$), perceived benefits (r = 0.130, $p < 0.001$), perceived barriers (r = 0.120, $p < 0.001$), and self-efficacy scores (r = 0.167, $p < 0.001$) (**Table 3**).

Table 4 presents the raw and standardized regression coefficients for each analysis step.

The SCSKS score explained 1.64, 1.12, 1.56, 1.17, and 1.34 of the variances in perceived susceptibility, perceived severity, perceived benefits, perceived barriers, and self-efficacy, respectively, after controlling for other variables.

Regarding perceived susceptibility, severity, and barriers, gender and SCSKS scores were significant in the final model (Model 2). Gender, training department, and SCSKS scores were significant for perceived benefits and self-efficacy. The training department, SCSKS score, and effective variables for perceived barriers were evaluated. Gender explained 1.58 of the variance in perceived benefits and 1.65 of the variance in self-efficacy, while the SCSKS score explained the majority of the remaining variables.

DISCUSSION

Skin Cancer and Sun Knowledge Scale

The mean SCSKS score of the participants was 14.91, indicating moderate knowledge (4.23 ± 1.08), with scores ranging between

Table 3. Mean SCSKS and HBMSSC score correlations ($n = 960$)

	PSus	PSev	PBen	PBar	SE
			r/p		
SP-SS	**0.083/0.010**	0.063/0.052	0.046/0.155	0.035/0.275	**0.075/0.044**
T-SS	**0.105/0.001**	**0.121/< 0.001**	0.060/0.062	**0.090/0.005**	**0.095/0.003**
SCP-SS	**0.165/< 0.001**	**0.119/< 0.001**	**0.105/0.001**	–0.047/0.148	**0.120/< 0.001**
SCRF-SS	**0.186/< 0.001**	**0.139/< 0.001**	**0.154/0.001**	**0.092/0.004**	**0.163/< 0.001**
SSC-SS	**0.087/0.007**	**0.085/0.009**	**0.840/0.009**	**0.076/0.018**	**0.090/0.005**
SCSKS	**0.193/< 0.001**	**0.176/< 0.001**	**0.130/< 0.001**	**0.120/< 0.001**	**0.167/< 0.001**

Pbar, perceived barriers; PBen, perceived benefits; PSev, perceived severity; PSus, perceived susceptibility; ***r***, Pearson correlation analysis; SCP-SS = Skin Cancer Prevention Subscale; SCRF-SS = Skin Cancer Risk Factors Subscale; SCSKS = Skin Cancer and Sun Knowledge Scale; SP-SS = Sun Production Subscale; SE, self-efficacy; SSC-SS = Symptoms of Skin Cancer Subscale; T-SS = Tanning. p < 0.05.

Table 4. Variables predicting students' attitudes and beliefs about skin cancer ($n = 960$)

Model 1	PSus				PSev				PBen				PBar				SE			
	$R = 0.190/R^2 = 0.036$ $F = 7.167/p = 0.000$)				$R = 0.167/R^2 = 0.028$ $F = 6.830/p = 0.000$				$R = 0.184/R^2 = 0.034$ $F = 8.375/p = 0.000$				—				$R = 0.212/R^2 = 0.045$ $F = 8.839/p = 0.000$			
	B	*SE*	*β*	*t/p*	*B*	*SE*	*β*	*t/p*	*B*	*SE*	*β*	*t/p*	*B*	*SE*	*β*	*t/p*	*B*	*SE*	*β*	*t/p*
Constant	27.567	1.412	—	19.529/ < 0.001	18.052	0.761	—	23.735/ < 0.001	25.223	1.089	—	23.165/ < 0.001	—	—	—	—	26.172	1.285	—	20.365/ 0.001
Gender	–3.589	0.700	–0.168	**–5.127/ < 0.001**	–1.909	0.414	–0.152	**–4.615/< 0.001**	–3.119	0.592	–0.172	**–5.268/ < 0.001**	—	—	—	—	–3.608	0.639	–0.185	**–5.650/ < 0.001**
Department	–0.322	0.252	–0.042	–1.279/ 0.201	–0.157	0.149	–0.035	–1.055/ 0.292	–0.501	0.213	–0.077	**–2.352/ 0.019**	—	—	—	—	–0.339	0.230	–0.057	–1.739/ 0.082
Class	0.587	0.226	0.083	**2.603/ 0.009**	—	—	—	—	—	—	—	—	—	—	—	—	0.561	0.206	0.087	**2.731/ 0.006**
Hair color	–0.084	0.225	–0.012	–0.373/ 0.709	–0.162	0.132	–0.040	–1.222/ 0.222	0.086	0.190	–0.015	–0.454/ 0.650	—	—	—	—	–0.138	0.204	–0.022	–0.605/ 0.500
Living region	–0.111	0.158	–0.023	–0.704 /0.481	–0.037	0.093	–0.013	–0.402/ 0.688	–0.091	0.134	–0.022	–0.678/ 0.498	—	—	—	—	–0.100	0.144	–0.022	–0.695/ 0.487
Model 2	$R = 0.249/R^2 = 0.062$ $F = 10.486/p = 0.000$				$R = 0.227/R^2 = 0.052$ $F = 10.390/p = 0.000$				$R = 0.215/R^2 = 0.046$ $F = 9.208/p = 0.000$				$R = 0.157/R^2 = 0.025$ $F = 12.025/p = 0.000$				$R = 0.249/R^2 = 0.062$ $F = 10.478/p = 0.000$			
Constant	21.002	1.895	—	11.084/ <0.001	14.112	1.101	—	12.817/ <0.001	21.183	1.586	—	13.357/ <0.001	12.834	0.684	—	18.753/ <0.001	21.268	1.734	–	12.266/ <0.001
Gender	–3.085	0.698	–0.145	**–4.421/ < 0.001**	–1.649	0.412	–0.131	**–4.001/ < 0.001**	–2.852	0.594	–0.158	**–4.805/ < 0.001**	—	—	—	—	–3.231	0.639	–0.165	**–5.053/ < 0.001**
Department	–0.356	0.249	–0.046	–1.433/ 0.152	–0.171	0.147	–0.038	–1.162/ 0.246	–0.516	0.212	–0.079	**–2.433/ 0.015**	0.399	0.127	0.100	**3.142/ 0.002**	0.427	0.206	0.066	**2.069/ 0.039**
Class	0.407	0.225	0.058	1.805/ 0.071	—	—	—	—	—	—	—	—	—	—	—	—	–0.425	0.228	–0.060	–1.867/ 0.062
Hair color	–0.039	0.222	–0.006	–0.176/ 0.860	–0.131	0.131	–0.033	–0.101/ 0.317	0.118	0.189	0.020	0.623/ 0.533	—	—	—	—	–0.105	0.203	–0.017	–0.519/ 0.604
Living region	–0.107	0.156	–0.022	–0.686/ 0.493	–0.037	0.092	–0.013	–0.396 /0.692	–0.090	0.133	–0.022	–0.675/ 0.500	—	—	—	—	–0.097	0.142	–0.022	–0.680/ 0.497
SCSKS	0.424	0.083	0.164	**5.112/ < 0.001**	0.238	0.049	0.156	**4.986/ < 0.001**	0.244	0.070	0.112	**3.486/ < 0.001**	0.155	0.042	0.117	**3.659/ < 0.001**	0.317	0.076	0.134	**4.171/ < 0.001**

Pbar = perceived barriers; PBen = perceived benefits; PSev = perceived severity; PSus = perceived susceptibility; SE = self-efficacy; ***SE*** = standard error; SCSKS = Skin Cancer and Sun Knowledge Scale.

0 and 25. Compared to other studies, such as Kasar et al., which reported a mean SCSKS score of 13.64 ± 2.91 for nursing students,[39] a study comprising medical students demonstrated higher knowledge levels.[40] However, this knowledge level was not as high as expected, especially considering the importance of health-related professions in educating the public about skin cancer. These results underscore the need for improved education on skin cancer for health science students in Turkey.

This study also identified that students training in the midwifery department and first-year students have lower SCSKS scores. This could be attributed to the limited exposure of first-year students to health education. However, the low scores among midwifery students, predominantly female, were unexpected. Given their role in providing health services and home health training, enhancing skin cancer education in midwifery programs is essential.[41] The average score of female students was higher than that of male students. Midwives, similar to nurses, play a crucial in providing preventive health services to society and home health training.[42] Therefore, these results highlight the importance of improving the education of midwifery students in Turkey, suggesting the need for more information on skin cancer in midwifery education programs.

Findings regarding the relationship between skin color and knowledge are inconclusive. While some studies found no difference based on hair color,[39,41,43] others suggested that individuals with light-colored hair tend to have more knowledge of skin cancer.[44,45] This study found that knowledge was higher among students with lighter skin. However, these differences may be influenced by the geographical region of the study.

Black-haired students obtained lower knowledge scores, although findings on the relationship between hair color and knowledge are mixed. While the results of this study are comparable with those of other studies,[41,45] they contradict others.[39] For instance, sensitivity to skin cancer risk factors, such as light hair, skin, and eye color, is well-documented.[46-47] Despite many participants having dark brown or black hair, typically considered advantageous for the treatment of skin cancer, black-haired students scored lower on skin cancer knowledge. These findings suggest a need for further research. Perhaps individuals with dark brown or black hair could benefit from information on the risks of skin cancer in their demographic.

Additionally, the mean DKGBÖ test scores of female students were significantly higher than those of male students. These results are consistent with those of previous research.[34,39,41,48] The results could be attributed to female students' heightened sensitivity to aesthetic concerns and body image, which may make them more receptive to such topics. Furthermore, the higher perceived susceptibility scores among female students further support this notion.

Attitudes and beliefs about skin cancer

Only one study has utilized this scale for university students,[37] thus the study results were compared with those of other studies.

The students' mean score for perceived susceptibility was 23.58 ± 7.79. Similar to a study conducted on university students,[37] the scores were positive. However, these results differ from those of a study involving medical students,[49] where the mean perceived susceptibility score was low. Therefore, we hypothesized that enhancing students' skin cancer risk education would increase their perceived susceptibility levels.[50]

In the Health Belief Model, perceived severity influences perceived disease threat, thereby increasing the likelihood of preventive action.[50] The students' perceived severity was moderate. The study results are comparable to those of medical students,[49] but higher than those of a study conducted on university students.[37] This difference may be attributed to the level of knowledge among individuals who keep up with health-related developments. Nonetheless, we anticipate an improvement in this regard. Moreover, this evaluation may indicate that many non-melanoma skin cancers are low-risk and easy to manage, whereas melanoma can be fatal in some cases.[51]

Skin cancer interventions primarily focus on community or individual campaigns.[52] Visual materials, such as ultraviolet (UV) photography, have been used to evaluate and influence skin cancer protection behaviors among university students.[53-55] A systematic review[53] found that UV photography significantly increasesd the perceived severity of photoaging. Furthermore, the authors recommended the use of UV photography and associated educational materials to enhance students' sun protection behavior.[53] Therefore, the findings suggest the need for alternative educational methods to enhance students' perceived severity.

Contrary to the literature,[49] the mean perceived benefit scores of the students in this study were lower and moderate. These results were unexpected, as we anticipated greater perceived benefits. This discrepancy may be attributed to the average level of skin cancer knowledge and sun exposure awareness in our research sample. Therefore, it is crucial to reflect on these findings when educating health science students. The findings demonstrate that alternative educational methods should be employed to enhance students' perceived benefits, as health professionals play a critical role in counseling patients on skin cancer and sun-protective behaviors.

The mean perceived barrier scores of the students in this study were positive, consistent with previous studies.[37,49] These findings indicate that perceived severity, benefits, and self-efficacy can be influenced. Another study on medical students identified a high level of knowledge about skin cancer but inadequate skin self-examination and sun protection behavior, primarily due to a lack of evaluation.[30]

Similar to the literature,[37,49] students' mean self-efficacy scores were moderate. However, we expected students who had received health-related education to demonstrate better self-efficacy. Self-efficacy is particularly important for the development of healthy lifestyle behaviors. Our findings suggest that alternative education programs could significantly impact attitudes and beliefs about skin

cancer among health science students. Visual educational materials such as brochures, videos, and PowerPoint presentations have been shown to enhance self-efficacy.[20,56] For instance, an educational intervention supported by visual materials increased skin self-examination behaviors among nursing students in Turkey.[57]

Relationship between knowledge, attitude, and belief

Gender and SCSKS scores were significant in the final model for perceived susceptibility and severity. Gender, training department, and SCSKS scores were significant for perceived benefits and self-efficacy. The training department, SCSKS score, and effective variables for perceived barriers were evaluated. Gender explained 1.58 of the variance for perceived benefits and 1.65 of the variance for self-efficacy, while the SCSKS score accounted for most of the variance for other variables.

The higher mean scores for perceived benefits and self-efficacy among female students in this study were expected. Female students, being more sensitive to aesthetic concerns and body image, may also be more attentive to the subject and better at self-monitoring. However, most students in this study were female and had only moderate skin cancer and sun protection knowledge, we consider skin cancer and sun protection knowledge to be significant variables in attitudes and beliefs regarding skin cancer.

Although the present study reveals important findings, it has several limitations. First, not all students participated because the study was voluntary. Second, the results may not be generalizable to all health science students as the sample included only health science students from one faculty. Third, the results were based on individual reports. Nonetheless, we believe that the data collection tools were effective in evaluating skin cancer and sun protection knowledge, attitudes, and beliefs regarding skin cancer.

CONCLUSION

This study revealed a moderate level of skin cancer and sun protection knowledge among health science students, however, their attitudes and beliefs regarding skin cancer were not as expected. While their perceived susceptibility and barriers to skin cancer were positive, their perceived severity, perceived benefits, and self-efficacy were moderate. Furthermore, female gender was a significant factor for perceived benefits and self-efficacy, while skin cancer and sun protection knowledge were significant variables for perceived susceptibility, severity, and barriers. These findings underscore the importance of a comprehensive educational approach to enhance skin cancer attitudes and beliefs among health science students, thereby fostering behavioral changes and promoting skin cancer protection. Effective training programs are crucial for the health and well-being of our study population and the patients they will serve as future health professionals.

REFERENCES

1. World Health Organization. 2024. Available from: https://www.who.int/health-topics/cancer#tab=tab_1. Accessed in 2024 (January 31).
2. Turkish Statistical Institute. 2022. Available from: https://data.tuik.gov.tr/Bulten/Index?p=Olum-ve-Olum-Nedeni-Istatistikleri-2022-9679#:~:text=%C3%96l%C3%BCmler%20nedenlerine%20g%C3%B6re%20incelendi%C4%9Finde%2C%202022,ile%20solunum%20sistemi%20hastal%C4%B1klar%C4%B1%20izledi.&text=Grafikteki%20rakamlar%2C%20yuvarlamadan%20dolay%C4%B1%20toplam%C4%B1%20vermeyebilir. Accessed in 2024 (January 31).
3. World Health Organization. 2022. Available from: https://www.who.int/news-room/fact-sheets/detail/cancer, Accessed in 2024 (January 31).
4. Morganroth PA, Lim HW, Burnett CT. Ultraviolet radiation, and the skin: An in-depth review. American Journal of Lifestyle Medicine. 2013; 7:168-181. https://doi.org/10.1177/1559827612460499.
5. Barbaric J, Sekerija M, Agius D, et al. Disparities in melanoma incidence and mortality in South-Eastern Europe: increasing incidence and divergent mortality patterns. Is progress around the corner?. Eur J Cancer. 2016; 55:47-55. PMID: 26773419; https://doi.org/10.1016/J.EJCA.2015.11.019.
6. World Health Organization. 2017. Available from: http://www.who.int/uv/faq/skincancer/en/index1.html. Accessed in 2024 (January 31).
7. Livingstone E, Windemuth-Kieselbach C, Eigentler TK, et al. A first prospective population-based analysis investigating the actual practice of melanoma diagnosis, treatment, and follow-up. Eur J Cancer. 2011; 47:1977–89. PMID: 21612915; https://doi.org/10.1016/j.ejca.2011.04.029.
8. Birch-Johansen F, Jensen A, Mortensen L. Trends in the incidence of nonmelanoma skin cancer in Denmark 1978–2007: rapid incidence increases among young Danish women. Int J Cancer. 2010; 127:2190–2198. PMID: 20473901; https://doi.org/10.1002/ijc.25411.
9. Karagas MR, Zens MS, Li Z, et al. Early-onset basal cell carcinoma and indoor tanning: a population-based study. Pediatrics. 2014; 34:4–12. PMID: 24958589; https://doi.org/10.1542/peds.2013-3559.
10. Cancer Research UK. 2014 Available from: https://www.cancerresearchuk.org/sites/default/files/sun_protection_trends_-_cruk.pdf. Accessed in 2024 (January 31).
11. Avsar G, Kasikci M. The condition of patient education in our country. Journal of Atatürk University School of Nursing. 2009; 12 (3):67-73.
12. Armstrong AW, Idriss NZ, Kim RH. Effects of video-based, online education on behavioral and knowledge outcomes in sunscreen use: A randomized controlled trial. Patient Educ Couns. 2011; 83:273–277. PMID: 20570081; https://doi.org/10.1016/j.pec.2010.04.033.
13. Stanton WR, Chakma B, O'Riordan DL, Eyeson-Annan M. Sun exposure and primary prevention of skin cancer for infants and young children during autumn/winter. Aust N Z J Public Health. 2000; 24(2):178-84. PMID: 10790938; https://doi.org/10.1111/j.1467-842x.2000.tb00139.x.
14. Wesson KM, Silverberg NB. Sun protection education in the United States: what we know and what needs to be taught. Cutis. 2003; 71(1):71-4. PMID: 12553634.

15. Makin JK, Warne CD, Dobbinson SJ, Wakefield MA, Hill DJ. Population and age-group trends in weekend sun protection and sunburn over two decades of the SunSmart programme in Melbourne, Australia. Br J Dermatol. 2013; 168:154–161. PMID: 23039760; https://doi.org/10.1111/bjd.12082.
16. Ergul S, Ozeren E. Sun protection behavior and individual risk factors of Turkish primary school students associated with skin cancer: A questionnaire-based study. Asian Pac J Cancer Prev. 2011; 12:765-770. PMID: 21627380.
17. Balyacı OE, Kostu N, Temel AB. Training program to raise consciousness among adolescents for protection against skin cancer through performance of skin self-examination. Asian Pac J Cancer Prev. 2012; 13(10):5011-7. PMID: 23244101; https://doi.org/10.7314/apjcp.2012.13.10.5011.
18. Aygun O, Ergun A. Validity, and reliability of sun protection behavior scale among Turkish adolescent population. Asian Nurs Res (Korean Soc Nurs Sci). 2015;9: 235-42. PMID: 26412628; https://doi.org/10.1016/j.anr.2015.04.006.
19. Sumen A, Oncel S. Effect of skin cancer training provided to maritime high school students on their knowledge and behaviour. Asian Pac J Cancer Prev. 2015; 16(17): 7769-7779. PMID: 26625796.
20. Erkin O, Temel. AB. Nurse-led school-based sun protection programme in Turkey. Cent Eur J Public Health. 2017; 25(4): 287-92. PMID: 29346851; https://doi.org/10.21101/cejph.a4975.
21. Kaymak Y, Tekbas ÖF, Simsek I. Knowledge, attitudes and behaviours of university students related to sun protection. Turkish Archives of Dermatology and Venereology. 2007; 41:81–5.
22. Cinar ND, Cinar S, Karakoc A, Ucar F. Knowledge, attitudes, and behaviors concerning sun protection/skin cancer among adults in turkey. Pakistan Journal of Medical Science. 2009; 25(1):108-112.
23. Celik S, Ilce A, Andsoy II. Knowledge and protective behaviors about skin cancer among nursing students in the west black sea region of Turkey. American Association for Cancer Education. 2017; 33(4):885-892.PMID: 28229313; https://doi.org/10.1007/s13187-017-1188-5.
24. Qiu D, Marugame T. Comparison of time trends in skin cancer incidence (1973–97) in East Asia, Europe, and USA, from cancer incidence in five continents. Jpn. J. Clin. Oncol. 2008; 4(8): 234-6. PMID: 18337321 https://doi.org/10.1093/jjco/hyn012.
25. Liu KE, Barankin B, Howard J, Guenther LC. One-year followup on the impact of a sun awareness curriculum on medical students' knowledge, attitudes, and behavior. J Cutan Med Surg. 2001; 5(3):193-200. PMID: 11685664; https://doi.org/10.1007/s102270000025.
26. Isvy A, Beauchet A, Saiag P, Mahé E. Medical students and sun prevention: knowledge and behaviours in France. J Eur Acad Dermatol Venereol. 2013; 27(2): e247-51. PMID: 22827632; https://doi.org/10.1111/j.1468-3083.2012.04621.x.
27. Forsea, AM, Popescu I, Turcu G, Giurcaneanu C, Geller AC. Knowledge, behavior and attitudes related to skin cancer prevention among final year medical students. Eur J Dermatol. 2012; 22(6): 790-792. PMID: 23131436; https://doi.org/10.1684/ejd.2012.1850.
28. Hymowitz MB, Hayes BB, Maury JJ, Geller AC. Evaluation of medical students' knowledge, attitudes, and personal practices of sun protection and skin self-examination. Arch Dermatol. 2006; 142(4), 523-524. PMID: 16618879; https://doi.org/10.1001/archderm.142.4.523.
29. Sopjani S, Sopjani I, Dushi O. A self-reported study toward melanoma knowledge, protective behavior and personal risk among nursing faculty students at AAB University of Kosovo. Med Arch. 2019; 73(3):201-204. PMID: 31404124; https://doi.org/10.5455/medarh.2019.73.201-204.
30. Ivanov NN, Swan A, Guseman EH, et al. Medical students' knowledge, attitudes, and behaviors with regard to skin cancer and sun-protective behaviors. J Am Osteopat Assoc. 2018; 118(7), 444-454. PMID: 29889933; https://doi.org/10.7556/jaoa.2018.098.
31. Patel SS, Nijhawan RI, Stechschulte S, Parmet Y, Rouhani P, Kirsner RS, et al. Skin cancer awareness, attitude, and sun protection behavior among medical students at the University of Miami Miller School of Medicine. Archives of Dermatology. 2010; 146(7): 797-800. PMID: 20644049; https://doi.org/10.1001/archdermatol.2010.140.
32. Iglesias-Puzas Á, Méndez Iglesias M, Diéguez Montes MP, Flórez Á. Assessment of sun-related behaviour, knowledge and attitudes among nursing students. Photodermatol Photoimmunol Photomed. 2019; 35(5), 304-312. PMID: 30907018; https://doi.org/10.1111/phpp.12466.
33. Boztepe A, Ozsoy S, Erkin O. The knowledge and practices of cleaning workers concerning sun protection. International Journal of Occupational Health and Public Health Nursing. 2014; 1(1):65-79.
34. Haney MO, Bahar Z, Beser A, Arkan G, Cengiz B. Psychometric Testing of the Turkish Version of the Skin Cancer, and Sun Knowledge Scale in Nursing Students. J Cancer Educ. 2016; 1:21-28. PMID: 27155664; https://doi.org/10.1007/s13187-016-1041-2.
35. Fitzpatrick T. The validity and practicality of sunreactive skin types I thorugh VI. Arch Dermatol. 1998;124:869-71. PMID: 3377516; https://doi.org/10.1001/archderm.124.6.869
36. Day AK, Wilson C, Roberts RM, Hutchinson AD. The skin cancer and sun knowledge (scsk) scale: validity, reliability, and relationship to sun-related behaviors among young western adults. Health Educ Behav. 2014; 41(4):440-8. PMID: 24722215; https://doi.org/10.1177/1090198114529129.
37. Dogan ES, Caydam OD. A Scale Development Study: Health Belief Model Scale in Skin Cancer among Turkish University Students. *Saudi J Nurs Health Care. 2021; 4*(8), 205-213. https://doi.org/10.36348/sjnhc.2021.v04i08.001.
38. Karasar N. Scientific Research Methods. Ankara: Nobel Academy Publishing, 2012.
39. Kasar KS, Yesilbalkan OU, Yildirim Y. Nursing student's awareness on skin cancer. International Journal of Caring Sciences. 2019; 12 (2): 1081-7.
40. Nahar V, Wilkerson AH, Ghafari G, et al. Skin cancer knowledge, attitudes, beliefs, and prevention practices among medical students: A systematic search and literature review. Int J Women's Dermatol.2018; 4(3): 139–149. PMID: 30175215; https://doi.org/10.1016/j.ijwd.2017.10.002.

41. Kocak AN, Adana F. The knowledge and behavior of university students about skin cancer and sun protection: a cross-sectional research. Journal of Anatolia Nursing and Health Sciences. 2021; 24(4): 486- 495. https://doi.org/10.17049/ataunihem.616340.
42. Hacivelioglu D, Demirci H. Health education activities the midwives in the primary health care services towards protection and promotion of women's health. Sağlık ve Toplum. 2022;32 (2) 49-60.
43. Ergin A, Bozkurt Al, Bostancı M, Onal O. Assessment of knowledge and behaviors of mothers with small children on the effects of the sun on health. Pamukkale Medical Journal. 2011; (2), 72- 78.
44. Sumen A, Oncel S. Investigation of the Research on Cancer and Sun Protection in Turkey. Turkiye Klinikleri Journal of Nursing Sciences. 2018; 10(1), 59-69. https://doi.org/10.5336/nurses.2017-56858.
45. Yilmaz M, Yavuz B, Subasi M, et al. Skin cancer knowledge and sun protection behavior among nursing students. Jpn J Nurs Sci. 2015;12(1):69-78. PMID: 24751212; https://doi.org/10.1111/jjns.12049.
46. Brokalaki H, Patelarou E, Vardavas C, et al. Current patterns of the sun protection measures adopted by nurses and the risk factors influencing their compliance. Open Journal of Nursing. 2011; 1: 43–50. https://doi.org/10.4236/ojn.2011.13006.
47. Nikolaou V, Stratigos AJ, Antoniou C, et al. Sun exposure behavior and protection practices in a mediterranean population: A questionnaire-based study. Photodermatol Photoimmunol Photomed. 2009; 25: 132–137. PMID: 19438991; https://doi.org/10.1111/j.1600-0781.2009.00424.x.
48. Patel SS, Nijhawan RI, Stechschulte S, et al. Skin cancer awareness, attitude, and sun protection behavior among medical students at the University of Miami Miller School of Medicine. Arch Dermatol. 2010; 146(7): 797-800. PMID: 20644049; https://doi.org/10.1001/archdermatol.2010.140.
49. Pearlman RL, Patel V, Davis RE, Ferris TS, Gruszynski K, Elledge T, et al. Effects of health beliefs, social support, and self-efficacy on sun protection behaviors among medical students: testing of an extended health belief model. Arch Dermatol Res. 2021; 313 (6): 445-452. PMID: 32780198; https://doi.org/10.1007/s00403-020-02123-9.
50. Rejeski WJ, Fanning J. Models and theories of health behavior and clinical interventions in aging: a contemporary, integrative approach. Clin Interv Aging. 2019: 14:1007. PMID: 31213787; https://doi.org/10.2147/CIA.S206974.
51. Brandt MG, Moore CC. Nonmelanoma skin cancer. Facial Plastic Surg Clin North Am. 2019; 27(1):1–13. PMID: 30420063; https://doi.org/10.1016/j.fsc.2018.08.001.
52. Roberts DC, Black D. Comparison of interventions to reduce sun exposure. Behav Med. 2009;35(2):67-76. PMID: 19433378; https://doi.org/10.3200/BMED.35.2.67-78.
53. Williams AL, Grogan S, Clark-Carter D, Buckley E. Appearance-based interventions to reduce ultraviolet exposure and/or increase sun protection intentions and behaviours: a systematic review and meta-analyses. Br J Health Psychol. 2013;18(1):182-217. PMID: 22989352; https://doi.org/10.1111/j.2044-8287.2012.02089.x.
54. Mahler HI, Kulik JA, Gibbons FX, Gerrard M, Harrell J. Effects of appearance-based interventions on sun protection intentions and self-reported behaviors. Health Psychol. 2003; 22(2):199-209. PMID: 12683740; https://doi.org/10.1037//0278-6133.22.2.199.
55. Mahler HI, Kulik JA, Gerrard M, Gibbons FX. Long-term effects of appearance-based interventions on sun protection behaviors. Health Psychol. 2007;26(3):350-360. PMID: 17500622; https://doi.org/10.1037/0278-6133.26.3.350.
56. Jeihooni AK, Rakhshani T. The effect of educational intervention based on health belief model and social support on promoting skin cancer preventive behavior rs in a sample of Iranian farmers. J Cancer Educ. 2019; 34(2):392-401. PMID: 29313300; https://doi.org/10.1007/s13187-017-1317-1.
57. Erkin O, Aygun O. Effects of an education intervention on nursing students' knowledge and attitudes regarding skin self-examination and skin cancer risks. J Nurs Res. 2020; 28(1): e62. PMID: 31935204; https://doi.org/10.1097/jnr.0000000000000326.

Authors' contributions: Dogan ES: data curation (equal), formal analysis (lead), project administration (equal), writing – original draft (lead); Caydam OD: data curation (equal), project administration (equal), writing – review, and editing (lead). All authors have reviewed and approved the final version of the manuscript submitted for publication.

Acknowledgment: We would like to thank the participants and ENAGO Language English Editing Services.

Sources of funding: None
Conflicts of interest: None

Date of first submission: March 05, 2024
Last received: May 13, 2024
Accepted: May 13, 2024

Address for correspondence:
Esin Sevgi Dogan
Department of Nursing, Manisa Celal Bayar University
Number: 8/4, 5526 Street, Uncubozkoy Neighborhood, Zip code: 45030, Manisa, Tukey.
Phone:+90535 691 53 19
E-mail: esinsevgi1990@hotmail.com

Editor responsible for the evaluation process:
Paulo Manuel Pêgo-Fernandes, MD, PhD

Reliability across content areas in progress tests assessing medical knowledge: a Brazilian cross-sectional study with implications for medical education assessments

Pedro Tadao Hamamoto Filho[I], Miriam Hashimoto[II], Alba Regina de Abreu Lima[III], Leandro Arthur Diehl[IV], Neide Tomimura Costa[V], Patrícia Moretti Rehder[VI], Samira Yarak[VII], Maria Cristina de Andrade[VIII], Maria de Lourdes Marmorato Botta Hafner[IX], Zilda Maria Tosta Ribeiro[X], Júlio César Moriguti[XI], Angélica Maria Bicudo[XII]

Universidade Estadual Paulista, Faculdade de Medicina de Botucatu, São Paulo, Brazil

[I]PhD. Physician, Assistant Professor, Departament of Neurology, Psychology and Psychiatry, Faculdade de Medicina de Botucatu, Universidade Estadual Paulista (UNESP), Botucatu (SP), Brazil.
https://orcid.org/0000-0001-6436-9307

[II]PhD. Physician, Assistant Professor, Departament of Pediatrics, Faculdade de Medicina de Botucatu, Universidade Estadual Paulista (UNESP), Botucatu (SP), Brazil.
https://orcid.org/0000-0001-6969-9161

[III]PhD. Biologist, Assistant Professor, Departament of Molecular Biology, Faculdade de Medicina de São José do Rio Preto (FAMERP), São José do Rio Preto (SP), Brazil.
https://orcid.org/0000-0003-4332-4059

[IV]PhD. Physician, Assistant Professor, Departament of Internal Medicine, Universidade Estadual de Londrina (UEL), Londrina (PR), Brazil.
https://orcid.org/0000-0002-9958-7213

[V]PhD. Physician, Assistant Professor, Departament of Internal Medicine, Universidade Estadual de Londrina (UEL), Londrina (PR), Brazil.
https://orcid.org/0000-0001-6624-2043

[VI]PhD. Physician, Assistant Professor, Departament of Tocogynecology, Universidade Estadual de Campinas (UNICAMP), Campinas (SP), Brazil.
https://orcid.org/0000-0003-4530-1109

[VII]PhD. Physician, Assistant Professor, Departament of Dermatology, Universidade Federal de São Paulo (UNIFESP), São Paulo (SP), Brazil.
https://orcid.org/0000-0002-5657-6645

[VIII]PhD. Physician, Assistant Professor, Departament of Pediatrics, Universidade Federal de São Paulo (UNIFESP), São Paulo (SP), Brazil.
https://orcid.org/0000-0003-4519-0613

[IX]PhD. Physician, Assistant Professor, Academic Assessment Center, Faculdade de Medicina de Marília (FAMEMA), Marília (SP), Brazil.
https://orcid.org/0000-0002-5471-4434

[X]PhD. Physician, Assistant Professor, Academic Assessment Center, Faculdade de Medicina de Marília (FAMEMA), Marília (SP), Brazil.
https://orcid.org/0000-0001-7368-3154

[XI]PhD. Physician, Associate Professor, Departament of Internal Medicine, Universidade de São Paulo (USP), Ribeirão Preto (SP), Brazil.
https://orcid.org/0000-0001-5499-3552

[XII]PhD. Physician, Full Professor. Departamentof Pediatrics, Universidade Estadual de Campinas (UNICAMP), Campinas (SP), Brazil.
https://orcid.org/0000-0003-3043-5147

KEYWORDS (MeSH terms):
Internal medicine.
Education, medical.
Educational measurement.

AUTHORS' KEYWORDS:
Reliability.
Progress test.
Medical education assessments.

ABSTRACT

BACKGROUND: Brazilian medical schools equitably divide their medical education assessments into five content areas: internal medicine, surgery, pediatrics, obstetrics and gynecology, and public health. However, this division does not follow international patterns and may threaten the examinations' reliability and validity.

OBJECTIVE: To assess the reliability indices of the content areas of serial, cross-institutional progress test examinations.

DESIGN AND SETTINGS: This was an analytical, observational, and cross-sectional study conducted at nine public medical schools (mainly from the state of São Paulo) with progress test examinations conducted between 2017 and 2023.

METHODS: The examinations covered the areas of basic sciences, internal medicine, surgery, pediatrics, obstetrics and gynecology, and public health. We calculated reliability indices using Cronbach's α, which indicates the internal consistency of a test. We used simple linear regressions to analyze temporal trends.

RESULTS: The results showed that the Cronbach's α for basic sciences and internal medicine presented lower values, whereas gynecology, obstetrics, and public health presented higher values. After changes in the number of items and the exclusion of basic sciences as a separate content area, internal medicine ranked highest in 2023. Individually, all content areas except pediatrics remained stable over time.

CONCLUSIONS: Maintaining an equitable division in assessment content may lead to suboptimal results in terms of assessment reliability, especially for internal medicine. Therefore, content sampling of medical knowledge for general assessments should be reappraised.

INTRODUCTION

Traditionally, Brazilian medical schools have divided general medical education assessments into five content areas: internal medicine, surgery, pediatrics, obstetrics and gynecology, and public health. This division was the consequence of a resolution passed in 2000 by the National Medical Residency Commission,[1] which defined the organization of the selection processes nationally. Despite the several modifications to the resolution in subsequent years, the equitable division of the number of items between the five content areas has remains untouched.

Therefore, all medical selection processes for general specialties (e.g., internal medicine, pediatrics, and general surgery) and direct-access specialties (e.g., anesthesiology, ophthalmology, and radiology) are legally obligated to use this division. Similarly, many undergraduate medical curricula follow this division, either for conducting assessments, such as inter-institutional progress testing,[2] or for organizing clerkship rotations.[3]

However, this equitable division of item numbers does not conform to international patterns. In the Netherlands, progress testing uses a two-dimensional blueprint that includes elements from disciplines (e.g., surgery, dermatology, pediatrics, and physiology) and categories (e.g., the respiratory and musculoskeletal systems).[4] The German Progress Test Medizin is blueprinted according to organ systems with different percentages for each (e.g., 11% for the cardiac system and 4.5% for skin).[5] Similarly, Step 2 of the United States Medical Licensing Examination includes differential weighing of content areas (e.g., 8–10% for the cardiovascular system and 4–6% for pregnancy, childbirth, and puerperium).[6]

Furthermore, the numbers of items across different content areas have implications for examination reliability, which is the reproducibility of assessment outcomes over time or on specific occasions, that is, the consistency of measurements. Therefore, owing to a large component of random errors, the data resulting from low-reliability assessments may threaten the generalization and interpretation of the results.[7]

OBJECTIVE

This study aimed to assess the reliability indices of the content areas of serial, cross-institutional progress test examinations conducted in the state of São Paulo between 2017 and 2023.

METHODS

Study design

We conducted an analytical, observational, cross-sectional study based on data from a retrospective database of inter-institutional progress test examinations held between 2017 and 2023 in nine public medical schools (mainly from the state of São Paulo). We considered only the grades achieved by sixth-year medical students as the test was designed at the level of a recently graduated physician. **Table 1** presents the number of participating students for each year.

Ethical considerations

We used only secondary data from the examinations and did not identify individual students; therefore, approval from an ethical review board was not necessary according to national legislation.

Settings and progress test information

The participating schools joining a consortium were Universidade Estadual Paulista (UNESP), Universidade Estadual de Campinas (UNICAMP), Universidade de São Paulo (USP – Ribeirão Preto), USP – Bauru, Universidade Federal de São Paulo (UNIFESP), Universidade Federal de São Carlos (UFSCAR), Faculdade de Medicina de Marília (FAMEMA), Faculdade de Medicina de São José do Rio Preto (FAMERP), and Universidade Estadual de Londrina (UEL). Universidade Regional de Blumenau (FURB) participated in the progress test examinations from 2017 to 2022. Further, Universidade de São Paulo, Bauru campus was inaugurated in 2018; consequently, their sixth-year students participated in the progress test examinations only in 2023.

Table 1. Number of participating sixth-year medical students across the observational period

Year	Number
2017	687
2018	742
2019	713
2020	712
2021	666
2022	726
2023	525
Total	4771

From 2017 to 2022, the progress test examination consisted of 120 multiple-choice questions equally divided into 20 items from basic sciences, internal medicine, pediatrics, surgery, gynecology and obstetrics, and public health. The use of basic sciences as a content area was related to the consortium's specific history. However, in 2023, basic sciences-related content was distributed among the other five areas, and the number of items was changed to emphasize internal medicine more. Therefore, in 2023, the items were 34 for internal medicine, 23 for pediatrics, 23 for surgery, 20 for gynecology and obstetrics, and 20 for public health. The items were based on clinical vignettes and focused on applied knowledge rather than on the retrieval of memorized information.

Data analysis

We calculated reliability indices using Cronbach's α coefficients,[8] which provide a measure of the internal consistency of a scale or test and range from 0 (low consistency) to 1 (high consistency). Tavakol and Dennick have stated that "*internal consistency describes the extent to which all the items in a test measure the same concept or construct and hence it is connected to the interrelatedness of the items within the test.*"[9] We calculated the α coefficients of each content area for each examination year using the following formula:

$$\alpha = \left(\frac{k}{k-1}\right) x \left(1 - \frac{\sum_{i=1}^{k} s_i^2}{s_{sum}^2}\right)$$

where k is the number of items in the test; s_1^2 is the variance of each item, and s_{sum}^2 is the variance in total scores for each respondent.

We tested the differences between the mean α coefficients using one-way analysis of variance (ANOVA) and calculated temporal trends in α coefficients using a simple linear regression model. The statistical significance level was set at P = 0.05. We performed statistical analyses using SPSS, version 24.0 (IBM Corp., Armonk, New York, United States) and Prism 9 for MacOS (version 9.5.0, GraphPad Software, San Diego, California, United States).

RESULTS

In terms of the absolute values of the α coefficients, basic sciences and internal medicine presented lower values, whereas gynecology and obstetrics, and public health presented higher values (**Figure 1**). After ranking the content areas according to a

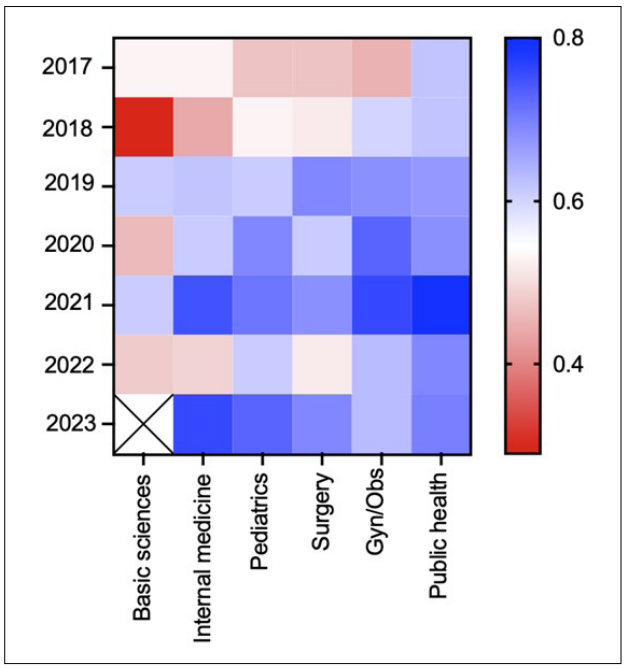


Figure 1. Heat map of alpha coefficient values for the six content areas between 2017 and 2023.

top-down classification of the α coefficients, we found that basic sciences ranked last in almost all years. Internal medicine had intermediate to low positions. Further, pediatrics and surgery had intermediate positions, while public health and gynecology and obstetrics were the highest-ranked areas. After the changes in the number of items and the absence of basic sciences as a separate content area in 2023, internal medicine had the highest position.

The mean α coefficients from 2017 to 2023 were 0.497, 0.600, 0.621, 0.597, 0.640, and 0.683 for basic sciences, internal medicine, pediatrics, surgery, gynecology and obstetrics, and public health, respectively. We found no statistically significant difference in the mean values ($F = 2.432$, $P = 0.054$).

Figure 2 shows the analysis of the temporal trends of each area, which revealed a significant difference in the intercept values of the lines, with basic sciences and internal medicine presenting the lowest values ($F = 2.897$, $P = 0.027$). That is, the initial values of the trend lines were significantly lower in these two content areas. Individually, all content areas except pediatrics remained stable over time, and pediatrics presented a significant upward trend despite a slight decrease in 2022.

Regarding the slopes, that is, the annual change in trend line characteristics, we found no difference between the content areas ($F = 0.206$, $P = 0.957$). Therefore, despite the differences in the initial values, the lines remained parallel to each other, with a pooled slope of 0.026, which indicates a slight increase in the examinations' overall consistency (**Table 2**).

DISCUSSION

The use of progress testing by medical schools is increasing in Brazil as feedback for students, faculty, and institutions effectively improves medical education.[2,10,11]

Created in the Netherlands and USA in the 1970s, progress testing began to be used in Brazil at Universidade de São Paulo and Universidade Estadual de Londrina between the late 1990s and early 2000s. The first progress testing examinations at Universidade de São Paulo consisted of 100–130 items divided into three areas: basic sciences, clinical sciences, and clerkship rotations. This division followed the traditional organization of medical curricula, and the number of items in each area was weighted according to the disciplines' workload.[11] At Universidade Estadual de Londrina, the test was divided into six areas: basic sciences, internal medicine, pediatrics, surgery, gynecology and obstetrics, and public health.[13]

This organization of curricula and assessments has been used in Brazil since the early 1990s owing to the immense efforts of the Interinstitutional Commission for the Evaluation of Medical Education (CINAEM).[14] This commission has played an important role in restructuring medical education in Brazil, especially in assessing medical school processes.[15] Their work culminated in the publication of the National Curricular Guidelines in 2001,[16] which was a landmark for medical education settings. The guidelines were reviewed years later in 2014 to emphasize other important domains for recently graduated general physicians, such as mental health, urgency, and emergencies.[17,18]

However, the equitable division of the number of items in general medical education assessments has not yet been adequately reappraised. The present results demonstrate that following this distribution may lead to suboptimal results in terms of assessment reliability, especially for internal medicine. This is why the consortium of public medical schools in the state of São Paulo changed the number of items across the content areas in progress testing in 2023. Consequently, the reliability index for internal medicine, which ranked highest, immediately increased. The increase in the number of items alone may have led to this result as the α coefficient is considerably influenced by the number of items.[19] While this may be true, it is only a part of the effect.

Following the well-accepted aphorism of biomedical research, increasing the sample size leads to more reliable results.[20] Twenty items do not seem sufficient to adequately sample all the content that medical students should know about internal medicine. In addition, if internal consistency refers to the extent to which different items measure the same construct, it is worth imagining how distant an item about acute myocardial infarction may be from another item about osteoarthritis. In contrast, for obstetrics, an item addressing gestational hypertension is expected to be similar to an item referring to HELLP syndrome (i.e., these two items probably measure the same construct).

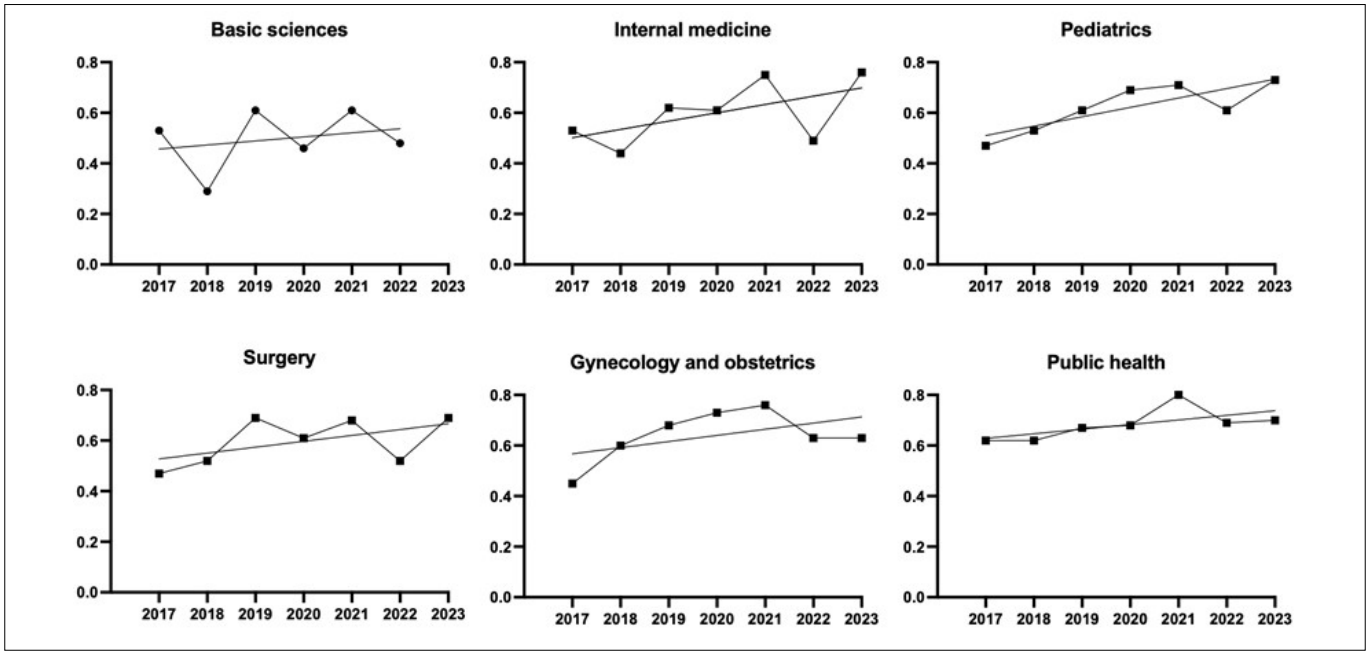


Figure 2. Alpha coefficient values (y axis) for each content area of progress testing between 2017 and 2023, with their respective trend lines. Basic sciences had the lowest intercept value and only pediatrics had a statistically significant upward trend.

Table 2. Linear regression models of temporal trends for each content area's reliability index

Area	Intercept	Slope	R^2	P value
Basic sciences	0.441	1.6%	0.063	0.632
Internal medicine	0.469	3.3%	0.332	0.176
Pediatrics	0.473	3.7%	0.691	**0.020**
Surgery	0.504	2.3%	0.288	0.214
Gynecology and obstetrics	0.543	2.4%	0.266	0.236
Public health	0.610	1.8%	0.420	0.116

The intercept refers to the point at which the regression line crosses the y axis. The slope refers to the annual percentage change. R^2 is the determination coefficient: the closer to "1," the better the adjustment of data to the regression. All areas showed a positive trend towards improvement in the reliability index, with a significant trend for Pediatrics ($P < 0.05$).

Incorporating basic sciences into the other content areas was a necessary adjustment to the test. As initially designed, progress tests must be structured at the graduate level, and therefore, writing items for "*first year students to get right*" is not adequate.[21] Therefore, items testing knowledge about basic sciences should be framed at the functional level of a recently graduated physician. Increasing the number of items in all content areas would be ideal; however, the extent to which tiredness undermines students' performance remains unclear. Therefore, we retained all 120 items.

We observed the best reliability indices for all six content areas in 2019, 2021, and 2023, and this is no coincidence. In those years, the progress test included pre-tested items, that is, items that had been previously used and selected based on their good psychometric properties. This finding highlights the benefits that medical schools can derive by supporting their faculty's ability to write good items that obtain better assessments[22]; this is especially important for basic sciences, whose faculties are lesser experienced with writing clinical-based items.[23] Good items have higher taxonomic levels and better psychometric behavior, and therefore, they provide more reliable results.[24,25] Thus, better assessment is the key to improving medical education as it steers learning along the right path.[26] Moreover, we observed that the α coefficients of all content areas has been increasing over the years, which indicates that this consortium of public medical schools in the state of São Paulo has improved the quality of the progress test examination.

Previous studies have highlighted the need to better explore the validity of assessments in medical education.[27,28] In this context, validity measures the truth of the inferences made from the results of an examination. Reliability is not sufficient to guarantee validity but is a condition for it.[29] Our study focused on a particular domain of validity—that is, a psychometric focus on reliability. Nevertheless, our results call attention to the importance of a broader perspective on medical education assessment and the need to reappraise content sampling of medical knowledge.

REFERENCES

1. Ministério da Educação. Resolução nº 01, de 14 de agosto de 2000. Available from: https://www.gov.br/mec/pt-br/residencia-medica/ementario-da-legislacao-da-residencia-medica. Accessed in 2023 (Nov. 01)
2. Bicudo AM, Hamamoto Filho PT, Abbade JF, Hafner MLMB, Maffei CML. Consortia of cross-institutional Progress Testing for all medical schools in Brazil. Rev Bras Educ Med. 2019;43(4):151-6. https://dx.doi.org/10.1590/1981-52712015v43n4RB20190018.
3. Zanolli MB, Streit DS, Maciel DT, et al. Differences in clerkship development between public and private Brazilian medical schools: an overview. BMC Med Educ. 2020 Sep 21;20(1):316. PMID: 32957972; https://doi.org/10.1186/s12909-020-02193-3.
4. Tio RA, Schutte B, Meiboom AA, Get al. The progress test of medicine: the Dutch experience. Perspect Med Educ. 2016;5(1):51-5. PMID: 26754310; https://doi.org/10.1007/s40037-015-0237-1.
5. Nouns ZM, Georg W. Progress testing in German speaking countries. Med Teach. 2010;32(6):467-70. PMID: 20515374. https://doi.org/10.3109/0142159x.2010.485656.
6. United States Medical Licensing Examination. Step 2 CK Content Outline & Specifications. Available from: https://usmle.org/prepare-your-exam/step-2-ck-materials/step-2-ck-content-outline-specifications. Accessed in 2023 (Nov. 01)
7. Downing SM. Reliability: on the reproducibility of assessment data. Med Educ. 2004;38(9):1006-12. PMID: 15327684. https://doi.org/10.1111/j.1365-2929.2004.01932.x.
8. Cronbach LJ. Coefficient alpha and the internal structure of tests. Psychometrika. 1951;16(3):297-334. https://dx.doi.org/10.1007/BF02310555.
9. Tavakol M, Dennick R. Making sense of Cronbach's alpha. Int J Med Educ. 2011;2:53-55. PMID: 28029643; https://doi.org/10.5116/ijme.4dfb.8dfd.
10. Cecilio-Fernandes D, Bicudo AM, Hamamoto Filho PT. Progress testing as a pattern of excellence for the assessment of medical students' knowledge - concepts, history, and perspective. Medicina (Ribeirão Preto). 2021;54(1):e-173770. http://dx.doi.org/10.11606/issn.2176-7262.rmrp.2021.173770.
11. Troncon LEA, Elias LLK, Osako MK, et al. Reflections on the use of the Progress Test in the programmatic student assessment. Rev Bras Educ Med. 2023;47(2):e076. https://dx.doi.org/10.1590/1981-5271v47.2-2022-0334.ing.
12. Tomic ER, Martins MA, Lotufo PA, Benseñor IM. Progress testing: evaluation of four years of application in the school of medicine, University of São Paulo. Clinics (Sao Paulo). 2005;60(5):389-96. PMID: 16254675. https://doi.org/10.1590/s1807-59322005000500007.
13. Sakai MH, Ferreira Filho OF, Almeida MJ, Mashima DA, Marchese MC. Progress testing and course evaluation: ten years of experience in the undergraduate medical course at the State University of Londrina. Rev Bras Educ Med. 2008;32(2):254-63. https://dx.doi.org/10.1590/S0100-55022008000200014.
14. Machado JLM. A participação da ANDES-SN na Cinaem: o processo de transformação das escolas médicas brasileiras. Interface (Botucatu). 1999;3(5):177–80. https://doi.org/10.1590/S1414-32831999000200025.
15. Falavigna A, Canabarro CT, Medeiros GS. Health system and medical education in Brazil: history, principles, and organization. World Neurosurg. 2013;80(6):723-7. PMID: 23333994. https://doi.org/10.1016/j.wneu.2013.01.079.
16. Ministério da Educação. Resolução CNE/CES nº 4, de 7 de Novembro de 2001. Brasilia: Ministério da Educação; 2001. Available from: http://portal.mec.gov.br/cne/arquivos/pdf/CES04.pdf. Accessed in 2023 (Nov. 01)
17. Ministério da Educação. Resolução CNE/CES nº 3, de 20 de Junho de 2014. Brasilia: Ministério da Educação; 2014. Available from: http://portal.mec.gov.br/cne/arquivos/pdf/CES04.pdf. Accessed in 2023 (Nov. 01)
18. Antunes Dos Santos R, Nunes MDPT. Medical education in Brazil. Med Teach. 2019;41(10):1106-1111. PMID: 31282823. https://doi.org/10.1080/0142159x.2019.1636955.
19. Agbo AA. Cronbach's alpha: review of limitations and associated recommendations. J Psychol Africa. 2010; 20(2):233-39. https://dx.doi.org/10.1080/14330237.2010.10820371.
20. Charter RA. Sample size requirements for precise estimates of reliability, generalizability, and validity coefficients. J Clin Exp Neuropsychol. 1999;21(4):559-66. PMID: 10550813. https://doi.org/10.1076/jcen.21.4.559.889.
21. Schuwirth LW, van der Vleuten CP. The use of progress testing. Perspect Med Educ. 2012;1(1):24-30. PMID: 23316456; https://doi.org/10.1007/s40037-012-0007-2.
22. Hamamoto Filho PT, Bicudo AM. Improvement of faculty's skills on the creation of items for progress testing through feedback to item writers: a successful experience. Rev Bras Educ Med. 2020;44(1):e018. https://dx.doi.org/10.1590/1981-5271v44.1-20190130.ING.
23. Feliciano CS, Elias LLK, Osako MK, Guimarães FS, Troncon LEA, Bollela VR. Workshop on item writing to assess basic sciences in health professional education: an experience report. Rev Bras Educ Med. 2023;47(2):e067. https://doi.org/10.1590/1981-5271v47.2-2022-0297.
24. Cecilio-Fernandes D, Kerdijk W, Bremers AJ, Aalders W, Tio RA. Comparison of level of cognitive process between case-based items and non-case-based items of the interuniversity progress test of medicine in the Netherlands. J Educ Eval Health Prof. 2018;15:28. PMID: 30541188; https://doi.org/10.3352/jeehp.2018.15.28.
25. Hamamoto Filho PT, Silva E, Ribeiro ZMT, Hafner MLMB, Cecilio-Fernandes D, Bicudo AM. Relationships between Bloom's taxonomy, judges' estimation of item difficulty and psychometric properties of items from a progress test: a prospective observational study. Sao Paulo Med J. 2020;138(1):33-39. PMID: 32321103; https://doi.org/10.1590/1516-3180.2019.0459.r1.19112019.
26. Norman G, Neville A, Blake JM, Mueller B. Assessment steers learning down the right road: impact of progress testing on licensing examination performance. Med Teach. 2010;32(6):496-9. PMID: 20515380. https://doi.org/10.3109/0142159x.2010.486063.

27. Kane MT. Validating the interpretations and uses of test scores. J Educ Meas. 2013;50(1):1-73. https://dx.doi.org/10.1111/jedm.12000.
28. Boursicot K, Kemp S, Wilkinson T, et al. Performance assessment: Consensus statement and recommendations from the 2020 Ottawa Conference. Med Teach. 2021;43(1):58-67. PMID: 33054524. https://doi.org/10.1080/0142159x.2020.1830052.
29. McLaughlin K, Lemaire J, Coderre S. Creating a reliable and valid blueprint for the internal medicine clerkship evaluation. Med Teach. 2005;27(6):544-7. PMID: 16199363. https://doi.org/10.1080/01421590500136113.

Authors' contributions: Hamamoto Filho PT: conceptualization (lead), data curation (lead), formal analysis (lead), funding acquisition (lead), investigation (lead), methodology (lead), project administration (lead), resources (lead), writing – original draft (lead); Hashimoto M: resources (equal), validation (equal), visualization (equal), writing – review and editing (equal); Lima ARA: resources (equal), validation (equal), visualization (equal), writing – review and editing (equal); Diehl LA: resources (equal), validation (equal), visualization (equal), writing – review and editing (equal); Costa NT: resources (equal), validation (equal), writing – review and editing (equal); Rehder PM: resources (equal), validation (equal), visualization (equal), writing – review and editing (equal); Yarak S: resources (equal), validation (equal), visualization (equal), writing – review and editing (equal); Andrade MC: resources (equal), validation (equal), writing – review and editing (equal); Hafner MLMB: resources (equal), visualization (equal), writing – review and editing (equal), Ribeiro ZMT: resources (equal), validation (equal), writing – review and editing (equal); Moriguti JC: resources (equal), supervision (equal), validation (equal), visualization (equal), writing – review and editing (equal); Bicudo AM: conceptualization (supporting), funding acquisition (supporting), project administration (supporting), resources (equal), supervision (lead), validation (lead), visualization (lead), writing – review and editing (lead). All authors reviewed and approved the final version submitted for publication

Acknowledgements: We thank the efforts of all faculties who have written new items to compose the progress testing examinations

Sources of funding: Pedro Tadao Hamamoto Filho and Angélica Maria Bicudo have received an award from the National Board of Medical Examiners (PA, PA, USA). GRANT_NUMBER: Proposal LAG5-2020. https://contributions.nbme.org/about/latinamerica-grants. The funders had no role in study design, data collection and analysis, decision to publish, or preparation of the manuscript

Conflict of interest: None

Date of first submission: August 18, 2023
Last received: March 25, 2024
Accepted: May 13, 2024

Address for correspondence:
Pedro Tadao Hamamoto Filho
Departamento de Neurologia, Psicologia e Psiquiatria, Faculdade de Medicina de Botucatu,
Universidade Estadual Paulista (UNESP)
Distrito de Rubião Jr, s/n - (SP), Brasil.
CEP 18618-686
Tel: +55 14 3880-1220
E-mail: pedro.hamamoto@unesp.br

Editor responsible for the evaluation process:
Paulo Manuel Pêgo-Fernandes, MD, PhD

Acute renal failure, COVID-19 and deaths, worrying rates in intensive care units: a cross-sectional study

Yoshimi José Ávila Watanabe[I], Lívia Maria Rezende Carvalho[II], João Victor Marques Guedes[III], André Oliveira Baldoni[IV], Vinícius Silva Belo[V], Alba Otoni[VI]

Universidade Federal de São João del-Rei (UFSJ), Divinópolis, MG, Brazil

[I]MD, MSc. Nefrologist, Physician, PhD Student, Postgraduate Program in Health Sciences, Campus Centro Oeste (CCO), Universidade Federal de São João del-Rei (UFSJ), Divinópolis (MG), Brazil.
https://orcid.org/0000-0002-6038-2501

[II]Undergraduate Nursing Student, Curso de Enfermagem, Campus Centro Oeste (CCO), Universidade Federal de São João del-Rei (UFSJ), Divinópolis (MG), Brazil.
https://orcid.org/0000-0003-1548-5330

[III]MSc. Pharmacist, External Research Partner, Postgraduate Program in Health Sciences Campus Centro Oeste (CCO), Universidade Federal de São João del-Rei (UFSJ), Divinópolis (MG), Brazil.
https://orcid.org/0000-0002-4812-7030

[IV]PhD. Pharmacist, Associate Professor, Campus Centro Oeste (CCO), Universidade Federal de São João del-Rei (UFSJ), Divinópolis (MG), Brazil.
https://orcid.org/0000-0001-6379-0415

[V]PhD. Biologist, Associate Professor, Campus Centro Oeste (CCO), Universidade Federal de São João del-Rei (UFSJ), Divinópolis (MG), Brazil.
https://orcid.org/0000-0003-0183-1175

[VI]PhD. Nurse, Associate Professor, Campus Centro Oeste (CCO), Universidade Federal de São João del-Rei (UFSJ), Divinópolis (MG), Brazil.
https://orcid.org/0000-0002-8126-3026

KEYWORDS (MeSH terms):
Acute kidney injury.
Death.
Intensive care units.
COVID-19.

AUTHOR KEYWORDS:
Kidney damage.
Intensive therapy.
Viral infection.
Pandemic.

ABSTRACT

BACKGROUND: Acute kidney failure is a serious consequence of coronavirus disease 2019 (COVID-19).

OBJECTIVES: To identify the prevalence of COVID-19, kidney failure, frequency of death, and associated factors in patients receiving intensive care.

DESIGN AND SETTING: Analytical cross-sectional study conducted in the intensive care unit (ICU) of a medium-sized philanthropic general hospital in center-west Minas Gerais.

METHODS: Adults and older individuals who underwent real-time polymerase chain reaction testing for severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) were evaluated by the nephrology team.

RESULTS: Among the 176 patients, the prevalence of COVID-19 and acute kidney injury (AKI) were 103 (58.5%) and 132 (75%), respectively, and 44 (25%) had chronic kidney disease (CKD) and 16 (15,5%) were positive for SARS-CoV-2. In the Charlson index classification, which estimates the risk of death, a statistically significant difference was identified in the percentages of groups with and without COVID-19 for indices 0, 1, and 2. There was a significant association between kidney disease and ICU mortality ($P < 0.05$). Patients with CKD had fewer fatal outcomes (13/97, 13.4%) than those with AKI (85/97, 87.6%).

CONCLUSIONS: COVID-19 rates remained high long after diagnosis and prevention of SARS-CoV-2 infection. In addition, a higher death rate among patients who developed AKI, whose prevalence was also greater than that in the national literature, regardless of the presence of COVID-19, revealed a worrying scenario and corroborated the need for early and judicious approaches to preserve the lives of patients with AKI admitted to intensive care units.

INTRODUCTION

Acute kidney failure is a serious consequence of severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) infection. Its occurrence can vary from 0.5% to 7% of the general population, being more frequent among those who are hospitalized and mainly in those who require intensive treatment.[1,2] During the coronavirus disease 2019 (COVID-19) pandemic, a greater number of patients with acute kidney injury (AKI) were observed in Brazil and worldwide.[3,4,5]

Specifically in Brazil, a study from Rio de Janeiro reported a high incidence of AKI in individuals with COVID-19 and an association with high mortality, highlighting the risk factors or predictors: acute respiratory distress syndrome, age, altered glomerular filtration rate, and systemic arterial hypertension.[6] In addition to AKI, the mortality rate was high for patients with chronic kidney disease (CKD), understood as abnormalities in the structure and/or function of the kidneys present for more than three months with implications for health, in Brazil.[7] The authors suggested that comorbid events, socioeconomic conditions, health system deficiencies, structural care inefficiencies, as well as social inequality allowed the advance of this pandemic infectious disease with a high frequency of lethal outcomes.[7]

People infected with SARS-CoV-2 have different outcomes, particularly when comparing those with and without known prior kidney disease. The reasons suggested for the different courses and outcomes are still inconclusive but suggest that there is an association with inflammatory "status" and response to infection, as the main motivator and promoter of the outcomes.[6]

Considering the severity and lethal impact of COVID-19, it is important to understand the epidemiological profile of patients affected by the disease and those with dysfunction or metabolic disorders involving the kidneys. Such information will be useful to better understand the evolutionary

course of this group of patients and, consequently, enable a better propaedeutic and therapeutic approach as well as logistical, financial, and operational management of the public health system.

OBJECTIVE

This study aimed to identify the prevalence of COVID-19, kidney failure, frequency of death, and associated factors in patients admitted to an intensive care unit (ICU).

METHODS

Outline

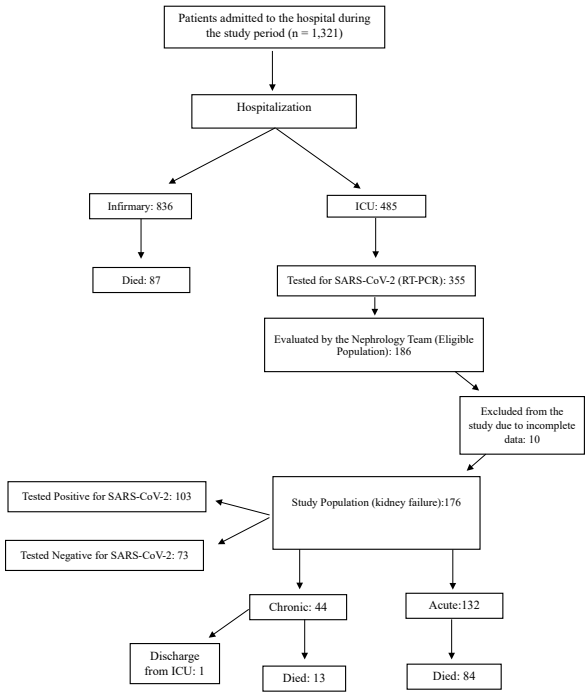
This cross-sectional study was conducted during the first half of 2022 in the intensive care unit of a large hospital complex in the Midwest region of Minas Gerais, Brazil. The Strengthening the Reporting of Observational Studies in Epidemiology (STROBE) guidelines were adopted to strengthen and guarantee the requirements of an observational study.[8] The Nephrology Service was activated to evaluate patients with renal alteration or metabolic dysfunction, with hospitalization ranging from zero to four days for those without COVID-19 (Tested Negative for SARS-CoV-2) and one to 11 days for the COVID-19 group (Tested Positive for SARS-CoV-2). Medical records were used for evaluation.

Participants and sample power calculation

Adult and older patients of both sexes who were admitted to the ICU in the first half of 2022 with evidence of renal impairment, which is subsequently referred to as kidney failure, and who underwent the real-time polymerase chain reaction (RT-PCR) test for SARS-CoV-2, were considered eligible, and those with incomplete information in their medical records were excluded.

During the study period, 1,321 patients were hospitalized. Of these, 485 were admitted to the ICU and 836 were admitted to the infirmary, of whom 87 died. Among those admitted to the IUC (485), 355 underwent tests for SARS-Cov-2, and 186 also had kidney failure. Therefore, this cohort was eligible for inclusion in this study. Of these, 10 were excluded because of incomplete data, hence the study cohort comprised 176 participants. Of these, 103 tested positive, and 73 tested negative for SARS-CoV-2. Among the same cohort of 176 patients who had kidney failure, 132 had AKI and 44 had CKD. Among those with CKD, one was discharged from the ICU and 13 died. It is noteworthy that only for the analysis of mortality, the patient with CKD who was discharged from the ICU was not included in this analysis (**Figure 1**).

The estimation of sample size was estimated using G*Power software, version 3.1.9.2. (Written by Franz Paul, University of Kiel, Kiel, Germany). The prevalence of kidney disease in patients without COVID-19 (73) and with COVID-19 (103) was considered at a significance level of 5% and the sample power was 92.7%.



ICU, intensive care unit; SARS-CoV-2, severe acute respiratory syndrome coronavirus 2 2019; RT-PCR, real-time reverse transcription polymerase chain reaction.

Figure 1. Flowchart of patients evaluated in the study and evolution to death.

Study variables of interest

The following outcomes were considered: the results of the SARCov-2 test (positive or negative) using RT-PCR. In addition, the outcome (fatal or nonfatal) was considered to assess the impact of kidney failure on death rates, with the presence or absence of CKD and AKI as the main explanatory variables, in addition to the other explanatory variables for both outcomes, as described below.

The explanatory variables were grouped into sociodemographic: age (continuous) and sex; and clinical: present or absent comorbidities; presence of Stage 3 acute kidney disease classified as creatinine ≥ 4.0 mg/dL or ≥ 3 times baseline, or decline in urine output by < 0.3 mL/kg/h for ≥ 24 h, or anuric for ≥ 12 h, and presence of CKD;[9] renal replacement therapy; and the Charlson Comorbidity Index, which uses 19 diseases that have a fixed weight assigned that vary between one and six points based on the severity of the condition.[10]

Statistical analysis

Frequency and dispersion measures were used to characterize the sociodemographic and clinical profiles of the cohort. Categorical variables are presented as absolute values and percentages and quantitative variables as medians and quartiles,

considering the asymmetric distribution of data, as indicated by the Shapiro-Wilk test.

Associations between sociodemographic and clinical variables and outcomes were analyzed using the Chi-square test or Fisher's Exact test. The association between quantitative variables and the outcomes was determined using the Mann–Whitney U test. For multiple analysis in the logistic regression models, all explanatory variables that were $P < 0.20$ in the bivariate association were included, and the backward technique was applied. For the final model, as well as for the statistical tests conducted, a significance level of $P < 0.05$ was adopted. All analyses were performed using Statistical Package for the Social Sciences, version 25 (SPSS, IBM, Armonk, New York, United States).

Ethical aspects

This study was approved by the Ethics Committee for Research involving Human Beings of the Universidade Federal de São João del-Rei (C.A.A.E. 11780919.8.0000.5545) with technical approval number: 3,359,799, on July 18, 2019. To guarantee the consent of the participants, an Informed Consent Form was presented to each patient, which was then signed.

RESULTS

Of the total participants, the majority were male (97 = 55.1%) and older with a median age of 60 years (Quartiles: 47-73). The frequencies of COVID-19, AKI, and CKD were, 103 (58.5%) 132 (75%), and 44 (25%), respectively. There were 73 (41,4%) patients without COVID-19. The frequency of AKI was significantly higher in patients with COVID-19 (**Table 1**).

In the Charlson Comorbidity Index, a statistically significant difference was identified between the COVID-19 group and the non-COVID-19 group in the proportions of individuals with indices 0, 1, and 2, which are considered lighter indices. There was a higher proportion of the zero index in the COVID-19 group and indices 1-2 had higher proportions in the non-COVID-19 group.

The bivariate analysis of the association between COVID-19 outcomes and explanatory variables is shown in **Table 1**.

With regard to the multivariate analysis, the variables with $P < 0.20$ and thus included in the model, were comorbidities (heart disease, vasculopathy, pneumopathy, oncology disorders, and obesity), kidney failure, Charlson Comorbidity Index, death, and renal replacement therapy. However, in the final model, none showed a significant association with the COVID-19 and non-COVID-19 outcomes.

When performing the bivariate analysis considering death as the outcome, a significant association was identified in the progression to death between patients with AKI and those with CKD ($P = .01$). Patients with CKD had a lower mortality rate (13/97, 13.4%) compared with those diagnosed with AKI (85/97, 87.6%) (**Table 2**). However, this association was not significant in the multivariate logistic regression. When patients simultaneously had COVID-19 and AKI (n = 87), the mortality rate was 69.0% (data not shown).

Table 1. Association between the presence and absence of coronavirus disease 2019 with sociodemographic and clinical variables in patients evaluated by nephrology, admitted to the intensive care unit of a large hospital in a city in the Midwest of Minas Gerais in the first half of 2022 (n = 176)

Variables	COVID-19 negative (n = 73)	COVID-19 positive (n = 103)	Total	P*
Sex				
Female	34 (46.6%)	45 (43.7%)	79 (44.9%)	0.70
Male	39 (53.4%)	58 (56.3%)	97 (55.1%)	
Age (median)	63 (55 – 73)	60 (47 – 71)		0.28
Cardiopathy				
No	54 (74.0%)	89 (86.4%)	143 (81.3%)	0.03
Yes	19 (26.0%)	14 (13.6%)	33 (18.8%)	
Vasculopathy				
No	63 (86.3%)	99 (96.1%)	162 (92.0%)	0.02
Yes	10 (13.7%)	4 (3.9%)	14 (8.0%)	
DM				
No	52 (71.2%)	78 (75.7%)	130 (73.9%)	0.50
Yes	21 (28.8%)	25 (24.3%)	46 (26.1%)	
SAH				
No	50 (68.5%)	69 (67.0%)	119 (67.6%)	0.83
Yes	23 (31.5%)	34 (33.0%)	57 (32.4%)	
Pneumopathy				
No	71 (97.3%)	91 (88.3%)	162 (92.0%)	0.04
Yes	2 (2.7%)	12 (11.7%)	14 (8.0%)	
Oncology disorders				
No	69 (94.5%)	103 (100.0%)	172 (97.7%)	0.02
Yes	4 (5.5%)	0 (0%)	4 (2.3%)	
Kidney disease				
Acute	45 (61.6%)	87 (84.5%)	132 (75.0%)	<0.01
Chronic	28 (38.4%)	16 (15.5%)	44 (25.0%)	
Charlson index				
0**	30 (41.1%)	60 (58.3%)	90 (51.1%)	0.04
1 – 2**	20 (27.4%)	12 (11.7%)	32 (18.2%)	
3 – 4	12 (16.4%)	16 (15.5%)	28 (15.9%)	
≥ 5	11 (15.1%)	15 (14.6%)	26 (14.8%)	
Obesity (n = 109)				
No	46 (93.9%)	47 (78.3%)	93 (85.3%)	0.02
Yes	3 (6.1%)	13 (21.7%)	16 (14.7%)	
ICU Death (n = 176)				
No	43 (58.9%)	35 (34.3%)	78 (44.6%)	<0.01
Yes	30 (41.1%)	67 (65.7%)	97 (55.4%)	
RRT (n = 119)				
No	34 (65.4%)	30 (44.8%)	64 (53.8%)	0.02
Yes	18 (34.6%)	37 (55.2%)	55 (46.2%)	

*Chi Square Test and Fisher's Test; **Statistically different values between COVID- and COVID+; ICU = intensive care unit; DM = diabetes mellitus; SAH = systemic arterial hypertension; RRT = Renal Replacement Therapy.

Table 2. Association between the presence and absence of death in the intensive care unit with sociodemographic and clinical variables in patients evaluated by nephrology, admitted to the intensive care unit of a large hospital in a city in the Midwest of Minas Gerais in the first half of 2022 (n = 175)

Variables	No (n = 78)	Yes (n = 97)	Total	P*
Sex				
Female	31 (39.7%)	48 (49.5%)	79 (45.1%)	0.19
Male	47 (60.3%)	49 (50.5%)	96 (54.9%)	
Age (median)	61 (49 – 72)	62 (48 – 70)		0.20
Cardiopathy				
No	63 (80.8%)	79 (81.4%)	142 (81.1%)	0.91
Yes	15 (19.2%)	18 (18.6%)	33 (18.9%)	
Vasculopathy				
No	71 (91%)	90 (92.8%)	161 (92.0%)	0.67
Yes	7 (9%)	7 (7.2%)	14 (8.0%)	
DM				
No	55 (70.5%)	74 (76.3%)	129 (73.7%)	0.38
Yes	23 (29.5%)	23 (23.7%)	46 (26.3%)	
SAH				
No	53 (67.9%)	65 (67.0%)	118 (67.4%)	0.89
Yes	25 (32.1%)	32 (33.0%)	57 (32.6%)	
Pneumopathy				
No	73 (93.6%)	88 (90.7%)	161 (92.0%)	0.48
Yes	5 (6.4%)	9 (9.3%)	14 (8.0%)	
Oncology disorders				
No	76 (97.4%)	95 (97.9%)	171 (97.7%)	0.99
Yes	2 (2.6%)	2 (2.1%)	4 (2.3%)	
Kidney disease				
Acute	48 (61.5%)	84 (87.6%)	132 (75.4%)	<0.01
Chronic	30 (38.5%)	13 (13.4%)	43 (24.6%)	
Charlson index				
0**	32 (41%)	58 (59.8%)	90 (51.4%)	0.01
1 – 2**	21 (26.9%)	10 (10.3%)	31 (17.7%)	
3 – 4	11 (14.1%)	17 (17.5%)	28 (16.0%)	
≥ 5	14 (17.9%)	12 (12.4%)	26 (14.9%)	
Obesity (n = 109)				
No	40 (93%)	53 (80.3%)	93 (85.3%)	0.09
Yes	3 (7%)	13 (19.7%)	16 (14.7%)	
COVID (n = 175)				
Negative	43 (55.1%)	30 (30.9%)	73 (41.7%)	<0,01
Positive	35 (44.9%)	67 (69.1%)	102 (58.3%)	
RRT (n = 119)				
No	24 (48%)	40 (58%)	64 (53.8%)	0.28
Yes	26 (52%)	29 (42%)	55 (46.2%)	

*Chi Square Test and Fisher's Test; **Statistically different values between death and non-death in the ICU only in the marked classes; DM = diabetes mellitus; SAH = systemic arterial hypertension; RRT = Renal Replacement Therapy.

DISCUSSION

The increased frequency of COVID-19 with simultaneous AKI in the ICU has revealed a worrying scenario. During the second wave of COVID-19 in Brazil, in which many severe cases were recorded, acute renal involvement was to be expected among people hospitalized with the SARS-CoV-2 virus but the prevalence rate found in this study was higher than the rates of AKI described in the current literature, which had a mean of approximately 60%.[5,12,13]

In a hospital study performed in China, whose objective was to evaluate the impact of AKI on the clinical evolution of COVID-19, an incidence of 12.9% of AKI was identified, increasing the risk of death for those hospitalized for COVID-19.[14] Corroborating these findings, a cohort developed in New York with 5,449 people identified that 1,993 (36.6%) developed AKI, 31.1% of these in Stage 3.[15]

In the Brazil, the percentage of patients with AKI has been variable, but still below that found in the present study. In a study performed in the state of Paraná/Brazil, it was found that 11.6% of patients developed AKI.[16] In contrast, a study performed in the state of Rio de Janeiro reported that 55.9% of patients with COVID-19 admitted to the ICU developed AKI, with the majority (66.7%) advancing to Stage 3.[4]

In view of the results of national surveys, it is necessary to reflect on the reason for such high rates of AKI in the patients involved in the current study, as well as the reason for the wide variety of AKI frequencies of acute kidney disease in ICUs. Such diverse perspectives can be explained by population demographics, comorbidities, and disease severity inherent to each patient profile and Brazilian regional location.

With regard to the pandemic period, many other factors could account for the high prevalence of AKI triggered by COVID-19, including the hyperinflammatory state due to the virus binding to angiotensin-converting enzyme 2 receptors, perfusion deficits, and the use of nephrotoxic drugs, which may favor tubulointerstitial nephritis and affect the kidney as a whole.[6] It is important to note that there is a consensus in the literature that the development of AKI in patients with COVID-19 decreases their survival and exponentially increases the risk of death.[4,17,18]

This consensus from the literature was corroborated by our findings, which, demonstrated the impact on the mortality of patients with COVID-19 and simultaneous AKI and revealed a mortality rate of almost 70%, higher than that reported in the literature.

Hirsch et al.[15] identified a 35% mortality rate among patients with COVID-19 and AKI and showed that mortality was higher among those classified as having Stage 3 acute renal impairment. In a study by Costa et al.[4] a significant difference was found in the mortality rates between patients with COVID-19 with and without renal involvement (33.3% and 9%, respectively). In another important study, Aroca et al.[17] reported that patients with COVID-19 who developed AKI had an 11.83 times greater risk of death than those without AKI.

It is also interesting to note that, although not common in national studies, international studies have emphasized the Charlson Comorbidity Index to weigh the risk of death and add

more solidity to the results related to mortality rates.[11] In this perspective, although the multivariate analysis of this study did not find significant associations between the Charlson Comorbidity Index and the presence of COVID-19 or between the Charlson Comorbidity Index and death, the consensus view in the literature is that most patients diagnosed with COVID-19 and comorbidities, most commonly heart disease, systemic arterial hypertension, diabetes mellitus, and obesity, have a higher mortality rate.[4,16,18,19,20]

Finally, considering the entire scenario presented based on the literature and aligned with our results, we can state that the evolution of COVID-19 combined with renal dysfunction contributes to the aggravation of the patient's condition, which may explain the failure of multiple organs and high death rate in this group.

Study limitations

The results of this study cannot be generalized because they were conducted on individuals admitted to a single hospital. It should be noted that the lack of official health records of information essential for conducting the study limited the inclusion of more participants. Brazil is still not effectively using official health records as a secondary and complete source of data. Most national studies point to the lack of data as a limiting factor for achieving a larger "n" and for more complex analyses.

Even so, it should be noted that the institution where the study was carried out is a reference hospital for COVID-19 for the population of 54 municipalities, which together represent approximately one million people, and therefore increases the representativeness of the results shown here.

CONCLUSION

This study revealed a high rate of COVID 19 simultaneously with a high rate of AKI, demonstrating that even after more than two and a half years of the pandemic there is still much to understand regarding the main measures to prevent complications, associated comorbidities, and effective approaches to this virus. The mortality rate among patients with AKI was also above expectations (87.6%), maintaining a rate of almost 70% in the presence of COVID-19. It is recommended that further studies with a longitudinal design and with a larger sample size be performed to determine, with certainty, solid evidence that explains the causes of such high rates of complications and mortality associated with AKI, as well as with COVID-19.

REFERENCES

1. Huang C, Wang Y, Li X, et al. Clinical features of patients infected with 2019 novel coronavirus in Wuhan, China. Lancet. 2020;395(10223):497-506. PMID: 31986264; https://doi.org/10.1016/s0140-6736(20)30183-5.
2. Wang D, Hu B, Hu C, et al. Clinical characteristics of 138 hospitalized patients with 2019 novel coronavirus–infected pneumonia in Wuhan, China. JAMA. 2020;323(11):1061-9. PMID: 32031570; https://doi.org/10.1001/jama.2020.1585.
3. Teixeira Júnior AAL, Neves PDMM, Lages JS, et al. Brazilian consortium for the study on renal diseases associated with COVID-19: a multicentric effort to understand SARS-CoV-2-related nephropathy. Front Med. 2020;7:584235. PMID: 33195337; https://doi.org/10.3389/fmed.2020.584235.
4. Costa RL, Sória TC, Salles EF, et al. Lesão renal aguda em pacientes com Covid-19 de uma UTI no Brasil: incidência, preditores e mortalidade hospitalar. Braz J Nephrol. 2021;43(3):349-58. https://doi.org/10.1590/2175-8239-JBN-2020-0144.
5. Wang F, Ran L, Qian C, et al. Epidemiology and outcomes of acute kidney injury in COVID-19 patients with acute respiratory distress syndrome: a multicenter retrospective study. Blood Purif. 2021;50(4-5):499-505. PMID: 33291098. https://doi.org/10.1159/000512371.
6. Pecly IMD, Azevedo RB, Muxfeldt ES, et al. A review of Covid-19 and acute kidney injury: from pathophysiology to clinical results. J Braz Nephrol. 2021;43(4):551-71. PMID: 34057983; https://doi.org/10.1590/2175-8239-jbn-2020-0204.
7. Pio-Abreu A, Nascimento MM, Vieira MA, et al. High mortality of CKD patients on hemodialysis with Covid-19 in Brazil. J Nephrol. 2020;33(5):875-7. PMID: 32770522; https://doi.org/10.1007/s40620-020-00823-z.
8. Malta M, Cardoso LO, Bastos FI, Magnanini MMF, Silva CMFP. STROBE initiative: guidelines on reporting observational studies. Rev Saude Publica. 2010;44(3):559-65. PMID: 20549022; https://doi.org/10.1590/s0034-89102010000300021.
9. Kidney Disease: Improving Global Outcomes. CKD Work Group. KDIGO 2012 Clinical practice guideline for the evaluation and management of chronic kidney disease. Kidney Int Suppl. 2013;3(1):1-150. https://doi.org/10.1038/kisup.2012.77.
10. Charlson ME, Pompei P, Ales KL, MacKenzie CR. A new method of classifying prognostic comorbidity in longitudinal studies: Development and validation. J Chronic Dis. 1987;40(5):373-83. PMID: 3558716; https://doi.org/10.1016/0021-9681(87)90171-8.
11. Martins M, Blais R. Evaluation of comorbidity indices for inpatient mortality prediction models. J Clin Epidemiol. 2006;59(7):665-9. PMID: 16765268; https://doi.org/10.1016/j.jclinepi.2005.11.017.
12. Lombardi R, Ferreiro A, Ponce D, et al. Latin American registry of renal involvement in COVID-19 disease. The relevance of assessing proteinuria throughout the clinical course. PLoS One. 2022;17(1):e0261764. PMID: 35085273; https://doi.org/10.1371/journal.pone.0261764.
13. Siqueira Junior DD, Morais TC, Portugal I, et al. Trends in COVID-19 mortality and case-fatality rate in the State of Paraná, South Brazil: spatiotemporal analysis over one year of the Pandemic. J Hum Growth Dev. 2021;31(3):549-61. https://doi.org/10.36311/jhgd.v31.12792.
14. Bao PL, Deng KL, Yuan AL, et al. Early renal impairment is associated with in-hospital death of patients with COVID-19. Clin Respir J. 2022;16(6):441-9. PMID: 35591765; https://doi.org/10.1111/crj.13496.

15. 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.
16. Pontes L, Danski MTR, Piubello SMN, Pereira JDFG, Jantsch LB, Costa LB, et al. Perfil clínico e fatores associados ao óbito de pacientes COVID-19 nos primeiros meses da pandemia. Esc Anna Nery. 2021;26:e20210203. https://doi.org/10.1590/2177-9465-EAN-2021-0203.
17. Aroca-Martínez G, Musso CG, Avendaño-Echavez L, et al. Diferenças entre pacientes com lesão renal aguda induzida por COVID-19 e pacientes com doença renal crônica. Braz J Nephrol. 2022;44(2):155-63. https://doi.org/10.1590/2175-8239-JBN-2021-0161.
18. Santos LG, Baggio JAO, Leal TC, et al. Prevalence of Systemic Arterial Hypertension and Diabetes Mellitus in Individuals with COVID-19: A Retrospective Study of Deaths in Pernambuco, Brazil. Arq Bras Cardiol. 2021;117(2):416-22. PMID: 34495244; https://doi.org/10.36660/abc.20200885.
19. Sottocornola SF, Silva RR, Barbosa SJ, et al. Renal replacement therapy in patients affected by Covid-19 in an Intensive Care Unit in the countryside of Rondônia. Res Soc Dev. 2021;10(17):e188101723921. https://doi.org/10.33448/rsd-v10i17.23921.
20. Wu YC, Chen CS, Chan YJ. The outbreak of COVID-19: An overview. J Chin Med Assoc. 2020;83(3):217-20. PMID: 32134861; https://doi.org/10.1097/jcma.0000000000000270.

Authors' contributions: Watanabe YJA: conceptualization (equal), data curation (equal), formal analysis (equal), funding acquisition (equal), investigation (equal), methodology (equal), project administration (equal), resources (equal), software (equal), supervision (equal), validation (equal), visualization (equal), writing – original draft (equal), writing – review and editing (equal); Carvalho LMR: conceptualization (equal), data curation (equal), formal analysis (equal), funding acquisition (equal), investigation (equal), methodology (equal), project administration (equal), resources (equal), software (equal), supervision (equal), validation (equal), visualization (equal), writing – original draft (equal), writing – review and editing (equal); Guedes JVM: conceptualization (equal), data curation (equal), formal analysis (equal), funding acquisition (equal), investigation (equal), methodology (equal), project administration (equal), resources (equal), software (equal), supervision (equal), validation (equal), visualization (equal), writing – original draft (equal), writing – review and editing (equal); Baldoni AO: conceptualization (equal), data curation (equal), formal analysis (equal), funding acquisition (equal), investigation (equal), methodology (equal), project administration (equal), resources (equal), software (equal), supervision (equal), validation (equal), visualization (equal), writing – original draft (equal), writing – review and editing (equal); Belo VS: conceptualization (equal), data curation (equal), formal analysis (equal), funding acquisition (equal), investigation (equal), methodology (equal), project administration (equal), resources (equal), software (equal), supervision (equal), validation (equal), visualization (equal), writing – original draft (equal), writing – review and editing (equal); Otoni A: conceptualization (equal), data curation (equal), formal analysis (equal), funding acquisition (equal), investigation (equal), methodology (equal), project administration (equal), resources (equal), software (equal), supervision (equal), validation (equal), visualization (equal), writing – original draft (equal), writing – review and editing (equal). All authors have reviewed and approved the final version of the manuscript submitted for publication.

Acknowledgements: We thank the Universidade Federal de São João Del Rei, the Conselho Nacional de Desenvolvimento Científico e Tecnológico (CNPq), and the Coordenação de Aperfeiçoamento de Pessoal de Nível Superior (CAPES), which made this research possible.

Sources of funding: None
Conflicts of interest: None

Date of first submission: May 16, 2023
Last received: March 15, 2024
Accepted: May 13, 2024

Address for correspondence:
Alba Otoni
Universidade Federal de São João del-Rei (UFSJ)
R. Sebastião Gonçalves Coelho, 400
Chanadour, Divinópolis – MG
CEP: 35501-296
Tel.: +55 37 99128-0746
E-mail: albaotoni@ufsj.edu.br

Editor responsible for the evaluation process:
Paulo Manuel Pêgo-Fernandes, MD, PhD

Perceptions of childhood immunization in São Paulo: quantitative-qualitative cross-sectional study

Lucas de Brito Costa[I], Carolina Nunes França[II], Luiz Henrique da Silva Nali[III], Patrícia Colombo-Souza[IV], Neil Ferreira Novo[V], Yára Juliano[VI]

Post-Graduation Program in Health Sciences, Universidade de Santo Amaro (UNISA), SP, BR

[I]MD. Physician, Master's student, Postgraduate Program in Health Sciences, Universidade de Santo Amaro (UNISA), São Paulo, Brazil
https://orcid.org/0000-0003-1360-5482

[II]PhD. Physiotherapist, Postgraduate Program Coordinator, Postgraduate Program in Health Sciences, Universidade de Santo Amaro (UNISA), São Paulo, Brazil
https://orcid.org/0000-0002-4167-4293

[III]PhD. Biologist, Professor, Postgraduate Program in Health Sciences Universidade de Santo Amaro (UNISA), São Paulo, Brazil
https://orcid.org/0000-0002-8365-9796

[IV]PhD. Dietitian, Professor, Postgraduate Program in Health Sciences Universidade de Santo Amaro (UNISA), São Paulo, Brazil
https://orcid.org/0000-0003-0247-4245

[V]PhD. Professor, Postgraduate Program in Health Sciences, Universidade de Santo Amaro (UNISA), São Paulo, Brazil
https://orcid.org/0000-0002-4033-721X

[VI]PhD. Professor, Post-Graduation Program in Health Sciences, Santo Amaro University, São Paulo, Brazil.
https://orcid.org/0000-0003-2894-0208

KEYWORDS (MeSH terms):
Vaccination.
Immunization.
Vaccine refusal.
Child.
COVID-19.

AUTHORS' KEYWORDS:
Vaccine-preventable diseases.
Vaccination coverage.
Anti-vaccine movements.

ABSTRACT

BACKGROUND: Vaccination hesitation spans from historical diseases such as smallpox to the current challenges with the coronavirus disease (COVID-19). In Brazil, vaccination faces obstacles related to trust and convenience. Despite the National Immunization Program, fear of adverse effects as well as misinformation challenge confidence in vaccines, and anti-vaccine movements have gained momentum.

OBJECTIVES: This study investigated childhood vaccine refusal, including COVID-19 vaccines, by comparing the reasons for and sociodemographic differences between vaccinated individuals and those who hesitated or refused immunization.

DESIGN AND SETTING: A cross-sectional study was conducted in São Paulo, Brazil, using questionnaires administered during pediatric consultations between January and April 2023.

METHODS: This study investigated vaccine hesitancy and the attitudes of parents and caregivers of children (0–12 years) towards vaccines. The questionnaire was administered during routine pediatric consultations at three different locations, each with 50 participants for a total of 150 participants, to avoid selection bias.

RESULTS: Marked differences were evident among caregivers in terms of sex, race, income, education, and religion, which influenced their attitudes toward vaccination. There was an increase in the refusal of seasonal vaccinations and a significant distrust of the efficacy of the COVID-19 vaccine (52%), with concerns about its side effects. Although most patients did not stop vaccination, significant delays occurred, especially in the clinical setting (58%).

CONCLUSIONS: This study emphasizes the importance of childhood health decisions, indicating the need to build trust in vaccines, tailor health policies, and investigate the causes of distrust to promote childhood immunizations.

INTRODUCTION

Issues of vaccine hesitancy are not exclusive to the 21st century. They have unfolded throughout history, from the smallpox vaccine to the measles, mumps, and rubella (MMR) vaccine in the 20th century, the human papillomavirus vaccine, and currently, the coronavirus disease (COVID-19) vaccine. Vaccination is the most effective way to prevent infectious diseases and has been responsible for completely eradicating smallpox and significantly reducing cases of measles, polio, and tetanus in many parts of the world.[1,2] Despite overwhelming evidence of vaccine effectiveness and safety, an increasing number of people hesitate to receive recommended vaccines or refuse them altogether.[2] It is a serious issue because it is linked to the resurgence of vaccine-preventable diseases, such as measles, in the United States and Europe. In Brazil, vaccination coverage for MMR has consistently decreased since 2013, raising concerns about increasing rates of unvaccinated individuals nationwide. This increases the risk of new disease outbreaks, which can be prevented using vaccines. In this context, understanding the vaccine confidence in Brazil is more crucial than ever.[3]

Figueiredo *et al.*[4] conducted a qualitative study involving interviews with families having children under 2 years old. Throughout these interviews, several barriers and influencing factors regarding vaccination were identified, addressing issues related to convenience, trust, and concerns about administering multiple vaccines simultaneously. Barbieri *et al.*[5] also conducted a study with middle-class parents in São Paulo and concluded that parents vaccinating their

children felt part of Brazil's "immunization culture," while those refusing vaccination felt that mandatory vaccination was incompatible with their lifestyle.

The Brazilian National Immunization Program (PNI) of the Pan American Health Organization (PAHO), a branch of the World Health Organization (WHO), has been cited as a global reference. Established by Law 6.259/75, this program provides 50 immunobiological products (serums, vaccines, and immunoglobulins) free of charge to all inhabitants of the Brazilian territory, including 33 vaccines, 19 of which are part of the National Vaccination Schedule to prevent over 20 infectious diseases across various age groups. Additionally, 10 special vaccines are available at Special Immunobiological Reference Centers (CRIEs) for groups with specific clinical conditions, such as people living with HIV.[6,7]

In this scenario, the fear of adverse events and the circulation of false information about immunobiological products overshadow knowledge about the importance and benefits of vaccines. Although not highly active in Brazil, antivaccine movements are becoming more frequent and persuasive, disseminating scientifically unfounded information on vaccine risks.

OBJECTIVE

This study aimed to analyze the frequency of vaccine refusal among parents and guardians regarding the available immunizations for the pediatric population, including those intended for COVID-19, to be administered to their children and/or wards in São Paulo, Brazil.

METHODS

This was a quantitative-qualitative cross-sectional study conducted in the city of São Paulo between January and April 2023, focusing on parents and caregivers of patients aged 0–12 years who attended routine pediatric consultations. Using the validated "Parental Attitudes on Childhood Vaccines" questionnaire, the study investigated vaccine hesitancy and caregivers' willingness to vaccinate their children, addressing vaccination behavior, safety, and confidence in vaccines. Sociodemographic information was collected and the research was conducted in three distinct locations within the same region of São Paulo city (Universidade Santo Amaro, UNISA; Basic Health Unit, BHU; and Medical Office), each with 50 participants, totaling 150, to mitigate selection bias.

Ethical Considerations

The study design and methodology were approved by the Research Ethics Committee of Santo Amaro University (5,770,898) on November 22, 2022. The study was conducted in accordance with the principles of the Declaration of Helsinki, and informed consent was obtained from all participants before the study commenced.

Statistical analysis

Categorical variables were analyzed using the chi-squared test. Statistical significance was set at $P < 0.05$.

RESULTS

In the study, a significant predominance of the female sex (82.7%) among the caregivers was observed across all settings, compared to male caregivers (chi-square test $X2 = 10.14$, $P = 0.0063$). Concerning race/ethnicity, the BHU and UNISA settings exhibited similarities, with a prevalence of Black and mixed-race individuals, whereas the Medical Office had a majority of White individuals (46%), which was a statistically significant difference ($P < 0.0001$, $X2 = 40.43$). Regarding family income, a higher percentage of families fell within the ranges of up to one minimum wage and two to four minimum wages compared to the group earning five to ten minimum wages, with statistically significant differences ($P < 0.0001$, $X2 = 75.40$). In terms of education, the Medical Office showed more caregivers with incomplete college education (36%), while BHU and UNISA had the majority with completed high school education (36% and 38%, respectively), with statistically significant differences ($P < 0.0001$, $X2 = 115.0$). Concerning religion, there was a predominance of Christian denominations across all settings, with Protestants (82%), followed by Catholics (60%), showing no statistically significant difference ($P = 0.3910$, $X2 = 12.70$). Additionally, the relationship between parents/guardians and partners was also significant ($P = 0.0147$, $X2 = 9.44$) (**Table 1**).

The results presented in **Table 2** show an increasing refusal of seasonal vaccinations for the flu, measles, and yellow fever. Refusal of the human rotavirus vaccine is influenced by age restrictions. Some children did not receive more than one vaccine, thereby increasing the absolute refusal rates. Although not statistically significant, there was a trend towards higher refusal rates in clinical settings than in the other studied scenarios ($X2 = 9.22$, $P = 0.3240$).

Regarding the reasons for refusing childhood vaccination, as shown in **Table 3**, the majority of respondents at BHU (60%) and UNISA (82%) denied having any concerns. However, in the medical office, the primary reason for refusal was distrust of the vaccine efficacy, which reached 52%. This data was significant, with $X2 = 47.33$ and $P < 0.0001$. Regarding immunization delays, 58% of caregivers at the medical office admitted to delays, while the overall average was 31%. The most significant delays occurred in the medical office (58%), followed by BHU and UNISA (26% and 10%, respectively), with $X2 = 27.76$ and $P < 0.0001$ in the chi-square test for this combined analysis.

In this study, amid the pandemic context, specific apprehensions regarding the coronavirus vaccine were also assessed, as shown in **Table 4**. At the private healthcare office, 74% of guardians of children aged 0–12 years expressed some level of concern

Table 1. Characterization of research participants according to demographic variables and study setting

	BHU		UNISA		Medical office		Total	
	n	%	n	%	n	%	n	%
Sex								
Female	47	94	42	84	35	70	124	82,7
Male	3	6	8	16	15	30	26	17,3
Total	50	100	50	100	50	100	150	100
Race								
White	8	16	9	18	23	46	40	26,7
Black	19	38	21	42	7	14	47	31,3
Mixed race	20	40	15	30	4	8	39	26
Yellow/indigenous	3	6	5	10	16	32	24	16
Total	50	100	50	100	50	100	150	100
Family income								
Up to 1 minimum wage	33	66	32	64	0	0	65	43,3
2 to 4 minimum wages	17	34	15	30	25	50	57	38
5 to 10 minimum wages	0	0	3	6	25	50	28	18,7
Total	50	100	50	100	50	100	150	100
Education								
Incomplete elementary school	6	12	1	2	0	0	7	4,6
Complete elementary school	16	32	11	22	0	0	27	18
Incomplete high school	9	18	18	36	0	0	27	18
Complete high school	18	36	19	38	11	22	48	32
Incomplete college	1	2	1	2	18	36	20	13,4
Complete college	0	0	0	0	14	28	14	9,4
Incomplete postgraduate	0	0	0	0	7	14	7	4,6
Total	50	100	50	100	50	100	150	100
Religion								
Catholic	18		21		21		60	
Protestant	31		27		24		82	
Buddhist	0		1		0		1	
Jewish	0		0		1		1	
Umbanda	1		0		0		1	
Spiritist	0		0		1		1	
Atheist	0		1		3		4	
Total	50		50		50		150	
Marital status								
With partner	24	48	29	58	38	76	91	60,7
Without partner	26	52	21	42	12	24	59	39,3
Total	50	100	50	100	50	100	150	100

BHU = basic health unit; UNISA = Universidade Santo Amaro.

about this particular vaccine, which can be explained by fear of side effects and disbelief in vaccine efficacy. The chi-square test for this analysis resulted in X2 = 32.31 and P < 0.0001. Concerning the COVID-19 vaccine, a high rate of complete administration of the available doses was observed at the BHU and an outpatient clinic linked to an educational institution. However, more than half of the patients in private medical offices (56%) completed the vaccination schedule. The chi-square test for this aspect resulted in X2 = 25.19 and P < 0.0001.

At the end of the questionnaire, parents and/or caregivers were asked whether they had missed vaccinating children under their care at any point. The results, shown in **Table 5**, indicate that a significant majority of those responsible for children at the BHU (84%) and UNISA (96%) stated that they had not missed vaccinating their children. In these results, it is important to note a distinction regarding vaccination delays. While delays still allowed for the possibility of updating overdue vaccines, this result considered only vaccines that were not offered or for which there was no longer an interest in receiving them. The statistical analysis for this question resulted in X2 = 27.89 and P < 0.0001.

DISCUSSION

The present study highlights the predominance of female caregivers across all settings, underscoring socioeconomic

Table 2. Acceptance or refusal of vaccination by available immunization in the National Immunization Program

	BHU		UNISA		Medical Office		TOTAL	
	n	%	n	%	n	%	n	%
VACCINES								
Bcg	0	0	0	0	0	0	0	0
Hepatitis	0	0	0	0	0	0	0	0
Pneumo 10	0	0	0	0	0	0	0	0
Pentavalent	0	0	0	0	0	0	0	0
Polio	0	0	0	0	0	0	0	0
Rotavírus	0	0	1	25	1	2,1	2	2,9
Meningococcal c	0	0	0	0	0	0	0	0
Measles, mumps, rubella (MMR)	0	0	0	0	0	0	0	0
Influenza	8	42,1	2	50	18	36,7	28	41,7
Yellow fever	1	5,2	0	0	4	8,2	5	7,4
Measles	0	0	0	0	0	0	0	0
Sarampo	2	10,6	0	0	4	8,2	6	8,9
Human papillomavirus (HPV)	0	0	0	0	0	0	0	0
COVID-19	8	42,1	1	25	22	44,8	31	46,2
Total	19	100	4	100	49	100	67	100

BHU = basic health unit; UNISA = Universidade Santo Amaro; COVID-19 = coronavirus disease.

Table 3. Reliability and vaccine refusal by available immunization in the National Immunization Program

	BHU		UNISA		Medical Office		TOTAL	
	n	%	n	%	n	%	n	%
Trust								
No fear	30	60	41	82	12	24	83	55,3
Fearful	12	24	9	18	12	24	33	22
Does not believe	8	16	0	0	26	52	34	22,7
Total	50	100	50	100	50	100	150	100
Vaccination delay								
Yes	13	26	5	10	29	58	47	31,3
No	37	74	45	90	21	42	103	68,7
Total	50	100	50	100	50	100	150	100

BHU = basic health unit; UNISA = Universidade Santo Amaro.

Table 4. Apprehension towards coronavirus disease vaccine and vaccination of children with available doses

	BHU		UNISA		Medical office		TOTAL	
	n	%	n	%	n	%	n	%
Apprehension for COVID-19 shots								
Yes	20	40	9	18	37	74	66	44
No	30	60	41	82	13	26	84	56
Total	50	100	50	100	50	100	150	100
Has recieved all COVID-19 doses								
Yes	42	84	49	98	28	56	119	79,3
No	8	16	1	2	22	44	31	20,7
Total	50	100	50	100	50	100	150	100

BHU = basic health unit; UNISA = Universidade Santo Amaro; COVID-19 = coronavirus disease.

Table 5. Overall outcome of vaccine refusal

	BHU		UNISA		Medical Office		TOTAL	
	n	%	n	%	n	%	n	%
Have missed/delayed any vaccine shot?								
Yes	8	16	2	4	22	44	31	20,7
No	42	84	48	96	28	56	118	78,7
Total	50	100	50	100	50	100	150	100

BHU = basic health unit; UNISA = Universidade Santo Amaro.

and educational differences. There has been a growing refusal of seasonal vaccinations, the influence of age restrictions on refusal of the human rotavirus vaccine, and a tendency toward higher refusal rates in clinical settings. The diverse reasons for refusal included distrust of the vaccine efficacy, notably in the medical office. Immunization delays were more frequent in medical offices, and reasons for hesitation regarding the coronavirus vaccine were emphasized. Various rates of complete administration of the COVID-19 vaccine were observed, while the majority of caregivers in healthcare units reported not having missed vaccinating their children, considering that vaccines were not offered, or lacking interest.

The predominance of women as caregivers across various environments suggests significant cultural and social influences, highlighting the need for a more detailed investigation of their impact on decisions concerning children's health. This finding aligns with a study conducted in Fortaleza, Ceará, which identified a predominance of females in caregiving roles, mainly mothers as the primary or sole caregivers of their children.[8] The racial disparity observed in different settings, with a higher representation of Black and mixed-race individuals in BHU and UNISA, and the prevalence of White individuals in private healthcare, underscore the influence of socioeconomic conditions on accessibility to healthcare services. The correlation between caregivers' family income and education in specific settings suggests the need for more comprehensive healthcare policies that cater to diverse socioeconomic and educational realities. Although the prevalence of Christianity across all settings did not demonstrate a statistically significant difference among religious groups, cultural aspects and beliefs may influence attitudes toward health and vaccination. It is crucial to explore how these factors impact adherence to immunization practices and preventive care; in some cases, non-vaccination is more closely related to healthcare service characteristics than to specific populations.[4]

The analysis revealed a progressive increase in refusal of seasonal vaccinations against influenza, measles, and yellow fever. This was particularly evident in the refusal of the human rotavirus vaccine, which was largely influenced by age-related restrictions. Furthermore, in some cases, children did not receive more than one vaccine, contributing to an absolute increase in refusal rates. In the study by Figueiredo et al.[4], one of the reasons for refusal was a lack of knowledge about the currently available vaccines. Interestingly, although not statistically significant, there was a tendency for higher refusal rates in clinical settings than in other analyzed contexts. This trend underscores the need to better understand the factors that influence vaccine acceptance or refusal, particularly in clinical settings, and to implement strategies that promote greater adherence to vaccination.

When analyzing the reasons for childhood vaccination refusal, different perspectives emerged across the healthcare settings under investigation. In the BHUs and at UNISA, the majority of respondents denied refusal, with rates of 60% and 82%, respectively. However, in medical offices, distrust of vaccine efficacy was identified as the primary cause, affecting 52% of the refusal decisions. The issue of mistrust aligns with the findings of another study conducted in São Paulo, which highlighted that major reasons for hesitancy were linked to trust, convenience, complacency, and other unknown reasons. The majority of doubts stemmed from trust issues.[3] In a 2017 technical report from the European Centre for Disease Prevention and Control, results showed vaccine hesitancy due to lack of trust, complacency, and vaccine convenience, labeled as the 3C model.[9]

Additionally, when exploring the issue of immunization delays, significant disparities were observed among different settings. In the medical office, 58% of caregivers admitted to delays, contrasting with the lower averages of 26% and 10% in the UBS and UNISA, respectively. This discrepancy underscores the need for targeted strategies to mitigate immunization delays, especially in clinical contexts where the prevalence of these delays has been shown to be more prominent.[5] In countries such as Italy, where childhood vaccination rates are decreasing, the strategy adopted involves stricter laws affecting school admission.[10]

Vaccine hesitancy is not a new phenomenon, yet the specific concern regarding the coronavirus vaccine amid the pandemic might have escalated as vaccine acceptance is higher when there is confidence in its effectiveness and safety,[9] something not witnessed in Brazil. Vaccine hesitancy during the COVID-19 pandemic may not be directly comparable to that in previous contexts. No virus in recent memory has so broadly disrupted social life and society as COVID-19.[11] However, in the clinic, a significant 74% of caregivers expressed concern about this vaccine, possibly linked to fear of side effects and distrust in vaccine effectiveness, cited as primary reasons for vaccination refusal or hesitation within this group. There was a disparity in the complete administration rate of COVID-19 vaccine doses among healthcare settings. While UBS and UNISA showed high completion rates, only about 56% of the patients at the clinic completed the process. In particular, compliance with containment measures might depend on the degree of trust in authorities and other healthcare services,[3,12] and fear of consequences, such as reporting to child protective services.[5]

Upon completing the data collection through questionnaires, parents and/or caregivers were asked about the potential cessation of vaccination in children under their care. The results revealed that a significant majority of guardians in the settings of the BHU and UNISA (84% and 96%, respectively) stated that they had not ceased vaccinating their children. It is relevant to note that this analysis distinguished itself from vaccination delays, focusing solely on situations where vaccines were not offered or when there was no interest in receiving them. This differentiation is crucial for understanding the dynamics between the explicit refusal of certain vaccines and delays, providing valuable insights for directing more effective strategies in the context of childhood vaccination.

It is of utmost importance to emphasize that socioeconomic status is a major issue that may impact hesitancy. Previous studies have described important inequalities that may imply access, decision, or delay in receiving the vaccination[13,14]. Since the Brazilian National Vaccination Program provides free vaccination to children on its schedule, lack of access does not seem to be a major problem but may be associated with misinformation that might be stimulated by the influence of social media[15], which may directly impact the perceived reliability of the vaccines. Regardless of the findings described on vaccines, fear of side effects, distrust of political involvement, and underestimation of the severity of infectious diseases, such as the COVID-19 pandemic are still frequent and present within the population[16,17]. Therefore, the implementation of strategic public health policies combined with well-planned and comprehensive vaccination campaigns is mandatory to reduce vaccination hesitancy and achieve greater vaccination coverage against COVID-19, and this should be applied to all other vaccines.

CONCLUSION

This study underscores the relevance of childhood healthcare decisions and their socioeconomic impact. This revealed vaccine hesitancy, particularly in clinical settings, emphasizing the importance of approaches to foster greater trust and information. These findings highlight the need for more inclusive healthcare policies tailored to diverse socioeconomic realities. An in-depth investigation into the roots of this hesitancy, considering cultural and demographic nuances, is necessary to achieve a comprehensive understanding of attitudes toward childhood vaccination. Furthermore, exploring specific strategies to enhance vaccine acceptance and adherence in various clinical contexts may be pivotal for advancing public health and childhood immunization.

REFERENCES

1. World Health Organization. Ten Threats to Global Health in 2019. Geneva: WHO; 2019. Available from: https://www.who.int./. Accessed in 2024 (Jun. 14).
2. Bianco A, Mascaro V, Zucco R, Pavia M. Parent perspectives on childhood vaccination: How to deal with vaccine hesitancy and refusal? Vaccine. 2019;37(7):984-90. PMID: 30655175. https://doi.org/10.1016/j.vaccine.2018.12.062.
3. Brown AL, Sperandio M, Turssi CP, et al. Vaccine confidence and hesitancy in Brazil. Cad Saude Publica. 2018;34(9):e00011618. PMID: 30281705. https://doi.org/10.1590/0102-311x00011618.

4. Figueiredo GL, Pina JC, Tonete VL, Lima RA, Mello DF. Experiences of families in the immunization of Brazilian children under two years old. Rev Lat Am Enferm. 2011;19(3):598-605. https://doi.org/10.1590/s0104-11692011000300020.
5. Barbieri CL, Couto MT, Aith FM. Culture versus the law in the decision not to vaccinate children: meanings assigned by middle-class couples in São Paulo, Brazil. Cad Saude Publica. 2017;33(2):e00173315. PMID: 28300971. https://doi.org/10.15900102-311x001733/15.
6. Monteiro PV, Miranda KC, Pereira ML, editors. Immunization manual and vaccination room: vaccination in the context of the National Immunization Program. Fortaleza: IMAC Editora; 2021. https://doi.org/10.22491/manual-imunizacoes.
7. Secretariat of Primary Health Care. PNI: understand how one of the largest vaccination programs in the world works. Brasília-DF, May 8, 2022. Available from: https://aps.saude.gov.br/noticia/18379. Accessed in 2024 (Jan. 17).
8. Menezes MS, Maia IB. The family's involvement in the care process of hospitalized children. Serv Soc Saude. 2020;19:e020005. https://doi.org/10.20396/sss.v19i0.8661082.
9. Ryan J, Malinga T. Interventions for vaccine hesitancy. Curr Opin Immunol. 2021;71:89-91. PMID: 34271335. https://doi.org/10.1016/j.coi.2021.05.003.
10. Bianco A, Mascaro V, Zucco R, Pavia M. Parent perspectives on childhood vaccination: How to deal with vaccine hesitancy and refusal? Vaccine. 2019;37(7):984-990. PMID: 30655175. https://doi.org/10.1016/j.vaccine.2018.12.062.
11. Lalot F, Abrams D, Heering MS, Babaian J, Ozkececi H, Peitz L, Davies Hayon K, Broadwood J. Distrustful Complacency and the COVID-19 Vaccine: How Concern and Political Trust Interact to Affect Vaccine Hesitancy. Polit Psychol. 2022:10.1111/pops.12871. PMID: 36718283; https://doi.org/10.1111/pops.12871.
12. Bargain O, Aminjonov U. Trust and compliance to public health policies in times of COVID-19. J Public Econ. 2020;192:104316. PMID: 33162621. https://doi.org/10.1016/j.jpubeco.2020.104316.
13. Hansen BT, Labberton AS, Kour P, Kraft KB. Coverage of primary and booster vaccination against COVID-19 by socioeconomic level: A nationwide cross-sectional registry study. Hum Vaccin Immunother. 2023;19(1)2188857. PMID: 36941785; https://doi.org/10.1080/21645515.2023.2188857.
14. Yao Y, Wu YS, Weng X, et al. Socio-economic disparities in exposure to and endorsement of COVID-19 vaccine misinformation and the associations with vaccine hesitancy and vaccination. Public Health. 2023;223:217-22. PMID: 37677851; https://doi.org/10.1016/j.puhe.2023.08.005.
15. Fujita DM, Nali LHS, Sartori GP, et al. Fake news and covid-19: a concern due to the low vaccine coverage in Brazil. Saude Soc. 2022;31(1):e210298. https://doi.org/10.1590/S0104-12902022210298.
16. Santos KCO, Junqueira-Marinho MF, Reis AT, et al. Social Representations of Hesitant Brazilians about Vaccination against COVID-19. Int J Environ Res Public Health. 2023;20(13):6204. PMID: 37444052; https://doi.org/10.3390/ijerph20136204.
17. Ojong N, Agbe E. "This is most likely not the correct vaccine": Analyzing COVID-19's viral spread and vaccine anxieties in Ghana, Cameroon, and Malawi. Soc Sci Med. 2023;329:116001. PMID: 37327597; https://doi.org/10.1016/j.socscimed.2023.116001.

Authors' contributions: Costa LB: conceptualization (lead), data curation (lead), investigation (lead), methodology (lead), project administration (lead), writing – original draft (lead); França CN: supervision (equal), validation (equal), writing – review and editing (equal); Nali LHS: validation (equal), visualization (equal); Souza PC: validation (equal), visualization (equal); Novo NF: data curation (equal), formal analysis (equal), methodology (equal); Juliano Y: supervision (equal), validation (equal), writing – review and editing (equal). All authors reviewed and approved the final version submitted for publication

Sources of funding: None
Conflict of interest: None

Date of first submission: April 4, 2024
Last received: March 28, 2024
Accepted: June 5, 2024

Address for correspondence:
Carolina Nunes França
Universidade de Santo Amaro (UNISA)
Rua Isabel Schmidt, 349
Santo Amaro, São Paulo (SP), Brasil
CEP 04743-030
Tel.: +55 11 21418584
E-mail: carolufscar24@gmail.com

Editor responsible for the evaluation process:
Marianne Yumi Nakai, MD, PhD (Associate Editor)
Paulo Manuel Pêgo-Fernandes, MD, PhD (Editor-in-Chief)

Accuracy and precision of non-invasive thermometers compared with the pulmonary artery temperature: a cross-sectional study

Rafael Lima Rodrigues de Carvalho[I], Mariana Avendanha Victoriano[II], Camila Claúdia Campos[III], Paula Frizera Vassallo[IV], Vandack Nobre[V], Flávia Falci Ercole[VI]

Universidade Federal de Minas Gerais, Belo Horizonte, MG, Brazil

[I]RN, PhD. Adjunct Professor, Nursing School, Universidade Federal da Bahia (UFBA), Salvador (BA), Brazil.
https://orcid.org/0000-0003-3576-3748

[II]RN, MSc. Education Manager, Proz Educação, São Paulo (SP), Brazil.
https://orcid.org/0000-0003-3123-9084

[III]RN, PhD. Professor, Faculdade Anhanguera, Belo Horizonte (MG), Brazil.
https://orcid.org/0000-0002-2398-7229

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

[V]MD, PhD. Titular Professor, Medicine School, Universidade Federal de Minas Gerais (UFMG), Belo Horizonte (MG), Brazil.
https://orcid.org/0000-0002-7922-0422

[VI]RN, PhD. Titular Professor, School of Nursing, Universidade Federal de Minas Gerais (UFMG), Belo Horizonte (MG), Brazil.
https://orcid.org/0000-0002-1356-0854

KEYWORDS (MeSH terms):
Thermometers.
Fever.
Temporal Arteries.

AUTHORS' KEYWORDS:
Axillary.
Tympanic.
Oral and Pulmonary Artery.

ABSTRACT

BACKGROUND: Temperature fluctuations are critical indicators of a patient's condition in intensive care units (ICUs). While invasive methods offer a more reliable measurement of core temperature, they carry greater risks of complications, limiting their use in most situations. This underscores the need for research evaluating the reliability of non-invasive temperature monitoring methods.

OBJECTIVES: This study aimed to assess the accuracy and precision of four non-invasive temperature measurement techniques compared to pulmonary artery temperature, considered the gold standard.

DESIGN AND SETTING: We conducted a cross-sectional clinical study with repeated measures in the ICUs at Hospital das Clínicas da Universidade Federal de Minas Gerais and Hospital Felício Rocho, Belo Horizonte, Brazil.

METHODS: All patients admitted with a pulmonary artery catheter were included. We simultaneously recorded temperatures from the pulmonary artery, axillary area, oral cavity, temporal artery, and tympanic membrane. Bland-Altman plots were employed to assess the agreement between the different temperature measurements.

RESULTS: A total of 48 patients participated, with a mean age of 54 years. Females comprised 66.67% of the sample. Compared to pulmonary artery temperature, the accuracy and precision (mean and standard deviation) of the non-invasive methods were: axillary (-0.42°C, 0.59°C), oral (-0.30°C, 0.37°C), tympanic membrane (-0.21°C, 0.44°C), and temporal artery (-0.25°C, 0.61°C). Notably, in patients with abnormal body temperature (non-normothermic), only oral and tympanic membrane methods maintained their accuracy and precision.

CONCLUSIONS: The non-invasive thermometers evaluated in this study demonstrated acceptable accuracy and precision (within the clinically relevant threshold of 0.5°C) compared to pulmonary artery temperature. Among the non-invasive methods, the tympanic membrane measurement proved to be the most reliable, followed by the oral method.

INTRODUCTION

Temperature monitoring is a crucial tool for hospitalized patients, especially those in intensive care units (ICUs).[1] Abnormalities in body temperature (BT) are a common clinical sign, alerting healthcare personnel to potential infectious and other conditions. Fever is the most frequent manifestation,[2] while hypothermia can also indicate poor outcomes.[3] Additionally, BT can be used therapeutically, such as controlled hypothermia after cardiac arrest.[4]

In adults, hyperthermia is defined as a BT of 38.0°C or higher.[2] Fever is typically defined as 38.3°C or above, although this may vary depending on patient characteristics, institutional protocols, and the measurement method use.[2]

Early detection of fever allows for prompt antibiotic therapy in life-threatening infections, particularly for vulnerable or critically ill patients.[2] Fever can also trigger broader diagnostic investigations, not just for infections but also for other possibilities.[2]

Invasive thermometers, like pulmonary artery (PA) and bladder catheters, offer reliable temperature monitoring.[1-2] However, despite their accuracy, invasive methods carry increased complication risks, limiting their routine use.[5]

While the literature lacks a consensus on the reliability of non-invasive methods, these technologies have seen advancements in algorithms improving their accuracy and precision.[1,6-7]

New thermometers and technologies are constantly emerging, but studies evaluating them remain scarce.[2]

Nurses and nurse assistants need to understand the appropriate type of temperature measurement for each clinical setting and patient, along with the associated reliability. This knowledge can lead to better patient assessments, allowing healthcare providers to identify patients with abnormal temperatures and intervene promptly.

OBJECTIVE

This study aimed to evaluate the accuracy and precision of four non-invasive thermometers (axillary [AT], oral [OT], tympanic membrane [TM], and temporal artery [TA]) compared to the gold standard of PA catheter measurements. We also investigated factors that might influence the accuracy of these non-invasive methods.

METHODS

This cross-sectional clinical study with repeated measures was conducted in three ICUs across two general hospitals in the southeast region of Brazil. Both hospitals are referral centers for high-complexity patients and have a total of 914 beds (Hospital 1: 486 beds, Hospital 2: 428 beds). Hospital 1 has a 16-bed mixed ICU unit. Hospital 2 has a 50-bed ICU unit further divided into 20 beds dedicated to cardiac patients and 30 mixed beds (surgical and medical).

This study was approved by the ethics committees of the Universidade Federal de Minas Gerais (71553317.7.0000.5149) and Hospital Felicio Rocho (71553317.7.3001.5125). Written informed consent was obtained from all patients or their next of kin.

Patients

From December 2017 to December 2018, all adult patients (aged 18 years or older) admitted consecutively to the participating ICUs were screened for eligibility. To be included, patients had to have a PA catheter inserted either upon ICU admission or immediately before, Patients were excluded if they had technical difficulties preventing one of the five temperature measurements or if their PA catheter was removed before the first measurement.

Temperature measurements were taken three times at two-hour intervals.

Study procedures

Four non-invasive thermometers were used: AT, OT, TM, and TA. An Omron® clinical thermometer (Tokyo, Japan) was used to measure AT. The probe was placed in direct contact with the patient's axillary skin at a 45º angle, the arm was closed, and the temperature was recorded after the beep. For OT, an Omron® clinical thermometer (Tokyo, Japan) was used. The probe was placed in the sublingual pocket until the beeped. TM temperature was obtained using a Braun Thermoscan® PRO 6000 (Kronberg im Taunus, Germany). The probe tip was placed in the ear canal as instructed by the manufacturer, the button was pressed, and the temperature was recorded. Finally, TA temperature was measured using an Exergen TAT 5000® (Watertown, USA) device. The thermometer was slid across the forehead in a straight line while the button was pressed to record the temperature. All measurements were performed by the lead researcher (RLRC), following the manufacturer's instructions.

Non-invasive temperatures were measured on the same side of the body every two hours, for a total of three measurements per patient. The site was chosen based on the patient's position and the presence of invasive devices (endotracheal tubes, intravenous lines, and monitors).

We collected demographic (sex and age) and clinical data from all participants, including body mass index (BMI), main diagnosis at admission, current use of medications that could interfere with BT (antipyretics, vasodilators, and sedatives), vasopressor or inotrope requirement, use of mechanical ventilation (MV), use of an oxygen catheter, diaphoresis at the time of temperature measurement, bath time, ingestion of liquids or solids, and presence of ear wax.

Statistical analysis

To assess the accuracy and precision of the non-invasive thermometers compared to the PA temperature, we calculated the difference between each device's reading and the PA temperature. The mean of these differences represents the bias between each non-invasive method and the PA temperature, which reflects the accuracy of the non-invasive measurement. The variance of these differences represents the precision of the non-invasive temperatures, expressed as the standard deviation of the differences. Furthermore, Bland-Altman graphs were constructed for each thermometer to visually evaluate their accuracy and precision compared to the PA temperature.

To identify factors influencing the accuracy of each non-invasive method, we built linear regression models. These models included variables with a p-value < 0.20 in the univariate analysis. The four final models, one for each non-invasive temperature method, were calculated using the stepwise backward method. Post-hoc tests were performed to verify the model adjustment. We set a significance level of $P < 0.05$ for all statistical analyses.

RESULTS

Fifty-eight patients were assessed for eligibility, of whom ten were excluded (**Figure 1**). Therefore, 48 participants were included in the final analysis, with 139 temperature measurements (mean of 2.9 measurements per patient).

Of the 48 patients, 15 were admitted to Hospital 1 and 33 to Hospital 2. Most patients were male (66.67%) with a mean age of 54 years (standard deviation ± 12.9). The primary characteristics of the 48 patients included in this study are presented in **Table 1**.

Most temperature measurements were performed while patients were receiving vasopressors: noradrenaline in 70.5% (98/139) and vasopressin in 13.7% (19/139) of measurements. Similarly, in 100 (71.94%) of the 139 temperature measurement episodes, patients were under MV. Finally, in 60 (43.12%) episodes, patients received sedatives, mainly fentanyl (39.57%).

Antipyretics were used four hours prior to temperature measurement in 19 episodes (13.87%), whereas a recent bath (less than one hour before temperature measurement) was recorded in eight (5.8%).

The mean temperature obtained by the PA catheter across all measurements was 36.94°C (standard deviation ± 0.78). Among the non-invasive methods, TM showed the highest accuracy (-0.22°C), followed by TA (-0.25°C). OT had the best precision (0.38°C). Detailed data on temperature measurements and Bland-Altman plots are presented in **Table 2** and **Figure 2**, respectively.

In the subgroup analysis restricted to abnormal temperature recordings (fever or hypothermia; n = 22), TM remained the most accurate (-0.17°C), followed by OT (-0.35°C). AT (0.41°C) and TA (-0.65°C) displayed lower accuracy. OT maintained the best precision (0.33°C), followed by TM (0.50°C). However, AT (0.90°C) and TA (0.99°C) showed greater bias compared to other methods.

We investigated factors potentially influencing the accuracy of each method compared to PA readings. The use of vasopressors, particularly nitroglycerin, negatively affected the accuracy of all four temperature measurement methods tested. Other vasoactive drugs like vasopressin and nitroprusside also impacted the accuracy of specific methods (OT and TA).

Interestingly, MV did not significantly alter the accuracy of OT (MV accuracy -0.300 vs non-MV accuracy -0.304, P = 0.95), and the presence of ear wax did not affect TM temperature accuracy (presence of ear wax accuracy -0.174 vs absence of ear wax accuracy -0.247, P = 0.350). **Table 3** provides a detailed breakdown of the identified factors influencing the accuracy of non-invasive thermometers compared to PA thermometers, as analyzed through multivariate linear regression **Table 3**.

DISCUSSION

This study compared the reliability of four non-invasive BT measurement methods to the gold standard, the PA catheter. Among the non-invasive methods, OT exhibited the greatest stability in

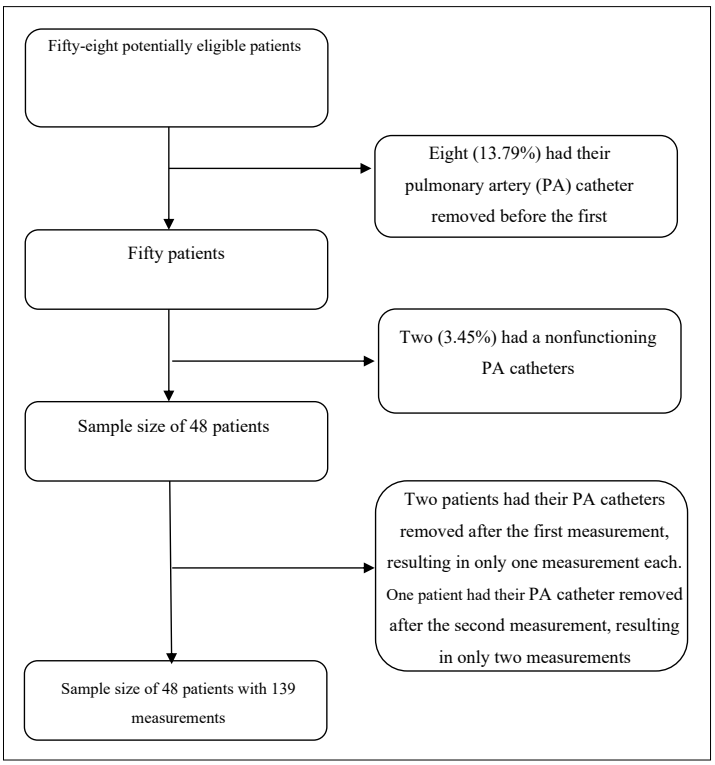


Figure 1. Flowchart of selection criteria and sample.

Table 1. Demographic and admittance data of 48 patients included in the study. Brazil, 2023

		n	%	Mean	Median	SD	IQR
Sex	Male	16	33,34	-	-	-	-
	Female	32	66,67	-	-	-	-
Age		-	-	54,36	56	12,96	50 – 62
Height (meters)		-	-	1.66	1.70	0.07	1.63 – 1.75
Weight (kg)		-	-	76.08	75	15.79	65 – 85
BMI		-	-	26.57	24.97	5.10	22.84 – 29.76
Hospital	1	15	31.25	-	-	-	-
	2	33	68.75	-	-	-	-
Diagnoses	Cirrhosis	31	64.58	-	-	-	-
	Other hepatic diseases	6	12.50	-	-	-	-
	Cardiovascular diseases	5	10.42	-	-	-	-
	Other diseases	6	12.08	-	-	-	-
Total		48	100%				

Table 2. Temperature measurements, accuracy, and precision of 139 non-invasive measurements and pulmonary temperature. Brazil, 2023

Method	Mean	Interval (°C)	Accuracy	Precision	LOA
Pulmonary artery	36.94	35.2 – 39.4	-	-	-
Axillary	36.51	34.3 – 39.9	-0.427	0.592	-1.59 – 0.73
Oral	36.63	34.8 – 38.9	-0.303	0.376	-1.04 – 0.43
Tympanic membrane	36,72	34,8 – 38,7	-0.219	0.449	-1.10 – 0.66
Temporal artery	36,67	35,6 – 38,3	-0.250	0.95	-1.45 – 0.95

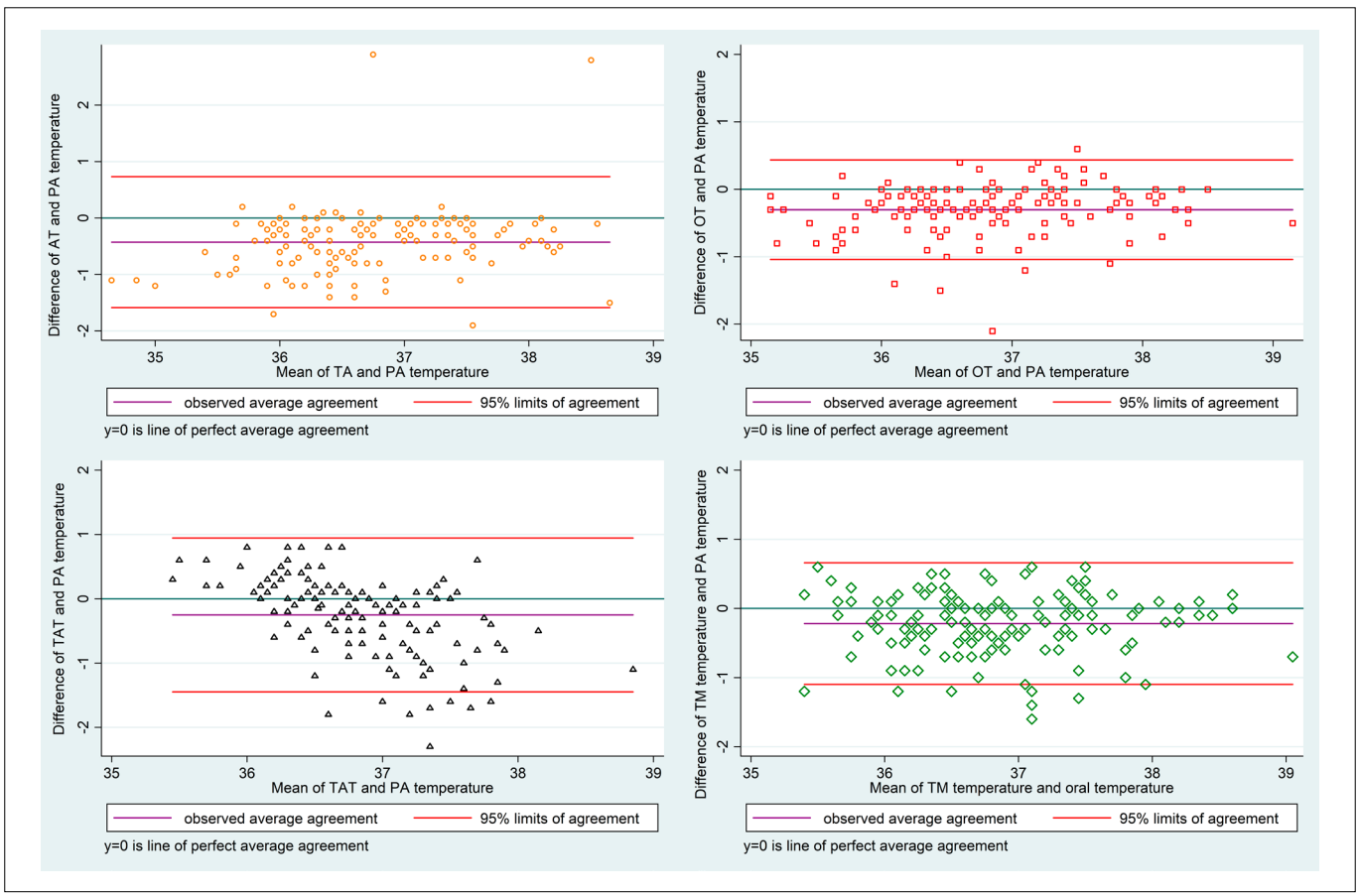


Figure 2. Bland-Altman plots of non-invasive temperature measurements compared to a pulmonary artery catheter.

Table 3. Factors that alter the accuracy of non-invasive measurements compared with pulmonary temperature after 139 measurements. Brazil 2023

Method	Factors that altered	Rate	P value
Axillary	BMI	0.02	0.038
	Bath before measurement	0.24	0.013
	Dose* of nitroglycerin	-0.02	< 0.001
Oral	Dose* of vasopressin	-0.01	0.008
	Dose* of nitroglycerin	-0.01	< 0.001
	Dose* of nitroprusside	-0.01	0.001
Tympanic membrane	Dose* of nitroglycerin	-0.01	< 0.001
Temporal artery	Age	0.01	0.02
	BMI	-0.04	< 0.001
	Dose* of vasopressin	-0.04	< 0.001
	Dose* of nitroglycerin	-0.02	< 0.001
	Dose* of nitroprusside	0.01	0.027

Dose is represented by the mg/hr of the drug infusion.

patients with abnormal body temperature (not normothermic). Notably, vasopressor use emerged as the primary factor influencing the accuracy of non-invasive thermometers, affecting all methods tested.

Many studies have been conducted to assess the accuracy and precision of non-invasive thermometers.[8-11] Most of these studies included a small sample of participants[8,12] and lacked the analysis of factors influencing accuracy.[8,10]

While some prior studies reported divergent results, it is important to consider specific testing conditions. For example, one meta-analysis found poor agreement with TM thermometers in comparison to central thermometers.[1] However, this finding may be specific to hypothermic patients, as other studies focusing on hypothermia also reported poor TM performance.[11,13] In contrast, our study, which included a broader temperature range, identified

TM as the most accurate non-invasive method. This aligns with other research highlighting the potential effectiveness of TM and OT for non-invasive temperature measurement.[6,8-9,14]

AT measurements showed mixed results, with good accuracy but poor precision compared to the PA catheter. This aligns with previous studies reporting similar findings.[1,2,5,9]

TA thermometers exhibited good accuracy (0.250°C) but lacked precision (0.950°C). This finding contributed to the ongoing discussion regarding TA reliability. While some studies advise against using TA in critical settings[1,2,5-6,15] and question its effectiveness in identifying fever,[15] others report its validity as a reliable method.[8,16]

This trend of good accuracy with poor precision for AT and TA contributed to the subgroup analysis of abnormal BTs (fever or hypothermia). While OT and TM remained the most reliable thermometers, AT and TA maintained good accuracy but lost precision.

The primary factor influencing temperature accuracy was the use of vasodilators (nitroglycerin and nitroprusside), affecting all four non-invasive methods. This aligns with previous research.[8-9] This phenomenon likely stems from altered blood flow in the outer skin of patients receiving these medications, leading to discrepancies in temperature readings. Other factors impacting accuracy included BMI and recent baths (within an hour) for AT measurements, and BMI and age for TA measurements.

BMI can influence temperature measurements because a thicker layer of adipose tissue impedes heat conduction from deeper skin layers to the surface.[17] Similarly, hot or cold baths before temperature measurement can alter skin blood flow and heat dissipation, potentially affecting AT readings.[18] Age may play a role, as thinner skin in older adults allows for easier heat transfer from deep tissues to the outer skin.[19]

Our study identified TM and OT as the most reliable non-invasive methods. While OT is the preferred method for critically ill patients in the United States,[2,6] it is less common in Brazil. Notably, the performance of both TM and OT remained relatively unaffected by fever or hypothermia. However, the small sample size of abnormal temperature measurements (22 of 139) limits definitive conclusions about their reliability in these specific conditions.

Our study employed a rigorous data collection methodology, utilizing advanced thermometers available in Brazil and including patients from two independent centers. One consideration for future research is to expand the sample size. While PA catheters are not routinely used in clinical practice, future studies might explore ways to recruit a larger patient population. Additionally, a larger sample size with a broader range of body temperatures, including more patients with fever or hypothermia, would allow for a more robust evaluation of accuracy and precision across diverse patient profiles.

CONCLUSION

Our findings suggest that TM and OT are the most accurate and precise non-invasive methods compared to the gold-standard PA catheter. While AT and TA measurements fell within the clinically acceptable threshold, they exhibited lower precision. These data support the use of TM and OT for non-invasive temperature assessment in clinical practice. However, caution is advised when using non-invasive methods on patients receiving vasodilators or presenting with fever or hypothermia.

REFERENCES

1. Niven DJ, Gaudet JE, Laupland KB, et al. Accuracy of peripheral thermometers for estimating temperature. Ann Intern Med. 2015;163(10):768-77. PMID: 26571241; https://doi.org/10.7326/m15-1150.
2. O'Grady NP, Alexander E, Alhazzani W, et al. Society of Critical Care Medicine and the Infectious Diseases Society of America Guidelines for Evaluating New Fever in Adult Patients in the ICU. Crit Care Med. 2023;51(11):1570-86. PMID: 37902340; https://doi.org/10.1097/ccm.0000000000006022.
3. Paal P, Pasquier M, Darocha T, et al. Accidental Hypothermia: 2021 Update. Int J Environ Res Public Health. 2022;19(1):501. PMID: 35010760; https://doi.org/10.3390/ijerph19010501.
4. Morrison LJ, Thoma B. Translating Targeted Temperature Management Trials into Postarrest Care. N Engl J Med. 2021;384(24):2344-5. PMID: 34133865; https://doi.org/10.1056/nejme2106969.
5. Hymczak H, Gołąb A, Mendrala K, et al. Core temperature measurement-principles of correct measurement, problems, and complications. Int J Environ Res Public Health. 2021;18(20):10606. PMID: 34682351; https://doi.org/10.3390/ijerph182010606.
6. Emergency Nurses Association. Clinical Practice Guideline: Non-invasive Temperature Measurement. Schaumburg: ENA; 2015. Available from: https://media.emscimprovement.center/documents/temperaturemeasurementcpg.pdf. Accessed in 2024 (Jun 17).
7. Yeoh WK, Lee JKW, Lim HY, et al. Re-visiting the tympanic membrane vicinity as core body temperature measurement site. PLoS One. 2017;12(4):e0174120. PMID: 28414722; https://doi.org/10.1371/journal.pone.0174120.
8. Lawson L, Bridges EJ, Ballou I, et al. Accuracy and precision of noninvasive temperature measurement in adult intensive care patients. Am J Crit Care. 2007;16(5):485-96. PMID: 17724246.
9. Rubia-Rubia J, Arias A, Sierra A, Aguirre-Jaime A. Measurement of body temperature in adult patients: Comparative study of accuracy, reliability and validity of different devices. Int J Nurs Stud. 2011;48(7):872-80. PMID: 21145551; https://doi.org/10.1016/j.ijnurstu.2010.11.003.
10. Basak T, Aciksoz S, Tosun B, Akyuz A, Acikel C. Comparison of three different thermometers in evaluating the body temperature of healthy young adult individuals. Int J Nurs Pract. 2013;19(5):471-8. PMID: 24093738; https://doi.org/10.1111/ijn.12097.

11. Shin J, Kim J, Song K, Kwak Y. Core temperature measurement in therapeutic hypothermia according to different phases: Comparison of bladder, rectal, and tympanic versus pulmonary artery methods. Resuscitation. 2013;84(6):810-7. PMID: 23306812; https://doi.org/10.1016/j.resuscitation.2012.12.023.
12. El-Radhi AS, Patel SP. Temperature measurement in children with cancer: an evaluation. Br J Nurs. 2007;16(21):1313-6. PMID: 18073667; https://doi.org/10.12968/bjon.2007.16.21.27716.
13. Krizanac D, Stratil P, Hoerburger D, et al. Femoro-iliacal artery versus pulmonary artery core temperature measurement during therapeutic hypothermia: an observational study. Resuscitation. 2013;84(6):805-9. PMID: 23200998; https://doi.org/10.1016/j.resuscitation.2012.11.022.
14. Ekers T, Adamson N, Wells A, Presneill J. A pilot study of agreement between noninvasive thermometers and the core temperature of postoperative cardiothoracic surgical patients. Aust Cri Care. 2023;36(5):782-6. PMID: 36123238; https://doi.org/10.1016/j.aucc.2022.08.008.
15. Haimovich AD, Taylor RA, Krumholz HM, Venkatesh AK. Performance of temporal artery temperature measurement in ruling out fever: implications for COVID-19 screening. J Gen Inter Med. 2020;35(11):3398-400. PMID: 32930937; https://doi.org/10.1007/s11606-020-06205-2.
16. Furlong D, Carroll DL, Finn C, et al. Comparison of temporal to pulmonary artery temperature in febrile patients. Dimensions of Critical Care Nursing. 2015;34(1):47-52. PMID: 25470268; https://doi.org/10.1097/dcc.0000000000000090.
17. Speakman JR. Obesity and thermoregulation. Handb Clin Neurol. 2018;156:431-43. PMID: 30454605; https://doi.org/10.1016/b978-0-444-63912-7.00026-6.
18. Kudo Y, Sasaki M, Kikuchi Y, et al. Effects of a warm hand bath on the blood flow in the shoulder, skin and deep body temperature, autonomic nervous activity, and subjective comfort in healthy women: an experimental cross-over trial. Jpn J Nurs Sci. 2019;16(1):88–100. PMID: 29920941; https://doi.org/10.1111/jjns.12216.
19. Macek P, Terek-Derszniak M, Biskup M, et al. Assessment of age-induced changes in body fat percentage and BMI aided by bayesian modelling: a cross-sectional cohort study in middle-aged and older adults. Clin Interv Aging. 2020;15:2301-11. PMID: 33335389; https://doi.org/10.2147/cia.s277171.

Authors' contributions: Carvalho RLR: conceptualization (lead), data curation (lead), formal analysis (lead), investigation (lead), methodology (lead), resources (lead), validation (lead), visualization (lead), writing – original draft (lead), writing – review and editing (lead); Victoriano MA: investigation (equal), writing – original draft (equal), writing – review and editing (equal); Campos CC: conceptualization (supporting), investigation (supporting), methodology (supporting), writing – original draft (equal), writing – review and editing (equal); Vassallo PF: supervision (equal), writing – original draft (equal), writing – review and editing (equal); Nobre V: methodology (equal), supervision (equal), writing – original draft (equal), writing – review and editing (equal); Ercole FF: project administration (lead), software (lead), supervision (equal), writing – original draft (equal), writing – review and editing (equal). All authors have reviewed and approved the final version of the manuscript submitted for publication.

Sources of funding: None
Conflict of interest: None

Date of first submission: November 17, 2023
Last received: April 9, 2024
Accepted: June 5, 2024

Address for correspondence:
Rafael Lima Rodrigues de Carvalho
Escola de Enfermagem, Universidade Federal da Bahia (UFBA)
R. Basílio da Gama, 241, Salvador (BA), Brasil
CEP: 40231-300
Tel.: +55 7132837600
E-mail: rafaelsjdr@hotmail.com

Editor responsible for the evaluation process:
Paulo Manuel Pêgo-Fernandes MD, PhD

Alcohol consumption habits and their impact on academic performance: analysis of ethanol patterns among health students. A cross-sectional study

Ana Paula Amaral de Brito[I], Aísa de Santana Lima[II], Átina Carneiro Rocha[III], Beatriz Muniz Gonçalves[IV], Dalila Maria Costa Baraúna de Freitas[V], Gleice de Jesus Oliveira[VI], Jamily Kaliny Azevedo Lima[VII], Katia de Miranda Avena[VIII]

Medicina Zarns, Salvador, BA, Brazil

[I]PhD. Professor, Departamento de Ciências da Vida, Universidade do Estado da Bahia (UNEB), Salvador (BA), Brazil; Professor, Estrutura e Função II, Medicina Zarns, Salvador, Bahia, Brazil.
https://orcid.org/0000-0002-7509-203X

[II]Physiotherapist, Escola de Ciências da Saúde, Universidade Salvador (UNIFACS), Salvador (BA), Brazil.
https://orcid.org/0000-0003-0252-2235

[III]Physiotherapist, Escola de Ciências da Saúde, Universidade Salvador (UNIFACS), Salvador (BA), Brazil.
https://orcid.org/0000-0002-4567-5285

[IV]MD. Physician, Escola de Ciências da Saúde, Universidade Salvador (UNIFACS), Salvador (BA), Brazil.
https://orcid.org/0000-0002-1622-2279

[V]MD. Physician, Escola de Ciências da Saúde, Universidade Salvador (UNIFACS), Salvador (BA), Brazil.
https://orcid.org/0000-0003-3777-6534

[VI]Physiotherapist, Escola de Ciências da Saúde, Universidade Salvador (UNIFACS), Salvador (BA), Brazil.
https://orcid.org/0000-0003-3655-7997

[VII]MD. Physician, Escola de Ciências da Saúde, Universidade Salvador (UNIFACS), Salvador (BA), Brazil.
https://orcid.org/0000-0001-9384-1017

[VIII]PhD. Professor Research Supervisor, Medicina Zarns, Salvador (BA), Brazil.
https://orcid.org/0000-0002-2179-3893

KEYWORDS (MeSH terms):
Alcohol drinking.
Binge drinking.
Alcohol drinking in college.
Alcoholism.
Students, health occupations.

AUTHORS KEYWORDS:
Drinking Behavior.
Epidemiology.
Global health.
Risk Assessment.
Risk Factors.
Student Drinking.

ABSTRACT

BACKGROUND: Studies have indicated a substantial increase in alcohol consumption among university students. Specifically, abusive consumption among health students can adversely affect their academic training and future professional practice.

OBJECTIVE: This study aimed to analyze alcohol consumption habits among healthcare students and investigate the associations between alcohol consumption patterns and sociodemographic and academic variables.

DESIGN AND SETTING: We performed this cross-sectional study at a private university located in the city of Salvador, Bahia.

METHODS: We conducted this study with 770 students using a printed, self-administered, anonymous questionnaire containing sociodemographic and academic performance data, as well as the Alcohol Use Disorders Identification Test (AUDIT) and Rutgers Alcohol Problems Inventory (RAPI).

RESULTS: We observed that the prevalence of alcohol consumption (65.1%) and binge drinking (57.5%) among Brazilian healthcare students was high, with more frequent consumption among men (73.1%), in medicine (83.0%) and veterinary medicine (79.1%) programs and in semesters beyond the fourth (71.7%). We found associations between drinking habits and sex ($P = 0.016$), religion ($P < 0.000$), course ($P < 0.000$) and semester ($P = 0.047$). Binge drinking was associated with attending academic activities without getting any sleep ($P < 0.000$), missing classes due to hangovers ($P < 0.000$), encountering issues with the institution's administration ($P = 0.028$), and failing to complete activities due to alcohol consumption ($P < 0.000$).

CONCLUSION: The prevalence of alcohol consumption and binge drinking among Brazilian healthcare students was high and associated with sex, religion, course, academic semester, risky behaviors, and negative academic impacts.

INTRODUCTION

Alcohol is the most widely used psychoactive drug globally despite economic, social, and cultural differences among countries worldwide.[1] Furthermore, it is the substance of choice for consumption among children and adolescents.[2] It is estimated that three million deaths occur annually worldwide as a result of the harmful use of alcohol, which account for 5.3% of global mortality.[1,2]

In Brazil, alcohol is the most consumed substance across all age groups, and its consumption is increasing among young people.[3,4] Estimates indicate that Brazilians' first experience with alcohol begins at the age of 12.[1-4] According to the Brazilian Center for Information on Psychotropic Drugs, approximately 20.5% of young people aged 18–24 years face alcohol dependency issues.[5] These statistics classify this age group as the second most affected, trailing only behind the 25–34-year-old age group, where the dependency rate reaches 23.3%.[5]

Specifically, alcohol consumption in young university students has significantly increased.[6] It is important to note that university students experience a critical and vulnerable phase in their lives, which may facilitate initial contact and persistence in the consumption of alcoholic beverages. Factors such as leaving the parents' homes to live alone or with friends and facing new social interactions and experiences can contribute to this scenario.[6]

University life brings about changes in lifestyle habits that may be associated with increased stress levels, more frequent socialization at parties, and exposure to alcoholic beverages.[6,7]

Furthermore, the combination of these social and emotional factors can increase young university students' susceptibility to occasional abusive alcohol consumption.

It is essential to emphasize that the abusive consumption of alcohol among students in the healthcare field can adversely affect not only their academic education but also their future professional practice, having an impact on both their own health and diagnostic and therapeutic skills.[6] Considering the inherent vulnerability of university students, identifying their alcohol consumption patterns is important to support the development of preventive interventions that align with harm reduction policies.[7]

OBJECTIVE

This study aimed to analyze alcohol consumption habits among healthcare students by investigating the associations between alcohol consumption patterns and sociodemographic and academic variables.

METHODS

We conducted a cross-sectional study with healthcare undergraduate students from a private university located in the city of Salvador, Bahia, from October 2015 to May 2016.

We included students from the Biomedical, Nursing, Pharmacy, Medicine, Veterinary Medicine, Nutrition, Psychology, and Social Work programs starting from the second semester onward. The non-inclusion criterion was being in the first semester of the program owing to the absence of a weighted average, which is a variable of interest in this study. We only included students over 18 years of age.

Sample selection was convenience-based and conducted through voluntary participation, requiring the signing of an informed consent form. We approached potential participants in person on university premises during class breaks and in the morning, afternoon, and evening shifts.

We utilized a printed, self-administered, anonymous questionnaire consisting of three parts. The first part assessed sociodemographic data (sex, age, marital status, and religion) and academic performance (semester-averaged weighted grade, frequency of attending or missing classes after alcohol intake, decrease in academic performance, and noncompletion of academic activities after alcohol intake).

In the second part, we administered the Test for the Identification of Alcohol Problems (AUDIT).[8,9] Developed by the World Health Organization, the test comprises 10 items aimed at screening alcohol use in the past 12 months, allowing the identification of risky use, harmful use, and alcohol dependence. The AUDIT consists of three questions measuring the quantity and frequency of regular or occasional alcohol use, another three investigating symptoms of dependence, and four related to harmful alcohol use. A score is generated for each of these questions, and risk levels are classified based on this score. Scores range from 0 to 40 points, with scores above 8 indicating the need for a more specific diagnosis.[8] The sum of the scores defines risk levels as follows: low-risk or abstainers (0–7 points), risky use (8–15 points), harmful use or high-risk use (16–19 points), and probable dependence (20–40 points).

The third part of the questionnaire included an inventory of problems and negative consequences related to alcohol and dependence (the Rutgers Alcohol Problems Inventory [RAPI]).[10] The RAPI indicates negative behaviors associated with alcohol use, revealing the impact on social functioning and health in the past 12 months and the last month. The instrument consists of 23 items, which are answered as 0 (*never*), 1 (*once or twice*), 2 (*3–5 times*), 3 (*6–10 times*), or 4 (*more than 10 times*). These responses represent the number of times a behavior occurred due to alcohol consumption. The sum of the scores generates a score ranging from 0 to 23 points.

For the analyses, we categorized the participants as drinkers or nondrinkers. Those who answered affirmatively to question 1 of the AUDIT[10] ("How often do you consume alcoholic beverages?") were considered drinkers. Subsequently, we classified drinkers as practitioners or nonpractitioners of binge drinking (a pattern of excessive alcohol consumption in a short period).[11,12] This was determined by considering the consumption of five or more alcoholic drinks (beer, wine, and/or spirits) for men or four or more for women on a single occasion.[13] Finally, we conducted a descriptive analysis of the study group according to the variables under investigation (sociodemographic variables, academic performance, and risky situations or undesirable events after alcohol use). Additionally, we considered risk behavior when students had an AUDIT score ≥ 8 and/or RAPI score ≥ 7 at any stage in the last 12 months or in the last month.[14]

We initially tabulated the data in Microsoft Office Excel (version 2010, Redmond, Washington, United States) and analyzed them in R software (version 4.0.2, Boston, Massachusetts, United States). We presented qualitative variables as absolute and relative frequencies. To investigate the association between outcome variables (drinking or not drinking /binge drinking or not binge drinking) and potential exposures (presence or absence of each variable) in the group, we performed the chi-square test or Fisher's exact test, with variables included in the model having a P value < 0.05.

The present study was performed under Resolutions 466/12 and 510/16 of the Brazilian National Health Council and approved by the Brazilian Research Ethics Committee (CAAE: 45396315.8.0000.5033, on September 17, 2015). The participants' autonomy, confidentiality, and privacy were respected. All study participants were informed of the research objectives and methods and signed an informed consent form.

RESULTS

A total of 770 students from the healthcare field at a private Brazilian university participated in the study. Among these, most were women (79.2%), aged between 18 and 25 years (82.2%), Catholic (36.0%), residing with family members (83.1%), and in their first two years of undergraduate studies (78.9%) (**Table 1**).

We observed that 65.1% of the interviewed students used alcoholic beverages, with this prevalence being high among both men (73.1%) and women (63.0%). Furthermore, alcohol consumption was more frequent among students in semesters beyond the fourth (71.7%), with notable rates in the fields of medicine (83.0%), veterinary medicine (79.1%), and nutrition (74.4%) (**Table 1**).

An analysis of the associations between sociodemographic and academic data and alcohol consumption revealed that sex (P = 0.016), religion (P < 0.000), course (P < 0.000), and semester (P = 0.047) were associated with drinking habits. Conversely, age and living situation were not significantly associated with such habits (**Table 1**).

Among the students who reported consuming alcoholic beverages, most exhibited low consumption levels; we classified these individuals as low-risk drinkers (64.9%) (**Table 2**).

We observed binge drinking in 57.5% of the participants who reported consuming alcoholic beverages and identified risky behavior in 63.9% of binge drinkers and 14.6% of non-binge drinkers. We observed a significant association between this practice and the adoption of risky behavior (P < 0.000) (**Table 3**).

When analyzing the sociodemographic and academic profiles of students who reported consuming alcoholic beverages and engaging in binge drinking, we found a significant association with the variable of religion (P = 0.002) but no associations between binge drinking and the other variables studied (**Table 4**).

When assessing the effects of alcohol consumption on academic life, we found that binge drinking was significantly associated with attending academic activities without getting any sleep (P < 0.000), missing classes due to hangovers (P < 0.000), encountering issues with the institution's administration (P = 0.028),

Table 1. Sociodemographic and academic characteristics of participating students, considering both the total sample and the grouping based on alcohol consumption (n = 770)

PROFILE*	PARTICIPANTS			P§
	TOTAL (n = 770)	ALCOHOL CONSUMPTION		
		YES (n = 501)	NO (n = 269)	
Sex				**0.016**
Men	160 (20.8)	117 (73.1)	43 (26.9)	
Women	610 (79.2)	384 (63.0)	226 (37.0)	
Age**				0.583
18–25 years old	544 (82.2)	355 (65.3)	189 (34.7)	
26–30 years old	63 (9.5)	40 (63.5)	23 (36.5)	
Over 30 years old	55 (8.3)	32 (58.2)	23 (41.8)	
Religion**				**<0.000**
No religion	104 (25.8)	83 (79.8)	21 (20.2)	
Catholic	145 (36.0)	104 (71.7)	41 (28.3)	
Protestant	92 (22.8)	31 (33.7)	61 (66.3)	
Spiritist	37 (9.2)	29 (33.7)	8 (21.6)	
African religions	3 (0.7)	3 (100.0)	0 (0.0)	
Eastern religions	1 (0.2)	1 (100.0)	0 (0.0)	
Others	21 (5.2)	10 (47.6)	11 (52.4)	
Residence**				0.093
With Family	343 (83.1)	227 (66.2)	116 (33.8)	
With Friends	29 (7.0)	24 (82.8)	5 (17.2)	
Alone	16 (3.9)	14 (87.5)	2 (12.5)	
Others	25 (6.1)	18 (72.0)	7 (28.0)	
Programs				**<0.000**
Biomedical	131 (17.0)	56 (42.7%)	75 (57.3%)	
Medicine	100 (13.0)	83 (83.0%)	17 (17.0%)	
Nursing	143 (18.6)	85 (59.4%)	58 (40.6%)	
Nutrition	129 (16.8)	96 (74.4%)	33 (25.6%)	
Pharmacy	19 (2.5)	1 (5.3%)	18 (94.7%)	
Psychology	26 (3.4)	17 (65.4%)	9 (34.6%)	
Social Work	136 (17.7)	95 (69.9%)	41 (30.1%)	
Veterinary Medicine	86 (11.0)	68 (79.1%)	18 (20.9%)	
Academic semester in progress**				**0.047**
≤ 4th	593 (78.9)	375 (63.2)	218 (36.8)	
> 4th	159 (21.1)	114 (71.7)	45 (28.3)	

*Data presented as absolute frequency (n) and relative frequency (%); **Relative frequency calculated considering the number of responses obtained for each variable (age: n = 662; religion: n = 403; residence: n = 413; semester: n = 752); §Chi-squared test or Fisher's Exact test.

Table 2. Alcohol consumption categorized using the Alcohol Use Disorders Identification Test (AUDIT)

ALCOHOL CONSUMPTION CLASSIFICATION	PARTICIPANTS* (n = 501)
Low Consumption	325 (64.9)
Risky Behavior	148 (29.5)
High Risk or Harmful Use	6 (1.2)
Dependence	22 (4.4)

* Data presented as absolute frequency (n) and relative frequency (%).

Table 3. Association between risky behavior and the practice of binge drinking among participating students who reported alcohol consumption (n = 501)

RISKY BEHAVIOR*	BINGE DRINKING**		P§
	YES (n = 288)	NO (n = 213)	
Presence	184 (63.9)	31 (14.6)	**< 0.000**
Absence	104 (36.1)	182 (85.4)	

*Risky behavior was considered when AUDIT ≥ 8 and/or RAPI ≥ 7 at any phase, in the last 12 months, or in the last month; ** Data presented as absolute frequency (n) and relative frequency (%); ** Chi-square test of independence.

and failing to complete activities due to alcohol consumption (P < 0.000). However, we observed no associations with attending the institution while intoxicated, achieving weighted averages less than 7.0 points in the last semester, or experiencing a decline in academic performance in the last semester (**Table 5**).

DISCUSSION

When investigating the alcohol habits of students, the present study demonstrated a substantial rate of alcohol consumption among Brazilian healthcare students, with relevant associations between sex, religion, course, academic semester, and drinking habits. Moreover, a considerable number of students disclosed their involvement in binge drinking—a behavior linked to high-risk conduct and adverse effects on academic achievement.

Studies conducted by several universities around the world have corroborated the prevalence of alcohol consumption shown in the present study, indicating that the frequency of alcohol intake among healthcare students ranges from 57.5%[6] to 85.0%.[12] These results are higher than the average for the general population, which is 40%.[1] Furthermore, in addition to demonstrating a prevalence of 81.6% alcohol consumption among university students, Pedrosa et al.[15] showed that alcohol consumption tends to increase over the years. It is important to note that while the onset of this behavior may precede university entrance, the academic environment can contribute to intensifying the habit of drinking.[16]

Regarding the profile of alcohol consumers, we observed a predominance of this practice among men, which is consistent with the findings of other studies.[5,17,18] Additionally, data from the Third National Survey on Drug Use by the Brazilian Population[5] indicate that dependence is 3.4 times more common in men than in women. This fact was also highlighted in the study by Silva et al.,[18]

Table 4. Association between the sociodemographic and academic profile of students who reported alcohol consumption and the practice of binge drinking (n = 501)

PROFILE*	BINGE DRINKING*		P**
	YES	NO	
Sex			0.710
Men	69 (59.0)	48 (41.0)	
Women	219 (57.0)	165 (43.0)	
Age			0.238
18–25 years old	202 (56.9)	153 (43.1)	
26–30 years old	21 (52.5)	19 (47.5)	
Over 30 years old	15 (46.9)	17 (53.1)	
Religion			**0.002**
No religion	39 (47.0)	44 (53.0)	
Catholic	65 (62.5)	39 (37.5)	
Protestant	11 (35.5)	20 (64.5)	
Spiritist	16 (55.2)	13 (44.8)	
African religions	0 (0)	3 (100.0)	
Eastern religions	0 (0)	1 (100.0)	
Others	9 (90.0)	1 (10.0)	
Residence			0.392
With Family	125 (55.1)	102 (44.9)	
With Friends	16 (66.7)	8 (33.3)	
Alone	6 (42.9)	8 (57.1)	
Others	12 (66.7)	6 (33.3)	
Programs			0.113
Biomedical	28 (50.0)	28 (50.0)	
Medicine	52 (62.7)	31 (37.3)	
Nursing	47 (55.3)	38 (44.7)	
Nutrition	47 (49.0)	49 (51.0)	
Pharmacy	0 (0)	1 (100.0)	
Psychology	11 (64.7)	6 (35.3)	
Social Work	65 (68.4)	30 (31.6)	
Veterinary Medicine	38 (55.9)	30 (44.1)	
Academic semester in progress			0.066
≤ 4th	224 (59.7)	151 (40.3)	
> 4th	57 (50.0)	57 (50.0)	

*Data presented as absolute frequency (n) and relative frequency (%);
** Chi-square test of independence.

Table 5. Association between binge drinking and the effects of alcohol consumption on the academic life of participating students

QUESTIONS	BINGE DRINKING*		P**
	YES	NO	
Have you ever attended academic activities without getting any sleep?			**< 0.000**
Yes	88 (80.7)	23 (50.0)	
No	21 (19.3)	23 (50.0)	
Have you ever skipped class due to a hangover?			**< 0.000**
Yes	68 (23.9)	24 (11.4)	
No	216 (76.1)	186 (88.6)	
Have you ever attended the educational institution while drunk?			0.195
Yes	33 (11.5)	17 (8.0)	
No	254 (88.5)	196 (92.0)	
Have you ever experienced issues with the school administration due to negative behaviors resulting from excessive drinking?			**0.028**
Yes	10 (3.5)	1 (0.5)	
No	274 (96.5)	212 (99.5)	
Have you ever failed to fulfill your responsibilities due to drinking?			**< 0.000**
Yes	44 (15.3)	11 (5.2)	
No	243 (84.7)	201 (94.8)	
Is your weighted average grade from the last semester less than 7 points?			0.141
Yes	11 (3.9)	14 (6.9)	
No	271 (96.1)	189 (93.1)	
Have you experienced a decrease in academic performance in the last semester?			0.443
Yes	23 (8.6)	13 (6.7)	
No	243 (91.4)	181 (93.3)	

*Data presented as absolute frequency (n) and relative frequency (%);
** Chi-square test of independence.

which, in addition to demonstrating a higher prevalence in men, showed a growing prevalence of abusive alcohol consumption in the Brazilian adult population. Specifically regarding the city of Salvador, recent data from the Vigitel 2023 survey[19] indicate that the capital of Bahia leads the country in alcohol abuse consumption, both for the general population and for men and women, surpassing national rates. In Brazil, the prevalence of alcohol abuse consumption in the general population is 20.8%, while in Salvador, it is 28.9%.[19] Given the high rate of alcohol abuse consumption in this population, this pattern of behavior may also be observed among the student participants in the study.

Although changes in social patterns favor behavioral convergence between sexes, resulting in increased alcohol intake among women over the years, it remains evident that a male predominance exists among alcohol consumers. According to Fachini et al.,[20] the intensity with which men drink is associated with positive cultural perceptions linked to use, such as the possibility of improved sexual performance.

Although the current study did not reveal substantial differences in alcohol consumption based on age, prior research has suggested a slight prevalence of alcohol consumption among university students aged 21–25 years.[21] Similarly, the housing variable did not significantly differ; however, we noted a trend toward a considerable percentage of alcohol consumption among students who lived alone or with friends. These findings corroborate studies indicating that students residing apart from family members often tend to exhibit elevated levels of alcohol consumption, which is potentially attributed to reduced parental oversight over their behavior.[22]

Regarding the course attended by university students, medical students have reported higher alcohol consumption, which aligns with the findings of Gomes et al.[23] According to Abreu et al.,[21] the pronounced susceptibility of this population to alcohol consumption may be associated with the characteristics of the course that predisposes individuals to stressful situations, such as a high workload combined with a large amount of content to study, excessive demands both inside and outside the academic environment, and delayed financial independence.

Considering that these young medical students will be future leaders in actions related to the prevention, diagnosis, and treatment of disorders associated with abusive alcohol consumption, it is concerning to find that this behavior can transcend graduation and potentially interfere with the quality of their professional practice. This problem is not limited to Brazilian students; a study conducted in the United States revealed that 12.9% of male medical students and 21.4% of female medical students met the criteria for alcohol abuse or dependence.[24]

Regarding the relationship between alcohol consumption and academic semester, the present study revealed that alcohol consumption was more frequent among students enrolled from the fifth semester onward. A similar finding was reported by Gomes et al.,[25] who demonstrated a progressive increase in alcohol consumption among medical students of both sexes over semesters, reaching 93.6% in the fifth semester.

Although the literature does not specify a period of greater vulnerability to drug use within the university, certain situations in the educational context, such as parties and stressful course conditions, vary throughout the semester and may provide greater access to alcoholic beverages.[22,26] Additionally, as they advance in their courses, healthcare students, who naturally acquire greater knowledge about the topic, may develop the conviction that they can manage any problems that may arise due to improper alcohol and drug use.[21]

In the present study, when analyzing the risk zones established by the AUDIT, more than half of the sample was classified in the low-risk zone, as in the study by Imai et al.[17] Furthermore, a minority of the study population fell into the categories of harmful use and probable dependence, which echoed the findings of Imai et al.[17] and Barbosa et al.[22]

In this context, the abusive and increasing consumption of psychoactive substances—especially alcohol—among young university students represents a considerable challenge for public health due to the interference of alcohol as a cause of disease, morbidity, and mortality worldwide.[27] Among university students, healthcare students are among the most vulnerable to binge drinking—a phenomenon characterized by consuming high doses of alcohol (four or more drinks for women and five or more for men) on a single occasion.[11,21,28]

The physiopathological, social, and economic impacts resulting from abusive alcohol consumption are widely documented. However, a better understanding of the underlying reasons that make healthcare students particularly vulnerable to this behavior is still necessary. The high rate of consumption and abuse in the academic environment may reflect the ease of accessing alcoholic beverages at frequent university parties and the adaptation mechanism to the academic environment, which ranges from its use as a means of social inclusion to a refuge from the stressful factors associated with courses.[12]

In the present study, a substantial portion of students engaged in binge drinking. Compared with other similar Brazilian studies, the prevalence of binge drinking varies widely, ranging from 15.6%[29] to 56.1%[12]; this suggests variability among regions and student populations, emphasizing the importance of specific prevention approaches for each situation.

Another relevant point is that heavy drinking habits can interfere with the development of these future professionals. According to a study by Cardoso et al.,[30] this habit can contribute to unpreparedness in providing healthcare. Thus, this unpreparedness in the

profession results from the interference of abusive use in essential work activities, such as learning, memory, psychomotor speed, and decision-making.[21]

We observed an association between religion and both drinking habits and binge drinking practices. University students who declared themselves Protestants had the lowest alcohol consumption, while those who were Catholic reported the highest consumption. Individuals without religious ties have a high prevalence of abusive alcohol use[29]; this characterizes religion as a protective factor against the adoption of risky behaviors, including the abusive use of substances such as alcohol. The fact that religiosity establishes norms and values that directly and indirectly influence individual attitudes may favor the rejection of drug use.

However, religions show differences with regard to the values that modulate the acceptance of consumption, which may be more or less permissive, especially about alcohol use. Therefore, Silva et al.[31] have concluded that religions with less permissive views on alcohol consumption, such as Protestantism, played a more determining role in preventing abusive use.

The present study demonstrated the negative effects of binge drinking on academics through practices such as attending academic activities while intoxicated, missing class due to hangovers, experiencing administrative issues with the educational institution, and not completing academic activities due to alcohol consumption. The impact of binge drinking on the academic environment, whether through absence from activities or impaired performance, was also identified in the study by Cardoso et al.[30] Furthermore, binge drinking practitioners can be considered to exhibit harmful behavior to individual and collective health. The concept of harmful behavior encompasses everything from dependence on health hazards and chronic diseases[32] as well as actions that directly affect society, such as legal problems and involvement in violent actions secondary to abusive use.[27] The importance of the topic is supported by the various negative effects of abusive use and its impact on public health, which significantly contribute to morbidity and mortality.

Given these findings, this study is expected to inform future research and facilitate the creation of university-based prevention policies that aim to mitigate the adverse effects of substance abuse, enhance students' quality of life, and support their professional development. This includes the implementation of preventive measures in educational institutions that disseminate information about the consequences of abusive consumption, as well as the identification of at-risk groups, so that therapeutic interventions can be offered.[22]

Finally, the limitations of this study include the low participation of students in semesters with few in-person classes at the institution due to more practical fieldwork, which limits the application of the data-collection instrument. As the questionnaire is self-administered and extensive, one must consider possible comprehension difficulties and fatigue in responding to all its questions. These factors may have contributed to some questions not being answered in their entirety by all participants in the sample. Despite these potential limitations, the findings presented in this study can be considered relevant to the scientific literature.

CONCLUSION

This study revealed high prevalence rates of alcohol consumption and binge drinking among healthcare students at a private university, with associations between these patterns of consumption and sex, religion, course, and academic semester. Additionally, these habits were associated with risky behaviors and negative impacts on academic performance due to noncompliance with curricular activities and the development of administrative problems with educational institutions.

REFERENCES

1. World Health Organization. Global status report on alcohol and health 2018. Geneva: World Health Organization; 2019. Available from: https://iris.who.int/handle/10665/274603. Accessed in 2024 (June 19).
2. Pan American Health Organization. Alcohol. Washington: PAHO; 2020. Available from: https://www.paho.org/pt/topicos/alcool. Accessed in 2024 (June 19).
3. Coutinho ESF, França-Santos D, Magliano ES, et al. ERICA: patterns of alcohol consumption in Brazilian adolescents. Rev Saude Publica. 2016;50(suppl 1):8s. PMID: 26910550; https://doi.org/10.1590/s01518-8787.2016050006684.
4. Paiva HN, Silva CJP, Galo R, Zarzar PM, Paiva PCP. Association between use of licit and illicit drugs, sex, and socioeconomic status among 12-year-old adolescents. Cad Saude Colet. 2018;26(2):153-9. https://doi.org/10.1590/1414-462X201800020048.
5. Bastos FIPM, Vasconcellos MTL, Boni RB, Reis NB, Coutinho CFS, orgs. Third national survey on drug use by the Brazilian population. Rio de Janeiro: ICICT/FIOCRUZ; 2017.
6. Baumgarten LZ, Gomes VLO, Fonseca AD. Alcohol consumption among university students in the health area of federal university of Rio Grande/RS: subsidy to the nursing. Esc Anna Nery. 2012;16(3):530-5. https://doi.org/10.1590/S1414-81452012000300015.
7. Stapleton JL, Turrisi R, Cleveland MJ, Ray AE, Lu SE. Pre-college matriculation risk profiles and alcohol consumption patterns during the first semesters of college. Prev Sci. 2014;15(5):705-15. PMID: 23928750; https://doi.org/10.1007/s11121-013-0426-2.
8. World Health Organization, Babor TF, Higgins-Biddle JC, Saunders JB, Monteiro MG. AUDIT: the alcohol use disorders identification test : guidelines for use in primary health care. Geneva: WHO; 2001. Available from: https://iris.who.int/handle/10665/67205. Accessed in 2024 (June 17).

9. Sousa KPA, Medeiros ED, Medeiros PCB. Validity and reliability of the Alcohol Use Disorders Identification Test (AUDIT) in students of a Brazilian university. Ciencias Psicológicas. 2020;14(2):e2230. https://doi.org/10.22235/cp.v14i2.2230.
10. White HR, Labouvie EW. Towards the assessment of adolescent problem drinking. J Stud Alcohol. 1989;50(1):30-7. PMID: 2927120; https://doi.org/10.15288/jsa.1989.50.30.
11. Sanchez ZM. Binge drinking among young Brazilians and the promotion of alcoholic beverages: a Public Health concern. Epidemiol Serv Saude. 2017;26(1):195-8. PMID: 28226021; https://doi.org/10.5123/s1679-49742017000100020.
12. Pelicioli M, Barelli C, Gonçalves CBC, Hahn SR, Scherer JI. Alcohol consumption and episodic heavy drinking among undergraduate students from the health area of a Brazilian university. J Bras Psiquiatr. 2017;66(3):150-6. https://doi.org/10.1590/0047-2085000000164.
13. National Institute on Alcohol Abuse and Alcoholism. Helping patients who drink too much: a clinician's guide. Bethesda: NIAAA; 2005. Available from: https://s21151.pcdn.co/wp-content/uploads/2016/11/Helping-Patients-who-Drink-Too-Much_A-Clinicians-Guide-2017.pdf. Accessed in 2024 (June 19).
14. Floripes TMF. Drinking while drunk (binge drinking): study of a population of university students who use risky alcohol. (Masters' dissertation). Botucatu: Universidade Estadual Paulista, Faculdade de Medicina de Botucatu; 2008. Available from: http://hdl.handle.net/11449/98450. Accessed in 2024 (June 19).
15. Pedrosa AAS, Camacho LAB, Passos SRL, Oliveira RVC. Alcohol consumption by university students. Cad Saude Publica. 2011;27(8):1611-21. PMID: 21877009; https://doi.org/10.1590/s0102-311x2011000800016.
16. Barros MSMR, Costa LS. Alcohol consumption between students. Rev Eletrônica Saúde Ment Álcool e Drog. 2019;15(1):4-13. https://doi.org/10.11606/issn.1806-6976.smad.2019.000353.
17. Imai FI, Coelho IZ, Bastos JL. Excessive alcohol consumption, smoking, and associated factors in a representative sample of undergraduate students from the Federal University of Santa Catarina, 2012: a cross-sectional study. Epidemiol Serv Saude. 2014;23(3):435-46. https://doi.org/10.5123/S1679-49742014000300006.
18. Silva LES, Helman B, Silva DCL, Aquino ÉC, Freitas PC, Santos RO, et al. Prevalence of heavy episodic drinking in the Brazilian adult population: National Health Survey 2013 and 2019. Epidemiol e Serv Saude. 2022;31(spe1):e2021378. PMID: 35792795; https://doi.org/10.1590/ss2237-9622202200003.especial.
19. Brazil. Vigitel Brazil 2023: Surveillance of risk and protective factors for chronic diseases by telephone survey: estimates on the frequency and sociodemographic distribution of risk and protective factors for chronic diseases. Brasília (DF): Ministério da Saúde; 2023. Available from: https://bvsms.saude.gov.br/bvs/publicacoes/vigitel_brasil_2023.pdf. Accessed in 2024 (June 19).
20. Fachin A, Furtado EF. Alcohol use and drinking expectations among college students: an analysis of sex differences. Psicol Teor Pesq. 2013;29(4):421-8. https://doi.org/10.1590/S0102-37722013000400008.
21. Abreu TT, Maurílio AO, Liguori CC, et al. The consumption of alcoholic beverages and binge drink among Medicine graduating in a Minas Gerais University. J Bras Psiquiatr. 2018;67(2):87-93. https://doi.org/10.1590/0047-2085000000190.
22. Barbosa FL, Barbosa RL, Barbosa MCL, Aguiar DL, Figueiredo IA, Ribeiro AC, et al. Alcohol Consumption Among Medical Students at the Federal University of Maranhão, Brazil. Rev Bras Educ Med. 2013;37(1):89-95. https://doi.org/10.1590/S0100-55022013000100013.
23. Gomes IP, Pereira RAC, Santos BF, Pinheiro MA, Alencar CH, Cavalcanti LPG. Factors associated with continued smoking addiction and alcohol consumption among medical students in capital city in the Northeast of Brazil. Rev Bras Educ Med. 2019;43(1):55-64. https://doi.org/10.1590/1981-52712015v43n1RB20180068.
24. Jackson ER, Shanafelt TD, Hasan O, Satele DV, Dyrbye LN. Burnout and alcohol abuse/dependence among U.S. Medical Students. Acad Med. 2016;91(9):1251-6. PMID: 26934693; https://doi.org/10.1097/acm.0000000000001138.
25. Gomes LS, Barroso CRD, Silvestre VA, Baylão ACP, Garcia SCM, Pacheco SJB. Alcohol consumption among South Fluminense medical students. Rev Med. 2018;97(3):260-6. https://doi.org/10.11606/issn.1679-9836.v97i3p260-266.
26. Santiago IS, Castro SC, Brito APA, Sanches D, Quintanilha LF, Avena KM, et al. Stress and exhaustion among medical students: a prospective longitudinal study on the impact of the assessment period on medical education. BMC Med Educ. 2024;24:630. PMID: 38844948; https://doi.org/10.1186/s12909-024-05617-6.
27. Terra Júnior AT, Santos JC, Pontes LF, Fernandes DR, Ribeiro DM. Consumption of alcohol and other psychoactive substances between university students and the practice of binge drinking. South Am Sci. 2021;2(2):e21105. https://doi.org/10.52755/sas.v2i2.105.
28. Reisdorfer E, Buchele F, Pires ROM, Boing AF. Prevalence and associated factors with alcohol use disorders among adults : a population-based study in southern Brazil. Rev Bras Epidomiol. 2012;15(3):582-94. PMID: 23090305; https://doi.org/10.1590/s1415-790x2012000300012.
29. Nunes JM, Campolina LR, Vieira MA, Caldeira AP. Alcohol consumption and binge drinking among health college students. Rev Psiquiatr Clin. 2012;39(3):94-9. https://doi.org/10.1590/S0101-60832012000300005.
30. Cardoso FM, Barbosa HA, Costa FM, Vieira MA, Caldeira AP. Factors associated with practice of binge drinking among students of health. Rev CEFAC. 2015;17(2):475-84. https://doi.org/10.1590/1982-021620158914.
31. Silva LVER, Malbergier A, Stempliuk VA, Andrade AG. Factors associated with drug and alcohol use among university students. Rev Saude Publica. 2006;40(2):280-8. PMID: 16583039; https://doi.org/10.1590/s0034-89102006000200014.

32. Melo APS, França EB, Malta DC, et al. Mortality due to cirrhosis, liver cancer, and disorders attributed to alcohol use: Global Burden of Disease in Brazil, 1990 and 2015. Rev Bras Epidemiol. 2017;20(Suppl 1):61-74. PMID: 28658373; https://doi.org/10.1590/1980-5497201700050006.

Authors contributions: Brito APA: conceptualization (equal), methodology (equal), project administration (equal), writing – original draft (equal), writing – review and editing (equal); Lima AS: conceptualization (equal), methodology (equal), project administration (equal), writing – original draft (equal), writing – review and editing (equal); Rocha AC: conceptualization (equal), investigation (equal), writing – original draft (equal), writing – review and editing (equal); Gonçalves BM: conceptualization (equal), investigation (equal), writing – original draft (equal), writing – review and editing (equal); Freitas DMCB: conceptualization (equal), investigation (equal), writing – original draft (equal), writing – review and editing (equal); Oliveira GJ: conceptualization (equal), investigation (equal), writing – original draft (equal), writing – review and editing (equal); Lima JKA: conceptualization (equal), investigation (equal), writing – original draft (equal), writing – review and editing (equal); Avena KM: formal analysis (equal), methodology (equal), writing – original draft (equal), writing – review and editing (equal). All authors reviewed and approved the final version submitted for publication.

Sources of funding: None
Conflicts of interest: None

Date of first submission: November 17, 2023
Last received: April 12, 2024
Accepted: June 6, 2024

Address for correspondence:
Ana Paula Amaral de Brito
Medicina Zarns
Avenida Luis Viana Filho, 3230 — Imbuí, Salvador (BA), Brasil
CEP 41720-200
Tel.: +55 71 3281-8000
E-mail: apabrito@uneb.br

Editor responsible for the evaluation process:
Paulo Manuel Pêgo-Fernandes MD, PhD

Relationship between angiogenic growth factors and atherosclerosis in renal transplantation recipients: a cross-sectional study

Melahat Çoban[I], Beyza Algul Durak[II], Mine Sebnem Karakan[III]

This study was conducted in Ankara Bilkent City Hospital nephrology clinic.

[I]PhD. Assistant Professor, Department of Nephrology, Ankara Bilkent City Hospital, Ankara, Turkey.
https://orcid.org/0000-0001-5761-7675

[II]MD. Department of Nephrology, Ankara Bilkent City Hospital, Ankara, Turkey.
https://orcid.org/0000-0002-3182-4382

[III]PhD. Professor, Department of Nephrology, Yıldırım Beyazıt University, Ankara, Turkey.
https://orcid.org/0000-0002-7499-1738

KEYWORDS (MeSH terms):
Atherosclerosis
Angiopoietin-2
Vascular endothelial growth factors

AUTHORS' KEYWORDS:
Renal resistive index.
Renal transplant recipients.
Renal failure

ABSTRACT

BACKGROUND: Accelerated development of atherosclerosis has been observed in renal transplant recipients (RTRs). Angiopoietin-2 (Ang-2) and vascular endothelial growth factor (VEGF) are vascular enzymes that play important roles in vascular development and angiogenesis.

OBJECTIVE: This study aimed to investigate the relationship between Ang-2 and VEGF and atherosclerosis in RTRs.

DESIGN AND SETTING: This study was conducted at Ankara City Hospital, Turkey.

METHODS: This cross-sectional study included 36 (37.5%) female and 60 (62.5%) male RTRs. All findings were compared with those of 70 healthy controls. Ultrasonographic measurements of the carotid artery intima-media thickness (CA-IMT) and renal resistive index (RRI) were used as indicators of atherosclerosis.

RESULTS: Log_{10} Ang-2, log_{10} VEGF, CA-IMT, and RRI levels were significantly higher in patients than in healthy controls. No significant differences were detected in CA-IMT and RRI between those with log_{10} Ang-2 ≥ 3.53 pg/mL and those with < 3.53 pg/mL. No significant differences were detected in CA-IMT and RRI between those with log_{10} VEGF ≥ 1.98 pg/mL and those with < 1.98 pg/mL. No correlation was detected between log_{10} Ang-2 and log_{10} VEGF, CA-IMT, or RRI.

CONCLUSIONS: Increased serum angiogenic growth factor levels and increased atherosclerosis development were detected in RTRs compared to healthy individuals. No relationship was observed between angiogenic growth factors and atherosclerosis. This may be due to the decreased synthesis and effect of angiogenic growth factor receptors synthesized from atherosclerotic plaques due to atherosclerosis, which improves after renal transplantation.

INTRODUCTION

Increased cardiovascular disease (CVD) has been observed in patients with chronic kidney disease (CKD), including renal transplant recipients (RTRs). Renal transplantation is the preferred treatment modality for patients with end-stage renal failure, providing significant survival and quality of life advantages over long-term dialysis. Although RTRs are highly susceptible to infection and have an increased tendency to develop malignancies, CVD is the main cause of mortality among RTRs. A 5-fold increase in cardiovascular (CV) mortality was detected one year after renal transplantation compared with that in the age-matched control group. In RTRs, the risk factors for CVD development are divided into two categories: traditional and non-traditional. Traditional risk factors are divided into two categories: immutable (age, sex, and inheritance) and variable (smoking, hyperlipidemia, hypertension, obesity, diabetes mellitus, physical activity, and stress). Non-traditional risk factors include transplantation and treatment (immunosuppressive agents, graft rejection, and viral infection) and chronic rejection (anemia, volume load, hyperhomocysteinemia, oxidative stress, secondary hyperparathyroidism, and microinflammation).[1]

Atherosclerosis is characterized by chronic, unrecoverable inflammation and cholesterol accumulation in the vascular walls of medium and large arteries. Neovascularization, unstable plaque formation, and rupture play important roles in its development. The presence of atherosclerosis can be assessed using renal Doppler ultrasonography with carotid artery intima-media thickness (CA-IMT) as a reproducible, noninvasive, and simple method. Increased CA-IMT may be regarded as an indicator of increased risk of CV events. The development of atherosclerosis, as determined by CA-IMT, is more common in RTRs than in the normal population.[2]

Determining the renal resistive index (RRI) using Doppler ultrasonography allows for the assessment of renal resistance and renal arteriolar damage. Values of ≥ 0.80 are indicative of adverse renal function and increased mortality,[3] but a decreased RRI may be a sign of renal stenosis. Chudek et al. reported that RRI is a sensitive but not specific marker for graft dysfunction.[4] Radermacher et al. reported that a high RRI may be used as a strong indicator of graft loss.[3] Kramann et al. reported that RRI obtained in the first 6 months after the transplantation failed to predict graft failure; however, RRI obtained 12-18 months may be useful in predicting long-term graft outcomes.[5] Shimizu et al. reported that RRI may be used as a reliable marker for atherosclerosis.[6] Calabia et al. found a significant relationship between RRI and CA-IMT and argued that this relationship could provide useful data on micro- and macrovascular damage.[7] For this reason, measuring RRI with ultrasonography can be considered an easy and non-invasive method to detect graft functions and the presence of atherosclerosis.

The balance between pro- and anti-angiogenic factors regulates angiogenesis, a process that requires an interaction between endothelial cells, extracellular matrix, and surrounding cells, mediated by a set of growth factors, their receptors, and intracellular signals. The angiopoietin (Ang)-Tie ligand receptor system consists of 2 receptor tyrosine kinases (Tie-1 and Tie-2) and four ligands (Ang-1, Ang-2, Ang-3, and Ang-4). Ang-2 is a ligand of Tie-2 receptor, a second-class vascular-specific receptor tyrosine kinase. Ang-2 is stored in granules called Weibel-Palade bodies (WPB) in endothelial cells. The Ang/Tie system tightly controls the endothelial phenotype during angiogenesis. Loss of vascular integrity, vascular leakage, and neutrophil migration occur due to Ang-2 effects. Therefore, it is considered a pro-inflammatory factor. Ang-2 is expressed at active vascular remodeling and angiogenesis sites, and is induced by various cytokines, including vascular endothelial growth factor (VEGF). Ang-2 acts as an agonist that stimulates angiogenesis by causing vascular destabilization in the presence of VEGF. Ang-2 competitively antagonizes Tie-2 phosphorylation in the absence of VEGF, causing vascular regression and endothelial cell death.[8] Thus, Ang-2 and VEGF act synergistically to form a stable and functional microvasculature. High serum Ang-2 levels are detected in patients with diabetes mellitus, arteriosclerosis, acute coronary syndrome, arterial hypertension, and acute renal injury.

As important regulators of angiogenesis, lymphangiogenesis, lipid metabolism, and inflammation, the VEGF family comprises of heparin-binding proteins that play a role in atherosclerosis and other CVDs development. The VEGF family consists of five gene products in humans, three of which regulate blood vessel growth (VEGF-A, VEGF-B, placental growth factor), and two of which regulate lymphangiogenesis (VEGF-C and VEGF-D). Additionally, there are three VEGF receptors: VEGF receptor 1 (VEGFR1) (FLT1 gene); VEGFR2 (KDR gene), which is mainly expressed in vascular endothelial cells; and VEGFR3 (FLT4 gene), which is expressed in lymphatic endothelial cells. The primary VEGF expression site is in the CV system (endothelial cells, angioblasts, and pericytes). However, it is also expressed in several other cell types during inflammation and hypoxia. VEGF receptors are distributed in vascular smooth muscle cells, osteoblasts, cardiomyocytes, myofibroblasts, neurons, and various tumor cells.[9] VEGF also plays roles in endothelial cell function, physiological angiogenesis (formation of blood vessels during tissue revascularization), and pathological angiogenesis (as a marker of ischemic diseases, inflammation, and microvascular occlusion). Increased VEGF levels induce endothelial cell proliferation and vascular permeability. VEGF also plays a dual role in atherosclerosis. However, it sometimes acts as a mitogen via re-endothelialization, causing harmful effects by preventing the repair of endothelial lesions that induce atherogenesis.

Although many studies have been conducted with stage 1-5 patients with CKD, few studies have investigated the development of atherosclerosis in RTRs and the relationship between growth factors and atherosclerosis.

OBJECTIVE

This study aimed to investigate the relationship between Ang-2 and VEGF and atherosclerosis, as determined by CA-IMT and RRI in RTRs.

METHODS

Patient selection

This cross-sectional study was conducted with 96 RTRs, including 36 female (37.5%) and 60 male (62.5%), who were followed up in the Organ Transplantation Polyclinic. The patient group was compared with a control group, which comprised 70 healthy volunteers with a similar distribution of age and sex. The exclusion criteria were as follows: refusal to participate in the study, active infection and malignancy, peripheral vascular disease, previous history of cardiac intervention (coronary angiography, valvular replacement, cardiac pacemaker), or history of heart disease detected echocardiographically (atrial fibrillation, left ventricular systolic dysfunction [LVEF] < 50%). The study was explained to the participants and approved by the Ethics Committee of Ankara City Hospital on March 20, 2024 (TABED 2-24 68)

Laboratory measurements

Venous blood samples taken from all participants after an 8-12 h overnight fasting were centrifuged at 4 °C for 10 min, and the supernatants were stored at -80 °C. Serum creatinine, total cholesterol (TC), high-density lipoprotein cholesterol (HDL-C), triglyceride, calcium (Ca), phosphate (P), 25 hydroxy(OH) vitamin(Vit) D_3 (25(OH)VitD_3), and parathyroid hormone (PTH) levels were analyzed according to standard methods.

Low-density lipoprotein cholesterol (LDL-C) levels were calculated using the Friedewald's formula. Ang-2 (Elabscience, Shanghai, China) and VEGF (Novex Life Technologies, Thermo Fisher Scientific, Germany) levels were measured using commercial enzyme-linked immunosorbent assay kits. For all parameters, %CV was < 10%; analytical range and analytical sensitivity values were 45.78-2970 pg/mL and 26.12 pg/mL for Ang-2 and 30.14-1989 pg/mL and 17.64 pg/mL for VEGF, respectively.

Measurement of CA-IMT

The right and left common carotid arteries (CCA) were visualized using a high-resolution B-mode ultrasonography (USI) device (Siemens, USA), using a 5-10 MHz linear probe. Measurements were performed in the supine position while the patient's neck was angled approximately 20° to the contralateral side at three points: right and left CCA, bifurcation, and the first 2 cm segment of the internal carotid artery. CA-IMT was measured by evaluating the posterior wall. CA-IMT was determined by longitudinal examination of the distance between the vascular lumen echogenicity and media/adventitia echogenicity. Each measurement was repeated three times, and the average of the left and right measurements was calculated.

Measurement of RRI

Measurements were performed using a high-resolution B-mode ultrasonography (USI) device (Siemens, Saint Paul, Minnesota, United States) and a 5 MHz vector probe. The examination was performed in the supine and/or prone position in transverse and longitudinal sections of the kidney from the straight segment of the renal artery near the hilus on the arcuate arteries (at the corticomedullary junction) or interlobar arteries (adjacent to medullary pyramids). No measurements were obtained from the accessory arteries. The RRI was calculated using the following formula: (maximum systolic flow rate - end-diastolic flow rate)/ maximum systolic flow rate. The RRI was determined at least three times for both kidneys and averaged to obtain the mean RRI value for each patient. The RRI values were calculated as the average of all determinations in the two kidneys. The normal range is 0.50-0.70. A high RRI (> 0.8) in native kidneys is associated with adverse CV events. The intraobserver coefficients of variance of RRI were 4.4% for the main renal artery and 5.1% for the interlobar artery.

Statistical analyses

The normality assumptions of the variables were examined using the Kolmogorov-Smirnov test. The Mann-Whitney U test was used to compare continuous variables that did not show a normal distribution between the groups, and the independent samples t-test was used to compare variables that had a normal distribution. The relationships between categorical variables were examined using chi-square or Fisher's exact tests, and the relationships between continuous variables were examined using Spearman's RHO correlation analysis. Multivariate regression analysis was used to determine the parameters predicting $\log_{10}$ VEGF and $\log_{10}$ Ang-2 variables. The IBM SPSS version 25 (IBM Corp., Armonk, NY, USA) was used for all analyses, with a significance level of $P < 0.05$.

RESULTS

Patients and healthy individuals

The study included 36 (37.5%) female and 60 (62.5%) male RTRs who had a mean age of 43.51 ± 11.51 years. The patients were compared with a group of 70 age- and gender-matched healthy controls who had a mean age of 44.94 ± 10.69 years. The mean time after transplantation was 40.8 ± 2.31 months. Nine (9.4%) patients had diabetes mellitus and 81 (84.4%) had hypertension. Mean creatinine, PTH, Ca, P, and 25(OH)VitD_3 were 1.24 ± 0.46 mg/dL, 102.21 ± 97.24 pg/mL, 9.28 ± 0.50 mg/dL, 3.20 ± 0.64 mg/dL, and 16.85 ± 7.22 ng/mL, respectively. TC, LDL-C, HDL-C, and triglyceride values were 186.01 ± 38.72 mg/dL, 105.00 ± 33.93 mg/dL, 49.01 ± 13.06 mg/dL, and 157.44 ± 87.84 mg/dL, respectively. Mean $\log_{10}$ Ang-2 was 3.48 ± 0.18 pg/mL and $\log_{10}$ VEGF was 1.88 ± 0.48 pg/mL. The mean CA-IMT was 0.91 ± 0.34 mm and RRI was 0.66 ± 0.06. Creatinine ($P < 0.001$), PTH ($P < 0.001$), triglyceride ($P < 0.001$), $\log_{10}$ Ang-2 ($P = 0.009$), $\log_{10}$ VEGF ($P = 0.029$), CA-IMT ($P < 0.001$), and RRI ($P < 0.001$) were significantly higher in the patients than in the healthy controls, and estimated glomerular filtration rate (eGFR) ($P < 0.001$), 25(OH)VitD_3 ($P < 0.001$), TC ($P = 0.004$), and HDL-C ($P < 0.001$) were significantly lower (**Table 1**).

Relationship between average growth factor values and atherosclerosis

The mean $\log_{10}$ Ang-2 was 3.53 pg/mL, and no significant differences were detected between those with $\log_{10}$ Ang-2 ≥ 3.53 pg/mL and those with $\log_{10}$ Ang-2 < 3.53 pg/mL regarding PTH, Ca, P, 25(OH)VitD_3, CA-IMT, and RRI (**Table 2**).

The mean $\log_{10}$ VEGF was 1.98 pg/mL, and no significant differences were detected between those with $\log_{10}$ VEGF ≥ 1.98 pg/mL and those with Log_{10} VEGF < 1.98 pg/mL regarding PTH, Ca, P, 25(OH)VitD_3, CA-IMT, and RRI (**Table 3**).

Relationship between growth factors and atherosclerosis

No correlation was detected between $\log_{10}$ Ang-2 and eGFR (**Figure 1**), CA-IMT (**Figure 2**), or RRI (**Figure 3**). No relationship was detected between $\log_{10}$ VEGF and eGFR (**Figure 4**), CA-IMT (**Figure 5**), or RRI (**Figure 6**) (**Table 4**). No relationships were found in the multivariate analysis between $\log_{10}$ Ang-2 and $\log_{10}$ VEGF, eGFR, CA-IMT, or RRI (**Table 5**).

Table 1. Clinical data, demographic characteristics, and laboratory values of patients and healthy controls

	Patients (n = 96) Mean ± SD / n (%)	Healthy control group (n = 70) Mean ± SD / n (%)	P
Age (years)	43.51 ± 11.51	44.94 ± 10.69	0.029
Female/Male	36 (37.5%)/60 (62.5%)	39 (55.7%) /31 (44.3%)	0.026
BMI (kg/m^2)	27.47 ± 5.82	25.53 ± 5.51	**0.003***
Time since transplant (months)	40.8 ± 2.31		
Diabetes mellitus	9 (9.4%)		
Hypertension	81 (84.4%)		
Cyclosporine-MMF/MNa-steroid	10 (10.4%)		
Tacrolimus-MMF/MNa-steroid	77 (80.2%)		
Everolimus-tacrolimus-steroid	9 (9.3%)		
Creatinine (mg/dL)	1.24 ± 0.46	0.82 ± 0.11	**< 0.001***
eGFR (mL/min/1.73 m^2)	63.69 ± 20.84	88.10 ± 13.28	**< 0.001****
PTH (pg/mL)	102.21 ± 97.24	43.38 ± 15.33	**< 0.001***
Ca (mg/dL)	9.28 ± 0.50	9.25 ± 0.33	0.810*
P (mg/dL)	3.20 ± 0.64	3.19 ± 0.50	0.801*
25(OH)VitD_3 (ng/mL)	16.85 ± 7.22	27.54 ± 14.10	**< 0.001***
TC (mg/dL)	186.01 ± 38.72	205.47 ± 41.00	**0.004***
LDL-C (mg/dL)	105.00 ± 33.93	124.27 ± 39.15	0.007*
HDL-C (mg/dL)	49.01 ± 13.06	60.26 ± 10.70	**< 0.001***
Triglyceride (mg/dL)	157.44 ± 87.84	105.51 ± 35.46	**< 0.001***
Log_{10} Ang-2 (pg/mL)	3.48 ± 0.18	3.47 ± 0.10	**0.009**
Log_{10} VEGF (pg/mL)	1.88 ± 0.48	1.79 ± 0.34	**0.029**
CA-IMT (mm)	0.91 ± 0.34	0.67 ± 0.07	**< 0.001***
RRI	0.66 ± 0.06	0.63 ±0 .04	**< 0.001***

*Mann Whitney U test; ** Independent samples t-test.

BMI = body mass index; MMF = mycophenolate mofetil; Mna = mycophenolate sodium; eGFR = estimated glomerular filtration rate; PTH = parathyroid hormone; Ca = calcium; P = phosphate; 25(OH)VitD_3 = 25 hydroxy(OH)vitamin(Vit) D_3; TC = total cholesterol; LDL-C = low density lipoprotein cholesterol; HDL-C = high density lipoprotein cholesterol; VEGF = vascular endothelial growth factor; Ang-2 = angiopoietin-2; CA-IMT = carotid artery intima-media thickness; RRI = renal resistivity index.

Table 2. Comparison of patient characteristics according to median of log_{10} angiopoietin-2

	Log10 Ang-2 < 3.53 (n = 51) Mean ± SD	Log10 Ang-2 ≥ 3.53 (n = 45) Mean ± SD	P
Time since transplant (months)***	128.24 ± 73.39	110.61 ± 61.38	0.200
eGFR (mL/min/1.73 m^2)****	62.92 ± 21.18	64.56 ± 20.65	0.704
PTH (pg/mL)****	102.78 ± 113.89	101.56 ± 75.34	0.280
Ca (mg/dL)****	9.15 ± 0.42	9.42 ± 0.55	0.006
P (mg/dL)****	3.30 ± 0.63	3.09 ± 0.64	0.117
25(OH)VitD_3 (ng/mL)***	16.39 ± 8.10	17.43 ± 5.97	0.499
CA-IMT (mm)****	0.93 ± 0.35	0.88 ± 0.33	0.621
RRI****	0.65 ± 0.06	0.66 ± 0.06	0.365

***Mann Whitney U test; ****t-test in independent samples

SD = standard deviation; Ang-2 = Angiopoietin-2; eGFR = estimated glomerular filtration rate; PTH = parathyroid hormone; Ca = calcium; P = phosphate; 25(OH) VitD_3 = 25 hydroxy(OH)vitamin(Vit) D_3; CA-IMT = carotid artery intima-media thickness; RRI = renal resistivity index.

Table 3. Comparison of patient characteristics according to median of log_{10} vascular endothelial growth factor

	Log10 VEGF < 1.98 (n = 48) Mean ± SD	Log10 VEGF ≥ 1.98 (n = 48) Mean ± SD	P
Time since transplant (months)***	122.90 ± 80.67	117.19 ± 53.56	0.791
eGFR (mL/min/1.73 m^2)****	67.42 ± 19.06	59.96 ± 22.05	0.079
PTH (pg/mL)****	82.90 ± 87.64	121.52 ± 103.29	0.102
Ca (mg/dL)****	9.18 ± 0.39	9.37 ± 0.58	0.128
P (mg/dL)****	3.25 ± 0.51	3.16 ± 0.76	0.654
25(OH)VitD_3 (ng/mL)***	17.00 ± 7.34	16.69 ± 7.18	0.838
CA-IMT (mm)****	0.94 ± 0.35	0.88 ± 0.32	0.272
RRI****	0.65 ± 0.06	0.67 ± 0.07	0.122

***Mann Whitney U test; ****t-test in independent samples

VEGF = vascular endothelial growth factor; SD = standard deviation; eGFR = estimated glomerular filtration rate; PTH = parathyroid hormone; Ca = calcium; P = phosphate; 25(OH)VitD_3 = 25 hydroxy(OH) vitamin(Vit) D_3; CA-IMT = carotid artery intima-media thickness; RRI = renal resistivity index.

Figure 1. Relationship between angiopoietin-2 and estimated glomerular filtration rate (r = 0.073, P = 0.479).

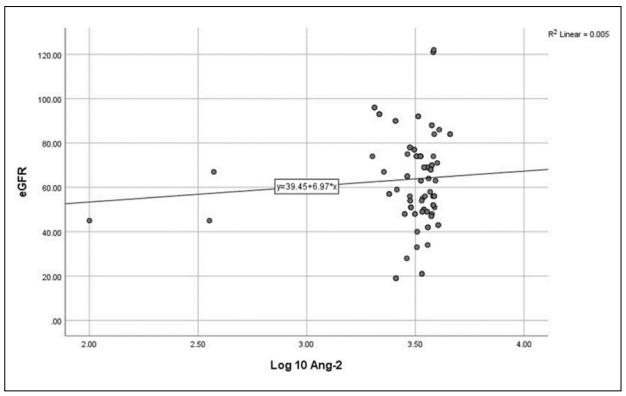


Figure 2. Relationship between angiopoietin-2 and carotid artery intima-media thickness (r = -0.067, P = 0.533).

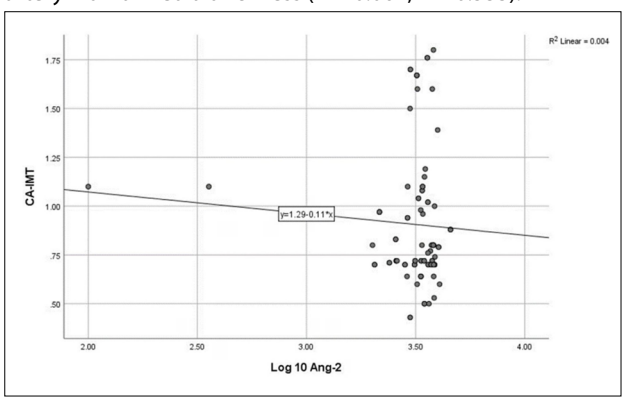


Figure 3. Relationship between angiopoietin-2 and renal resistivity index (r = - 0.172, P = 0.097).

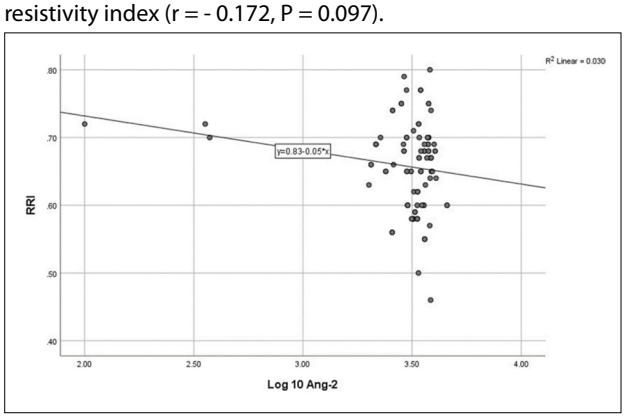


Figure 4. Relationship between vascular endothelial growth factor and estimated glomerular filtration rate (r = -0.130, P = 0.205).

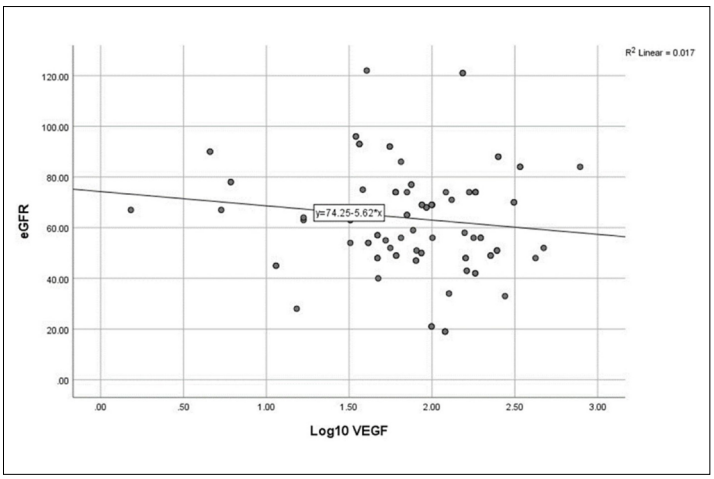


Figure 5. Relationship between vascular endothelial growth factor and carotid artery intima-media thickness (r = 0.111, P = 0.299).

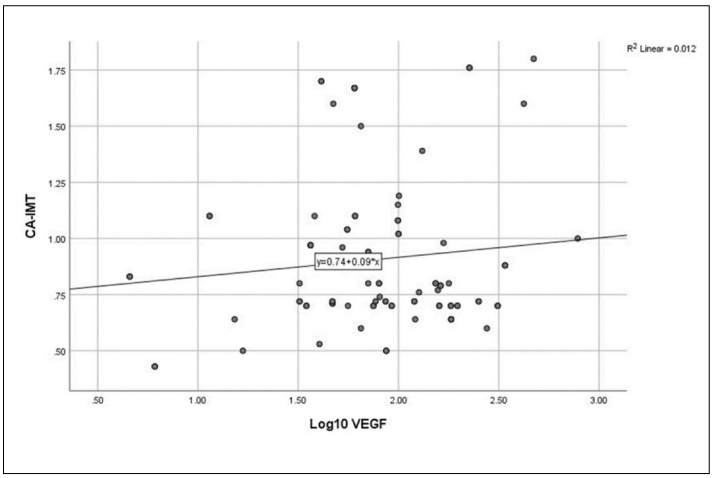
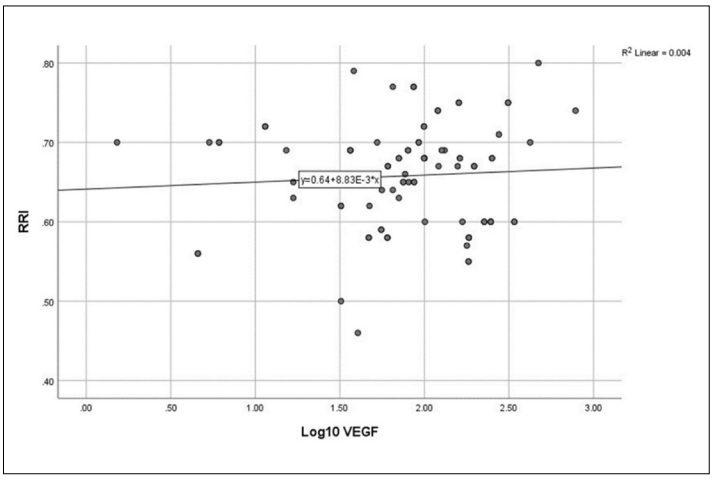


Figure 6. Relationship between vascular endothelial growth factor and renal resistivity index (r = 0.067, P = 0.522).



DISCUSSION

Increased serum Ang-2 and VEGF levels were detected in RTRs compared to those in healthy individuals in our study. In addition, increased atherosclerosis development, as determined by CA-IMT and RRI, was found in RTRs compared to those in

Table 4. Correlation between serum growth factors and atherosclerosis

	Log10 VEGF r	Log10 VEGF P	Log10 Ang-2 r	Log10 Ang-2 P
Time since transplant (months)	0.053	0.610	-0.117	0.260
eGFR (mL/min/1.73 m²)	-0.130	0.205	0.073	0.479
PTH (pg/mL)	0.134	0.194	0.014	0.890
Ca (mg/dL)	0.170	0.197	0.216	0.350
P (mg/dL)	-0.134	0.193	-0.070	0.498
25(OH)VitD_3 (ng/mL)	0.016	0.879	0.102	0.338
CA-IMT (mm)	0.111	0.299	-0.067	0.533
RRI	0.067	0.522	-0.172	0.097

Mann Whitney U test; Spearman correlation test
VEGF = vascular endothelial growth factor; Ang-2 = Angiopoietin-2; eGFR = estimated glomerular filtration rate; PTH = parathyroid hormone; Ca = calcium; P = phosphate; 25(OH)VitD_3 = 25 hydroxy(OH)vitamin(Vit) D_3; CA-IMT = carotid artery intima-media thickness; RRI = renal resistivity index.

Table 5. Association between serum angiogenic growth factors and atherosclerosis in multivariate analysis

	β	SE	P
Log10 VEGF			
eGFR (mL/min/1.73 m²)	0.000	0.002	0.868
CA-IMT (mm)	0.024	0.133	0.859
RRI	0.896	0.705	0.207
Log10 Ang-2			
eGFR (mL/min/1.73 m²)	0.000	0.001	0.707
CA-IMT (mm)	-0.053	0.068	0.437
RRI	-0.489	0.361	0.179

SE = standard error; VEGF = vascular endothelial growth factor; Ang-2 = Angiopoietin-2; eGFR = estimated glomerular filtration rate; CA-IMT = carotid artery intima-media thickness; RRI = renal resistivity index.

healthy individuals. No relationship was found between Ang-2 and VEGF and atherosclerosis.

Patients with CKD show increased atherosclerosis, as determined by CA-IMT; however, results regarding the effects of renal transplantation on atherosclerosis development are conflicting. In a study conducted with 178 RTRs, Yilmaz et al. reported an improvement in atherosclerosis 6 months after the transplantation and that the improvement was associated with the accompanying increase in eGFR, but the values were still higher when compared to healthy individuals.[10] Nafar et al. reported that the CA-IMT value increased gradually 2, 4, and 6 months after the transplantation.[11] Pinho et al. reported accelerated atherosclerosis development after renal transplantation.[12] Junarta et al. detected no relationships between eGFR and atherosclerosis and observed increased atherosclerosis development determined by CA-IMT in RTRs.[13] Basinatria et al. reported that the CA-IMT value was higher in young RTRs than in healthy individuals and that the development of subclinical atherosclerosis was observed concerning sex and cumulative calcitriol dose.[14] Kasiske et al. reported an acceleration in the atherosclerotic process after the transplantation in RTRs who did not have atherosclerotic disease before the transplantation.[15] Lindholm et al. reported that atherosclerotic complications were significantly higher in RTRs than in the normal population.[16] Turkmen et al. found increased atherosclerosis, determined by CA-IMT, in RTRs when compared to healthy individuals, and this was associated with increased oxidative stress, expression of pro-inflammatory and prothrombotic molecules, and decreased endothelial repair ability.[17] Increased atherosclerosis determined by CA-IMT was observed in RTRs compared to healthy individuals in the present study.

Renal dysfunction (anatomical and functional changes in the microcirculation of the kidney) implies increased RRI values because of a decreased number and area of postglomerular capillaries. An increased RRI is associated with the degree of renal impairment as a measure of increased microvascular tonus. Scarring in the kidneys causes a decrease in the area of intrarenal vessels, which causes an increase in intrarenal vascular resistance.[3] Calabia et al. reported that the mean RRI value was 0.69 ± 0.08 and RRI values were significantly higher in patients with CKD.[7] Shimizu et al. reported significant relationships between RRI and carotid atherosclerosis.[6] Radermacher et al. reported that increased RRI value was associated with increased mortality in RTRs.[3] Heine et al. reported that RRI was a complex integration of arterial compliance, pulsatility, and peripheral resistance in RTRs and was associated with subclinical atherosclerotic vascular damage and traditional CV risk factors; therefore, it is a marker of not only renal but also general vascular atherosclerosis.[18] Akgul et al. reported a relationship between RRI and CV risk factors and atherosclerosis determined by CA-IMT in RTRs.[19] Brennan et al. reported a significant relationships between RRI and traditional CV risk factors and subclinical atherosclerosis in renal transplantation.[20] Köger et al. found a significant correlation between mean renal transplantation RRI and mean internal carotid artery RRI in RTRs and noted that RRI was associated with overall atherosclerosis. They also reported that traditional CV risk factors and markers of subclinical atherosclerosis were associated with elevated RRI in RTRs.[21] Increased atherosclerosis determined by RRI was observed in RTRs compared with healthy individuals in the present study.

In the present study, increased serum Ang-2 levels were detected in RTRs compared with those in healthy individuals. David et al. reported an inverse relationship between serum Ang-2 levels and eGFR in patients with CKD, and showed that circulating Ang-2 levels increased in patients with stage 1-5 CKD and patients on dialysis, and also reported that Ang-2 levels increased shortly after nephrectomy in a group of 15 healthy renal donors and correlated with a decrease in eGFR. They noted that the high Ang-2

levels returned to normal 3 months after renal transplantation. Endothelial WBP, synthesized from activated endothelial cells in patients with CKD, is the primary source of Ang-2. WBP secretion is activated by physical damage (hypoxia and trauma), endogenous chemicals (reactive oxygen species, histamine, and serotonin), and proteins (thrombin, VEGF, etc.). As the only known inhibitor of WBP exocytosis, nitric oxide is decreased in patients with CKD.[22] In vivo studies have shown that pharmacological inhibition of nitric oxide production increases endothelial WPB exocytosis. Increased Ang-2 levels may result from excessive WPB exocytosis because of decreased nitric oxide in patients with CKD.[23] Yang et al. reported higher serum Ang-2 levels in peritoneal dialysis patients than in healthy individuals, suggesting that increased Ang-2 levels resulted from excessive WPB exocytosis because of decreased nitric oxide production. Ang-2 expression has also been detected in high glucose and tumor necrosis factor-alpha levels in dialysis patients in vitro.[24]

Tsai et al. showed an independent association between increased serum Ang-2 levels and all-cause mortality and adverse CV events in patients with CKD.[25] David et al. reported a relationship between increased Ang-2 and increased CV mortality in patients with CKD.[26] Iribarren et al. reported that increased serum Ang-2 levels may be associated with CV disease progression and could be used as a marker for CV events that might develop.[27] Le et al. reported that Ang-2 was elevated in vascularized and rupture-prone human atherosclerotic plaques.[28] El-Asrar et al. reported that Ang-2 was a significant independent risk factor for atherosclerosis because of its role in vascular dysfunction in patients with type 1 diabetes mellitus.[29] Yang et al. reported a relationship between Ang-2 and atherosclerosis in peritoneal dialysis patients and that high Ang-2 levels would independently predict fatal and non-fatal CV events.[24] Shroff et al. studied children undergoing dialysis treatment and found an association between increased serum Ang-2 levels and atherosclerosis as assessed by CA-IMT.[30] Mayer et al. reported that Ang-2 showed an increase with advancing disease stage in patients with CKD, and caused increased atherosclerosis.[31] David et al. reported that Ang-2 was a marker of atherosclerosis in patients with CKD and that Ang-2-induced endothelial activation had important roles in the pathogenesis of atherosclerosis.[22] No relationships were found between Ang-2 and atherosclerosis determined by CA-IMT and RRI in RTRs in the present study. Ahmed et al. reported that Ang-2 inhibits atherosclerosis by limiting LDL oxidation over a nitric oxide-dependent pathway by stimulating the release of nitric oxide from endothelial cells.[32] David et al. reported that elevated Ang-2 was an indicator of atherosclerosis in dialysis patients and that Ang-2 was not a marker of atherosclerosis in renal transplantation, attributing this to the disappearance of atherosclerotic changes after renal transplantation.[33]

In the present study, increased serum VEGF levels were observed in RTRs compared to healthy individuals. Blann et al. reported elevated serum VEGF levels in diabetic patients.[34] Liu et al. suggested an increased serum VEGF levels in patients with CKD compared to healthy individuals probably due to decreased excretion because of decreased renal function or VEGF being closely associated with CKD pathogenesis.[35] Nguyen et al. reported that VEGF was inversely correlated with eGFR in patients with diabetic stage 3-5 CKD and increased serum VEGF levels were detected when compared to healthy individuals.[36] Pilmore et al. reported an increased serum VEGF levels in RTRs because of hypoxia and decreased renal blood flow in chronic rejection.[37] Rintala et al. reported that VEGF ligands and receptors increased after renal transplantation in mice.[38]

The role of VEGF in the molecular mechanisms underlying atherosclerotic lesions remains controversial. Angiogenesis mediates plaque growth, promoting the influx of erythrocytes and inflammatory cells, resulting in plaque rupture and deterioration of atherosclerosis. Hypoxia and inflammation in atherosclerotic plaques trigger VEGF synthesis in macrophages. Felmeden et al. reported a relationship between high serum VEGF levels and endothelial damage/dysfunction and CV risk in hypertensive patients.[39] Celletti et al. suggested that VEGF potentially enhanced the development of early atherosclerotic plaques and contributed to plaque destabilization and atherosclerosis deterioration.[40] Inoue et al. noted that VEGF promoted the development of atherosclerosis by stimulating monocyte chemotaxis and plaque neovascularization.[41] Celletti et al. showed that VEGF promotes atherosclerotic plaque formation in mice[40] and Ohtani et al. showed that it stimulated the development of atherosclerosis through the infiltration of macrophages and mobilization of myelocytes in rabbits.[42] Yu et al. suggested that VEGF could be defined as a marker of atherosclerosis, based on their experiment in rabbits.[43] Kimura et al. reported that serum VEGF could be used as a prognostic marker for atherosclerosis development in humans.[44] In the present study, no relationships were detected between VEGF and atherosclerosis determined by CA-IMT and RRI in RTRs. VEGF inhibits media thickening by accelerating vascular endothelial cell regeneration and improving endothelial function. Milasan et al. reported that VEGF inhibits the inflammatory response, and prevents the progression of atherosclerosis by stimulating the expansion and proliferation of lymphatic vessels and reducing oxidative stress.[45] Heinonen et al. reported that VEGF causes decreased atherosclerosis development by reducing plasma lipoprotein lipase activity and accumulating chylomicrons, LDL, and triglycerides in large lipoprotein granules.[46] Lim et al. reported that VEGF and Ang-2 levels increased in diabetic patients, but detected no relationships between them and endothelial damage and atherosclerosis.[47] Sánchez-Escuredo et al.

reported that although an independent relationship was detected between interleukin-8 and C-reactive protein, which are inflammation markers, and increased CA-IMT and CV mortality after renal transplantation, such a relationship was not detected with VEGF.[48] After renal transplantation, secondary to the decreased atherosclerosis[49], a decrease in the receptors and effects of angiogenic growth factors synthesized from atherosclerotic plaques may occur. Fiedler et al.[50] reported that Ang may be responsible for the development of CV events by triggering microinflammatory events on the endothelium without causing atherosclerosis.

The present study has some limitations. First, the study had a cross-sectional design, was conducted in a single center, and included a limited number of patients. Because this study had a small sample size, it was difficult to uncover the traditional and non-traditional risk factors that cause atherosclerosis development. Second, serum Ang-2 and VEGF-A levels and ultrasonographic findings were determined only at the beginning of the study, and follow-up values were not obtained because the study was cross-sectional. Third, no comparisons were made based on serum angiogenic growth factor levels and CA-IMT values in patients who received peritoneal dialysis or hemodialysis treatment before transplantation. Serum angiopoietin and VEGF levels, and atherosclerosis findings were determined only at the beginning of the study, and follow-up values were not obtained. Therefore, the relationship between growth factors and atherosclerosis was not examined in RTRs during the follow-up periods. Additionally, antihypertensive and antihyperlipidemic medications were continued for ethical reasons. Therefore, it is not possible to rule out the direct effects of these drugs on endothelial function. This may have affected the actual atherosclerosis rates in the patients included in this study. Finally, other subtypes of growth factors, tissue receptors, and inflammatory parameters and their effects on atherosclerosis have not been investigated.

CONCLUSION

Increased serum angiogenic growth factor levels and atherosclerosis development were detected in RTRs. No relationship was detected between the angiogenic growth factors and atherosclerosis. This may be due to decreased levels of serum angiogenic growth factors and receptors synthesized from atherosclerotic plaques that resolved after transplantation. Further multicenter studies with a larger number of patients are needed because of conflicting results.

REFERENCES

1. Sarnak MJ, Levey AS, Schoolwerth AC, et al. Kidney disease as a risk factor for development of cardiovascular disease: a statement from the American Heart Association Councils on Kidney in Cardiovascular Disease, High Blood Pressure Research, Clinical Cardiology, and Epidemiology and Prevention. Circulation. 2003;108(17):2154-69. PMID: 14581387; https://doi.org/10.1161/01.cir.0000095676.90936.80.
2. Recio-Mayoral A, Banerjee D, Streather C, Kaski JC. Endothelial dysfunction, inflammation and atherosclerosis in chronic kidney disease--a cross-sectional study of predialysis, dialysis and kidney-transplantation patients. Atherosclerosis. 2011;216(2):446-51. PMID: 21414625; https://doi.org/10.1016/j.atherosclerosis.2011.02.017.
3. Radermacher J, Mengel M, Ellis S, et al. The renal arterial resistance index and renal allograft survival. N Engl J Med. 2003;349(2):115-24. PMID: 12853584; https://doi.org/10.1056/nejmoa022602.
4. Chudek J, Kolonko A, Król R, et al. The intrarenal vascular resistance parameters measured by duplex Doppler ultrasound shortly after kidney transplantation in patients with immediate, slow, and delayed graft function. Transplant Proc. 2006;38(1):42-5. PMID: 16504659; https://doi.org/10.1016/j.transproceed.2005.12.013.
5. Kramann R, Frank D, Brandenburg VM, et al. Prognostic impact of renal arterial resistance index upon renal allograft survival: the time point matters. Nephrol Dial Transplant. 2012;27(10):3958-63. PMID: 22247231; https://doi.org/10.1093/ndt/gfr772.
6. Shimizu Y, Itoh T, Hougaku H, et al. Clinical usefulness of duplex ultrasonography for the assessment of renal arteriosclerosis in essential hypertensive patients. Hypertens Res. 2001;24(1):13-7. PMID: 11213024; https://doi.org/10.1291/hypres.24.13.
7. Calabia J, Torguet P, Garcia I, et al. The relationship between renal resistive index, arterial stiffness, and atherosclerotic burden: the link between macrocirculation and microcirculation. J Clin Hypertens. 2014;16(3):186-91. PMID: 24548343; https://doi.org/10.1111/jch.12248.
8. Barr MP, Bouchier-Hayes DJ, Harmey JJ. Vascular endothelial growth factor is an autocrine survival factor for breast tumour cells under hypoxia. Int J Oncol. 2008;32(1):41-8. PMID: 18097541.
9. Shibuya M. Vascular endothelial growth factor and its receptor system: physiological functions in angiogenesis and pathological roles in various diseases. J Biochem. 2013;153(1):13-9. PMID: 23172303; https://doi.org/10.1093/jb/mvs136.
10. Yilmaz MI, Sonmez A, Saglam M, et al. A longitudinal study of inflammation, CKD-mineral bone disorder, and carotid atherosclerosis after renal transplantation. Clin J Am Soc Nephrol. 2015;10(3):471-9. PMID: 25542907; https://doi.org/10.2215/cjn.07860814.
11. Nafar M, Khatami F, Kardavani B, et al. Atherosclerosis after kidney transplantation: changes of intima-media thickness of carotids during early posttransplant period. Urol J. 2007;4(2):105-10. PMID: 17701931.
12. Pinho A, Sampaio S, Pestana M. Accelerated atherosclerosis after renal transplantation: an unsuspected cause of uncontrolled hypertension. Int J Nephrol Renovasc Dis. 2014;7:295-6. PMID: 25053893; https://doi.org/10.2147/IJNRD.S69358
13. Junarta J, Hojs N, Ramphul R, et al. Progression of endothelial dysfunction, atherosclerosis, and arterial stiffness in stable kidney transplant patients: a pilot study. BMC Cardiovasc Disord. 2020;20(1):6. PMID: 31914943; https://doi.org/10.1186/s12872-019-01309-y.

14. Basiratnia M, Fazel M, Lotfi M, et al. Subclinical atherosclerosis and related risk factors in renal transplant recipients. Pediatr Nephrol. 2010;25(2):343-8. PMID: 19911201; https://doi.org/10.1007/s00467-009-1345-0.
15. Kasiske BL. Risk factors for accelerated atherosclerosis in renal transplant recipients. Am J Med. 1988;84(6):985-92. PMID: 3287917; https://doi.org/10.1016/0002-9343(88)90302-6.
16. Lindholm A, Albrechtsen D, Frödin L, et al. Ischemic heart disease--major cause of death and graft loss after renal transplantation in Scandinavia. Transplantation. 1995;60(5):451-7. PMID: 7676492; https://doi.org/10.1097/00007890-199509000-00008.
17. Turkmen K, Tonbul HZ, Toker A, et al. The relationship between oxidative stress, inflammation, and atherosclerosis in renal transplant and end-stage renal disease patients. Ren Fail. 2012;34(10):1229-37. PMID: 23025491; https://doi.org/10.3109/0886022x.2012.723580.
18. Heine GH, Gerhart MK, Ulrich C, Köhler H, Girndt M. Renal Doppler resistance indices are associated with systemic atherosclerosis in kidney transplant recipients. Kidney Int. 2005;68(2):878-85. PMID: 16014069; https://doi.org/10.1111/j.1523-1755.2005.00470.x.
19. Akgul A, Sasak G, Basaran C, et al. Relationship of renal resistive index and cardiovascular disease in renal transplant recipients. Transplant Proc. 2009;41(7):2835-37. PMID: 19765450; https://doi.org/10.1016/j.transproceed.2009.07.023.
20. Brennan DC, Lentine KL. Is there a correlation between atherosclerosis and renal resistive indices in kidney transplant recipients? Nat Clin Pract Nephrol. 2006;2(2):64-5. PMID: 16932391; https://doi.org/10.1038/ncpneph0090.
21. Köger P, Engelberger S, Thalhammer C, et al. Association of intrarenal resistance index and systemic atherosclerosis after kidney transplantation. In Vivo. 2021;35(6):3369-75. PMID: 34697171; https://doi.org/10.21873/invivo.12635.
22. David S, Kümpers P, Lukasz A, et al. Circulating angiopoietin-2 levels increase with progress of chronic kidney disease. Nephrol Dial Transplant. 2010;25(8):2571-6. PMID: 20179005; https://doi.org/10.1093/ndt/gfq060.
23. Schmidt RJ, Baylis C. Total nitric oxide production is low in patients with chronic renal disease. Kidney Int. 2000;58(3):1261-6. PMID: 10972689; https://doi.org/10.1046/j.1523-1755.2000.00281.x.
24. Yang X, Zhang H, Shi Y, et al. Association of serum angiopoietin-2 with malnutrition, inflammation, atherosclerosis and valvular calcification syndrome and outcome in peritoneal dialysis patients: a prospective cohort study. J Transl Med. 2018;16(1):312. PMID: 30445969; https://doi.org/10.1186/s12967-018-1687-0.
25. Tsai YC, Lee CS, Chiu YW, et al. Angiopoietin-2 as a prognostic biomarker of major adverse cardiovascular events and all-cause mortality in chronic kidney disease. PLoS One. 2015;10(8):e0135181. PMID: 26274392; https://doi.org/10.1371/journal.pone.0135181.
26. David S, John SG, Jefferies HJ, et al. Angiopoietin-2 levels predict mortality in CKD patients. Nephrol Dial Transplant. 2012;27(5):1867-72. PMID: 21976741; https://doi.org/10.1093/ndt/gfr551.
27. Iribarren C, Phelps BH, Darbinian JA, et al. Circulating angiopoietins-1 and -2, angiopoietin receptor Tie-2 and vascular endothelial growth factor-A as biomarkers of acute myocardial infarction: a prospective nested case-control study. BMC Cardiovasc Disord. 2011;11:31. PMID: 21672190; https://doi.org/10.1186/1471-2261-11-31.
28. Le Dall J, Ho-Tin-Noé B, Louedec L, et al. Immaturity of microvessels in haemorrhagic plaques is associated with proteolytic degradation of angiogenic factors. Cardiovasc Res. 2010;85(1):184-93. PMID: 19620132; https://doi.org/10.1093/cvr/cvp253.
29. El-Asrar MA, Elbarbary NS, Ismail EA, Bakr AA. Circulating angiopoietin-2 levels in children and adolescents with type 1 diabetes mellitus: relation to carotid and aortic intima-media thickness. Angiogenesis. 2016;19(3):421-31. PMID: 27236773; https://doi.org/10.1007/s10456-016-9517-6.
30. Shroff RC, Price KL, Kolatsi-Joannou M, et al. Circulating angiopoietin-2 is a marker for early cardiovascular disease in children on chronic dialysis. PLoS One. 2013;8(2):e56273. PMID: 23409162; https://doi.org/10.1371/journal.pone.0056273.
31. Mayer G. Capillary rarefaction, hypoxia, VEGF and angiogenesis in chronic renal disease. Nephrol Dial Transplant 2011;26(4):1132-7. PMID: 21330358; https://doi.org/10.1093/ndt/gfq832.
32. Ahmed A, Fujisawa T. Multiple roles of angiopoietins in atherogenesis. Curr Opin Lipidol. 2011;22(5):380-5. PMID: 21881497; https://doi.org/10.1097/mol.0b013e32834b26b3.
33. David S, Kümpers P, Hellpap J, et al. Angiopoietin 2 and cardiovascular disease in dialysis and kidney transplantation. Am J Kidney Dis. 2009;53(5):770-8. PMID: 19268412; https://doi.org/10.1053/j.ajkd.2008.11.030.
34. Blann AD, Belgore FM, McCollum CN, et al. Vascular endothelial growth factor and its receptor, Flt-1, in the plasma of patients with coronary or peripheral atherosclerosis, or Type II diabetes. Clin Sci. 2002;102(2):187-94. PMID: 11834138.
35. Liu Y, Hong K, Weng W, et al. Association of vascular endothelial growth factor (VEGF) protein levels and gene polymorphism with the risk of chronic kidney disease. Libyan J Med. 2023;18(1):2156675.
36. Nguyen TTU, Kim H, Chae YJ, Jung JH, Kim W. Serum VEGF-D level is correlated with renal dysfunction and proteinuria in patients with diabetic chronic kidney disease. Medicine. 2022;101(7):e28804. PMID: 35363168; https://doi.org/10.1097/md.0000000000028804.
37. Pilmore HL, Eris JM, Painter DM, et al. Vascular endothelial growth factor expression in human chronic renal allograft rejection. Transplantation. 1999;67(6):929-33. PMID: 10199746; https://doi.org/10.1097/00007890-199903270-00024.
38. Rintala SE, Savikko J, Rintala JM, von Willebrand E. Vascular endothelial growth factor (VEGF) ligand and receptor induction in rat renal allograft rejection. Transplant Proc. 2006;38(10):3236-8. PMID: 17175233; https://doi.org/10.1016/j.transproceed.2006.10.049.
39. Felmeden DC, Spencer CG, Belgore FM, et al. Endothelial damage and angiogenesis in hypertensive patients: relationship to cardiovascular risk factors and risk factor management. Am J Hypertens. 2003;16(1):11-20. PMID: 12517677; https://doi.org/10.1016/s0895-7061(02)03149-7.

40. Celletti FL, Waugh JM, Amabile PG, et al. Vascular endothelial growth factor enhances atherosclerotic plaque progression. Nat Med. 2001;7(4):425-9. PMID: 11283668; https://doi.org/10.1038/86490.
41. Inoue M, Itoh H, Ueda M, et al. Vascular endothelial growth factor (VEGF) expression in human coronary atherosclerotic lesions: possible pathophysiological significance of VEGF in progression of atherosclerosis. Circulation. 1998;98(20):2108-16. PMID: 9815864; https://doi.org/10.1161/01.cir.98.20.2108.
42. Ohtani K, Egashira K, Hiasa K, et al. Blockade of vascular endothelial growth factor suppresses experimental restenosis after intraluminal injury by inhibiting recruitment of monocyte lineage cells. Circulation. 2004;110(16):2444-52. PMID: 15477409; https://doi.org/10.1161/01.cir.0000145123.85083.66.
43. Yu ZM, Deng XT, Qi RM, et al. Mechanism of chronic stress-induced reduced atherosclerotic medial area and increased plaque instability in rabbit models of chronic stress. Chin Med J. 2018;131(2):161-70. PMID: 29336364; https://doi.org/10.4103/0366-6999.222322.
44. Kimura K, Hashiguchi T, Deguchi T, et al. Serum VEGF--as a prognostic factor of atherosclerosis. Atherosclerosis. 2007;194(1):182-8. PMID: 17141247; https://doi.org/10.1016/j.atherosclerosis.2006.07.025.
45. Milasan A, Smaani A, Martel C. Early rescue of lymphatic function limits atherosclerosis progression in Ldlr-/- mice. Atherosclerosis. 2019;283:106-19. PMID: 30851674; https://doi.org/10.1016/j.atherosclerosis.2019.01.031.
46. Heinonen SE, Kivelä AM, Huusko J, et al. The effects of VEGF-A on atherosclerosis, lipoprotein profile, and lipoprotein lipase in hyperlipidaemic mouse models. Cardiovasc Res. 2013;99(4):716-23. PMID: 23756254; https://doi.org/10.1093/cvr/cvt148.
47. Lim HS, Lip GY, Blann AD. Angiopoietin-1 and angiopoietin-2 in diabetes mellitus: relationship to VEGF, glycaemic control, endothelial damage/dysfunction and atherosclerosis. Atherosclerosis. 2005;180(1):113-8. PMID: 15823283; https://doi.org/10.1016/j.atherosclerosis.2004.11.004.
48. Sánchez-Escuredo A, Pastor MC, Bayés B, et al. Inflammation, metalloproteinases, and growth factors in the development of carotid atherosclerosis in renal transplant patients. Transplant Proc. 2010;42(8):2905-7. PMID: 20970566; https://doi.org/10.1016/j.transproceed.2010.07.076.
49. Yilmaz MI, Sonmez A, Saglam M, et al. A longitudinal study of inflammation, CKD-mineral bone disorder, and carotid atherosclerosis after renal transplantation. Clin J Am Soc Nephrol. 2015;10(3):471-9. PMID: 25542907; https://doi.org/10.2215/cjn.07860814.
50. Fiedler U, Reiss Y, Scharpfenecker M, et al. Angiopoietin-2 sensitizes endothelial cells to TNF-alpha and has a crucial role in the induction of inflammation. Nat Med. 2006;12(2):235-9. PMID: 16462802; https://doi.org/10.1038/nm1351.

Authors contributions: Melahat Coban: Conceptualization, Data curation, Formal Analysis, Funding acquisition, Investigation, Methodology, Project administration, Writing-original draft, Writing-review and editing; Beyza Algül Durak: Resources, Software, Supervision; Mine Sebnem Karakan: Validation, Visualization. All authors reviewed and approved the final version submitted for publication

ACKNOWLEDGEMENTS: We would like to thank all of the participants who volunteered their time to participate in this study

Sources of funding: None
Conflicts of interest: None

Date of first submission: April 4, 2024
Last received: April 4, 2024
Accepted: June 5, 2024

Address for correspondence:
Melahat Coban
Department of Nephrology, Ankara Bilkent City Hospital
Universiteler Str. No:1 Cankaya — 06800, Ankara, Turkey.
Tel: +90 5065101449
E-mail: melahatcoban@hotmail.com

Editor responsible for the evaluation process:
Marianne Yumi Nakai, MD, PhD (Associate Editor)
Paulo Manuel Pêgo-Fernandes, MD, PhD (Editor-in-chief)

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).

CQH 2024

XXIV CONGRESSO BRASILEIRO DE QUALIDADE EM SERVIÇOS DE SAÚDE

VII Congresso Brasileiro de Medicina Preventiva e Social e Administração em Saúde

Ação climática, inteligência artificial e gestão de pessoas. Qual o desafio para a **ÁREA DE SAÚDE?**

07 • NOV ON-LINE **08 • NOV** HÍBRIDO

Nos dias 07 e 08 de novembro de 2024, o CQH retorna com a **vigésima quarta edição do Congresso Brasileiro de Qualidade em Serviços da Saúde**. Te convidamos a participar deste evento inovador em sua área, disseminando a cultura da qualidade em hospitais, fortalecendo a sua organização e incentivando a inovação em gestão em saúde.

Neste ano, trazemos pautas atuais para o desenvolvimento de novos processos de trabalho em unidades de saúde, com foco em Ação Climática, Inteligência Artificial e Gestão de Pessoas.

12 HORAS
de conteúdo científico com certificado

Atualização **PROFISSIONAL**

Discussões de práticas **INOVADORAS** na qualidade e gestão

Escaneie o **QR code** e Não deixe de acompanhar o **#CQH2024**

11 3188-4281 | 11 96410-4330 | eventos@apm.org.br

www.apm.org.br/congresso-cqh-24

Médico Técnico Científico Responsável pelo evento: Dr. Milton Osaki | CRM 38982

CQH Compromisso com a Qualidade Hospitalar Excelência APM

ABRAMPAS Associação Brasileira de Medicina Preventiva e Social e Administração em Saúde

SOMPAS Sociedade Paulista de Medicina Preventiva e Administração e Saúde

APM ASSOCIAÇÃO PAULISTA DE MEDICINA

SulAmérica Médicos

O primeiro plano hospitalar com seguro de vida[1] exclusivo para médicos.

Planos a partir de R$335[2]
com benefícios especiais.

SulAmérica Saúde

Simule seu plano

Conheça as opções de planos que se ajustam a você, sua família e seu consultório.

3188-4200

Qualicorp Adm. de Benefícios ANS nº 417173

SulAmérica ANS nº 005622

quali corp

APM ASSOCIAÇÃO PAULISTA DE MEDICINA

[1]Consulte condições com o Consultor. [2]R$ 335,20 - Plano Especial 100 Adesão Trad. 23 F (ANS 496.356/23-3) da operadora SulAmérica, segmentação Hospitalar com obstetrícia, faixa etária até 18 anos, com coparticipação e acomodação individual, abrangência geográfica nacional (tabela de agosto/2024 - Titular + 2 ou mais dependentes).