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São Paulo Medical Journal
EVIDENCE FOR HEALTH CARE

INDEX

Editorial

Original article

Short communication

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Translational Medicine and Implementation Science

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In the past, numerous groundbreaking discoveries remained confined to basic sciences, taking decades to translate into diagnostic tools or treatments applicable to clinical practice.

A prime example is the association between cholesterol and atherosclerosis. Between 1908 and 1913, Russian researchers made the first observation of cholesterol-induced atherosclerosis in rabbits.[1] The Framingham Heart Study,[2] published in 1961, provided the first human evidence supporting this link. However, it was not until 1976 that the first statin drug was developed, beginning the modern era of atherosclerosis treatment.[3] This significant delay, mirrored in numerous other instances, represents a loss of valuable knowledge and human lives.

Translational Medicine emerged to address this challenge, encompassing three primary areas: a) accelerating the transfer of knowledge from basic research to clinical application; b) elucidating the causal mechanisms and pathophysiology of clinical observations through interaction with basic science; and c) implementing basic knowledge and concepts derived from clinical and experimental research into the general population, a field known as Implementation Science.

Implementation science demands consideration of multiple factors.

PERSONALIZED MEDICINE

Currently, medication prescriptions are based on research that has identified effective drug dosages. This approach fails to consider individual responses, focusing on the average rather than differentiating between responders and non-responders. Side effects are also reported in this manner. Randomized studies, on the contrary, exclude patients with comorbidities and only represent 6%–8% of the affected population, failing to reflect real-world scenarios. These limitations lead to errors and challenges in dose adjustment.

Pharmacogenetics offers a more precise understanding of patient responses to external agents, enabling personalized treatment strategies, such as preventing allergic reactions. In essence, understanding the human genome and bodily responses will pave the way for personalized treatments, taking into account individual reactions to contrast media, intolerance to external agents, salt sensitivity, and responses to antiplatelet and anticoagulant medications. While this is not yet standard practice, it is poised to become the norm in the near future.

SOCIOECONOMIC INEQUALITIES INFLUENCE DISEASES

The Whitehall Study,[4] conducted in the 1980s, demonstrated an association between lower job satisfaction and increased mortality. Subsequent research consistently shows that educational level, financial resources, and social status significantly impact disease prevalence and mortality rates.[5] The underlying mechanisms extend beyond psychological factors. Individuals with higher socioeconomic status are generally more informed about health issues, have access to better medical facilities, and can afford healthcare expenses. This universal issue, deeply intertwined with economic and social development, manifests in disparate health outcomes.

AGE AFFECTS THE COURSE OF ALL DISEASES

The global population is aging at an unprecedented rate. Comorbidities, such as cancer, cardiovascular diseases, rheumatic disorders, renal diseases, metabolic disorders, inflammatory diseases, urological disorders, respiratory diseases, neurological disorders (including dementia

and Alzheimer's), and psychiatric disorders, are highly prevalent among the older population. It is increasingly rare to find an older patient with only one disease, which underscores the need for multiple experts to collaborate and determine the most effective treatment approach in increasingly complex cases.[6,7] Consistent with this idea, a meta-analysis concluded that teamwork positively correlates with clinical outcomes.[8]

RISKS *VERSUS* BENEFITS OF MODERN TECHNOLOGIES

New technological advances in healthcare offer a multitude of benefits but also carry inherent risks. For instance, the ability to detect minimal thyroid, breast, and prostate lesions has led to unnecessary "preventive" interventions,[9] potentially causing harm and anxiety to patients. Similarly, imaging techniques such as scintigraphy, coronary computed tomography angiography, and percutaneous interventions can be misused, overburdening healthcare systems, escalating costs, and causing distress in patients.

Countries like the United Kingdom and Canada have already implemented measures to curb excessive use of these technologies. In Brazil too, we should adopt strategies to evaluate the quality of professional medical practice, similar to the assessments conducted by the Brazilian Bar Association. Implementing such measures is crucial, considering the limited federal budget, which falls short of meeting the needs of the majority who rely on the public health system (SUS), and cannot afford wastage.

Teaching hospitals play an essential role in this regard, as they provide a platform for critically assessing innovative techniques, and ensuring new technologies are adopted responsibly and effectively.

FOUNDATION OF PREVENTIVE MEDICINE: HEALTHY LIFESTYLE

When translating medical knowledge into practical applications for the general population, emphasizing the concept of a healthy lifestyle is paramount, particularly within the context of preventive medicine.

Most cardiovascular events, including myocardial infarction and death, are associated with modifiable risk factors such as dyslipidemia, smoking, hypertension, and diabetes.[5] Genetic factors play a minor role in most cases. The Whitehall Study, conducted in England,[4] demonstrated that public sector workers in lower hierarchical positions had a three to four times higher mortality rate than those in higher positions, further highlighting the influence of lifestyle on health outcomes.

The foundation of preventive medicine lies in adopting a healthy lifestyle, encompassing a diet rich in vegetables, fruits, and fish, coupled with reduced consumption of red meats and carbohydrates. Regular aerobic and strength exercises, at least 150 min/week, are strongly recommended, including for the protection of cognitive functions and the prevention of Alzheimer's disease.[5]

Exercise and diet are crucial for preventing and treating diabetes, hypertension, and obesity. Numerous smoking cessation programs are available with considerable success rates. In the book "The Blue Zones,"[10] American researchers examined the lifestyle of the five longest-living populations globally: Okinawa (Japan), Sardinia (Italy), Ikaria (Greece), Loma Linda (California), and Nicoya (Costa Rica). Common practices include a diet rich in grains, fruits, vegetables, and fish, with minimal red meat; a vibrant social life; spirituality; a strong emphasis on family; regular physical labor such as walking, tending to animals, cooking, and housekeeping; and limited use of medications. Genetic factors do not seem to be the sole explanation for this longevity, as the populations are from different countries with no familial relation.

Emotional stress from any source is a well-established causal factor in cardiovascular events. The exponential increase in such conditions during the coronavirus disease pandemic confirms this association.[11,12]

A unique challenge in promoting a healthy lifestyle lies in its implementation in adults, posing a significant obstacle for the third component of translational medicine: the general population. For instance, outcomes from initiatives to instill healthy habits in children and adolescents, as evidenced in Brazil and other countries,[13,14] are striking—with children monitoring their parents to ensure they avoid smoking, exercise, and maintain a healthy diet. Hulsegge *et al*.[15] found that individuals who sustained four to five healthy habits over 5 years had a 2.5-fold reduction in the risk of cardiovascular diseases and overall mortality compared to those who did not maintain these habits.

It is crucial to consider the setting in which such implementation takes place, whether in hospitals, educational programs, within the SUS, in private medical practice, during online consultations, or elsewhere. Different strategies are required depending on the context.

TEAMWORK

Given the complexity of certain cases, comorbidities, varying institutional capabilities, and individual experiences, working in multidisciplinary teams is an effective strategy to provide comprehensive patient care. In the field of cardiology, a typical team should include a clinician, an interventionalist, a surgeon, or an electrophysiologist.[16]

In practice, the recommendation of procedures is influenced by individual experience. For instance, hemodynamicists may favor percutaneous interventions, whereas surgeons might prefer surgical procedures. There are arguments supporting either procedure based on its non-invasive nature, longitudinal outcome data, the efficacy of pharmacological treatments, and patient lifestyle considerations. Furthermore, the swift advancement of research techniques and treatments, along with the unique expertise of physicians and medical centers, may also lead to variations in opinions. Therefore, the heart team aims to reduce these biases. In these circumstances, it is essential to ensure that the patient is informed and consulted regarding their preferences.

ESSENCE OF THE TRANSLATIONAL PROCESS: HIGH-QUALITY RESEARCH

The preceding arguments underscore the fundamental importance of scientific rigor throughout the translational medicine process. From the meticulous collection of experimental data in vitro, ex vivo, or in vivo, through the rigorous design and execution of clinical studies ranging from Phase I to III, to the responsible application of knowledge in the general population, scientific integrity must be paramount. Ideally, randomized clinical trials with well-defined, clinically relevant outcomes, adequate patient numbers, and appropriate follow-up duration are the preferred study design. However, implementing randomized trials is often hindered by substantial costs and delays in obtaining results.

Several factors clearly impact the translation of best practices into healthcare delivery for the population, including the off-label use of drugs, economic considerations, and misconceptions about exercising medical autonomy. Nevertheless, contemporary methods such as Mendelian randomization, Genome-Wide Association Studies, and big data analytics, enhanced by artificial intelligence, computational advances, and novel statistical techniques such as propensity score analysis, enable more comprehensive investigations that shed light on underlying causes and pathophysiological mechanisms.[17-19]

In the realm of interventions, clinical efficacy remains the primary concern for physicians. Ultimately, the credibility of medicine rests firmly on the principles of the scientific method.

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Diagnostic criteria and outcome measures in randomized clinical trials on carpal tunnel syndrome: a systematic review

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ABSTRACT

BACKGROUND: The diagnostic criteria for carpal tunnel syndrome (CTS) lack uniformity. Moreover, because CTS is a syndrome, there is no consensus as to which signs, symptoms, clinical and complementary tests are more reproducible and accurate for use in clinical research. This heterogeneity is reflected in clinical practice. Thus, establishing effective and comparable care protocols is difficult.

OBJECTIVE: To identify the diagnostic criteria and outcome measures used in randomized clinical trials (RCTs) on CTS.

DESING AND SETTING: Systematic review of randomized clinical trials carried out at the Federal University of São Paulo, São Paulo, Brazil.

METHODS: We searched the Cochrane Library, PubMed, and Embase databases for RCTs with surgical intervention for CTS published between 2006 and 2019. Two investigators independently extracted relevant data on diagnosis and outcomes used in these studies.

RESULTS: We identified 582 studies and 35 were systematically reviewed. The symptoms, paresthesia in the median nerve territory, nocturnal paresthesia, and special tests were the most widely used clinical diagnostic criteria. The most frequently assessed outcomes were symptoms of paresthesia in the median nerve territory and nocturnal paresthesia.

CONCLUSION: The diagnostic criteria and outcome measures used in RCTs about CTS are heterogeneous, rendering comparison of studies difficult. Most studies use unstructured clinical criteria associated with ENMG for diagnosis. The Boston Questionnaire is the most frequently used main instrument to measure outcomes.

REGISTRATION: PROSPERO (CRD42020150965- https://www.crd.york.ac.uk/prospero/display_record.php?RecordID=150965).

INTRODUCTION

Carpal tunnel syndrome (CTS) is the most prevalent peripheral neuropathy in the world.[1,2] Although some patients are treated conservatively, most require surgical treatment, which generates spending more than US$ 2 billion/year.[2]

The socioeconomic impact of the disease drove numerous randomized clinical trials (RCTs) to determine the best treatment for CTS. To identify effective interventions, accurate and relevant outcomes for the patient are needed.[3-6] There is extensive literature about objective outcomes (e.g., loss of strength) and variables derived from nerve conduction studies. However, how these outcomes translate into tangible benefits to the patients remains unclear.[3-6]

In CTS, the lack of uniform criteria poses a challenge in diagnosis. Thus, Graham proposed well-defined criteria, based on a robust methodology.[7] Moreover, because CTS is a syndrome, experts do not agree on which signs, symptoms, clinical and complementary tests are more reproducible and accurate in clinical research.[8]

This heterogeneity is reflected in clinical practice and has led to difficulty in establishing effective and comparable care protocols.[9,10] Thus, studies must use precise diagnostic methods and clarify the main post-surgical outcomes to be evaluated in patients with CTS.

Systematic reviews promote synthesis, provide a comprehensive view, and recommend the best available evidence on a topic. Diagnostic and rational management criteria are of interest.[8,10] Importantly, evaluation outcomes should reflect the impact of treatments on body structure and function, including activity limitations and participation restrictions, through a broad evaluation model.[11-13] The Classification of Functioning and Disability and Health (ICF), approved in 2001 by the World Health Organization, proposed a comprehensive assessment from both individual

and social perspectives.[14,15] The model aimed to recognize the abnormalities in the body structure, identify the consequences on function, and describe the repercussions and adaptations to such changes in the individual's social dynamics.[14] A previous systematic review on the subject was published in 2006.[8] Given the importance of the topic, we sought to give an update.

OBJECTIVE

The objective of this systematic review is to compare the diagnostic criteria and outcome measures based on ICF used in CTS over the past 15 years.

METHODS

This systematic review was approved by the Research Ethics Committee (no. 2248181019) and developed in accordance with the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) statement. The protocol was published a priori in the PROSPERO database (CRD42020150965 - https://www.crd.york.ac.uk/prospero/display_record.php?RecordID=150965).

Search strategy

We conducted a search of works published in English, from 2006 to 2019, at the Cochrane Library, Medline (via PubMed), and Embase (via Ovid). The search was performed independently by RLS and AFZ. We use the terms: carpal tunnel syndrome and randomized controlled trial along with the Boolean term AND for free search of Cochrane Library and Embase. For Medline, we searched the MeSH term carpal tunnel syndrome and randomized controlled trial; we then used the PubMed Search Builder tool to combine terms.

Criteria for selection of studies and procedures

After the initial screening based on the title and abstract, the full-text articles were independently reviewed by RLS and AFZ. These were included if they met the eligibility criteria enumerated below. Disagreements were resolved by a third author, VYM.

The inclusion criteria were: 1. Type of study: randomized clinical trials with follow-up longer than three months; 2. Patients: adults (>18 years) with initial diagnosis of CTS.

Exclusion criteria

1. Studies not published in English.
2. Studies that did not involve at least one surgical intervention

Data extraction

We extracted the following data: 1. Study design (country and year of publication); 2. Experimental and control interventions; 3. Sample size; 4. Follow-up time; 5. Blinding; 6. Diagnostic criteria; 7. Pre- and post-operative outcome measures.

Methodological quality assessment

We use the Cochrane Collaboration Risk-of-Bias tool,[51] which evaluates: 1. random sequence generation (selection bias); 2. Allocation Concealment (selection bias); 3. Blinding of participants and staff (performance bias); 4. Blinding of assessments and outcome (detection bias); 5. Incomplete outcomes (friction bias); 6. Selective outcome reporting (reporting bias) and 7. Other sources of bias (other biases).

Assessment of outcomes based on the International Classification of Functioning, Disability and Health (ICF)

This classification facilitates understanding of health determinants and health-related effects through a standardized and comprehensive terminology.[15] Correlating the pathophysiology of CTS with its clinical manifestations (i.e., signs and symptoms) assists in identifying specific structures and functions of the body altered by the disease (first domain of ICF). Additionally, patients may also have disabilities or limitations in performing activities of daily life (second domain of ICF), which impact situations of social life and satisfaction (third domain of ICF).[8,14]

Data analysis

The data collected were presented in tables. Each study was labelled according to its author. The data was managed in Excel 2020 (Microsoft Corporation, Redmond, Washington, United States).

RESULTS

From the 582 studies screened, 35 were included in the systematic review (**Figure 1**).[16-50] **Table 1** provides a meta-summary of the characteristics of the studies included.[16-50]

The outcome measures reported in the RCTs were classified according to the domains of the ICF: A) Body functions and structures (**Table 2**);[16-50] B) Activity limitations (**Table 3**)[16-50] and C) Social life/Satisfaction (**Table 3**).[16-50]

Characteristics of studies and evaluated outcomes

We analyzed studies that evaluated the effectiveness of different surgical and conservative techniques; some studies used more than one intervention. In the experimental group, classical open carpal ligament (CLL) release (12; 34%), modified open CLL release (12; 34%) and endoscopic CT release (6; 17%) were used. In addition, conservative interventions such as physiotherapy (5; 14%) and the use of drugs (3; 8%) were also tested. As control, classical open CT release (20; 57%), modified open CT release (7; 20%), endoscopic CT release (1; 3%), open surgery (1; 3%), physiotherapy (3; 8%) and drugs (6; 17%) were used. A total of 3,007 patients and 3138 hands were studied (some patients received

treatments for both hands). The follow-up time ranged from 3 to 60 months. The average follow-up was 12 months; five reported follow-up longer than 13 months. From the total, 25 studies (71%) showed adequate blinding.

The studies analyzed the following clinical diagnostic criteria for CTS: paresthesia in the territory of the median nerve, night paresthesia, and Phalen's and Tinel's tests (part of the six criteria described by Graham) (18 studies; 51%), the Katz diagram (3; 9%) and all the Graham criteria - CTS-6 (2; 6%). Other studies (12; 34%) did not specify the diagnostic method used (**Table 1**). Studies that used only part of the six criteria described by Graham[7] were classified as paresthesia and special tests.

Electroneuromyography (ENMG) was a complementary examination in 31 studies (89%) and ultrasonography in only one (3%). The studies that used ENMG were then classified based on the use of the Padua criteria,[52] used by 22 (71%). Three other studies (9%) did not use any type of complementary examination (**Table 1**).[16-50]

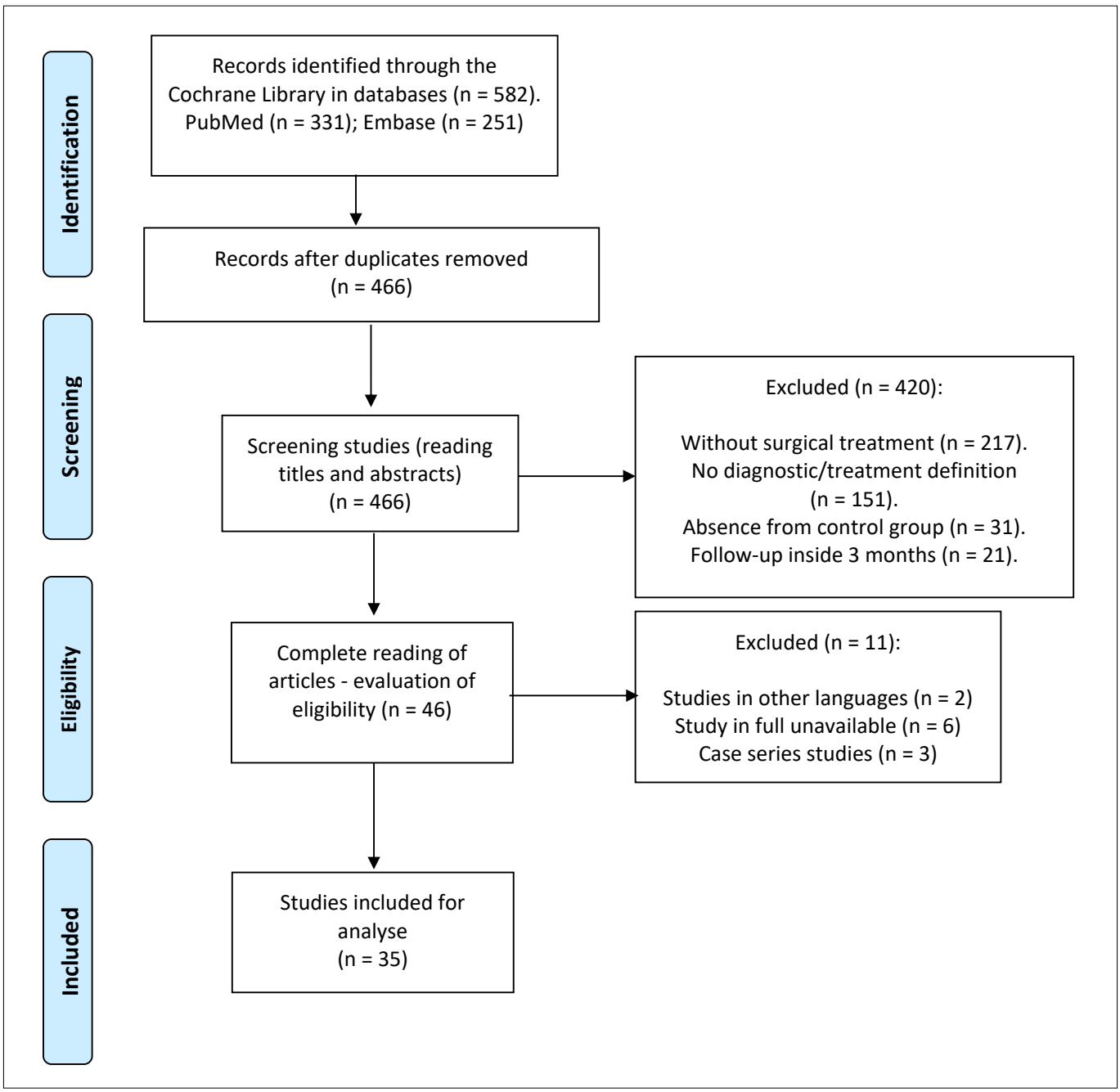

Figure 1. Flow diagram of eligible studies.[16-50]

Table 1. Summary of the included randomized controlled trials

First Author	Country	Diagnostic Criteria		Experimental studies	Intervention Control	Sample Size		Follow-up (months)	Blinding
		Clinics	Complementary examinations			Patients	Hands		
Rab[16]	Austria	Paresthesia + special tests	ENMG (Non-Padua criteria)	Endoscopic	Classic open CTD release	10	20	12	
Siegmeth[17]	United Kingdom	Paresthesia + special tests	-	CTD open modified release	Classic open CTD release	42	84	6	x
Zyluk[18]	Poland	Unspecified	ENMG (Non-Padua criteria)	CTD open modified release	CTD open modified release	65	73	12	x
Forward[19]	United Kingdom	Graham Criteria (CTS-6)	ENMG (Non-Padua criteria)	Classic open CTD release	CTD open modified release	112	112	3	x
Atroshi[20]	Sweden	Diagram Katz	ENMG (Non-Padua criteria)	Endoscopic	Classic open CTD release	128	128	12	x
Huemer[21]	Austria	Unspecified	ENMG (Non-Padua criteria)	Classic open CTD + release Small bandage	Classic open CTD release + Bulky bandage	50	50	3	
Pomerance[22]	United States	Paresthesia + special tests	ENMG (Non-Padua criteria)	Classic open CTD release + Physiotherapy	Classic open CTD release	150	150	6	x
Atroshi[23]	Sweden	Katz Diagram	ENMG (Non-Padua criteria)	Endoscopic	Classic open CTD release	126	126	60	
Gordon[24]	Canada	Unspecified	ENMG (Non-Padua criteria)	Physiotherapy	Classic open CTD release	21	21	12	
Faraj[25]	Iraq	Paresthesia + special tests	ENMG (Non-Padua criteria)	CTD open modified release	Classic open CTD release	40	40	3	
Nabhan[26]	Germany	Unspecified	ENMG (Non-Padua criteria)	Classic open CTD release + local anaesthesia	Classic open CTD release + regional anesthesia	43	43	6	x
Eriji[27]	Japan	Paresthesia + special tests	ENMG (Non-Padua criteria)	Endoscopic	Open Surgery	79	101	3	x
Uçar[28]	Turkey	Unspecified	ENMG (Non-Padua criteria)	CTD open modified release	CTD open modified release	90	90	30	
Larsen[29]	Denmark	Unspecified	ENMG (Non-Padua criteria)	CTD open modified release	Endoscopic	90	90	6	x
Tarallo[30]	Italy	Paresthesia + special tests	ENMG (Non-Padua criteria)	CTD open modified release	Classic open CTD release	120	120	12	
Ullah[31]	Pakistan	Paresthesia + special tests	ENMG (Non-Padua criteria)	Classic open CTD release	Pharmacological	40	40	13	x
Andreu[32]	Spain	Katz Diagram	ENMG (Non-Padua criteria)	Classic open CTD release	Pharmacological	95	95	12	
Vanni[33]	Italy	Paresthesia + special tests	ENMG (Non-Padua criteria)	CTD open modified release	Classic open CTD release	220	220	12	x
Peñas[34]	Spain	Paresthesia + special tests	ENMG (Non-Padua criteria)	Physiotherapy	Classic open CTD release	111	111	12	x
Sadatsunel[35]	Brazil	Paresthesia + special tests	ENMG (Non-Padua criteria)	Classic open CTD release + Pharmacological	Classic open CTD release + Pharmacological	37	37	6	x

Continue...

Table 1. Continuation.

First Author	Country	Diagnostic Criteria		Experimental studies	Intervention Control	Sample Size		Follow-up (months)	Blinding
		Clinics	Complementary examinations			Patients	Hands		
Rojo-Manaute[36]	Arab Emirates	Unspecified	ENMG (Non-Padua criteria)	CTD open modified release	CTD open modified release	82	82	12	x
Acar[37]	Turkey	Paresthesia + special tests	ENMG (Non-Padua criteria)	Classic open CTD release	CTD open modified release	113	159	24	x
Gumustas[38]	France	Unspecified	ENMG (Non-Padua criteria)	Endoscopic	Classic open CTD release	50	50	-	x
Cho[39]	South Korea	Paresthesia + special tests	ENMG (Non-Padua criteria)	CTD open modified release	CTD open modified release	79	79	24	x
Herold[40]	United Kingdom	Paresthesia + special tests	-	Physiotherapy	Classic open CTD release	93	93	3	x
Peñas[41]	Spain	Paresthesia + special tests	ENMG (Non-Padua criteria)	Classic open CTD release	Physiotherapy	120	120	12	x
Logli[42]	United States	Unspecified	ENMG (Non-Padua criteria)	Physiotherapy	Classic open CTD release	249	249	12	x
Peñas[43]	Spain	Paresthesia + special tests	ENMG (Non-Padua criteria)	Classic open CTD release	Physiotherapy	100	100	12	x
Peñas[44]	Spain	Paresthesia + special tests	ENMG (Non-Padua criteria)	Physiotherapy	Classic open CTD release	95	95	12	x
Boriani[45]	Italy	Paresthesia + special tests	ENMG (Non-Padua criteria)	Classic open CTD release + Pharmacological	Classic open CTD release + Pharmacological	64	64	3	x
Kleermaeker[46]	Germany	Paresthesia + special tests	ENMG (Non-Padua criteria)	Classic open CTD release	Physiotherapy and Pharmacology	43	43	6	x
Kanchanathepsak[47]	Thailand	Unspecified	-	CTD open modified release	Classic open CTD release	33	36	3	x
Oh[48]	South Korea	Unspecified	Ultrasonography	Endoscopic	CTD open modified release	67	67	6	
Rimdeika[49]	Germany	Unspecified	ENMG (Non-Padua criteria)	CTD open modified release	Classic open CTD release	104	104	4	
Zhang[50]	China	Paresthesia + special tests	ENMG (Non-Padua criteria)	CTD open modified release	Pharmacological	46	46	3	x
TOTAL n = 35						**3,007**	**3,138**		
Average ± SD						**82 ± 51**	**90 ± 51**	**12 ± 11**	

CDT = carpal transverse ligament; ENMG = electroneuromyography; SD = standard deviation.

Diagnostic criteria

Risk of bias - Cochrane Collaboration

Figure 2 presents the risk of study bias.[16-50] Because surgical intervention was involved, blinding was difficult; most were classified as having uncertain or high risk of bias.

Categorization of the outcomes analyzed based on the International Classification of Functionality, Disability and Health (ICF)

The outcomes reported in the ECR were categorized according to the three domains of the ICF.

A) Body functions and structures (Table 2): Among the outcomes analyzed, symptoms (paresthesia in the territory of the median and nocturnal nerve) were the most frequently employed (26 studies; 74%).[16-50]

Standardized questionnaires were used in 25 studies (71%): the Boston Questionnaire (BQ) (17; 65%), Disabilities of the Arm, Shoulder and Hand (Dash score) (4; 15%), Patient Evaluation Measure (PEM score) (2; 8%), Michigan Hand Outcomes Questionnaire (MHQ) (2; 8%), and QuickDash score (1; 4%). Only one study used more than one questionnaire.

Table 2. Outcomes in randomized clinical trials - body functions and structures

First Author	Symptoms	Motor Functions			Sensitive Functions			Body Structures			
	Paresthesia in the territory of the median and nocturnal nerve	Manual Grasping Force	Tweezers	Pick-up Test	2 Point Discrimination	Monofilament	Vibration	Nerve Conduction (sensitive and motor)	Wound Complications	Local Sensitivity Disorders	Causalgia
	Standard questionnaire used										
Rab[16]	Boston Questionnaire	x	x		x	x		x			
Siegmeth[17]	PEM score	x								x	
Zyluk[18]	Boston Questionnaire	x	x		x	x					
Forward[19]	PEM score	x	x								
Atroshi[20]	Boston Questionnaire	x	x		x	x				x	
Huemer[21]	-	x		x	x			x		x	
Pomerance[22]	Dash score	x	x								
Atroshi[23]	-										
Gordon[24]	Boston Questionnaire						x	x			
Faraj[25]	-								x		
Nabhan[26]	MHQ										
Eriji[27]	-	x	x		x	x		x		x	
Uçar[28]	Boston Questionnaire										
Larsen[29]	-	x									
Tarallo[30]	Boston Questionnaire	x	x		x				x	x	
Ullah[31]	-										
Andreu[32]	-								x		
Vanni[33]	Boston Questionnaire										
Peñas[34]	-							x			
Sadatsunel[35]	-										x
Rojo-Manaute[36]	Quickdash score	x								x	
Acar[37]	-							x		x	
Gumustas[38]	Boston Questionnaire							x			
Cho[39]	Boston Questionnaire									x	
Herold[40]	MHQ			x	x	x	x			x	
Peñas[41]	Boston Questionnaire										
Logli[42]	Dash score	x							x		
Peñas[43]	Boston Questionnaire										
Peñas[44]	Boston Questionnaire		x								
Boriani[45]	Boston Questionnaire				x			x			
Kleermaeker[46]	Boston Questionnaire										
Kanchanathepsak[47]	Boston Questionnaire	x	x		x	x		x	x		
Oh[48]	Boston Questionnaire + Dash score										
Rimdeika[49]	Dash score	x	x		x	x					
Zhang[50]	Boston Questionnaire							x			

PEM score = Patient Evaluation Measure; Dash = Disabilities of the Arm, Shoulder and Hand; MHQ = Michigan Hand Outcomes Questionnaire.

Motor functions, included in 16 studies (46%), were operationally defined as manual grasping force (14; 88%), tweezers (10; 62%) and pick-up test (2; 12%).

Sensory function was evaluated in 11 studies (31%). The most studied variable was two-point discrimination (10; 91%), followed by the monofilament test (8; 73%) and vibration (1; 10%).

Finally, the body structures were analyzed in 18 studies (51%), through sensory and motor nerve conduction (12; 67%), local sensitivity disorders (9; 50%), wound complications (3; 17%) and causalgia (1; 6%).

B) Limitations of activity (Table 3): Twenty-four (69%) studies evaluated activity limitations. The functional status scale of the BQ was the most frequently used outcome (17; 71%). The use of hands in daily life activities was analyzed in nine (38%) and dexterity in only two studies (8%).[16-50]

C) Restrictions of activities of social life/satisfaction (Table 3): Participation restrictions were analyzed in 12 studies (34%). Satisfaction was the most frequent outcome (6; 50%), followed by time off work (4; 33%) and aesthetic (4; 33%).[16-50]

DISCUSSION

This systematic review mapped the diagnostic criteria and outcome measures used in CTS ECRs. Paresthesia, in conjunction with special tests (part of Graham's criteria)[7], was the most widely used diagnostic clinical criterion, together with the complementary ENMG examination (mostly without the use of structured classification, such as that of Padua).[52] Various outcome measures were found; these categorized according to the domains of the ICF. For body functions and structures, symptoms (paresthesia

Table 3. Outcomes in randomized clinical trials - activity and social life limitations/satisfaction

First author	Activities (limitations)			Social life/Satisfaction		
	Dexterity	Use of hands in AVD's	Functional Status Scale - Boston Questionnaire	Time away from work	Satisfaction	Aesthetics
Rab[16]			Applied			
Siegmeth[17]		x	Not applied			x
Zyluk[18]			Applied			
Forward[19]			Not applied			
Atroshi[20]		x	Applied	x		
Huemer[21]			Not applied			
Pomerance[22]			Not applied	x		
Atroshi[23]			Not applied		x	
Gordon[24]	x		Applied			
Faraj[25]			Not applied		x	
Nabhan[26]		x	Not applied	x	x	x
Eriji[27]		x	Not applied			
Uçar[28]			Applied			
Larsen[29]			Not applied			
Tarallo[30]			Applied		x	x
Ullah[31]			Not applied			
Andreu[32]		x	Not applied			
Vanni[33]			Applied			x
Peñas[34]			Not applied			
Sadatsunel[35]			Not applied			
Rojo-Manaute[36]			Not applied	x		
Acar[37]			Not applied			
Gumustas[38]		x	Applied			
Cho[39]			Applied		x	
Herold[40]	x	x	Not applied			
Peñas[41]		x	Applied		x	
Logli[42]			Not applied			
Peñas[43]			Applied			
Peñas[44]			Applied			
Boriani[45]			Applied			
Kleermaeker[46]			Applied			
Kanchanathepsak[47]			Applied			
Oh[48]			Applied			
Rimdeika[49]		x	Not applied			
Zhang[50]			Applied			

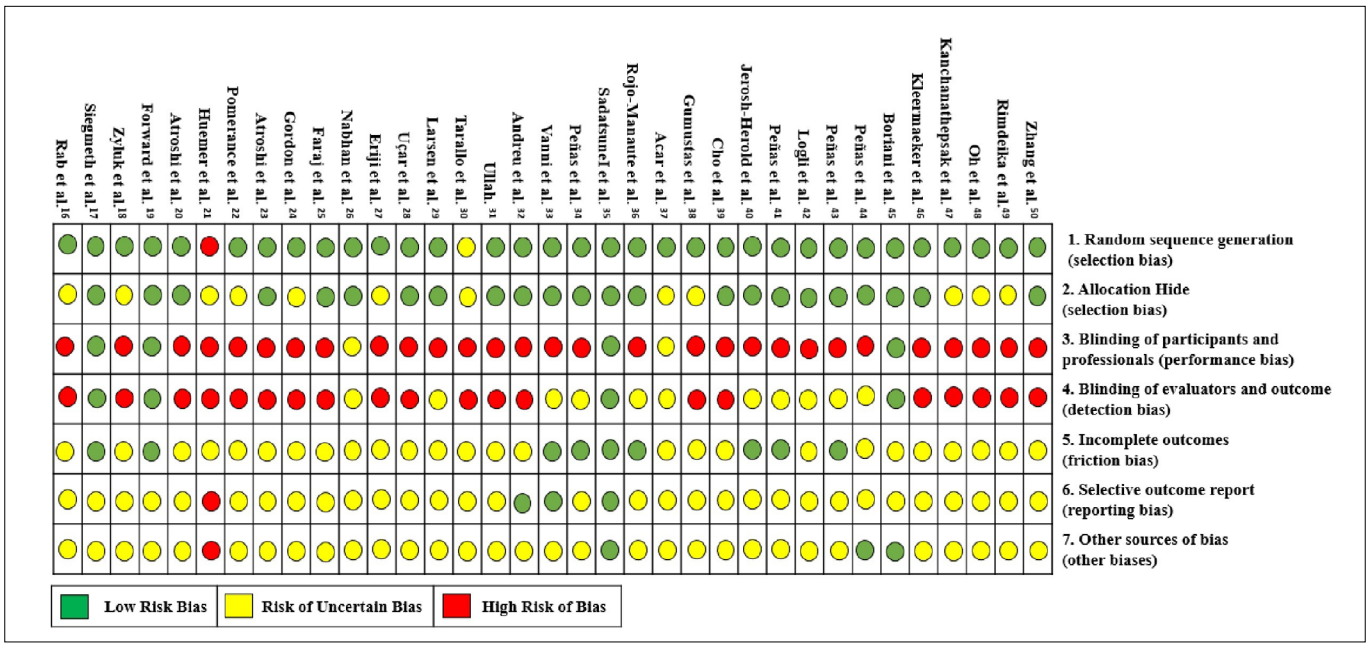

Figure 2. Risk of bias of randomized clinical trials included in the study - Cochrane Collaboration Tool.

in the territory of the median and nocturnal nerve) were the most evaluated outcomes, measured predominantly by means of BQ. The functional status scale of the BQ was the outcome of the highest evaluation in assessing activity limitations. Finally, participation/satisfaction restrictions were mainly evaluated through patient satisfaction.

Research for diagnostic methods (clinical and complementary) of CTS is important because of the high prevalence and potential disability resulting from the disease.[1,2] The presence of classical signs and symptoms (numbness and tingling in the distribution of the median nerve with nocturnal worsening) is appropriate for the diagnosis in most patients,.[53] However, clinical and complementary tests are important in most cases to determine the suitability of surgical or conservative management.[53] Graham's criteria are widely recommended.[7] However, systematic reviews challenge the use of two-point discrimination (one of Graham's criteria), due to its low diagnostic sensitivity for CTS.[54] Our results suggest the same, because most of the studies do not use two-point discrimination.

ENMG is widely used as a complementary quantitative method and is considered an important tool for analyzing and monitoring CTS intensity.[52,54,55] Few studies utilized ENMG to predict outcomes for CTS.[52,55,56] The ENMG Padua criteria (Electroneuromyography classification for stratification of median nerve involvement in CTS), is one of the most widely used tools.[52] However, although ENMG was a predominant complementary examination in the included studies, most did not use the quantitative criteria of Padua fully.

In addition to effective diagnostic methods, the correct definition of primary and secondary outcomes in RCTs allows the generation of responses to the hypotheses previously defined in these studies.[8,10] The focus of the included studies was the outcomes of body function and structure, with less attention to activity limitation and participation restriction. BQ was the most widely used, being an important outcome measure for assessing symptoms (body function and structure) and functional capacity (activity limitations). BQ has good psychometric properties in patients with CTS.[57-59] Thus, its use should replace other non-standardized methods.[59]

Similarly, previous systematic reviews were less focused on outcomes related to activity limitations and participation restriction.[8,60] Gummesson et al. reviewed 92 studies of upper limb dysfunction. The authors demonstrated that the outcomes of body function and structure were used in all studies, while only 41% of these also used measures of activity and participation.[60]

Jerosch-Herold et al.,[8] investigated the most valid and accurate tools to assess the clinical outcomes of the CTS. The authors also reported that most of the variables evaluated (sensory functions, pain sensations, motor functions and sleep functions), were concentrated in body functions and structures. Outcomes related to activity limitations and participation restrictions were evaluated less frequently and included the functional status scale of the BQ, timed manual dexterity test, and reported time to resume activities of daily living. The only participation restriction measures were the number of days to return to work and patient satisfaction.

Considering these findings, our review informs the selection of precise outcomes for future CTS ECRs and highlights the most utilized clinical and complementary diagnostic instruments. Future RCTs should use paresthesia in the median nerve territory, nocturnal paresthesia, and special tests (i.e., the Phalen's and Tinel's tests), and ENMG with quantitative Padua criteria as

diagnostic criteria for CTS. To reflect the impact of treatment on the three domains of analysis of ICF (body functions and structures, activity limitations and participation restrictions), BQ and participation restriction measures (e.g., number of days to return to work and patient satisfaction) should be standardized as main outcomes of analysis.

This is the first systematic review aimed at identifying the diagnostic criteria and the outcome measures used in ECR on CTS. The protocol was previously published in the PROSPERO database, restricting biases in methodology and enhancing credibility.[6] In addition, in order to improve the quality of the report of this systematic review, the PRISMA statement was used.

Our review has several limitations. We only looked for studies written in English. Because we eliminated studies with less than three months follow-up to eliminate anesthesiology papers, studies of surgical interest may have been lost. We considered only RCTs, due to the greater ability to identify of the outcome. However, longitudinal studies also report results of surgical processes, and their non-inclusion may have generated the loss of important outcome and diagnostic measures.

CONCLUSION

Almost half of the high-level methodological studies do not support diagnosis based on structured clinical criteria, such as Graham's. Most use ENMG as a complementary examination. Contrary to the literature, most studies do not prioritize patient-reported outcomes as relevant or primary outcomes. A task force is needed to standardize CTS research.

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Which anthropometric equation to predict body fat percentage is more strongly associated with maximum oxygen uptake in adolescents? A cross-sectional study

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ABSTRACT

BACKGROUND: Identifying the relationship between maximum consumption of oxygen and body fat percentage is important due to increased cardiovascular risk factors.

OBJECTIVE: This study aimed to verify the association between body fat percentage determined by three predictive equations using anthropometric measures (Lohman, Boileau, and Slaughter) and maximum oxygen uptake (VO_2max). We also aimed to estimate the capacity of these equations for explaining VO_2max variations in adolescents according to sex.

DESIGN AND SETTING: This was a cross-sectional study conducted in high schools in São José, Southern Brazil.

METHODS: This study included 879 adolescents (14–19 years) from Southern Brazil. Aerobic fitness was assessed using the modified Canadian Aerobic Fitness Test. The independent variable was body fat percentage predicted by the Lohman, Boileau, and Slaughter equations. Analyses adjusted for sociodemographic variables, physical activity level, and sexual maturation were performed with P value < 0.05.

RESULTS: All anthropometric prediction equations used to estimate body fat percentage explained VO_2max variations in adolescents. In male adolescents, both regression models based on the Boileau et al.[12] and Lohman[10] equations revealed higher explanatory power for VO_2max (20%) compared with that based on the Slaughter et al.[13] equation (19%). In female adolescents, the model based on the anthropometric equation of Slaughter et al.[13] showed the greatest explanatory power for VO_2max (18%).

CONCLUSION: The inverse relationship between VO_2max and body fat intensifies the need for effective intervention programs that prioritize maintenance of appropriate body fat and aerobic fitness levels because inadequate levels of both factors result in negative health consequences.

INTRODUCTION

Aerobic fitness is defined as the ability to supply oxygen to the muscles for generating energy during physical exercise.[1] Although it is a physiological determinant of running performance, aerobic fitness is not only restricted to sports performance, but also used as a diagnostic measure of health and physical exercise prescription.[1]

An adequate aerobic fitness level is an important marker of health in children and adolescents and strongly associated with disease prevention including obesity, hypertension, and diabetes at all stages of life.[2,3] On the other hand, low aerobic fitness levels have been reported to be associated with increased cardiovascular risk factors that may occur during adolescence, such as hypertension, insulin resistance, and metabolic risk factors.[2]

Research conducted in 2015 throughout Brazil indicated that approximately three million adolescents aged 13–17 years were overweight.[4] The world estimates reported that in the year 2025, approximately 75 million children and adolescents will be overweight and obese.[5] In Latin America, approximately 21 million adolescents (between 2008 and 2013) and one-third of adolescents in the United States (in 2003 and 2004) had body fat above healthy recommended levels. This is of concern because overweight was found to be a risk factor for cardiovascular and pulmonary diseases; diabetes mellitus; biliary disorders; and certain types of cancer.[6,7]

The gradual decrease in aerobic fitness levels in adolescents[8] is even more worrying when associated with excess body adiposity. Studies have identified that one of the possible explanations for various cardiovascular changes and occurrence of chronic diseases in individuals with overweight may be related to low aerobic fitness levels.[2,3] These findings seem independent of the

method used to predict excess adiposity,[9] regardless of the technique used to measure body composition, excess body fatness is a predictor of low aerobic fitness levels.

One way to identify excess body adiposity is through anthropometric measurement.[10] This practice is widely used in epidemiological studies because it is easy to apply and has low cost and good validity indexes compared with more accurate methods.[3] Since body fat percentage prediction equations using skinfolds are non-invasive methods that systematically measure body dimensions and proportions, they are well accepted and widely used in population research. These equations help detect changes in body pattern; health conditions; and performance and functional capacity.[11]

Analyzing the explanatory capacity of body fat percentage prediction equations for estimating maximum oxygen uptake (VO_2max), it is possible to identify whether equations that use only two skinfolds (triceps and subscapular) could be sufficient to predict VO_2max variation in adolescents. In addition, this study could allow for the identification and comparison of the relationship of each equation with aerobic fitness, thus helping to choose the most efficient equation according to sex.

OBJECTIVE

This study aimed to verify the association between body fat percentage analyzed by three different anthropometric predictive equations[10,12,13] and VO_2max and estimate the explanatory capacity of these equations to explain VO_2max variations in adolescents according to sex.

METHODS

Participants

This cross-sectional, school-based research was part of the macro-project entitled "Brazilian Guide for the Assessment of Physical Fitness Related to Health and Life Habits - Stage I". The study was approved by the Human Research Ethics Committee of the Universidade Federal de Santa Catarina on 14th August 2014 (CAAE Protocol: 33210414.3.0000.0121) and conducted between August and November 2014.

The study population recruited 5,182 high school students aged 14–19 enrolled in high schools in the city of São José southern Brazil, distributed across 11 eligible schools and 170 high school classes.

The sample process was determined at two stages: (i) stratified by state public high schools (n = 11) and (ii) class conglomerates considering study shift and school grade (n = 170 classes). At stage 2, all students enrolled in high schools who were present in the classroom on days of data collection were invited to participate in the study.

Regarding sample size calculation, unknown prevalence for the outcome (50%), tolerable error of five percentage points, 95% confidence level, and design effect of 1.5 were considered, adding 20% for losses and refusals and a further 20% for the association study. A sample size of 751 adolescents was found to be large enough in this study. However, due to conglomerate sampling, all students were invited to participate in the survey (1,132 students).

Eligibility was defined as being: enrolled in the state education network, present in classroom on the day of data collection, and aged 14–19 years. All adolescents who participated in the survey provided written informed consent signed by parents or responsible persons (for the participants under 18 years of age) or the participants themselves (if aged above 18 years). Students who did not want to participate in the research were considered refusals. Moreover, those with incomplete questionnaires or who did not undergo one or more physical tests were considered losses.

Measures

The dependent variable VO_2max was estimated using the modified Canadian Aerobic Fitness Test (mCAFT),[14] validated in comparison with indirect calorimetry in men and women aged 15–69 years.[15] Considering the test, adolescents had to complete one or more stages of three minutes each, where they had to go up and down two steps (20.3 centimeters). The stage and initial velocity were predetermined according to the participants' sex and age. The rhythm for performing the steps within each stage of the test was performed with musical cadence, indicating that when the adolescent should go up and down the steps.[14] The test was finalized only when the participants reached 85% of the maximal heart rate (determined by the formula 220 - age),[14] which was measured using a Polar H7 Bluetooth heart rate monitor (Kempele, Finland). If the participants did not reach 85% of the maximal heart rate at a given stage, a new stage was started shortly after the last stage until 85% of the maximum heart rate was reached at the end of the test. The final stage of the test was considered the one in which the adolescent was able to perform completely: if 85% of the maximum heart rate was reached during a certain stage, the stage prior to the adolescent 's performance was recorded as the final stage.

The oxygen expenditure during exercise and reference values for determination of the beneficial health zone for aerobic fitness were determined by the Canadian battery.[14] The aerobic fitness score equation determined by the Canadian battery was: *Score = 10 [17.2 + (1.29 x Oxygen expenditure) - (0.09 x weight in kg) - (0.18 x age in years)*.

The score was divided by 10 to obtain the value estimated for VO_2max,[14] which was continuously analyzed.

The independent variables were the anthropometric equations used for predicting body fat percentage. The Boileau et al.,[12] Slaughter et al.[13] and Lohman[10] equations (**Table 1**) were used. The Pires-Neto and Petroski[16] (the information is at https://osf.

io/4evdf/) constants were used for the Lohman[10] equation. Sociodemographic data were collected using self-administered questionnaires. Skin color was auto-referred according to the Brazilian Institute of Geography and Statistics[17] and dichotomized in "White" and "Brown/Black/Yellow/Indigenous". Age was categorized as "14–16 years" and "17–19 years." Economic level was identified using the questionnaire of the Brazilian Association of Research Companies[18] and dichotomized as "High" ("A1," "A2," "B1," "B2") and "Low" ("C1"; "C2"; "D"; "E").

Physical activity level was assessed using the following question: "During the past seven days, on how many days were you physically active for at least 60 minutes a day?" Adolescents who practiced physical activity five days or more a week were classified as "physically active (≥ 300 minutes per week)" and less than five days/week as "little physically active (< 300 minutes per week).[19]"

Sexual maturation was evaluated according to the criteria proposed by Tanner,[20] validated and reproducible for the Brazilian population.[21] Stages were determined by self-assessment (figures) of breast (female participants) and genital (male participants) development after individual and previous explanations of the instrument by the researcher, always of the same sex as the adolescent. Due to the low frequency of adolescents in the pre-pubertal stage (0.2%), categories were "Pre-pubertal/Pubertal" and "Post-pubertal." This variable was fitted in the multivariate analysis in discrete continuous form.

Statistical analysis

The mean values, standard deviations, and frequency distributions were used for the descriptive analysis of the variables. Data distribution normality was tested using asymmetry and kurtosis analyses. The highest asymmetry value was for the body mass index (asymmetry = 1.2), and the highest kurtosis value was for the subscapular skinfold (kurtosis = 2.3). The other variables exhibited asymmetry and kurtosis values close to zero. According to the literature, such asymmetry and kurtosis values referred to normal data distribution.[22] Thus, Student's t-test was applied to verify differences between means according to sex. Pearson's correlation was used to verify the relationship between the anthropometric equations to predict body fat percentage and VO_2max according to sex.

Simple and multiple linear regression analyses were used to identify the relationship between the anthropometric equations for predicting body fat percentage and VO_2max. Using multiple linear regression analysis, a model was constructed for each equation separately and adjusted for sociodemographic factors (skin color, age, and economic level); physical activity level; and sexual maturation. The significance level was set to 5%. Analyses were performed using the SPSS version 22.0 (IBM, New York, United States), considering the design effect and sample weight, which were stratified by sex.

RESULTS

Of the 1,132 adolescents evaluated, 253 were excluded from the study because they did not perform the aerobic fitness test. Therefore, a total 879 adolescents with a mean age of 16.22 ± 1.14 years were finally included in the study. The mean height and VO_2max were significantly higher in boys than in girls (**Table 2**). The mean triceps and subscapular skinfold, sum of the triceps and subscapular skinfold values, and body fat percentage predicted by the three anthropometric equations were significantly higher in girls than in boys (**Table 2**). In both sexes, VO_2max was negatively correlated with body fat percentage, as estimated using the three equations analyzed (**Figure 1**).

Using simple and multiple linear regression analyses, it was found that as body fat percentage increased, regardless of the anthropometric prediction equation,[10,12,13] VO_2max values of adolescents of both sexes decreased. The male participants presented standardized β values of -0.41, -0.41 and -0.28 for Boileau et al.,[12] Lohman[10] and Slaughter et al.[13] equations, respectively. The magnitude of decrease in VO_2max in female participants was -0.26, -0.26, and -0.19, for the Boileau et al.,[12] Lohman[10] and Slaughter et al.[13] equations, respectively (**Table 3**).

Multiple linear regression analysis revealed that regardless of sociodemographic factors (skin color, age, and economic level); physical activity level; and sexual maturation, anthropometric equations used to predict body fat percentage presented explanatory

Table 1. Equations for predicting the percentage of body fat in children and adolescents

Reference	Year	Sex	Predictive equation's
Boileau et al.[12]	1985	Male	$\%FAT = 1.35\ (TR + SE) - 0.012\ (TR+SE)^2 - 4{,}4$
		Female	$\%FAT = 1.35\ (TR + SE) - 0.012\ (TR + SE)^2 - 2{,}4$
Lohman[10]	1986	Male and female (all ages)	$\%BF = 1.35\ (TR + SE) - 0.012\ (TR + SE)^2 - I^a$
Slaughter et al.[13]	1988	Male ∑BF < 35mm (all ages)	$\%BF = 1.21\ (TR + SE) - 0.008\ (TR + SE)^2 + I^b$
		Female ∑BF < 35mm (all ages)	$\%BF = 1.33\ (TR + SE) - 0.013\ (TR + SE)^2 - 2.5$
		Male ∑BF ≥ 35 mm (all ages)	$\%BF = 0.783\ (TR+SE) + 1.6$
		Female ∑BF ≥ 35 mm (all ages)	$\%BF = 0.546\ (TR+SE) + 9.7$

%FAT = fat percentage; TR = triceps skinfold; SE = subscapular skinfold; %BF = body fat percentage; I^a = Intercept based on sex, age and ethnicity proposed by Lohman;[10] ∑BF = sum of body fat; I^b = Intercept substitutions based on maturation and ethnicity for boys proposed by Slaughter et al. (1988).

power for VO_2max above 14% (R^2) in both sexes. In male participants, both regression models based on the Boileau et al.[12] and Lohman[10] equations presented explanatory power for VO_2max of 20%, which was greater than the regression model based on the Slaughter et al.[13] equation (19%). The regression models based on the Boileau et al.[12] and Lohman[10] equations presented greater explanatory power for VO_2max. In female participants, the equation that presented the highest explanatory power ($R^2 = 0.18$) for VO_2max was proposed by the Slaughter et al.[13] equation (**Table 3**).

DISCUSSION

All anthropometric prediction equations used to estimate body fat percentage explained the VO_2max variations in adolescents in the present study. In male participants, both regression models based on the Boileau et al.[12] and Lohman[10] equations presented higher explanatory power for VO_2max compared with the regression model based on the Slaughter et al.[13] equation. Therefore, the models with the Boileau et al.[12] and Lohman[10] equations were those that obtained the greatest explanatory power (R^2) for

Table 2. Total and stratified by sex of the mean and standard deviation of age, height, body mass, anthropometric indicators and VO_2max of adolescents

Variables	Total sample	Males	Females	P value	Cohen's d
	Mean ± SD	Mean ± SD	Mean ± SD		
Age (years)	16.22 ± 1.14	16.28 ± 1.19	16.16 ± 1.10	0.15	0.10
Height (cm)	166.56 ± 8.81	172.59 ± 7.35	161.17 ± 6.09	< 0.01*	1.69
Body mass (kg)	61.67 ± 12.20	65.43 ± 12.07	58.31 ± 11.32	0.25	0.60
BMI (kg/m²)	22.16 ± 3.72	21.89 ± 3.44	22.41 ± 3.95	0.25	0.14
TR (mm)	14.94 ± 7.34	10.75 ± 5.13	18.70 ± 6.99	< 0.01*	1.29
SE (mm)	13.32 ± 6.73	10.76 ± 4.86	15.60 ± 7.33	< 0.01*	0.77
ΣTR+SE (mm)	28.26 ± 13.49	21.51 ± 9.53	34.30 ± 13.66	< 0.01*	1.08
Boileau equation's[12]	23.05 ± 7.42	18.02 ± 5.87	27.57 ± 5.51	< 0.01*	1.67
Lohman equation's[10]	21.21 ± 7.53	15.99 ± 5.87	25.89 ± 5.52	< 0.01*	1.73
Slaughter equation's[13]	22.82 ± 10.57	15.69 ± 8.32	29.23 ± 7.96	< 0.01*	1.66
VO_2max (ml/kg/minutes)	38.80 ± 5.83	42.68 ± 5.34	35.33 ± 3.66	< 0.01*	1.60

SD = standard deviation; BMI = body mass index; TR = triceps skinfold; SE = subscapularis skinfold; ΣTR + SE: sum of triceps and subscapularis skinfolds; VO_2max = maximum oxygen uptake; *P ≤ 0.05 (Student's t test).

Table 3. Simple and multiple linear regression for the association between VO2max and percentage of body fat analyzed by different anthropometric equation in boys and girls

Variables	Male										
	Simple		Multiple†			Multiple§			Multiple‡		
	β	CI 95%	β	CI95%	R^2						
					0.20			0.20			0.19
Skin color	0.80	(-0.14; 1.76)	0.88	(-0.18; 1.95)		0.89	(-0.17; 1.96)		0.92	(-0.14; 2.00)	
Age	0.48	(-0.44; 1.41)	0.37	(-0.65; 1.40)		0.19	(-0.84; 1.22)		0.23	(-0.79; 1.27)	
Economic level	-0.01	(-1.16; 1.14)	-0.16	(-1.33; 1.00)		-0.16	(-1.33; 1.00)		-0.14	(-1.32; 1.03)	
Physical activity level	**-1.19**	**(-2.22; -0.16)**	**1.55**	**(-2.68; -0.42)**		**-1.55**	**(-2.68; -0.42)**		-1.54	(-2.67; -0.40)	
Sexual maturation	**-1.31**	**(-2.38; 0.25)**	**-1.43**	**(-2.63; -0.24)**		**-1.43**	**(-2.62; -0.23)**		-1.35	(-2.55; -0.15)	
Boileau equation's*[12]	**-0.41**	**(-0.49; -0.33)**	**-0.38**	**(-0.47; -0.29)**							
Lohman equation's*[10]	**-0.41**	**(-0.49; -0.33)**				**-0.38**	**(-0.47; -0.29)**				
Slaughter equation's*[13]	**-0.28**	**(-0.34; -0.22)**							**-0.27**	**(-0.33; -0.20)**	
					Female						
Skin color	0.73	(0.09; 1.36)	0.69	-0.01; 1.40	0.14	0.69	-0.01; 1.40	0.14	0.74	0.04; 1.43	0.18
Age	-0.31	**(-0.93; 0.31)**	**-0.40**	**(-1.10; 0.29)**		**-0.53**	**(-1.23; 0.16)**		-0.87	-1.56; -0.18	
Economic level	0.36	(-0.32; 1.05)	0.45	-0.25; 1.16		0.44	-0.26; 1.15		0.55	-0.14; 1.24	
Physical activity level	-0.76	**(-1.57; 0.03)**	**-0.47**	**(-1.37; 0.42)**		**-0.46**	**(-1.36; 0.42)**		-0.44	-1.31; 0.43	
Sexual maturation	-0.18	**(-0.87; 0.50)**	**-0.44**	**(-1.20; 0.31)**		**-0.45**	**(-1.20; 0.31)**		**-0.19**	**(-0.95; 0.56)**	
Boileau equation's*[12]	-0.26	**(-0.32; -0.21)**	**-0.24**	**(-0.30; -0.17)**							
Lohman equation's*[10]	-0.26	**(-0.32; -0.20)**				**-0.23**	**(-1.21; 0.31)**				
Slaughter equation's*[13]	-0.19	**(-0.23; -0.15)**							**-0.18**	**(-0.23; -0.14)**	

B = slope coefficient; CI = confidence interval 95%; R^2 = determination coefficient; *Adjusted analysis for skin color, age, economic level, physical activity level and sexual maturation. †Adjusted model for percentage of body fat estimated by Boileau equation's;[12] §Adjusted model for percentage of body fat estimated by Lohman equation's;[10] ‡Adjusted model for percentage of body fat estimated by Slaughter equation's.[13]

VO_2max. In female participants, the model with the Slaughter et al.[13] anthropometric equation obtained the greatest explanatory power for VO_2max.

The inverse relationship between body fat and VO_2max could be explained by the fact that individuals with higher amounts of body fat might tend to experience locomotion difficulties, which results in less frequent walking and stability during walking and/or running.[23] These aspects influence the movement economy, resulting in greater energy expenditure and precipitated fatigue during low-intensity activities.[24]

The three anthropometric equations used to predict body fat percentage[10,14,15] were derived from the same sample,[25] and this may explain why the differences between them in the explanation of VO_2max in adolescents in the present study were not greater. The original study that proposed these prediction equations involved 310 American, Caucasian, and African children, adolescents, and adults. This original study was conducted in Illinois, United States, and replicated in Arizona, United States.[10,14,15] However, the equations differ among themselves. The first equation was proposed by Boileau et al.[12] and was established to cover the age range between 8 and 29 years, being stratified by sex (the information is at https://osf.io/4evdf/). The Lohman[10] equation (the information is at https://osf.io/4evdf/) included an age range between 7 and16 years and used constants different from that in the Boileau et al.[12] equation. The anthropometric equation for the prediction of body fat percentage proposed by Slaughter et al.[13] covered the age group of 8–18 years (the information is at https://osf.io/4evdf/). However, this equation, unlike the Boileau et al.[12] and Lohman[10] equations, considered the sexual maturation stage in children and adolescents in addition to skin color and sex.

The models used for body fat prediction created by Boileau et al.[12] and Lohman[10] were the equations that obtained greater explanatory power for VO_2max variations in boys in the present study. In girls, the Slaughter et al.[13] equation was that best explained VO_2max variations. Possible justification for these findings is that the Slaughter et al.[13] equation was the only one of the three equations that used variables of sexual maturation and the puberty process in the prediction model and. Consequently, sexual maturation seems to influence more female adolescents.[26] The reason is that, in addition to girls being at greater risk for early pubertal development, considering that the prevalence of delayed puberty was more common in male participants, female children and adolescents tended to have higher fat mass levels and higher leptin levels during childhood.[26] Plasma leptin concentrations (responsible for body weight and energy balance regulation) are related to changes in VO_2max and body composition during the puberty process.[27]

In male participants, leptin concentrations decrease throughout the pubertal period. However, VO_2max increases throughout puberty to adulthood due to the higher concentration of fat-free mass in boys, according to the oxidative potential of muscle fibers.[28] The opposite occurs in female individuals because, during puberty, girls gain fat mass, leading to increased leptin concentrations.[26] In addition, VO_2max increases in girls only at the onset until the end of puberty, with no change from late puberty to adulthood, as they have higher body fat concentration compared with boys.[29] In this sense, the Boileau et al.[12] and Lohman[10] equations responded better to male participants because they did not comprise the variable of sexual maturation, unlike the Slaughter et al.[13] equation, which seems to be more suitable for female individuals when the purpose is to identify associations with aerobic fitness.

The use of equations that consider only two skinfolds (triceps and subscapula) may be a limitation of this study. However, it is important to stress that the use of only two skinfolds to identify the body fat percentage makes the application simple with lower chance of error. In addition, the fact that VO_2max was estimated using a submaximal test may be another limitation, considering that the use of submaximal protocols to estimate VO_2max is less precise compared with maximum protocols. However, submaximal tests are more practical to apply to samples with a larger number of individuals.[30] In addition, submaximal indirect tests using heart rate may be used to assess VO_2max in adolescents with low physical fitness or in those who do not support maximum-effort tests.[3]

Regardless of the equation used to predict body fat percentage in this study,[10,14,15] all equations were able to explain VO_2max variations in adolescents. This intensifies the need for effective intervention programs that prioritize the maintenance of satisfactory body fat and aerobic fitness levels, considering that both factors result in inadequate levels that cause negative consequences and health damage, such as a predisposition to development of cardiovascular diseases. In addition, sexes responded differently to each prediction equation when associated with VO_2max. Therefore, actions should be taken in a cautious and sex-specific manner, considering factors that directly influence VO_2max and body fat differently in male and female individuals, such as sexual maturation.

CONCLUSION

All anthropometric prediction equations used to estimate body fat percentage explained VO_2max variations in adolescents in the present study. In male participants, the Boileau et al.[12] and Lohman[10] equations showed the greatest explanatory power for VO_2max. In female participants, the model with the Slaughter et al.[13] anthropometric equation revealed the greatest explanatory power for VO_2max.

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Autonomic dysfunction in COVID-19 patients receiving mechanical ventilation: A cross-sectional study

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ABSTRACT

BACKGROUND: Coronavirus disease 2019 (COVID-19) can damage cardiac tissue by increasing troponin levels and inducing arrhythmias, myocarditis, and acute coronary syndrome.

OBJECTIVES: To analyze the impact of COVID-19 on cardiac autonomic control in mechanically ventilated intensive care unit (ICU) patients.

DESIGN AND SETTING: This cross-sectional analytical study of ICU patients of both sexes receiving mechanical ventilation was conducted in a tertiary hospital.

METHODS: Patients were divided into COVID-19-positive (COVID(+)) and COVID-19-negative (COVID(-)) groups. Clinical data were collected and heart rate variability (HRV) records obtained using a heart rate monitor.

RESULTS: The study sample comprised 82 subjects: 36 (44%) in the COVID(-) group (58.3% female; median age, 64.5 years) and 46 (56%) in the COVID(+) group (39.1% females; median age, 57.5 years). The HRV indices were lower than the reference values. An intergroup comparison identified no statistically significant differences in the mean normal-to-normal (NN) interval, standard deviation of the NN interval, or root mean square of successive differences in NN intervals. The COVID(+) group had an increased low frequency ($P = 0.05$), reduced high frequency ($P = 0.045$), and increased low frequency/high frequency (LF/HF) ratio ($P = 0.048$). There was a weak positive correlation between LF/HF and length of stay in the COVID(+) group.

CONCLUSION: Patients who received mechanical ventilation had lower overall HRV indices. COVID(+) patients who received mechanical ventilation had lower vagal HRV components. These findings likely indicate clinical applicability, as autonomic control impairments are associated with a greater risk of cardiac death.

INTRODUCTION

Breathing difficulties with severe hypoxemia, caused by infection with the severe acute respiratory syndrome (SARS) virus, is the most important manifestation of coronavirus disease 2019 (COVID-19).[1] In addition to the possibility of a pulmonary lesion, COVID-19 may directly cause heart damage in the form of myocarditis, heart failure, cardiogenic shock, acute coronary syndrome, and cardiac arrhythmias. Clinical manifestations are also accompanied by increased cardiac biomarker levels. The mechanisms that cause these cardiovascular disorders are not yet clear; however, they are believed to be related to excessive inflammatory responses, hypoxemia, thromboembolic phenomena, and endothelial dysfunction.[2,3] The severity of infection increases simultaneously with the activation of the inflammatory pathways that trigger cytokine storm.[4]

Cardiac autonomic control can be studied through heart rate variability (HRV), which is the physiological phenomenon of variation in the time interval between heartbeats.[5,6] Decreased HRV is a sign of abnormal and insufficient adaptation of the autonomic nervous system (ANS) and may indicate physiological malfunctioning in some clinical conditions.[7-10] Autonomic dysfunction is common in various disorders that occur in patients with critical conditions, such as multiple organ dysfunction syndrome, sepsis, myocardial infarction, decompensated heart failure, and severe brain injury.[11-14]

Furthermore, depressed parasympathetic activity has been implicated in the pathogenesis of diseases associated with excessive inflammatory responses.[15] These changes may be clarified by the inflammatory reflex theory – i.e., activation of the vagus nerve and consequently reduced inflammatory responses in septic and aseptic inflammation models.[16] Reduced HRV may be an independent predictive factor of 30-day all-cause mortality in intensive care unit (ICU) patients.[15,17-19]

OBJECTIVE

Given the likely cardiac damage caused by COVID-19, the objective of this study was to analyze the impact of this disease on cardiac autonomic control in ICU patients.

METHODS

Study design

This cross-sectional analytical study was conducted between August 2020 and February 2021 in an ICU that exclusively treated adult SARS patients. The following data were collected from the medical records: sample characterization (such as sex, age, vital signs (heart rate [HR], systolic arterial pressure, diastolic arterial pressure, peripheral oxygen saturation [SpO_2]), history of current disease, pre-existing diseases, and ICU length of stay).

Additionally, ventilatory parameters (positive end-expiratory pressure, pressure support [PS], fraction of inspired oxygen [FiO_2], and arterial pressure of oxygen/FiO_2 ratio [PaO_2/FiO_2]) and ventilatory muscle function data (maximum inspiratory pressure, maximum expiratory pressure, and rapid and shallow breathing index) were collected.

The samples were obtained for convenience. Participants in the study included patients receiving mechanical ventilation (MV) who underwent reverse transcription-polymerase chain reaction (RT-PCR) for COVID-19 diagnosis. Those with positive and negative results were included, and their groups were denoted COVID(+) and COVID(−), respectively. Patients with complex arrhythmias, second- or third-degree atrioventricular block, cardiac pacemakers, heart transplants, or those taking antiarrhythmic drugs were excluded.

This study was approved by the Research Ethics Committee of the HUOC/PROCAPE Hospital Complex (no. CAAE 13364019.5.0000.5192) on June 26, 2019. The patients or their legal guardians signed an informed consent form.

Heart rate variability

HRV was measured with a Polar V800 heart rate monitor (Polar Electro Oy, Kempele, Finland), with a Polar H10 heart rate sensor (Polar Electro Oy) positioned at the patient's xiphoid process with a Polar Pro strap (Polar Electro Oy). The final data were exported to Kubios HRV Standard software (release 3.3.1, 2019; Kubios Oy, Kuopio, Finland), in which normal-to-normal intervals (NNi) were processed and digitally filtered to eliminate artifacts. The Task Force of the European Society of Cardiology and North American Society of Pacing and Electrophysiology recommendations were followed.[20]

All patients received invasive pressure support MV and were always assessed in the morning, between 8 o'clock and noon, to avoid the influence of the circadian rhythm. The subjects were lying in bed in the supine position, with the headrest angled at 45º. Time and frequency domains were analyzed with the highest quality and fewest-artifact 5-minute extracts.

The following HRV data were investigated in the time domain: mean NNi (ms), standard deviation of the NN interval (SDNN, ms), and the root mean square of successive differences in NN intervals (RMSSD, ms). For the frequency domain, low frequency (LF, in normalized units [nu]), high frequency (HF, nu), and the LF/HF ratio were analyzed.

Statistical analysis

The statistical analysis was performed using SPSS software (release 22.0, 2013; SPSS Inc., Chicago, Illinois, United States, Release 22.0, 2013). Initially, normality was verified using the Kolmogorov-Smirnov test and homoscedasticity using Bartlett's test. Given the results and considering the nature of the study, continuous variables were presented as medians (first quartile – third quartile) (minimum value – maximum value) and categorical variables as absolute and relative frequencies. The Mann-Whitney U test compared the results of the continuous variables between the two groups, while the Pearson chi-square test (χ^2) analyzed the proportions of categorical variables. The measures of central tendency and dispersion presented in the study by Nunan were taken as normal reference values of the HRV parameters analyzed in the present study.[21] A linear regression was performed to evaluate possible confounding factors. All analyses were bilateral and performed at the 5% significance level. When calculated, P values and 95% confidence intervals were precise.

RESULTS

The study comprised 82 individuals divided into two groups based on RT-PCR results for SARS-CoV-2. The COVID(-) group had 36 (44%) subjects with a median age of 64.5 (56.0–70.0) years; 21 (58.3%) were female. The COVID(+) group had 46 (56%) subjects with a median age of 57.5 (42.8–73.0) years; 18 (39.1%) were female. The groups were homogeneous, and the sample characterization data are presented in **Table 1**.

No difference in vital signs was observed between the two groups, except for SpO_2, which was significantly lower in the COVID(+) than COVID(-) group (95.5% versus 97.0%; P = 0.035). Nonetheless, both values were normal. Among the ventilatory parameters, the FiO_2 used was higher in the COVID(+) group (P = 0.024). There was no significant intergroup difference in ventilatory muscle function.

The main comorbidities found in the COVID(+) group were systemic arterial hypertension (52.2%) and diabetes mellitus (39.1%), with a statistically similar prevalence, in contrast to the COVID(-) group. The patients' length of stay by the day

Table 1. Characterization of positive and negative patients for COVID-19 admitted to an intensive care unit between August 2020 and February 2021 under mechanical ventilation (n = 82)

Variables	Negative COVID (n = 36) Median (1Q–3Q) [Min-Max]	Positive COVID (n = 46) Median (1Q–3Q) [Min-Max]	P
Age, years	64.5 (56.0–70.0)[28.0–81.0]	57.5 (42.8–73.0)[31.0–88.0]	0.472
Heart rate, bpm	93.0 (81.3–101.0)[58.0–119.0]	88.0 (73.0–104.0)[55.0–147.0]	0.492
Systolic blood pressure, mmHg	137.0 (113.8–156.5)[67.0 - 189.0]	128.5 (108.8–142.5)[64.0–166.0]	0.071
Diastolic blood pressure, mmHg	74.5 (66.3–86.8)[47.0–100.0]	69.5 (60.0–84.0)[48.0–117.0]	0.184
Peripheral capillary oxygen saturation, %	97.0 (95.0–98.0)[93.0–100.0]	95.5 (94.0–98.0)[91.0–100.0]	0.035
Length in intensive care unit, days	5.0 (3.0–10.8)[1.0–26.0]	9.0 (4.0–14.0)[1.0–34.0]	0.024
Positive end-expiratory pressure, cmH_2O	6 (6–8)[5–10]	6 (6–8)[5–10]	0.795
Pressure support, cmH_2O	10 (10–10)[8–18]	10 (10–12)[8–16]	0.682
Fraction of inspired oxygen, %	21 (21–30)[21–35]	25 (21–35)[21–50]	0.024
PaO_2/FiO_2 ratio	366 (310–471)[201–666]	356 (277–419)[140–633]	0.168
Maximal inspiratory pressure, cmH_2O	-60 (-47 – -80)[-20 – -120]	-60 (-60 – -100)[-30 – -120]	0.282
Maximal expiratory pressure, cmH_2O	80 (46–100)[20 – 170]	70 (48–100)[20–150]	0.828
Rapid shallow breath index	44 (36–66)[12–110]	46 (37–66)[24–85]	0.602
Female sex, n (%)	21 (58.3%)	18 (39.1%)	0.084
Systemic arterial hypertension, n (%)	24 (66.7%)	24 (52.2%)	0.186
Diabetes mellitus, n (%)	19 (52.8%)	18 (39.1%)	0.218
Chronic obstructive pulmonary disease, n (%)	6 (16.7%)	5 (10.9%)	0.523

COVID-19 = coronavirus disease 2019; 1Q = first quartile; 3Q = third quartile; Min-Max = minimum-maximum; PaO_2 = oxygen blood pressure; FiO2 = fraction of inspired oxygen.

of assessment was significantly longer in the COVID(+) group (P = 0.024) than in the negative group (**Table 1**).

All HRV parameter values for the patients in both groups were significantly lower than the reference values. In contrast, the comparison of time domain indicators between the COVID(+) and COVID(-) groups revealed no statistical difference in mean NNi, SDNN, or RMSSD values. In the frequency domain, comparison between the groups revealed a significant increase(P = 0.05) in LF, a significant decrease (P = 0.045) in HF, and an increase in the LF/HF ratio (P = 0.048) in the COVID(+) group (**Table 2**).

The indices in the frequency domain that showed a significant difference in the COVID(+) group were subjected to linear regression to analyze possible confounding factors, and a weak positive correlation was observed between LF/HF and days spent in the ICU (P = 0.01; r2 = 0.14) (**Figure 1**).

DISCUSSION

This study observed changes in cardiac autonomic control interactions in ICU patients receiving invasive MV, whose RT-PCR test was positive for COVID-19. These patients had lower vagal activity and sympathetic hyperactivity in the frequency domain than non-infected patients.

Strong hyperimmune reactions due to COVID-19 produce a large adrenergic release, which is mainly modulated by the sympathetic nervous system.[2,3] Consequently, a modulated compensatory response occurs via the cholinergic anti-inflammatory pathway of the parasympathetic nervous system.[4,5] Thus, the ANS participates in regulating this inflammatory reflex, and its balance is essential for maintaining physiological homeostasis.[11,12]

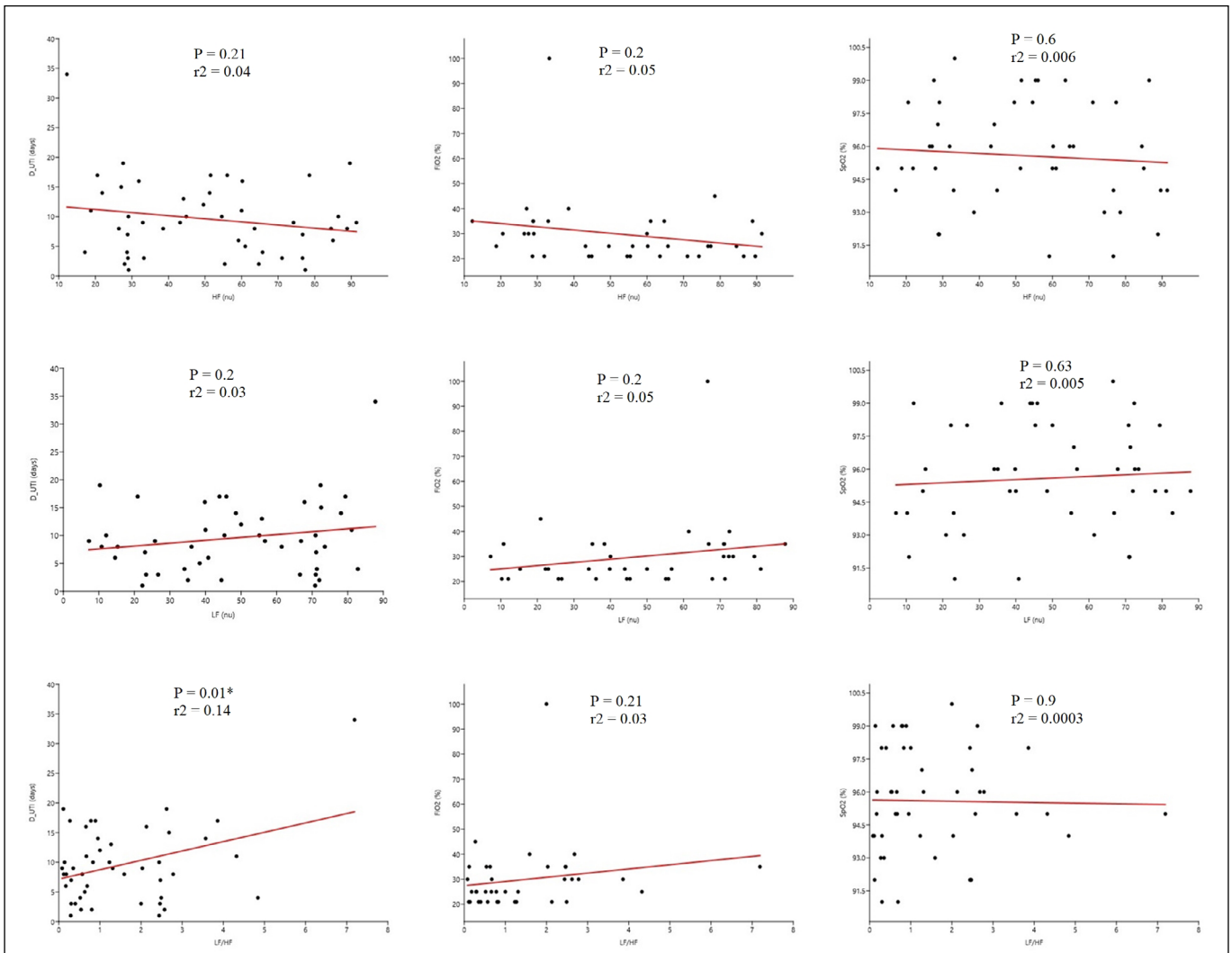
The vagus nerve is an important neuroimmunomodulator of the anti-inflammatory pathway.[22] When working properly, this regulatory anti-inflammatory response limits viral infection dissemination and is vital for controlling and treating COVID-19. However, when vagal activity is reduced, the inflammatory response may get out of control, contributing to hyperinflammation – the so-called cytokine storm.[23] In this regard, the results of this research show decreased HF in the COVID(+) group, demonstrating that these patients' vagal component is reduced. Hence, unregulated immune responses observed in severe cases of COVID-19 (those which cause inflammation and SARS) may result from impaired vagal activity in inflammation regulation.[22]

Various previous studies have already researched the correlation between HRV and inflammatory markers.[24-26] Tateishi et al. found that interleukin-6 (IL-6) was negatively correlated with LF in septic ICU patients.[24] Papaioannou et al. reported an

Table 2. Measures of heart rate variability of positive and negative patients for COVID-19, admitted to the intensive care unit under mechanical ventilation (n = 82)

Variables	Negative COVID (n = 36) Median (1Q–3Q) [Min-Max]	Positive COVID (n = 46) Median (1Q–3Q) [Min-Max]	P
NNi medium, ms	639.5 (572.3–764.8)[451.0–1191.0]	653.0 (571.8–800.8)[8.6–1321.0]	0.581
SDNN, ms	8.1 (4.5–25.9)[3.0–65.0]	10.4 (6.2–21.3)[2.5–46.3]	0.562
RMSSD, ms	12.1 (4.5–32.2)[2.1–98.0]	12.9 (7.9–27.3)[2.0–68.6]	0.695
LF, nu	33.6 (24.8–55.4)[9.2–87.2]	47.2 (26.4–71.0)[7.2–87.8]	0.050
HF, nu	66.8 (44.3–74.9)[12.8–90.2]	51.4 (28.9–71.8)[12.2–91.4]	0.045
LF/HF ratio	0.5 (0.3–1.3)[0.1–6.8]	0.9 (0.4–2.5)[0.1–7.2]	0.048

COVID-19 = coronavirus disease 2019; 1Q = first quartile; 3Q = third quartile; Min-Max = minimum-maximum; HF = high frequency; LF = low frequency; NNi = N-N interval; RMSDD = square root of the mean squared differences of successive N-N intervals; SDNN = standard deviation of the N-N interval.



D_UTI = length in intensive care unit; FiO_2 = fraction of inspired oxygen; SpO_2 = peripheral capillary oxygen saturation; LF = low frequency; HF = high frequency.

Figure 1. Linear regression analysis between indices in the frequency domain and possible confounding factors days of ICU stay, SpO_2, and Fio2.

inverse correlation between LF and LF/HF and C-reactive protein levels.[25]

Previous studies examining the role of HRV in COVID-19 found that a reduction in HRV preceded an increase in inflammatory markers. However, these studies used small sample sizes and did not statistically adjust for important confounders such as age and comorbidities.[27,28]

One of the first studies examining the potential role of HRV as a surrogate marker for vagus nerve activity in COVID-19 showed that age is a predictor of death only in cases of reduced HRV. This suggests that the vagus nerve plays an important moderating and protective role in COVID-19 and may even weaken the prognostic role of aging.[27]

Among the HRV parameters analyzed in the time domain, SDNN and RMSSD are markers of parasympathetic tone. Their values were low in both groups in the present study, demonstrating that parasympathetic activity was reduced in patients with severe disease who were receiving MV. This reduction was sharper in the COVID(-) group, although the difference was not statistically significant. A cross-sectional analytical study conducted in India also found significantly higher RMSSD and SDNN values in the COVID(+) group.[29] However, that study neither included severe patients nor used oxygen therapy.

Jarczok et al. observed in a cross-sectional study that daytime RMSSD values below 25 (±4) ms indicate high cardiovascular risk.[30] Hence, the low RMSSD values found in this study suggest that ICU patients, with or without a confirmed COVID-19 diagnosis, were at an increased cardiovascular risk.

HRV reductions have been associated with disease severity and increased mortality in ICU patients.[11] Papaioannou et al. observed that less clinically stable patients have a lower LF/HF ratio and decreased overall variance; they also pointed out that patients recovered from such reduction as they improved and were discharged from the ICU.[25] Likewise, LF/HF values in the present study were lower in both groups, demonstrating that the sample patients were in a severe condition.

The average length of stay for the COVID(+) group was 9 days. It is known that in the first two weeks of infection, the defense mechanisms are deregulated and the severity of the disease increases as the cytokine storm is activated.[4,31] A retrospective study conducted in China analyzed chest computed tomography (CT) scans of 121 patients with COVID-19 and showed the most extensive disease approximately 10 days after the onset of symptoms.[32] A study in Mexico of COVID-19 patients observed that the interval between the first symptoms and death was a mean 9 (range, 5–13) days.[33] Thus, the weak positive correlation between LF/HF and days spent in the ICU observed in the COVID(+) group may be related to the greater dysregulation of the anti-inflammatory reflex observed in the initial 10 days of the disease.

Limitations

This study has some limitations. The pandemic period and difficulty in obtaining an interruption-free HRV record due to electronic equipment causing interference in the ICU environment compromised the recruitment of a larger sample, which may have limited the generalization of our findings. Recent studies have shown that short-term recordings of HRV indices in the time domain may not be monitored to interpret oscillations in autonomic and regulatory nervous systems. This may explain the lack of significant differences in the RMSSD and SDNN between the groups in the present study.

Although HRV spectral analysis is an accepted, valid, and reliable noninvasive indicator of ANS balance, no other measures (such as catecholamine serum levels or baroreflex sensitivity) were used to collect data on autonomic activity.

CONCLUSIONS

ICU patients who received MV had lower overall HRV measures. HF reduction was particularly sharper in COVID-19 patients receiving MV, which demonstrates the role of cardiac autonomic control in the pathogenesis of diseases characterized by excessive inflammatory responses. Hence, HRV measurements with spectral analysis can be promising markers of the inflammatory response, aiding future studies on new anti-inflammatory treatments. The findings of the present study are likely to be clinically applicable, as autonomic control impairments are associated with a greater risk of cardiac death. Further studies are required to confirm these results.

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Appraising epidemiology data and antimicrobial resistance of urinary tract infections in critically ill adult patients: a 7-year retrospective study in a referral Brazilian hospital

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AUTHORS' KEYWORDS:
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Etiology.
Multi-resistant.

ABSTRACT

BACKGROUND: Urinary tract infections (UTI) are highly preventable and have significant clinical and financial impact on the patient and the health care system.

OBJECTIVE: To investigate UTIs in critically ill adult patients and the relationship of antimicrobial consumption and multidrug-resistant isolate.

DESIGN AND SETTING: A cohort study performed in a Brazilian tertiary-care university hospital in the city of Uberlandia (MG), located at the Federal University of Uberlandia, southeast region of the country.

METHODS: We analyzed a cohort of 363 patients with first episode of UTIs from the adult intensive care unit (ICU), from January 2012 to December 2018. The daily doses of antimicrobial administered were calculated.

RESULTS: The incidence rate of UTI was 7.2/1000 patient days, with 3.5/1000 patient-days of bacteriuria, and 2.1/1000 patient-days of candiduria. Of 373 microorganisms identified, 69 (18.4%) were Gram-positive cocci, 190 (50.9%) Gram-negative bacilli, and 114 yeasts (30.7%). *Escherichia coli* and *Candida* spp. were the most common. Patients with candiduria had higher comorbidity score (Charlson Comorbidity Index ≥ 3), longer length of stay (P = 0.0066), higher mortality (P = < 0.0001) severe sepsis, septic shock, and were immunocompromised when compared with patients with bacteriuria. We observed correlation between antibiotics consumption and multidrug-resistant (MDR) microorganisms.

CONCLUSION: The UTIs incidence was high and was mainly caused by Gram-negative bacteria that were resistant to common antibiotics. We observed increase in the consumption of broad-spectrum antibiotics in ICU correlating with MDR microorganisms. In general, ICU-acquired candiduria may be associated with critical illness and poor prognosis.

INTRODUCTION

Urinary tract infections (UTI) are the most frequently reported healthcare associated infection (HAI), accounting for up to 40% of all HAIs.[1,2] The risk of these infections increases with hospitalization in intensive care units (ICUs), where incidence rates range between 15.5% and 37.6% in low- and middle-income countries, such as Brazil.[3-5]

UTI is closely correlated with use of indwelling urinary catheters HAIs,[1,2] and according to the Centers for Disease Control and Prevention approximately 75% of UTIs have this association.[6] In countries, such as Brazil UTI continue to prevail and represent a major safety concern for patients.[5,7] It is estimated that in Brazil, 16.6% to 37.6% of all ICU-acquired infections are UTI resulting in 10.7%–20.0% related deaths.[3,4,8,9]

Two important aspects about these infections are: (I) in recent years the frequent use of antibiotics in the treatment of asymptomatic infections, has resulted in the urinary tract becoming a major reservoir of resistant pathogns;[10,11] and (II) these infections can be associated with secondary bloodstream infections (BSI), an infection that develops subsequent to a documented infection of the blood with the same organism.[12]

OBJECTIVE

In this study, we investigated the characteristics of patients and microorganisms involved in UTIs in critically ill adult patients and the relationship of antimicrobial consumption and the number of multidrug-resistant (MDR) isolate.

METHODS

Patients, study, and data collection

A 7-year retrospective observational study was conducted, from January 2012 to December 2018, for the detection of patients with UTI with first episode of positive urine culture (≥ 10^5 colony forming unite, [CFU]/mL) after 48 hours of hospitalization in adult mixed ICU (30-bed), in Brazilian tertiary-care university hospital. In this surveillance, two groups were analyzed: patients with candiduria and bacteriuria. We collected the following patient data from electronic database of clinicians and the Infection Control Service Records: age, sex, comorbidities, acute physiology score,[12] chronic comorbidity Charlson Comorbidity Index (CCI),[13] incidence of sepsis,[14] and septic shock,[15] immunosuppression (age ≥ 60, blood neoplasia, use of corticosteroids, or immunocompromising disease), use of invasive devices, length of unit stay (LOS), use of urinary catheterization, previous use of antibiotics and multidrug-resistant isolate.

Definitions

UTI was defined as an infection in a patient using urinary catheter for a period ≥ 48 hours with positive urine culture of no more than two organisms.[16,17] In Brazil these infections are defined in UTI and Catheter-associated Urinary Tract Infections following National Health Surveillance Agency (Agência Nacional de Vigilância Sanitária) criteria.[18] BSI was defined by clinical criteria and documented by a positive culture result.[18,19] The ICU-acquired positive BSI culture was considered to be associated with urinary tract infection if there was a concurrent or subsequently positive culture with the same organism within a 14-day period.[17] MDR was defined as an acquired infection nonsusceptibile to at least one agent in three or more antimicrobial categories, including beta-lactams, aminoglycosides, and fluoroquinolones for Gram-negative bacilli (GNB); oxacillin/methicillin for *Staphylococcus* sp.; and *Enterococcus* sp.[20] Previous use of antibiotics was considered when patients received antimicrobial therapy 72 hours after hospital admission and before the diagnosis of microbial infection.[21] The outcomes were classified as death or survival during hospitalization; however, it was not ascertained if the death happened during their stay in the ICU.

Clinical, microbiological, and antibiotic resistant profile

Microbial identification and antimicrobial susceptibility test were performed on a VITEK II system (bioMérieux, Brazil) for the following antimicrobials: aminoglycoside (gentamicin and amikacin), carbapenems (imipenem, meropenem, and ertapenem), cephalosporin (cefazolin, ceftriaxone, cefuroxime, and cefepime), glycopeptides (vancomycin and teicoplanin), rifampicin, fluoroquinolone (ciprofloxacin), polymyxin (E and B), and penicillin plus β-lactamase inhibitors (piperacillin-tazobactam, tetracyclines, and ampicillin-sulbactam). Data on antifungal susceptibility tests were not available. Quality-control protocols were used according to the standards of the Clinical and Laboratory Standard Institute.[22] The isolate with intermediate susceptibility were considered resistant.[20]

Calculation of incidence infection rates and density

$$\text{UTI/1000 patient-day} = \frac{\text{Number of UTIs}}{\text{Total number of patient-days}^{A}} \times 100$$

[A]Patient-day = P x B x O

P = Period of observation in days

B = Beds available in the unit

O = Occupancy rate in the period considered (%)

Defined daily dose of antimicrobial (DDD) per 1000 patient-days

The most used antibiotics were selected for calculations per 1000 patient-days: cefepime, ceftriaxone, imipenem, meropenem, tigecycline, and polymyxin B. The density of DDD per 1000 patient-days was obtained by the following formula:

$$\text{DDD} = \frac{\text{Antibiotic consumption in grams}}{\text{Defined daily dose}^{23}}$$

$$\text{DDD/100 patient-days} = \frac{\text{DDD}}{\text{Total number of patient-days}} \times 100$$

Statistical analysis

The Chi-square tests or Fisher's exact test were used to compare discrete variables. Fisher's exact test was used instead of the Chi-square test when one or more expected values in the 2 × 2 contingency table were equal or less than 5. The comparison of two quantitative variables was made using the Mann–Whitney test for nonparametric variables and the Students-*t* test for parametric variables. Two-sided tests were used for all analyses. All P value < 0.05 was considered statistically significant. The Pearson's correlation coefficient test was used to describe the relationship between antibiotic consumption and bacterial resistance rate (GraphPad Prism version 6.0 [La Jolla, California, United States]). The epidemiological data were analyzed through using the GraphPad Prism 6.0 (La Jolla, California, United States) and BioEstat 5.0 (Tefé, Amazonas, Brazil).

Ethical considerations

Data and the samples analyzed in the present study were obtained according to the standards approved by the Institutional Ethics

Committee of the Universidade Federal de Uberlândia (Protocol number 1.627.990, July 5, 2016).

RESULTS

During a 7-year period (2012–2018), a cohort of 363 critical patients with first episode of UTI were included in the study, of these 252 (69.4%) were caused by bacteria and 109 (30.0%) by *Candida* sp. Further, two episodes of infection had a fungal etiology of the genus *Trichosporon* (0.5%), and these were not included in the comparative analyzes between bacteriurias and candidurias. The incidence rate of UTI was 7.2/1000 patient-days with 3.5/1000 patient-days for bacteriuria and 2.1/1000 patient-days for candiduria (**Table 1**). Overall, only 10/363 (2.7%) episodes were polymicrobial.

The most common characteristics of the patients were: women (58.6%), clinical patient (67.7%), cardiopathy (53.1%) and nephropathy (52.0%). Majority of the patients had high acute and chronic illness severity scores with average severity index score (ASIS) ≥ 4 (74.6%) and high score for chronic comorbidity CCI (54.5%), severe sepsis (29.2%), septic shock (42.9%), and used invasive procedures and broad-spectrum antibiotics therapy (96.9%; **Table 2**). The average length of hospitalization and that after diagnosis were prolonged, 15 (standard deviation [SD] ± 13.29) and 11 days (SD ± 12.52), respectively. The crude mortality rate was 38.8% and was more frequently among those with candiduria (55.0%) than those with bacteriuria (31.3%; **Table 2**).

There was significant difference in patient characteristics between those with bacteriuria and candiduria. The patients with candiduria were women (68.6%, P = 0.0086), older (58.3 years, SD 58.35 ± 20.55, P = < 0.0001), had more severe illness, had diabetes mellitus (P = 0.0012) and nephropathy (P = 0.0014), with presence of septic shock (P = 0.0002). Moreover, patients with candidemia showed more ICU-LOS than those with bacteriuria, > 15 days (62.3% versus 46.8%, P = 0.0066). Furthermore, traumatic patients were most frequently observed in the group of patients with bacteriuria (P = 0.0034). In addition, high frequency of mechanical ventilation in both groups was observed; however, it was not statistically significant (**Table 2**). Majority of the patients were using a bladder catheter (90.9%) for a longer period, with an average of 13 days (SD ± 13.29; **Table 2**).

Of the 373 microorganisms identified, 69 (18.4%) were Gram-positive cocci, with a predominance of *Enterococcus faecalis* (n = 30, 43.4%) and *Staphylococcus epidermidis* (n = 12, 17.3%), 190 (50.9%) were GNB, with a predominance of *Escherichia coli* (n = 68, 35.7 %), and 114 (30.7%) were *Candida* sp. Although the number of non-fermenting GNB isolated was low (17.8), a high rate of carbapenem-resistant *Acinetobacter baumannii* (73.1%) was found as well MDR strains (63.1%). MDR rates in *K. pneumoniae* and *E. coli* were 62.2% and 32.3%, respectively. Meanwhile, the rate of multidrug resistance of Gram-positive bacteria was low (17.3%). However, 66.6% of *Staphylococcus haemolyticus* strains and 36.3% of *S. aureus* were MDR (**Table 3**).

In the study 41.3% (150/363) patients had BSI, and 26.1% of these patients had the infection after the first episode of UTI. The urinary tract was the probable focus of infection, i.e., had the same microorganisms in blood and urine in only 11.5% (11/95) of these patients. These infections were caused mainly by bacteria in 7/11 (63.3%) cases, and the yeast genus *Candida* in 4/11 (26.3%) cases. It is important to highlight that among these patients who presented fungemia three died (75.0%; data not demonstrated).

Figure 1 shows the relationship between the defined daily dose of antibiotics/1000 patient-days and the number of patients with MDR microorganisms UTI/1000 patient-days. A variation of 104–196.7 per 1000 patient-days in the consumption of broad spectrum cephalosporins, fluoroquinolones, ertapenem, imipenem, polymyxin, and tigecycline was observed during the study period. On the other hand, there was an increase in the consumption of meropenem (data non demonstrated). Despite this, a positive correlation was observed between the increase in MDR isolate and the consumption of meropenem (r = 0.4611 and P = 0.0063) and polymyxin (r = 0.2959 and P = < 0.0001; **Figure 1**).

DISCUSSION

In this retrospective analysis, we attempted to investigate the characteristics of critical patients with candiduria and bacteriuria and the relationship of antimicrobial consumption and the

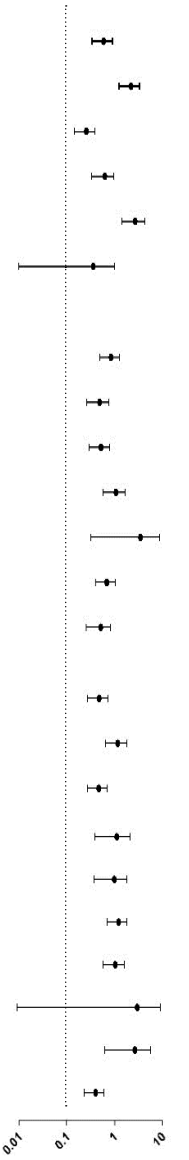
Table 1. Incidence of Urinary Tract Infections per 1.000/patient-days

Variables	Epidemiological indicators/ years							
	2012	2013	2014	2015	2016	2017	2018	Total
UTI/1.000 patient-day	3.92	5.11	4.01	8.9	14.4	7.8	6.5	**7.2**
Bacteriuria/1.000 patient-day	2.83	3.65	3.01	6.3	9.3	5.9	4.2	**3.5**
Candiduria/1.000 patient-day	1.09	1.36	0.82	2.6	5.0	1.8	2.2	**2.1**
Use of IDC (%)	95.0	93.3	80.0	89.9	93.6	92.6	95.7	**90.9**
Mortality crude (%)	23.0	37.5	31.8	44.8	39.8	20.9	37.5	**38.8**

UTI = Urinary Tract Infection; IDC = Indwelling Urinary Catheter.

Table 2. Epidemiological characteristics of patients with first episode positive urinary culture and comparison between candiduria and bacteriuria

Characteristics	Total patients = 363	Bacteriuria n = 252	Candiduria n = 109	P[1]	OR[2] CI-95%
Sex					
Woman	213 (58.6)	136 (53.9)	75 (68.8)	0.0086*	
Male	152 (41.8)	116 (46.0)	34 (31.1)	0.0086*	
Ages, year (mean) ± SD[3]	55.91 ± 19.03	54.81 ± 18.25	58.35 ± 20.55	< 0.0001*	
Patient					
Clinical	246 (67.7)	161 (63.8)	83 (76.1)	0.0223*	
Traumatic	112 (30.8)	90 (35.7)	22 (20.1)	0.0034*	
Surgical	5 (1.3)	1(0.3)	4 (3.6)	0.0146*	
Comorbidities					
Cardiopathy	193 (53.1)	128 (50.7)	63 (57.7)	0.2209	
Diabetes mellitus	86 (23.6)	48 (19.0)	38 (34.8)	0.0012*	
Nephropathy	189 (52.0)	118 (46.8)	71 (65.1)	0.0014*	
Neuropathy	89 (24.5)	61 (24.2)	28 (25.6)	0.7643	
HIV[4]+	9 (2.4)	7 (2.7)	2 (1.8)	0.5978	
Immunocompromised Score Clinical	175 (48.2)	113 (44.8)	62 (56.8)	0.0356*	
Asis[5] ≥ 4	271 (74.6)	179 (71.0)	92 (84.4)	0.0070*	
Charlson ≥ 3	198 (54.5)	123 (48.8)	75 (68.8)	0.0005*	
Severity of infection					
Sepsis	106 (29.2)	74 (29.3)	32 (29.3)	0.9989	
Septic shock	156 (42.9)	93 (36.9)	63 (57.7)	0.0002*	
ICU-LOS[6] ≥15 days	187 (51.5)	118 (46.8)	68 (62.3)	0.0066*	
Invasive procedures					
Indwelling bladder catheter	330 (90.9)	228 (90.4)	100 (91.7)	0.7014	
Mechanical ventilation	322 (88.7)	223 (88.4)	99 (90.8)	0.5120	
Tracheostomy	146 (40.2)	103 (40.8)	43 (39.4)	0.8003	
Hemodialysis	92 (25.3)	54 (21.4)	36 (33.0)	0.6714	
IDC[7] (mean/days) ± SD	13 ± 13.29	12.29 ± 0.85	14.67 ± 12.55	0.2903	
Previous use of antimicrobials	352 (96.9)	245 (97.2)	104 (95.4)	0.3786	
Mortality	141 (38.8)	79 (31.3)	60 (55.0)	< 0.0001*	



[1]Statistically significant < 0.05; [2]OR = odds ratio; CI = confidence interval; [3]SD = standard deviation; [4]HIV = human immunodeficiency virus; [5]ASIS= Average Severity Index Score. [6]ICU-LOS = Intensive Care Unit-Length of Hospital Stay; [7]IDC = indwelling urinary catheter.

number of multidrug-resistant isolate. In total, 363 cases of UTI were observed and 373 microorganisms were isolated. Our findings indicate that the presence of UTI was associated with diagnosis of admission as trauma in bacteriuria patients and older age, severe illness, diabetes mellitus, and nephropathy in candiduria patients. These infections are a problem in ICU because they are the second most important healthcare-associated infection in critically ill patients,[17] associated with high morbidity and costs.[1-3] The situation is more serious in countries like Brazil, which already has higher rates of HAI, in addition to the constant lack of financial resources to invest in the control and prevention of these.[3,4]

Overall, the higher UTI indicators found in this study's ICU compared with that by Aubron et al.[17] may be due to high and inappropriate use of urinary catheter. Although there are few studies that describe the differences between bacteriuria and candiduria, in a recent study Ding et al.[1] did not find differences between these two groups. However, our study found significant differences between them. Patients with ICU-acquired candiduria had higher comorbidities score (CCI ≥ 3), presented

Table 3. Pathogens responsible for positive urine culture in intensive care unit (ICU)

Microorganisms/ resistance profile	n total = 373/total MDR (%)
Gram-negative Bacilli	190 (50.9)
carbapenem resistant/ MDR[1]	76 (40.0)/82 (43.6)
Escherichia coli	68/190 (35.7)
carbapenem resistant /MDR	55 (80.8)/22 (32.3)
ESBL[2]	5/55 (7.3)
Klebsiella pneumoniae	45/190 (23.6)
carbapenem resistant/ MDR	4 (8.8)/28 (62.2)
ESBL	8/45 (17.7)
Pseudomonas aeruginosa	15/190 (7.8)
carbapenem resistant/ MDR	3 (20.0)/4 (26.6)
*Acinetobacter baumanni*i	19/190 (10.0)
Carbapenem resistant/ MDR	14 (73.6)/12 (63.1)
Others[3]	43/190 (22.6)
MDR	17/43 (39.5)
Gram-positive Cocci	69 (18.4)
oxacillin resistant/ MDR	10 (14.4)/12 (17.3)
*Staphylococcus aureu*s	11/69 (16.0)
oxacillin resistant/ MDR	4 (36.3)/4 (36.3)
Staphylococcus epidermidis	12/69 (17.3)
oxacillin resistant/ MDR	2 (16.6)/2 (17.0)
Staphylococcus haemolyticus	6/69 (9.0)
oxacillin resistant/ MDR	4 (66.6)/4 (66.6)
Enterococcus faecalis	30/69 (43.4)
Others[4]	11/69 (14.6)
MDR	2/11 (20.0)
Yeasts	114 (30.7)
Candida albicans	65/114 (57.0)
Candida tropicalis	25/114 (21.9)
Candida glabrata	9/114 (7.8)
Others[5]	15/114 (13.1)

[1]MDR = Multidrug-resistance; [2]ESBL = Extended-spectrum beta-lactamase; *[3]Klebsiella oxytoca, Enterobacter cloacae, Enterobacter gergoviae, Enterobacter aerogenes, Citrobacter koseri, Citrobacter freundii, Hafnia alvei, Serratia marcescens, Proteus mirabilis, Stenotrophomonas maltophilia, Raoultella planticola; [4]Sphylococccus capitis, Staphylococcus hominis, Staphylococcus saprophyticus, Enterococcus faecium, Enterococcus hirae, Streptococcus agalactiae; [5]Candida guillermondii, Candida krusei, Candida utilis, Candida lamata, Trichosporon sp.*

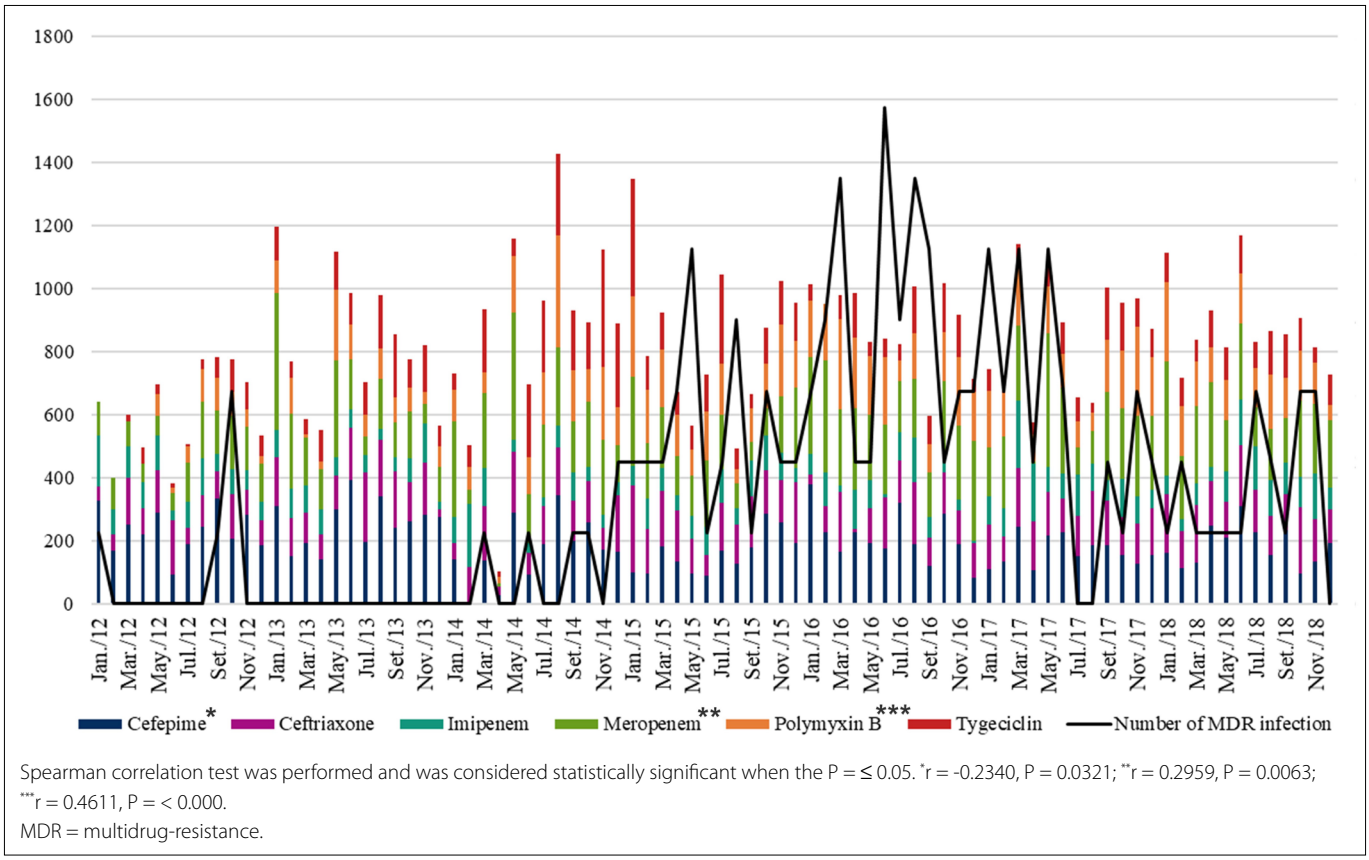
severe sepsis, septic shock, and were immunocompromised when compared with patients with bacteriuria. Higher incidence of mortality and a longer ICU-LOS, as reported in another study,[17] was also observed.

The overuse and misuse of antimicrobials in hospital settings, has caused increased bacterial resistance over time, particularly in lower and middle-income countries.[3,4,17,24] In Brazil, a rising number of scientific articles have shown high frequencies of bacterial resistance especially among infections due to *K. pneumoniae*, *P. aeruginosa,* and *A. baumannii*.[3,4] Historically, the literature describes the urinary tract as a reservoir of MDR microorganisms.[25,26]

These microorganisms were common in our cohort; High rate of occurrence of bacteria from the Enterobacteriaceae family and *Candida* spp., especially *C. albicans* (57.0%) was observed. This increase in fungal infections has been reported by other studies.[17] The impact of antibiotic therapy on microbiological ecology contributes to the emergence of these pathogens. In addition, a high frequency of *E. faecalis* was also found among Gram-positive species (43.4%). This is an interesting finding, since in developing countries and particularly in Brazil, these infections are primarily caused by GNB.[24]

Moreover, in this cohort we found alarming frequencies of MDR *A. baumannii* and *P. aeruginosa* strains, as well as high intensity consumption of the broad-spectrum cephalosporins followed by carbapenems. In addition, positive correlation was found between the consumption of polymyxin B and meropenem with multidrug-resistant infections. This positive correlation between carbapenems and MDR infections was also demonstrated in other studies.[27,28] In general, the quantity of antibiotics for general use in the evaluated ICU was higher than that compared to other countries.[29-31] Our results reinforce that the ICU is a favorable environment for the emergence of resistant microorganisms, and it is necessary for countries to invest in strategies to prevent these infections. Likewise, the importance of urine as a source of these phenotypes has also been demonstrated.

Although unexpected, we found a high mortality rate in our cohort (38.8%); however, this was attributed to several factors, such as BSI occurring concomitantly or after UTIs and the severity of acute clinical diseases. As previously mentioned, *Candida* sp. were very common in our investigation and patients with candiduria had higher mortality rates. Thus, our results suggest an association between candiduria and increased patient morbidity, which is likely to be a marker of patient severity, as noted by Horan et al.[16] In general, our results indicate that efforts to prevent nosocomial UTI (candiduria or bacteriuria) are required as although they are often not considered serious infections, our findings show otherwise. Likewise, it is extremely necessary and urgent to implement protocols for the conscious consumption of antimicrobials which are evaluated frequently as high consumption rates of these drugs and alarming rates of MDR pathogens have been observed. This reinforces the need for governments to invest in surveillance and control of these infections in developing countries.



Spearman correlation test was performed and was considered statistically significant when the P = ≤ 0.05. *r = -0.2340, P = 0.0321; **r = 0.2959, P = 0.0063; ***r = 0.4611, P = < 0.000.
MDR = multidrug-resistance.

Figure 1. Relationship between the defined daily dose of antimicrobials per 1.000 patient-days and the number of patients with multidrug-resistant urinary tract infections per 1.000 patient day in the intensive care unit of hospital.

CONCLUSION

In conclusion, the data presented in this report fortify the fact that UTIs caused by MDR GNB organisms and *Candida* sp. in adult ICUs are a challenge for the patient safety. The UTI rates and the consumption of antimicrobials found in our study were higher than that from of countries. Better strategies for the effective and systematic surveillance and prevention of this problem is required for greater adherence to infection control measures and antimicrobials use in ill patients.

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Photodynamic therapy for infected foot ulcers in people with diabetes mellitus: a systematic review

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AUTHORS' KEYWORDS:
Laser therapies.
Phototherapies.
Foot ulcers.

ABSTRACT

BACKGROUND: Ulceration of the feet in patients with diabetes is a frequent complication that increases morbidity, mortality, hospitalization, treatment costs, and non-traumatic amputations.

OBJECTIVE: To present a systematic review of the treatment of patients with diabetes mellitus and infected foot ulcers using photodynamic therapy.

DESIGN AND SETTING: A systematic review was performed in the postgraduate program in nursing at the Universidade da Integração Internacional da Lusofonia Afro-Brasileira, Ceará, Brazil.

METHODS: PubMed, CINAHL, Web of Science, EMBASE, Cochrane Library, Scopus, and LILACS databases were screened. The methodological quality, risk of bias, and quality of evidence of each study were assessed. Review Manager was used for the meta-analysis.

RESULTS: Four studies were included. They highlighted significantly better outcomes in patient groups treated with photodynamic therapy than those in the control groups that were treated with topical collagenase and chloramphenicol ($P = 0.036$), absorbent ($P < 0.001$), or dry covers ($P = 0.002$). Significant improvements were noted in terms of the microbial load in the ulcers and tissue repair, with a reported reduction in the need for amputation by up to 35 times. Photodynamic therapy resulted in significantly better outcomes between the experimental and control groups ($P = 0.04$).

CONCLUSION: Photodynamic therapy is significantly more effective in treating infected foot ulcers than standard therapies.

SYSTEMATIC REVIEW REGISTRATION: International Prospective Register of Systematic Reviews (PROSPERO) - CRD42020214187, https://www.crd.york.ac.uk/prospero/display_record.php?RecordID=214187.

INTRODUCTION

Ulcers in the feet of patients with diabetes mellitus (DM) are a frequent complication and a relevant cause of morbidity and mortality, increased rates of hospitalization and higher treatment costs, and non-traumatic amputations of lower limbs.[1] Approximately 60% of people who undergo amputations do so for infected ulcers in the feet.[2]

Infection is one of the leading causes of amputations in patients with DM; due to delayed healing in DM, infections promote exudate, swelling, microbial growth, friability, and hemorrhagic granulation tissue.[3,4] Moreover, when not treated correctly, it increases the risk of osteomyelitis or sepsis.[5] Therefore, antibiotic therapy should be implemented immediately after identifying the infection in the wound bed to avoid severe complications, such as amputation.

The standard treatment for diabetic foot ulcers (DFU) generally includes cleaning and removal of the necrotic tissue, improving blood circulation, maintenance of a moist environment, and infection control.[6] However, the classic topical therapies for DFU are costly and include low efficacy in the presence of multidrug-resistant bacteria.[4,7] Additionally, topical therapies are cytotoxic and delay healing.[8] Therefore, for DFU, the standard treatment alone is not sufficient for adequate healing and prevention of infections. This fact highlights the relevance of implementing new adjuvant therapies in the treatment of complex ulcers, such as DFU.[3,9]

Several studies have suggested photodynamic therapy as a viable option for treating infections in the treatment and healing of DFU.[9-11] Photodynamic therapy (PDT) involves the topical application of photosensitizers followed by illumination with Light Amplification by Stimulated Emission of Radiation (LASERs) or Light Emitter Diode (LED) light, which along with tissue oxygen induces the formation of reactive oxygen species and a high local cytotoxic effect, thus fighting the local infection.[12]

Systematic reviews, meta-analyses, and integrative and narrative reviews have been published regarding the effects of DFU in animal, human, and *in vitro* studies. These studies considered wounds of several etiologies. However, to date, there is no systematic review and meta-analysis concerning the effectiveness of PDT in DFU.

Although there are favorable reports regarding the application of PDT,[11,12] newer investigations can provide additional evidence about the effectiveness of PDT in the treatment of DFU.[13] A study identified that health professionals, even those with qualifications to operate LASERs, have doubts regarding the dosage, wavelength, time, and number of applications to be used.[14] Therefore, it is important that health professionals, especially wound experts, understand the new approach of PDT in treating infected ulcers and incorporate it into their practice to promote optimized healing and reduce the number of complications due to DFU.[1,15]

The study is relevant in combining the effects and protocols of DFU as an adjuvant therapy in infection reduction, optimizing DFU healing, and offering scientific evidence to reduce bacterial resistance and amputations.

OBJECTIVE

This study aimed to provide a systematic review and meta-analysis of the effectiveness of PDT in the treatment of infected DFU.

METHODS

Protocol and registry

This systematic review was performed according to the guidelines of the Joanna Briggs Institute (JBI) and the Preferred Reporting Items for Systematic reviews and Meta-analyses (PRISMA).[16,17] It was registered in PROSPERO (CRD42020214187) https://www.crd.york.ac.uk/prospero/display_record.php?RecordID=214187.

Focal issue

The research question "What is the effectiveness of PDT in the reduction of infection and healing process of infected foot ulcers in patients with DM?" was formulated using the acronym population, intervention, comparison, results, and studies (PICOS).

Study selection

Clinical trials without limitations on the time of publication or language were included if their data were completely available. The following studies were excluded: incomplete studies in annals of events, studies in animal or *in vitro* models, and studies with ulcers secondary to injuries of other etiologies.

Research strategy and search for scientific evidence

The search was performed between August and December 2020 and reviewed in June 2022. The databases of PubMed, CINAHL, Web of Science, EMBASE, Cochrane Library, Scopus, and LILACS were searched using descriptors, entry terms, and keywords in association with the Boolean operators "AND" and "OR" (**Table 1**).

Screening and selection of studies

The screening and selection of studies were performed independently by two reviewers using Rayyan software (Qatar Foundation, Qatar).[18] The complete texts of the selected publications were analyzed by the two reviewers. They evaluated the methodological rigor[19] and capacity to answer the research question. Disagreements were resolved by a third reviewer.

Data extraction

An instrument for data extraction was developed by the authors for the following factors: identification, methodological attributes, PDT protocol, results, limitations, and article recommendations.

Evaluation of the risk of bias, methodological quality, and evidence quality

The risk of bias was graded as low risk of bias, high risk of bias, or uncertain risk of bias using the Cochrane Review Manager v5.4 (Cochrane; London, United Kingdom).[20] The methodological quality was evaluated using a checklist for randomized controlled trials.[19] The evidence quality was evaluated as high, moderate, low, or very low using GRADEpro GDT https://www.gradepro.org/ (Evidence Prime, Kraków, Poland).

Data overview

The extracted data were organized in tables. Review Manager as used for the meta-analyses using a randomized effect model and different averages. Heterogeneity was evaluated statistically using the I^2 test. The meta-analysis was conducted using forest plots.

Table 1. Search terms used for each database

Databases	Search strategy
PubMed, CINAHL, Web of Science e Scopus	("Photochemotherapy" [MeSH] OR "Photochemotherapy" [All fields] OR "Photodynamic therapy" OR "PDT") AND ("Diabetic Foot" [MeSH] OR "Diabetic Foot" [All Fields] OR "Foot Ulcer")
EMBASE	("Photochemotherapy" OR "Photodynamic therapy" OR "PDT") AND ("diabetic foot" OR "foot ulcer")
Cochrane Library	("Photochemotherapy" OR "Photochemotherapy" OR "Photodynamic therapy" OR "PDT") AND ("Diabetic Foot" OR "Diabetic Foot" OR "Foot Ulcer")
LILACS	*(Fotoquimioterapia OR "Terapia Fotodinâmica") AND ("Pé diabético")*

RESULTS

Description of the included studies

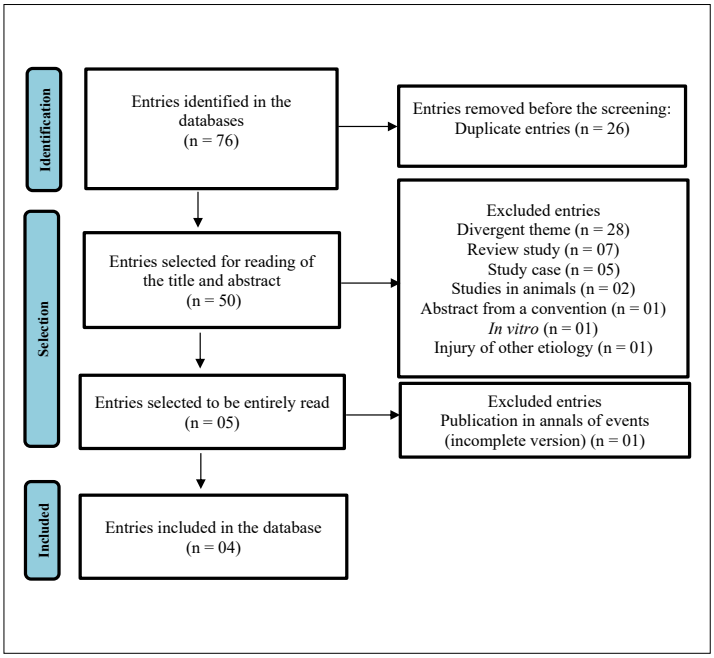
Four of the 76 studies identified were included in the analysis. Other studies only included ulcers of other etiologies or deviated from the eligibility criteria of this meta-analysis **(Flow chart 1)**. Two evaluated studies did not perform real randomization or hidden allocation. In three cases, blinding was not clear (**Table 2**). In the risk evaluation of bias, the distribution was mainly classified as low-risk (**Graphic 1**).

Participants

The participants were between 18 and 35 years of age with a confirmed diagnosis of DM and at least one foot ulcer.

Treatment groups

In all studies, PDT was only used in the experimental groups, whereas the control groups were treated with collagenase and chloramphenicol;[21] systemic antibiotics and simple dry bandages;[22] oral antibiotics and gauze embedded in vaseline;[23] or an absorbent cover **(Table 3)**.[24]

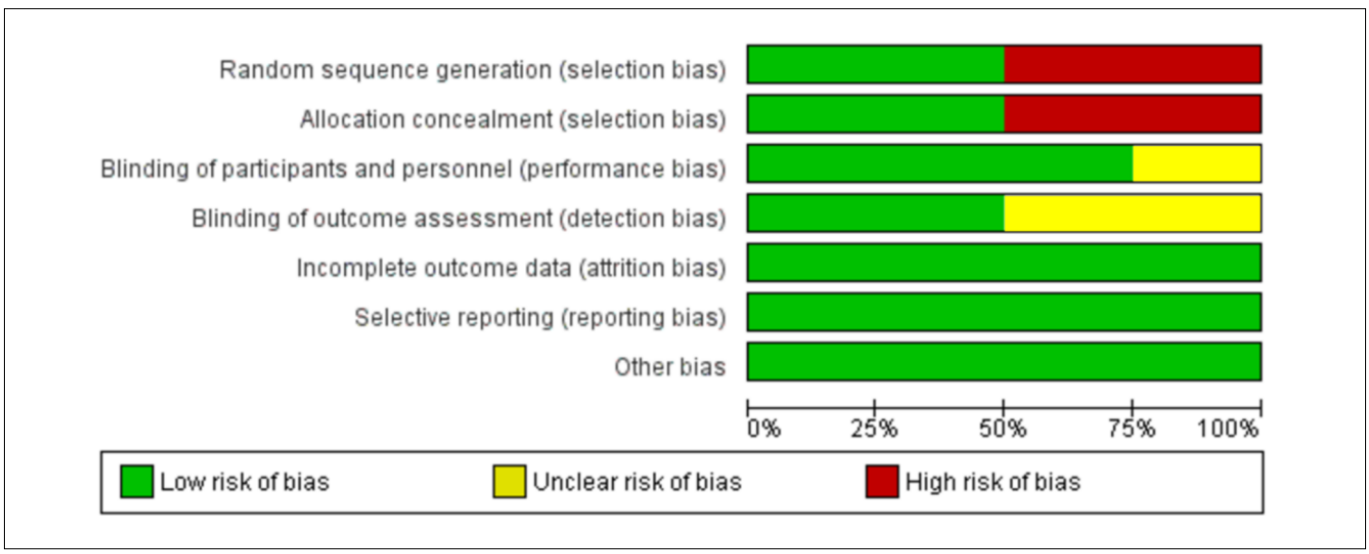


Flow chart 1. Flow chart depicting the study selection using Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) 2020 guidelines.

Table 2. Quantitative evaluation of the methodological quality

Authors / Article	Critical analysis of the Methodological Quality													Total Yes
	Questions													
	Q1	Q2	Q3	Q4	Q5	Q6	Q7	Q8	Q9	Q10	Q11	Q12	Q13	
Carrinho et al.[21]– A1	✗	✗	✓	✓	?	✓	✓	✓	✓	✓	✓	✓	✓	11
Tardivo et al.[22]– A2	✗	✗	✓	✓	✗	?	✓	✓	✓	✓	✓	✓	✓	09
Mannucci et al.[23]– A3	✓	✓	✓	✓	✓	?	✓	✓	✓	✓	✓	✓	✓	11
Morley et al.[24]– A4	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓	13

(Yes) ✓ (No) ✗ (Unclear) ?



Graphic 1. Distribution of risk of bias.

Table 3. Description of the studies included in the systematic review

Article	Local	Study design Evidence level	Population	Groups	Outcome measurement	Main results
A1	Brazil	Non-randomized clinical trial controlled with placebo 1.d	12	Experimental group Sample: 06 Intervention: PDT protocol and primary cover with collagenase 0.6 U/g + chloramphenicol 0.01 g/g. Control group Sample: 06 Intervention: primary cover with collagenase 0.6 U/g + chloramphenicol 0.01 g/g.	- Nominal analysis of the ulcers - Healing index of the ulcer	- There was an improvement in tissue repair in the patients treated with PDT, especially in the macroscopic aspects of neovascularization, epithelialization, and reduction of the wound's affected area. - A significant difference in the nominal size of the wounds pre- and post-treatment with PDT was observed along with the wound's affected area (P = 0.036).
A2	Brazil	Non-randomized clinical trial controlled with placebo 1.d	34	Experimental group Sample: 18 Intervention: PDT protocol, systemic antibiotics (clindamycin 300 mg every 8 hours and ciprofloxacin 500 mg every 12 hours) for 10 days and simple dry bandages. Control group Sample: 16 Intervention: systemic antibiotics (clindamycin 300 mg every 8 hours and ciprofloxacin 500 mg every 12 hours) for 10 days and simple dry bandages.	- Photographic analysis -Simple radiographies of the bones from the feet - Wagner's classification	- Only one of the patients from the experimental group required amputation. At least two participants in the PDT group recovered from resistant bacterial strains (*Pseudomonas aeruginosa* and *Klebsiella pneumoniae*). - In the control group, every participant underwent amputation. - The amputation rate in the PDT group was 0.029 times the rate of the control group (P = 0.002), with an amputation rate 35 times lesser in the former than that in the latter.
A3	Italy	Non-randomized clinical trial controlled with placebo 1.c	55	Experimental group Sample: 42 Intervention: PDT protocol, 875 mg of oral Amoxicillin + clavulanic acid 125 mg, three times per day, for 7 days and cover with gauze embedded in Vaseline. Control group Sample: 13 Intervention: 875 mg of oral Amoxicillin + clavulanic acid 125 mg, three times per day, for 7 days and cover with gauze embedded in Vaseline.	- Microbiological analysis - Nominal analysis of the ulcers - PEDIS score	- A reduction in the total microbial load immediately after illumination, with a progressive fading of the effect during follow-up. - No significant changes were observed in the ulcer's dimensions following PDT.
A4	United Kingdom	Non-randomized clinical trial controlled with placebo 1.c	16	Experimental group Sample: 08 Intervention: PDT protocol and cover with absorption action. Control group Sample: 08 Intervention: cover with absorption action.	- Microbiological analysis - Nominal analysis of the ulcers	- The treatment was well-tolerated without reports of pain. - There was a significant statistical reduction (P < 0.001) in the bacterial load immediately after PDT; in contrast, there was no significant reduction in the placebo group. - There was a better healing process—measured using the wound size—in patients who received PDT in comparison with those in the control group.

PDT = photodynamic therapy.

Outcomes

Two studies[22,24] reported reduced microbial load as the primary outcome and changes in tissue repair as the secondary outcome. Carrinho et al.[21] evaluated the changes in tissue repair as the primary outcome. Tardivo et al.[22] evaluated foot amputation as the primary outcome and changes in tissue repair as the secondary outcome. To measure the effects of PDT on the microbial load, microbiological analyses of ulcer swabs were performed.[23,24] Healing was evaluated using photographs,[22] assessments of the area affected,[21,23] and perfusion, extent, depth, infection and sensation (PEDIS) score.[23] Radiological assessments and Wagner's classification analysis were used to identify the need for amputation.[22]

Main results of PDT in the treatment of foot ulcers

PDT resulted in significant improvements in microbial load and tissue repair compared to the interventions in the control groups. The clinical evolution of the ulcer also demonstrated a significant improvement (P = 0.036) with the use of PDT.[21] PDT also promoted improvements in infection control (P < 0.01).[24] PDT was well-tolerated when compared with the interventions in the control groups.[23] The amputation rate was 35 times lower in the group that received PDT in comparison with the groups that received other treatments (P = 0.002).[22] The most common photosensitizer was methylene blue (0.01% to 1%). The wavelength ranged from 560 nm to 689 nm with doses of 6–30 J/cm^2. The number of PDT sessions varied from one to 23. The longest follow-up post-PDT was 90 days (**Table 4**).

Quality of evidence

The evidence regarding the outcomes concerning the reduction in the microbial load, improvements in tissue repair, and reduction in amputations was of "moderate quality," and the outcomes were considered clinically critical (essentials) for the patients. Therefore, there is moderate confidence in the estimated effect but more clinical trials can improve the confidence (**Table 5**).

Table 4. Description of the main parameters of the photodynamic therapy (PDT) protocols

Article	Photosensitive composite	Concentration / Rest period	Wavelength	Dose (J)	Application period	Total number of sessions	Frequency of applications	Follow-up period
A1	Methylene blue	0.01% 5 minutes	660 nm	6 J/cm^2	8 seconds per cm^2	10 sessions	3 times a week	22 days
A2	Methylene blue and tolonium chloride	1% Did not report	560 and 640 nm	6 J/cm^2 and 30 J/cm^2	10 minutes in every area	Average of 16 sessions (9–23)	2 times a week	Did not report
A3	Methylene blue	0.10, 0.30, and 0.50% 60 minutes	689 ± 5 nm	60 J/cm^2	8 minutes and 30 cm^2	Unique application	-	15 days
A4	Methylene blue	Did not report 15 minutes	570–670 nm	50 J/cm^{-2} (Total)	Did not report	Unique application	-	90 days

Table 5. Quality of evidence of the outcomes

EVALUATION OF THE QUALITY OF OUTCOMES								
Number of studies	**Study design**	**Risk of bias**	**Inconsistence**	**Indirect evidence**	**Imprecision**	**Other considerations**	**Quality of the evidence**	**Importance**
Outcome 1 – Reduction in the microbial load								
02	Clinical trials	not serious	not serious	not serious	serious[a]	none	⊕⊕⊕◯ MODERATE	CRITICAL
Outcome 2 – Progress in tissue repair								
04	Clinical trials	serious[b]	not serious	not serious	not serious	none	⊕⊕⊕◯ MODERATE	CRITICAL
Outcome 3 – Reduction in amputations due to diabetic foot								
01	Clinical trials	serious[b]	not serious	not serious	not serious	none	⊕⊕⊕◯ MODERATE	CRITICAL

[a]Microbial load assessment using the swab technique (inaccurate for diabetic foot ulcers [DFU] microbial assessment); [b]No real randomization (blinding of intervention applicators).

Effectiveness of PDT in the treatment of foot ulcers with infections

Numerous variabilities were noted in terms of the control groups and the methods of analysis of the evaluated outcomes between the studies. The studies used different parameters in their evaluations, which resulted in high heterogeneity (I^2 = 99%). Therefore, the outcomes of tissue repair were verified in this meta-analysis. However, nested meta-analyses were not performed. The effect of PDT on tissue repair was significant, thus suggesting the benefits of using PDT protocols in DFU. There were significant differences between the treatments (PDT protocol and standard therapy), and the intervention favored the experimental group (P = 0.04) **(Graphic 2)**.

DISCUSSION

There is a consensus regarding the superiority of PDT treatment for DFU over other therapies in control groups. This finding may be related to PDT's capacity to induce cell death in pathogens, decrease inflammation, and stimulate the proliferation of fibroblasts, collagen, and elastin.[25,26] Owing to its mechanism of action, low invasiveness, and absence of significant collateral effects, PDT offers an alternative treatment for DFU.[27]

In the studies evaluated, patients treated with PDT demonstrated a significant reduction in the microbial load.[23,24] Other studies have corroborated this result.[12,28,29] An *in vitro* study demonstrated that PDT exerted bactericidal effects on resistant bacteria and biofilms through oxidative stress.[10] This is a relevant result as biofilm bacteria and deep DFU cultures have broad bacterial resistance.[30,31] It is worth highlighting that increasing antimicrobial resistance has restricted the therapeutic arsenal to face this type of infection,[32] which reinforces the need for new treatments with antimicrobial action and reduce the clinical indications for antibiotics.[33]

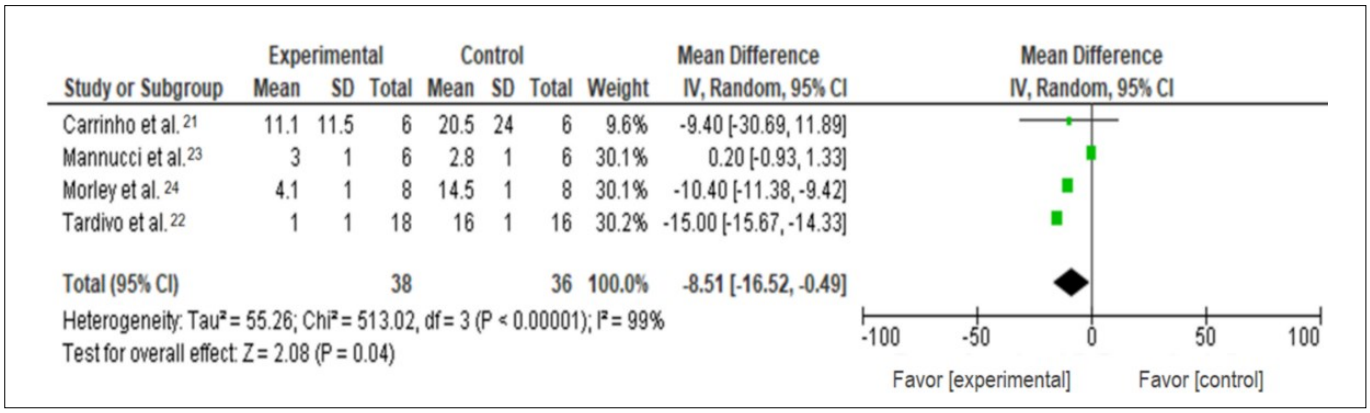
Several studies have confirmed that PDT is a promising adjuvant approach in the deactivation of resistant bacteria and bacterial biofilms.[10,25,34-36] In two studies, bacterial colonies were decreased shortly after the first PDT session.[23,24] This finding is a relevant benefit since a decrease in the colonies that form the biofilm around the ulcer provides a favorable environment for the formation of healthy granular tissue.[37] Consequently, this deactivation contributes to tissue repair.[12] A better healing process of ulcers was noted with PDT.[21-24]

These findings demonstrate that PDT has several advantages in wound healing, especially in DFU.[1,11] PDT is an adjuvant therapy that can substantially improve the healing process in DFU because it facilitates tissue repair through an immediate reduction in bacterial colonies.

In this study, we identified that through its antimicrobial effects and contribution to the healing process of infected ulcers, PDT can decrease the risk of amputation. Previous studies have reported similar results.[22,38] This finding highlights PDT's relevance as an adjuvant therapy because it demonstrated the potential to minimize the risk of amputation and decrease treatment costs and hospitalizations.[33]

Despite the convergent and positive results of PDT, each study used varying parameters for photosensitizer activation. Consequently, it was not possible to determine the optimal parameters for PDT in the treatment of DFU. Further efforts have been made to standardize the PDT protocols.[39] However, the most recent studies used lower doses for light irradiation.[21,22] Reduction of the dose of light in the PDT protocol has been suggested to exert better biostimulatory effects in cells. Cells enriched with low amounts of photosensitizer composites may also proliferate better following light exposure with the correct wavelength and appropriate time window.[40]

No adverse events were associated with PDT. A recent study inferred that with the correct choice of PDT parameters, this approach is safe and reliable.[34] For the three outcomes analyzed, the quality of evidence was considered moderate for an essential clinical outcome. In the meta-analysis, the intervention favored the experimental group. One study corroborated that PDT may be a promising procedure in the management of infected ulcers



Graphic 2. Meta-analysis regarding the outcome of tissue repair.

with a higher probability of healing, lower risk of amputation, and an important clinical outcome.[9]

However, it is pertinent to discuss the importance of health education with the patients during therapy, especially regarding glycemic control, foot care, use of appropriate shoes, and a healthy lifestyle to improve the success of PDT.[13]

The current study contributes to improving the awareness of healthcare professionals regarding new protocols and medical therapies using adjuvant technologies with better cost-benefit relationships, such as PDT. Furthermore, PDT protocols validated by clinical trials that are identified in this review can be used by health professionals safely. Despite the limited research on PDT in DFU, the findings of this study highlight the relevance of antimicrobial therapy that can be used along with standard treatments to decrease bacterial resistance and non-traumatic amputations.

More clinical studies are needed with microbiological evidence of the effectiveness of PDT in decreasing the microbial load as well as identifying the most effective PDT parameters in the treatment of DFU. This is essential for determining the precise mechanisms of action of PDT and the interactions between light and injured tissues as well as selecting the appropriate LASER parameters and concentration of the photosensitizer to avoid thermal discomfort in the irradiated tissues or phototoxicity.

CONCLUSION

PDT is significantly more effective in treating infected DFU than standard care. A significant reduction in the infection rate was noted soon after the first session of PDT along with an improvement in healing. The three outcomes analyzed were supported by a moderate quality of evidence and essential clinical outcomes. In the meta-analysis, the intervention significantly favored the groups treated with PDT.

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Arrival time at a referral hospital and functional disability of people with stroke: a cohort study

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ABSTRACT

BACKGROUND: Stroke is a major cause of death and functional disability worldwide. Knowledge of the associated factors is essential for defining education, management, and healthcare strategies.

OBJECTIVE: To analyze the association between arrival time at a neurology referral hospital (ATRH) and functional disability in patients with ischemic stroke 90 days after the event.

DESIGN AND SETTING: Prospective cohort study conducted at a public institution of higher education in Brazil.

METHODS: This study included 241 people aged ≥ 18 years who presented ischemic stroke. The exclusion criteria were death, inability to communicate without companions who could answer the research questions, and > 10 days since ictus. Disability was assessed using the Rankin score (mR). Variables for which associations showed a P value ≤ 0.20 in bivariate analysis were tested as modifiers between ATRH and disability. Significant interaction terms were used for multivariate analysis. Multivariate logistic regression analysis was performed with all variables, arriving at the complete model and adjusted beta measures. The confounding variables were included in the robust logistic regression model, and Akaike's Information Criterion was adopted to choose the final model. The Poisson model assumes a statistical significance of 5% and risk correction.

RESULTS: Most participants (56.0%) arrived at the hospital within 4.5 hours of symptom onset, and 51.7% presented with mRs of 3 to 5 after 90 days of ictus. In the multivariate model, ATRH ≥ 4.5 hours and females were associated with more significant disability.

CONCLUSIONS: Arrival at the referral hospital 4.5 hours after the onset of symptoms or wake-up stroke was an independent predictor of a high degree of functional disability.

INTRODUCTION

Stroke is a major cause of death and functional disability worldwide. Estimates from the Global Burden of Disease have shown that the global burden of stroke continues to increase, resulting in the loss of more than 100 million years of life.[1]

Despite advances in treating the acute phase of stroke, mortality, and disability rates remain high.[2] In 2017, there were 5.5 million stroke survivors in Latin America, 0.6 million new strokes, more than 0.26 million deaths, and approximately 5.5 million years of life lost to disability.[3] In the face of population aging, the magnitude of the disease is expected to worsen, compromising the sustainability of cerebrovascular disease care policies, which are still based on supportive therapy in most cases.[4]

Besides the early deaths, the impact on health and social security systems due to the reduction of the active and productive part of society, stroke affects the loss of autonomy among adults and older adults, and consequent dependency.[4,5] Stroke victims are limited by their motor functions and the compromise in managing their personal, professional, and family life.[6]

Delays in the search for adequate healthcare services for stroke can compromise early diagnosis, treatment options, and the prognosis of people affected in terms of functional disability.[7] However, other variables also influence this outcome. Studies have reported that low levels of income and education are related to unfavorable prognoses in stroke.[4,5] Sex, age,[8] stroke severity assessed by the National Institute of Health Stroke Scale (NIHSS),[2] length of hospitalization[4], admission to a specialized unit, and thrombolysis[9,10] were also associated with differences in functional disability due to the disease.

Moreover, despite advances in the epidemiology, etiology, risk factors, and treatment of ischemic stroke, cohort studies that associate arrival time at a referral hospital with the outcome of functional disability remain insufficient. No study has investigated sociodemographic and clinical variables as potential modifiers or confounders of this association.

It is necessary to know the factors that influence the association between arrival time at a referral hospital and functional disability after an ischemic stroke to promote public awareness and develop strategies to reduce presentation time and, consequently, unfavorable outcomes.

OBJECTIVE

To analyze the association between the arrival time at a neurology referral hospital (ATRH) and functional disability in patients with ischemic stroke 90 days after the event.

METHODS

Type and place of study

This prospective cohort study was conducted at a public hospital in Bahia, Brazil, which is officially a Reference Center of High Complexity in Neurology.

Ethical aspects

This study was part of the Matrix Project and approved by the Ethics Committee (protocol number 3.159.694). We assured the participants of the objectives, personal confidentiality, privacy, the right to withdraw from the research at any stage, and clarification of the Informed Consent Form.

Sample

The access population was composed of 320 people hospitalized at the study site from March to October 2019 who met the inclusion criteria, such as a clinically confirmed diagnosis of acute ischemic stroke, registered in the patient's record with a compatible imaging exam, and a minimum age of 18. The exclusion criteria were death, symptoms that prevented verbal communication in the absence of companions who could answer the research questions, and > 10 days of ictus, owing to the possibility of memory bias.

Of the 320 participants, 38 were excluded due to intrahospital death or up to 90 days post-ictus (n = 20), and 12 had symptoms that prevented verbal communication and were not accompanied by someone who could answer the research questions and/or were > 10 days of ictus due to the possibility of memory bias. Nine participants were lost to follow-up because they could not be reached via phone. Thus, we obtained a sample of 241 participants.

The power of the sample was estimated for two-sample comparison of proportions, where p1 is the proportion in group 1 (p1 = 0.623), p2 is the proportion in group 2 (p2 = 0.437), alpha of 0.05 (two-sided), and sample size n1 = 106 and n2 = 135 with n2/n1 = 1.27. The estimated power was 0.80 (80%).

Data collection procedures and instruments

Instrument I - Sociodemographic and clinical characterization data

We used an instrument formed by closed, multiple-choice, and semi-structured questions for data collection on sociodemographic (age, sex, race/color, marital status, education, monthly family income) and clinical characteristics (systemic arterial hypertension, dyslipidemia, diabetes mellitus, atrial fibrillation, previous stroke, previous myocardial infarction, smoking, NIHSS, and venous thrombolysis).

The instrument also included a space for recording the date and time of onset of symptoms or wake-up stroke, date and arrival time at the first healthcare service sought, study site, and hospital discharge, including death cases. These data allowed us to calculate the independent variable, ATRH (the time elapsed between the onset of symptoms or wake-up stroke until arrival at the study site).

Instrument II - Rankin Scale (mRs)

Another instrument used was the mRs, translated and culturally adapted to Brazil and validated for application by telephone.[11] This scale was applied to assess previous functional incapacity (pre-morbid mRs). It was also conducted via telephone 90 days after the ictus using a call protocol.

Instrument III - Telephone call protocol

The protocol was developed to standardize the telephone approach used by the researchers, with items for registering the identification of the participants, confirmation of the premorbid mRs, occurrence of death, and mRs for assessing disability after 90 days of ictus.

Collection of data procedures

The data were collected in three phases. Phase I occurred between March and October 2019. This corresponded to the identification of eligible participants, explanation of the objectives and importance of the study, and invitations to participate. Sociodemographic and clinical data were collected through interviews. Medical charts indicated the NIHSS score at admission, date, and arrival time at the study site. Patients also had atrial fibrillation, diabetes mellitus, systemic arterial hypertension, dyslipidemia, and thrombolysis. When an eligible participant did not have the clinical, cognitive, or emotional conditions to interact with the researcher, their partner was approached.

Phase II, which began in March 2019 and lasted until January 2020, corresponded to the follow-up of the participants during hospitalization to identify the inpatient units visited and the length of stay until hospital discharge, transfer, or death.

Phase III, which took place from June 2019 to January 2020, corresponded to participants' follow-up 90 days after stroke. We contacted them by phone to apply the mRs. During the phone call, we also identified the occurrence of death, excluding the participant from this study. The participants answered the scale or, if not possible, the accompanying person/family members who participated in their care at home.

Treatment and data analysis

Clinical and sociodemographic variables and ATRH were analyzed in terms of absolute and relative frequencies. ATRH, the primary independent variable, was dichotomized into ≤ 4.5 hours and > 4.5 hours from symptom onset or wake-up stroke. Based on mRs, the disability outcome was dichotomized from 0 to 2 (asymptomatic to mild disability) and 3 to 5 (moderate to severe disability).

We then performed a bivariate analysis using Pearson's chi-squared test or Fisher's exact test to verify the association between sociodemographic, clinical, and ATRH variables and functional disability. The variables for which associations showed a P value ≤ 0.20 were tested, one by one, as potential interaction (modifier) variables between ATRH and functional disability. Therefore, the interaction terms with P value ≤ 0.20 (NIHSS score and diabetes mellitus) were simultaneously included in the multivariate analysis with the variables statistically associated with functional disability in the bivariate analysis. In multivariate analysis, the two interaction terms were not statistically significant.

We performed a multivariate logistic regression analysis with all variables in the complete model, obtaining their adjusted beta measures. Potential confounders of the association between the primary independent and dependent variables were verified by comparing the reduced models, which tested each specific variable and obtained the respective association measures (beta). One confounding variable showed a difference between the beta values of the complete model and those of the reduced model greater than or equal to 7.0%. In this analysis, confounding variables were sex, first healthcare service sought, thrombolysis performance, and admission to the Stroke Unit. These confounding variables were included in the multivariate robust logistic regression model with the primary independent variable (ATRH) by adopting the backward procedure. Akaike's Information Criterion (AIC) and a statistical significance level of 5% were used to select the best model.

Considering that the disability outcome was common to the studied group, risk correction was adopted by applying the Poisson Model to obtain the prevalence ratio estimates and their respective confidence intervals.

Analyses were performed using StataCorp software (2011, Statistical Software: Release 12; StataCorp, LP, College Station, Texas, United States).

RESULTS

The study sample comprised 241 participants. Regarding sociodemographic characteristics, male predominance (51.9%), age ≥ 60 years (66.0%), no partner (53.1%), up to eight years of schooling (66.8%), and a monthly family income of up to three minimum wages (88.2%) were observed. Regarding race/color, 85.8% of the participants self-reported as Brown and Black and were classified as Black, and 14.2% self-reported as White, Asian, and Indigenous and were classified as Non-Black (**Table 1**).

Regarding the clinical characteristics of the participants (**Table 2**), the most prevalent comorbidity was systemic arterial hypertension (78.0%), followed by dyslipidemia (33.2%), diabetes mellitus (27.8%), and atrial fibrillation (7.3%). Regarding previous events, 30.8% of the patients reported stroke, and 11.3% reported myocardial infarction. A total of 40.3% of participants reported being smokers or former smokers. Most of them had an NIHSS score greater than or equal to six (77.7%), first sought health care services other than the referral hospital (83.8%), did not undergo venous thrombolysis (73.9%), and were in the Stroke Unit at some point during hospitalization (74.2%) (**Table 2**).

Most patients (56.0%) arrived within 4.5 hours of the onset of symptoms or wake-up stroke at the neurology referral hospital, and 51.7% had moderate to severe disability after 90 days of ictus. When comparing functional disability before and after 90 days, 94.6% of the sample was asymptomatic, had no significant dysfunction, or had mild disability, and 6.4% had moderate to severe disability. Therefore, 45.3% of the participants demonstrated a change from being asymptomatic to exhibiting mild-to-moderate-to-severe disabilities (**Table 2**).

A statistically significant difference of 5% was observed in the bivariate analysis between functional disability and sex, marital status, and monthly family income at minimum wage. The analysis illustrated that female participants without a partner, and lower income presented worse outcomes (mRs ≥ 3) (**Table 1**).

Bivariate analysis showed a statistically significant association at 5% between ATRH and mRs after 90 days of ictus, with a higher percentage of scores of 3 to 5 (62.3%) for those who arrived at the referral hospital within 4.5 hours of symptom onset or wake-up stroke (P = 0.004).

For participants with hypertension, previous stroke, NIHSS ≥ 14, and not submitted to thrombolysis, a higher percentage was observed with mRs 3 to 5, with these associations being statistically significant at 5%.

Table 1. Association between sociodemographic variables and functional disability of participants. Salvador, Bahia, Brazil, 2021

Sociodemographic variables	n (%)	Disability (n = 241)		P value*
		mRs 0-2 n (%)	mRs 3-5 n (%)	
Age group				
< 60 years	82 (34.0)	44 (53.7)	38 (46.3)	0.218
≥ 60 years	159 (66.0)	72 (45.3)	87 (54.7)	
Gender				
Male	125 (51.9)	69 (55.2)	56 (44.8)	**0.023**
Female	116 (48.1)	47 (40.5)	69 (59.5)	
Self-reported race/color n = 240				
Non-black	34 (14.2)	14 (41.2)	20 (58.8)	0.367
Black people	206 (85.8)	102 (49.5)	104 (50.5)	
Marital status				
With a partner	113 (46.9)	65 (57.5)	48 (42.5)	**0.006**
Without a partner	128 (53.1)	51 (39.8)	77 (60.2)	
Education n = 238				
Eight years of schooling	79 (33.2)	42 (53.2)	37 (46.8)	0.336
up to 8 years of schooling	159 (66.8)	74 (46.5)	85 (53.5)	
Monthly family income** n = 237				
≤ 3 minimum wages	212 (89.5)	96 (45.3)	116 (54.7)	**0.031**
> 3 minimum wages	25 (10.5)	17 (68.0)	8 (32.0)	

*P value of dichotomous variables obtained by Pearson's Chi-square test; **Minimum wage for 2020: R$ 1040,00 = U$192.

For participants with dyslipidemia and diabetes mellitus who were not admitted to the Stroke Unit and who did not choose the Mobile Emergency Care Service (SAMU) as the first health service, we also noted a higher percentage with worse outcomes, but without a statistically significant association at 5% (**Table 2**).

The variables with a P value ≤ 20% in the bivariate analyses were tested as potential modifiers between ATRH and functional disability. The potential modifiers identified were diabetes mellitus and the NIHSS score. However, the interaction terms were not significant when analyzed with the other variables. Thus, there was no justification for stratification of the model.

Thus, all variables were tested as potential confounders of the primary association of interest, including sex, first healthcare service sought, thrombolysis performance, and admission to the Stroke Unit. These variables comprised the multivariate model of robust logistic regression, proceeding to the exclusion of each one, and identifying sex and admission to the stroke unit as the best final model (lowest AIC value) (**Table 3**).

In this model, we observed that participants who arrived at the referral hospital 4.5 hours after symptom onset had 1.4 times more moderate to severe functional disability compared to those who arrived up to 4.5 hours, with statistical significance (prevalence ratio [PR] 1.40; 95% confidence interval [CI] 1.09–1.79). When this model was adjusted for sex and admission to the Stroke Unit, it showed that female participants had 1.3 times more moderate to severe disability (PR 1.33; 95% CI 1.04–1.69). Although not significant, those not admitted to the Stroke Unit had 1.1 times worse outcomes (PR, 1.12; 95% CI 0.86–1.44).

DISCUSSION

In this study regarding stroke and disability, dominant characteristics of patients presenting with stroke included male sex, older age, without partners, Black, and low education and income levels. These characteristics are similar to those found in other studies,[4,12-1] except for the predominantly self-reported race/color, which can be explained by regional specificities.

Sociodemographic variables were also significantly associated with a greater level of functional disability in the bivariate analyses. This study showed a worse outcome in female patients after stroke, corroborating other investigations.[2,15] Although no studies have related marital status to functional disability, it is worth mentioning that identifying people without a partner with a higher degree of disability after stroke is worrisome; this is because the impairment extends beyond mobility and interferes with physical and mental abilities, making the affected people dependent on care, which the spouses could often provide.[16] Having a stroke prevents patients from seeking treatment, and other people around the individual, such as spouses, must often recognize the signs and

Table 2. Association of ATRH and clinical characteristics with functional disability of participants. Salvador, Bahia, Brazil, 2021

ATRH and clinical variables	n = 241 (%)	Disability		P value*
		mRs 0-2 n (%)	mRs 3-5 n (%)	
Arrival time at the site				
≤ 4.5 hours	135 (56.0)	76 (56.3)	59 (43.7)	**0.004**
> 4.5 hours	106 (44.0)	40 (37.7)	66 (62.3)	
Systemic arterial hypertension				
Yes	188 (78.0)	83 (44.1)	105 (55.9)	**0.020**
No	53 (22.0)	33 (62.3)	20 (37.7)	
Dyslipidemia				
Yes	80 (33.2)	32 (40.0)	48 (60.0)	**0.075**
No	161 (66.8)	84 (52.2)	77 (47.8)	
Diabetes mellitus n = 237				
Yes	66 (27.8)	27 (40.9)	39 (59.1)	**0.169**
No	171 (72.2)	87 (50.9)	84 (49.1)	
Atrial fibrillation n = 232				
Yes	17 (7.3)	6 (35.3)	11 (64.7)	0.282
No	215 (92.7)	105 (48.8)	110 (51.2)	
Previous stroke n = 240				
Yes	74 (30.8)	26 (35.1)	48 (64.9)	**0.008**
No	166 (69.2)	89 (53.6)	77 (46.4)	
Previous AMI n = 239				
Yes	27 (11.3)	11 (40.7)	16 (59.3)	0.390
No	212 (88.7)	105 (49.5)	107 (50.5)	
Smoking				
Never smoked	144 (59.7)	72 (50.0)	72 (50.0)	0.762
Smoker	32 (13.3)	15 (46.9)	17 (53.1)	
Former smoker	65 (27.0)	29 (44.6)	36 (55.4)	
NIHSS n = 206				
≤ 5	62 (30.1)	42 (67.7)	20 (32.3)	**< 0.001**
6 to 13	98 (47.6)	50 (51.0)	48 (49.0)	
≥ 14	46 (22.3)	7 (15.2)	39 (84.8)	
Venous thrombolysis				
Yes	63 (26.1)	37 (58.7)	26 (41.3)	**0.050**
No	178 (73.9)	79 (44.4)	99 (55.6)	
Admission due to stroke n = 240				
Yes	178 (74.2)	91 (51.1)	87 (48.9)	**0.093**
No	62 (25.8)	24 (38.7)	38 (61.3)	
1st health service sought				
Study site	39 (16.2)	16 (41.0)	23 (59.0)	**0.149**
SAMU	52 (21.6)	31 (59.6)	21 (40.4)	
Other type of service	150 (62.2)	69 (46.0)	81 (54.0)	

*P value of the dichotomous variables obtained by Pearson's chi-square, except for the variable prior mRs, the first health care service sought, and smoking, for which the applied test was Fisher's Exact Test.

Thirty-five participants had no record of this scale score on their medical charts.

ATRH = arrival time at a neurology referral hospital; AMI = myocardial infarction; NIHSS = National Institute of Health Stroke Scale; SAMU = mobile emergency care service.

Table 3. Association of ATRH variables and functional disability shown in Poisson regression model. Salvador, Bahia, Brazil, 2021

Variables	PR	P value	(95% CI)
ATRH > 4.5 hours	1.40	0.007	**1.09–1.79***
Female gender	1.33	0.023	**1.04–1.69***
Not having been admitted to the stroke unit	1.12	0.394	0.86–1.44
AIC		271.4098	

* Statistically significant.
ATRH = arrival time at a neurology referral hospital; PR = prevalence ratio; CI = confidence interval; AIC = Akaike information criterion.

symptoms and trigger the health care service. A study in China also concluded that people with a lower socioeconomic status had worse outcomes after the event.[18]

More than half of the participants arrived to the neurology referral hospital within 4.5 hours of symptom onset or wake-up stroke. However, only 26.1% of patients benefited from thrombolytic therapy, and more than half presented with moderate-to-severe disability 90 days after ictus. Considering that at least 45.3% of the sample changed from being asymptomatic to having mild to moderate to severe disability, this reinforces the idea that the sequelae resulting from stroke imply a higher degree of dependence and loss of autonomy, reducing the active and productive part of society.[4]

In the bivariate analysis, arriving at the referral hospital 4.5 hours after the onset of ischemic stroke symptoms and not performing thrombolysis were significantly associated with a higher mRs. First, it is noteworthy that late arrival at the referral hospital may have impeded the institution from introducing thrombolytic therapy. Although there are already studies regarding extending the therapeutic window to 9 hours, depending on strict eligibility criteria and advanced neuroimaging tests,[13] the recommendation for its application remains up to 4.5 hours from symptom onset.[19] Moreover, patients treated with recombinant tissue-plasminogen activator present fewer sequelae than those undergoing conservative treatment, resulting in less productivity loss and lower social security and rehabilitation costs.[9] However, although thrombolysis is available in all Latin American countries, only approximately 1% of the population of these countries has access to this treatment.[3]

Other clinical variables were also associated with worse outcomes, with statistical significance at 5%, such as having systemic arterial hypertension, report of a previous stroke, NIHSS score greater than or equal to six, and not having performed thrombolysis. Systemic arterial hypertension is the leading risk factor for stroke and predicts a poorer quality of life after the event.[9,20] Similar to hypertension, a previous stroke has been cited as a risk factor for a new event.[14] However, its connection with functional disability after the new stroke has not been established. A study that analyzed the association of NIHSS scores up to 24 hours of admission with the prognosis after 90 days found that systolic blood pressure was related to variation of this score, and this variation was a predictor of functional capacity after stroke.[21] Another study showed that the difficulty in reintegrating into the community was associated with impaired functional capacity and greater severity of stroke measured by NIHSS.[5] We also highlight a survey in Northeast Brazil that identified the NIHSS as an independent predictor for functional disability after 90 days, reinforcing our findings.[22]

Other variables were associated with a higher degree of disability with a statistical significance of 20%, such as dyslipidemia, diabetes mellitus, not being admitted to the Stroke Unit, and not being assisted by the SAMU; these variables have also been reported in other studies.[14,23,24] For instance, Kuster et al. found that patients with ischemic stroke admitted to hospitals from emergency services, such as the SAMU, had shorter neuroimaging diagnosis entry times and received thrombolytic therapy more frequently.[25]

No independent variable was a modifier of the connection between functional disability and arrival time at the referral hospital. Confounders remained in the final multivariate model, as identified by the lowest AIC, ATRH, sex, and hospitalization in the Stroke Unit.

It was observed that arrival After 4.5 hours at the referral hospital contributed significantly to worse outcomes, adjusted according to sex and admission to the Stroke Unit. As mentioned, arrival within 4.5 hours at a referral hospital is closely linked to the possibility of performing intravenous thrombolysis, which has time-dependent benefits. Thus, early therapeutic intervention is crucial for reversing or reducing the area of injury and progression of infarction. Notably, stroke morbidity and mortality are minimized by the early infusion of thrombolytics[26-29] and appropriate therapeutic management. Proper therapeutic management includes etiological investigation, early rehabilitation, clinical stability,[30] prescription of appropriate drugs according to the etiology of the ischemic stroke,[31,32,] and hospitalization in stroke units.[23]

In the final model, it was also seen that female sex was statistically significantly associated with worse outcomes, adjusted for ATRH and admission to the Stroke Unit. A study from France that analyzed the difference between sexes in the outcome of ischemic stroke patients also observed that women had a worse prognosis than men.[15] Research from Spain that complemented these findings observed that women had higher mRs scores and were less likely to be admitted to a stroke unit than men, possibly influencing their outcomes.[2] Another study revealed that nontraditional stroke symptoms are more common in women at risk of delayed awareness and treatment.[17]

Although the association between admission to the stroke unit and disability was not significant in the final multivariate model, the worst mRs for participants who were not admitted to

the stroke unit were more frequent. The reduction in the degree of disability and mortality after implementing the stroke unit has been evidenced,[23] and the functional improvement and longer life with quality of life after the assistance of ischemic stroke victims in specific units and those who received thrombolytic treatment.[10]

The reduction in prehospital delay directly influences the possibility of providing adequate therapy and outcomes after the event. Therefore, through well-defined flows and detailed procedures, immediate and qualified care for people with acute stroke events is vital to ensure survival and a good prognosis.[19] Healthcare efforts are essential to promote public awareness about the signs and symptoms of stroke and reduce pre-hospital delay. Agile and qualified care is critical for those who arrive within the therapeutic window of the hospital.

It is worth noting that the difference identified between the sexes in this study points to the need for special attention in female stroke victims. Dealing with clinical presentation and treatment delays may be a significant avenue for reducing stroke morbidity and mortality.[17]

Moreover, after the event, the impact of the number of affected people who remain disabled in Latin American countries, including Brazil, requires concentrated actions by governments, health professionals, and society to improve primary prevention, acute care, and rehabilitation.[3] Training primary health care professionals to prevent a stroke and help patients recognize the disease early[33] may improve their quality of life and reduce readmissions caused by disabilities.[6] Nurses who work with stroke patients should guide them in the main difficulties by mainly educational actions.

It is necessary to produce knowledge to understand and help stroke victims who develop functional disability because it is a complex condition linked to significant changes in daily life, generating the need for adaptation in various contexts.[6]

Limitations and strengths of the study

The limitations of this study include data collection in a single public hospital in Bahia, making it impossible to generalize the results to other profiles. Telephone follow-up for the evaluation of the outcome after 90 days might result in a possible loss of follow-up.

The main contribution of this study is that it is the first to prospectively investigate the association between ATRH and functional disability in patients with stroke and its connection with the variables of interest.

CONCLUSIONS

Higher ATRH and female sex were significantly associated with higher functional disability in the multivariate model. Arriving at the referral hospital within 4.5 hours of symptom onset or wake-up stroke was an independent predictor of higher degrees of functional disability.

The results revealed the need for advances in the healthcare network to ensure early access of people with stroke to specialized units and effective treatments to minimize negative repercussions on the lives of individuals and families.

Health education to recognize the event and early search for treatment in an adequate health service, targeting specific audiences, may achieve positive results by reducing arrival time at referral hospitals for treatment.

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Cross-sectional evaluation of the saccharin transit time test for primary ciliary dyskinesia: did we discard this tool too soon?

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ABSTRACT

BACKGROUND: Primary ciliary dyskinesia (PCD) is a rare and heterogeneous disease that is difficult to diagnose and requires complex and expensive diagnostic tools. The saccharin transit time test is a simple and inexpensive tool that may assist in screening patients with PCD.

OBJECTIVES: This study aimed to compare changes in the electron microscopy findings with clinical variables and saccharin tests in individuals diagnosed with clinical PCD (cPCD) and a control group.

DESIGN AND SETTING: An observational cross-sectional study was conducted in an otorhinolaryngology outpatient clinic from August 2012 to April 2021.

METHOD: Patients with cPCD underwent clinical screening questionnaires, nasal endoscopy, the saccharin transit time test, and nasal biopsy for transmission electron microscopy.

RESULTS: Thirty-four patients with cPCD were evaluated. The most prevalent clinical comorbidities in the cPCD group were recurrent pneumonia, bronchiectasis, and chronic rhinosinusitis. Electron microscopy confirmed the clinical diagnosis of PCD in 16 of the 34 (47.1%) patients.

CONCLUSION: The saccharin test could assist in screening patients with PCD due to its association with clinical alterations related to PCD.

INTRODUCTION

Primary ciliary dyskinesia (PCD) is an autosomal recessive disease in which ciliary motility is compromised by mucus accumulation, changes in the microbiota of the airways, infection, structural changes with consequent functional worsening, and important clinical repercussions.[1,2]

The clinical changes secondary to ciliary motility dysfunction include defects in laterality (situs inversus, situs inversus totalis, and dextrocardia), infertility, chronic rhinosinusitis (CRS), chronic otitis media, and recurrent infections of the upper and lower airways.[1-3] In the lungs, changes in mucociliary clearance are related to respiratory failure in the neonatal period, recurrent pneumonia, bronchiectasis, and chronic cough.[1,3-5]

There is no gold standard for PCD diagnosis.[1,2] It is a rare disease that affects approximately 1:10,000 live births.[1] Furthermore, it is a constantly evolving condition in terms of diagnosis, and some PCD phenotypes are not yet fully established.[1,2]

Currently, guidelines from the American Thoracic Society (ATS) and the European Respiratory Society (ERS) suggest diagnostic confirmation through a combination of different clinical suspicion and diagnostic methods such as nasal nitric oxide (nNO), transmission electron microscopy (TEM), high-speed video microscopy, and genetic screening for pathogenic variants in PCD-related genes.[1,6] Clinical scores such as the Primary Ciliary Dyskinesia Rule (PICADAR) and ATS clinical screening questionnaires can help in diagnosing this disorder.[1,6,7]

TEM involves the analysis of ciliated epithelium samples. In this analysis, alterations in the ciliary ultrastructure were evaluated, and approximately 70% of patients with PCD presented with alterations within the TEM.[8] Some patients with PCD may not present obvious defects under TEM, even with changes in ciliary function.[2,8]

Infectious and inflammatory processes can affect mucociliary transport, so false positives can be found in these cases.[9] On the other hand, patients with normal ciliary ultrastructure may present functional defects of ciliary motility.[8]

The saccharin test allows for a rough evaluation of mucociliary function. It is a screening test that is widely available outside specialized centers; it is simple, inexpensive, easy to implement, and can be a useful tool for general practitioners.[10-12] Nevertheless, it is a subjective test that may be normal in patients with dyskinetic beating cilia and difficult to perform in children younger than 12 years.[12]

Adequate diagnostic evaluation remains a challenge for the management and follow-up of patients with PCD.[1,2,13,14] There have been many changes in the diagnostic criteria and methods since the prior studies on the use of saccharin transit time tests were conducted.[1,2] Therefore, this study is justified, as it could verify the saccharin test as a screening prospect.

OBJECTIVE

This study aimed to compare changes in TEM, clinical variables, and the saccharin transit time in individuals with a clinical PCD diagnosis.

METHODS

This cross-sectional prospective observational study included patients from the Hospital de Clínicas of the Universidade Estadual de Campinas (HC-UNICAMP). Before beginning the study, all participants and their guardians signed an informed consent form. The study was approved by the ethics committee of UNICAMP (CAAE:1109.0.146.000-11 approved on January 17, 2011, and CAAE: #31498020.8.0000.5404 approved on June 4, 2020).

Patients with a clinical PCD (cPCD) diagnosis based on otorhinolaryngology, pneumopediatrics, and pulmonology between August 2012 and April 2021 were included in the cPCD group. The clinical diagnosis was based on the characteristic symptoms described by the ERS task force criteria: defects of laterality, family history of PCD, persistent rhinorrhea, CRS, neonatal respiratory failure, productive cough, bronchiectasis, chronic otitis (chronic otitis media, serous otitis media, conductive hearing loss), and infertility.[1]

Patients diagnosed with cystic fibrosis, alpha-1-antitrypsin deficiency, or immunodeficiencies, and smokers were excluded. Patients with insufficient material for TEM were excluded. Patients who presented with acute upper airway infections on the day of the appointment were rescheduled.

Because PCD is a rare disease, the sample size was based on a convenience sample of patients who agreed to participate in the study.

All patients answered a clinical form containing demographic data, characteristic PCD symptoms, and personal history, and those evaluated after 2016 answered the PICADAR and ATS clinical screening questionnaires.[6,7]

All patients underwent nasal endoscopy, and the main findings were documented. This examination allowed the nasal fossa to be biopsied and tested, excluding obstructive factors.

The saccharin test was performed as described previously.[10,11,15] A sodic saccharin fragment measuring 1 mm in diameter was placed on the surface of the head of the inferior nasal turbinate 1 cm posterior to the nasal vestibule to avoid the squamous epithelium area. The participants remained seated, breathing normally, without sneezing or blowing their nose. The time between the placement of saccharin and the beginning of the sensation of sweet taste was measured in minutes. If the patient did not report a sensation of taste after 60 minutes, the test was interrupted. The test was considered altered when the result was greater than 30 minutes.[11]

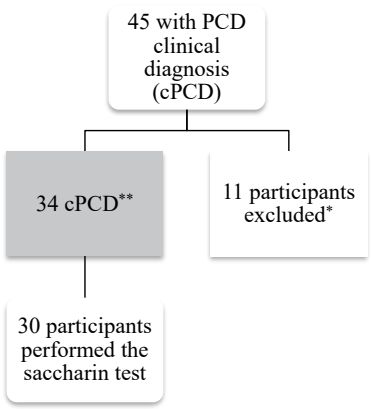
For the TEM evaluation, the material was collected through cytological brushing of the inferior turbinate. The material was placed in as container with a glutaraldehyde fixing solution of 3% and kept at 4 °C for three hours. The biopsy specimens were processed, washed, and placed in a phosphate buffer container. The samples were analyzed by two researchers (MDCT and EO) according to the international consensus guideline for reporting TEM (BEAT PCD TEM criteria).[16] Changes in the ultrastructure were based on the observation of at least 100 cilia, being evaluated in cross-sections.[1] Abnormalities found in less than 10% of the cilia were considered within the normal range.[17] Described alterations associated with PCD were analyzed, such as the absence of the internal and external arm of dynein, translocations, and absences of central microtubules, compound cilia, ciliary disorientation, and alterations of peripheral and central microtubules.[18,19]

The BEAT PCD TEM criteria consist of class 1 alterations: hallmark defects such as more than 50% of axonemes with outer dynein arm (ODA) defects with or without inner dynein arm (IDA) defects or microtubular disorganization (MD) with IDA defects, and class 2 alterations: cilia alterations that confirm PCD diagnosis in the presence of other supporting evidence which include: central complex defects, mislocalization of basal bodies with few or no cilia (Oligocilia), MD defect with IDA present or ODA defect with or without IDA defect in 25-50% of cross-sections.[16]

Descriptive analyses were performed using categorical data and absolute and relative frequencies. Numerical data are presented as the median, minimum, and maximum values and interquartile intervals. The normality of the numerical data was evaluated using the following techniques: (i) analysis of descriptive measures for central tendency and (ii) statistical tests (normality tests): Kolmogorov-Smirnov and Shapiro-Wilk. The data collected from the biopsies were compared between the groups using statistical analysis of contingency (chi-square), Fisher's exact test, and the Wilcoxon-Mann-Whitney test. The significance level was set at $P < 0.05$.

RESULTS

A total of 45 individuals were evaluated. Eight patients with cPCD were excluded because of insufficient material for TEM. Three patients were excluded after testing positive for the cystic fibrosis transmembrane conductance regulator gene. After exclusion, 34 patients were included in this study. Moreover, four patients were unable to complete the saccharin transit time test because of a lack of understanding or reactive sneezing during the test. **Figure 1** shows a flowchart of the inclusion of patients, and **Table 1** shows the main clinical characteristics of the study participants. The median age of the participants was 15.5 years (range: three to 60 years). The most common clinical features were bronchiectasis, recurrent pneumonia, and CRS.



*Eleven participants with a clinical diagnosis of primary ciliary dyskinesia (cPCD) were excluded: eight due to insufficient material for TEM and three for positive genetic testing for cystic fibrosis. **34 patients were included in the cPCD group; however, it was not possible to perform the saccharin test in four cases.

Figure 1. Flow chart of the inclusion of participants in the study.

Table 1. Main characteristics of participants with a clinical diagnosis of primary ciliary dyskinesia (cPCD)

	cPCD group n = 34
Median age	15.5
Sex: male	22 (64.7%)
Recurrent pneumonia	23 (67.6%)
Laterality defects	9 (26.5%)
Fertility disorders	4 (11.8%)
Chronic rhinosinusitis	19 (55.9%)
Chronic otitis media	13 (38.2%)
Bronchiectasis	26 (76.5%)
Asthma	15 (44.1%)
Allergic rhinitis	17 (50%)
Saccharin transit time > 30 minutes*	7 (23.3%)

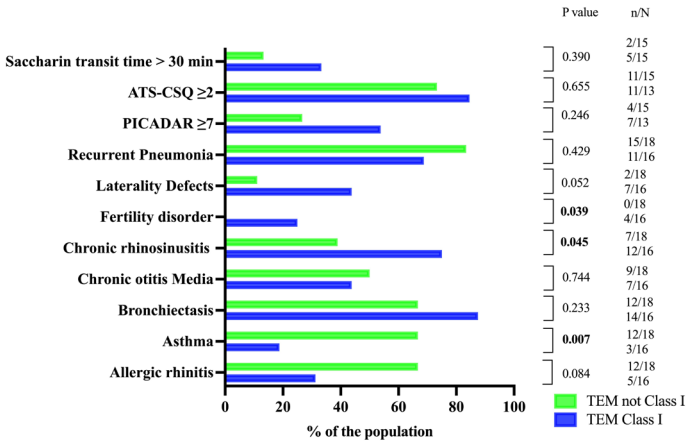
*In the cPCD group, only 30 patients were able to complete the saccharin transit time test.

Twenty-seven (79.4%) individuals presented with changes in ciliary ultrastructure, and seven (20.6%) had no alterations on TEM. When classifying these alterations according to the BEAT PCD TEM criteria,[16] 16 patients (47.1%) presented class I alterations, five patients (14.7%) presented class II alterations, and 13 patients (38.2%) did not present alterations compatible with the PCD diagnosis. **Figure 2** shows the clinical alterations, clinical scores of the PICADAR and ATS-CSQ, and saccharin transit time in the groups with or without class I alterations.

Patients with cPCD present with the following alterations in ciliary ultrastructure: absence of dynein's inner arm, absence of dynein's external arm, ciliary disorientation, compound cilia, central microtubule translocation, extra peripheral microtubules, extra central microtubules, absence of cilia, absence of peripheral microtubules, and absence of central microtubules.

The median saccharin progression time was 11.5 minutes. **Figure 3** shows the distribution of the results for the participants who completed the saccharin transit time test. No association was found between the altered saccharin test results and changes in TEM in general or according to the BEAT PCD TEM criteria.

No association was found between PICADAR ≥ 7 or the ATS clinical score ≥ 2 and saccharin test greater than 30 minutes. Also, there was no association between PICADAR ≥ 7 or the ATS clinical score ≥ 2 and TEM class I defects.



TEM class I represents patients with hallmark ultrastructural defects of PCD, while TEM, not class I, represents either normal or other TEM alterations. Statistical analyses were performed using the Fisher's exact test. An alpha of 0.05 was set in all analyses.

Figure 2. Clinical characteristics, clinical scores of PICADAR and ATS-CSQ (American Thoracic Society clinical screening questionnaire), and alteration in the saccharin progression time test (> 30 min) of individuals clinically classified with primary ciliary dyskinesia (cPCD), divided by the transmission electron microscopy (TEM) findings.

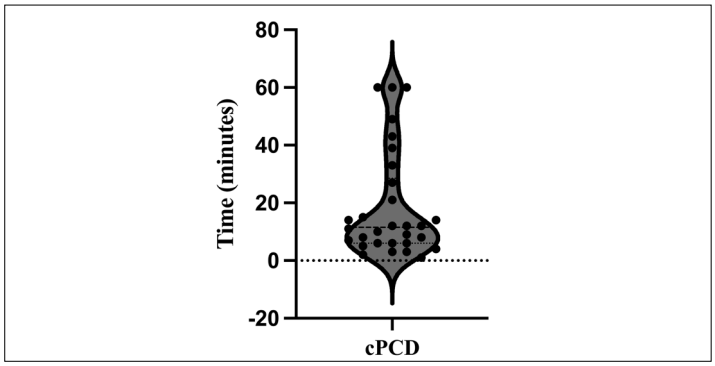


Figure 3. Violin plot for the saccharin progression time (minutes) of individuals clinically classified with primary ciliary dyskinesia (cPCD).

DISCUSSION

The diagnosis of PCD remains a major challenge in clinical practice due to the need for a combination of tools, which often require sophisticated techniques available in only a few centers in a limited number of countries.[13] The investigation of this disease becomes even more difficult due to the low incidence and great variability of genotypes and phenotypes.[7] In Brazil, few studies have been conducted that evaluate the diagnosis and clinical characteristics of patients with PCD.[20]

Due to this phenotypic unpredictability, great heterogeneity may be observed in the clinical characteristics of these patients. In this study, clinical variability was observed in the cPCD group, and the most frequent features were recurrent pneumonia, bronchiectasis, and CRS.

Identifying children with suspected PCD at an early age can improve the prognosis and delay pulmonary remodeling, leading to a decrease in pulmonary function.[6,21] However, complex and expensive screening and diagnostic tests may delay PCD diagnosis. Pediatric European centers demonstrated a 5.3-year median age at diagnosis.[21] However, Braun et al. demonstrated a median age of 17 years at PCD diagnosis in a retrospective 30-year analysis of a single center,[22] similar to the results of this study.

Three meta-analyses of studies with patients with PCD showed differences in the prevalence of clinical features such as CRS, bronchiectasis, situs inversus, otitis media, and recurrent pneumonia. There is great heterogeneity in the prevalence of clinical characteristics.[5,23-25]

Seventy-seven percent of the patients with clinical characteristics compatible with PCD presented with alterations in the ciliary ultrastructure on TEM analysis. This result was consistent with a meta-analysis, which reported a detection rate of 83%.[25] In the literature, approximately 30% of PCD cases present normal TEM.[8]

The findings of this study concerning TEM were similar to those of a study by Demarco et al. in the Brazilian population, which showed 54% alterations in dynein arms (internal, external, or associated) and 14% ciliary aplasia.[9]

However, when analyzing the criteria published by the International Consensus of TEM (BEAT PCD TEM criteria) in 2020, 61.8% of our patients were classified as having either class I or II TEM alterations.[16]

Previously, the saccharin test was disregarded in the new diagnostic guidelines of 2017 and 2018 because of its technical difficulty, especially in children.[1,26] A previous study demonstrated a sensitivity of up to 95% in identifying a normal ciliary ultrastructure.[17] However, our results showed no relationship between the altered saccharin test and TEM. Patients with ciliary beat alterations may also present false negatives, which may be true in other diagnostic tests, such as TEM and genetic screening.[11,27]

Although several guidelines state that the saccharin transit time test is unreliable in children younger than 12 years old,[11] studies have shown reliable results when testing patients aged three to 11 years old for other conditions such as adenoid hypertrophy and even healthy children.[27-29]

Our study found no association between altered clinical scores, such as the PICADAR and ATS-CSQ, and alterations in the saccharin test or TEM. Clinical scores have gained great relevance in the diagnostic algorithm, especially in the ATS guidelines, where patients with a clinical screening questionnaire score of less than two should not continue the investigation.[2] The positive predictive value of these scores in previous studies was similar to that of nNO, but these scores require multicentric and multidisciplinary validation.[13]

The complete diagnostic algorithm for PCD can cost €653 to €2,097 per patient, which can be challenging in countries with limited resources and social heterogeneity, such as Brazil. This is not only due to the costs but also the lack of reference centers with staff able to perform the required tests and analyses.[26,30]

Thus, physicians should pay attention to patients with severe or atypical symptoms and individually evaluate each patient's clinical history.[1] In this context, the assessment of the saccharin transit time may be an additional tool to corroborate subjective clinical decisions, particularly in primary and secondary care centers.

Our study has some limitations because it examined a rare disease and reduced the number of patients evaluated per year. In the nine years of analysis included in this study, there were changes in the diagnostic criteria, especially concerning the TEM criteria, and scores such as the PICADAR and ATS clinical questionnaire were incorporated before 2016. In addition, evaluating other tools is challenging because of the lack of a reference test for PCD diagnosis. Access to nNO, ciliary beat analysis through video microscopy, and genetic testing may be useful in future studies that diagnostic and screening tools.

CONCLUSION

Due to the genotypic and phenotypic complexity of PCD, this study showed that the saccharin transit time test and TEM may be complementary to other more specific tools. Nevertheless, the saccharin transit time cannot be used as a diagnostic test because of its lack of association with TEM alterations.

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Intravenous zoledronate for postmenopausal women with osteopenia and osteoporosis: a systematic review and metanalysis

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ABSTRACT

BACKGROUND: Osteoporosis compromises bone strength and increases the risk of fractures. Zoledronate prevents loss of bone mass and reduces the risk of fractures.

OBJECTIVES: To determine the efficacy and safety of zoledronate in postmenopausal women with osteopenia and osteoporosis.

DESIGN AND SETTINGS: A systematic review and meta-analysis was conducted within the evidence-based health program at the Universidade Federal de São Paulo.

METHODS: An electronic search of the CENTRAL, MEDLINE, Embase, and LILACS databases was performed until February 2022. Randomized controlled trials comparing zoledronate with placebo or other bisphosphonates were included. Standard methodological procedures were performed according to the Cochrane Handbook and the certainty of evidence for the Grading of Recommendations Assessment, Development, and Evaluation Working Group. Two authors assessed the risk of bias and extracted data on fractures, adverse events, bone turnover markers (BTM), and bone mineral density (BMD).

RESULTS: Twelve trials from 6,652 records were included: nine compared zoledronate with placebo, two trials compared zoledronate with alendronate, and one trial compared zoledronate with ibandronate. Zoledronate reduced the incidence of fractures in osteoporotic [three years: morphometric vertebral fractures (relative risk, RR = 0.30 (95% confidence interval, CI: 0.24–0.38))] and osteopenic women [six years: morphometric vertebral fractures (RR = 0.39 (95%CI: 0.25–0.61))], increased incidence of post-dose symptoms [RR = 2.56 (95%CI: 1.80–3.65)], but not serious adverse events [RR = 0.97 (95%CI: 0.91–1.04)]. Zoledronate reduced BTM and increased BMD in osteoporotic and osteopenic women.

CONCLUSION: This review supports the efficacy and safety of zoledronate in postmenopausal women with osteopenia for six years and osteoporosis for three years.

PROSPERO REGISTRATION NUMBER: CRD42022309708, https://www.crd.york.ac.uk/prospero/display_record.php?RecordID=309708.

INTRODUCTION

Osteoporosis is a silent disease that compromises the density and quality of bones, increasing the risk of fractures. Advanced age and female sex are important risk factors for osteoporosis.[1]

Approximately 200 million women worldwide are observed to have osteoporosis,[2] representing one-fifth of individuals over the age of 50 years.[3] Although osteoporosis is responsible for a significant number of fractures, most fractures occur in individuals with osteopenia or with normal bone mineral density (BMD), which can be explained by the high number of people in this T-score range. Therefore, BMD results should be combined with other clinical risk factors for an accurate assessment of fracture risk and to guide treatment decisions.[4,5] The most common sites where an osteoporotic fracture can occur are the vertebrae, hip, and distal forearm; however, the incidence of occurrence at other sites is also high.[6,7]

Drugs that increase bone mass do so by affecting bone metabolism. There are three categories: anti-catabolic (bisphosphonates, hormone therapy, selective estrogen-receptor modulators (raloxifene), and calcitonin), anabolic (teriparatide and abaloparatide), and both anabolic and anti-catabolic (romosozumab).[4]

Bisphosphonates are one of the first treatment choices for postmenopausal osteoporosis.[4,8] They bind to hydroxyapatite in the bone mineral, inhibit the activity of osteoclasts, and prevent bone resorption.[9]

Zoledronic acid (or zoledronate) is an intravenous bisphosphonate that has a high affinity to the mineralized bone.[10] It reduces the blood levels of bone turnover markers (BTM) (produced by osteoclasts) and increases bone mass (observed through densitometry).[10] These findings are observed to correlate with a reduction in the number of new fractures.[10]

Prolonged use of bisphosphonates has been associated with complications, such as osteonecrosis of the jaw, excessive suppression of bone remodeling, atypical fractures of the femur, and atrial fibrillation.[11]

As the incidence of osteoporotic fractures continues to increase, global health demands therapies to reduce the risk of fractures. This systematic review helps to evaluate the evidence on the efficacy and safety of zoledronate in postmenopausal women, presenting an accessible updated synthesis to clinicians, researchers, health policy makers, and consumers, contributing to decision-making for preventing fractures.

OBJECTIVE

To determine the efficacy and safety of zoledronate in postmenopausal women with osteopenia and osteoporosis.

METHODS

The protocol was registered in PROSPERO (number CRD42022309708; https://www.crd.york.ac.uk/prospero/display_record.php?RecordID=309708).

Study selection

All randomized controlled trials (RCTs) of a duration of at least one year comparing zoledronic acid (5 mg) to a placebo or other anti-catabolic agents in postmenopausal women were included. The inclusion criteria for RCTs for osteoporosis were: postmenopausal women with a previous fragility fracture and women with osteoporosis defined by densitometry (BMD T-score ≤ -2.5 standard deviation [SD]), with or without previous fragility fractures; and for osteopenia were: postmenopausal women without fragility fractures and with a T-score < -1 SD and > -2.5 SD. Trials that investigated women with secondary osteoporosis (bone loss caused by specific diseases, including malignancy, or medications) were excluded.

Search methods for the identification of studies

On May 13, 2021, and February 15, 2022, electronic databases, such as the Cochrane Central Register of Controlled Trials (CENTRAL), MEDLINE (via PubMed); EMBASE (via Ovid), and LILACS (Latin American and Caribbean Health Science Information database) were searched for all relevant RCTs, regardless of language or publication status. In addition, trial registers for study protocols, ongoing trials, and conference abstracts were searched.

Study outcomes

The primary outcomes were fractures and adverse reactions each year. The fractures were classified as follows: incidence of clinical and morphometric vertebral fractures, non-vertebral fractures, hip fractures, and all fractures. For adverse reactions, the following were considered: non-serious and serious adverse events (SAE), total mortality, atrial fibrillation, post-dose symptoms or influenza-like symptoms, increase in serum creatinine (a rise of more than 0.5 mg per deciliter (or 44 μmol/L) compared with the baseline level), osteonecrosis of the jaw, atypical femoral fractures, and eye disorders (uveitis, iritis, episcleritis).

The secondary outcomes were percent change in BTM, such as CTX (C-terminal telopeptide of type 1 collagen) and P1NP (Procollagen type 1 N propeptide) after 6 months and after each year, and percent change in BMD of the lumbar spine, femoral neck, and total hip after each year.

Data collection

Data were extracted systematically in a predefined and standardized manner according to the instructions given in the Cochrane Handbook for Systematic Reviews of Interventions.[12] Two review authors independently selected the studies that matched the inclusion criteria, screened titles and abstracts, selected reports to read in full text, and independently extracted all data from the studies. In addition, the risk of bias was assessed using domain-based evaluation criteria and was judged as low, with some concerns, or a high risk of bias. When necessary, a third reviewer was consulted to settle any disagreements.[12]

Data analysis

Risk ratios (RR) were calculated for dichotomous variables with 95% confidence intervals (CI), and the relative percent change was calculated and expressed as a percentage. The number needed to treat for a benefit or the number needed to cause harm was calculated for significant outcomes.[12,13] The mean difference (MD) in the percent change from baseline with 95% CI was calculated for continuous data.[12,13] The WebPlotDigitizer program (https://github.com/ankitrohatgi/WebPlotDigitizer, version 3, Pacifica, California, United States) was used to extract values from graphics when the data were not available in the text.[14]

Meta-analyses were performed in a random-effects model to avoid 'between-study' variations when the data were clinically and statistically homogeneous, as recommended in the Cochrane Handbook for Systematic Reviews of Interventions.[13]

Heterogeneity was assessed using the chi-square test (with the significance set at a P value of 0.05) and measured through I^2 (I^2 > 50% was considered to signify substantial heterogeneity).[13]

The overall certainty of the evidence was independently assessed by two authors using the specific evidence grading system developed by the Grading of Recommendations Assessment, Development, and Evaluation (GRADE) Working.[15] The GRADE approach specifies four levels of certainty of evidence (high, moderate, low, or very low).

A minimum significant reduction value for fractures was established in this review to consider zoledronate effective. The values varied according to the fracture type: 30% for vertebral and hip fractures, 15% for non-vertebral fractures and all clinical fractures.[16] Any increase in serious adverse events or a 10% increase in non-serious adverse events was considered significant.[16]

A minimal significant reduction in the BTM levels (CTX and P1NP) of 30%, a minimal significant increase in the BMD values measured by dual-energy X-ray absorptiometry of 5% at the lumbar spine, and a 4% increase at the femoral neck and total hip were considered.[16]

RESULTS

Results of the search

A total of 6,652 records were identified. After removing duplicates (1,787 records), 12 RCTs met the eligibility criteria,[17-29] and 11 RCTs were included in the meta-analysis (**Figure 1**). One RCT published data in more than one article.[17,18] Six RCTs compared zoledronate yearly with placebo,[17-23] two RCTs compared zoledronate with alendronate,[27,28] one RCT compared zoledronate

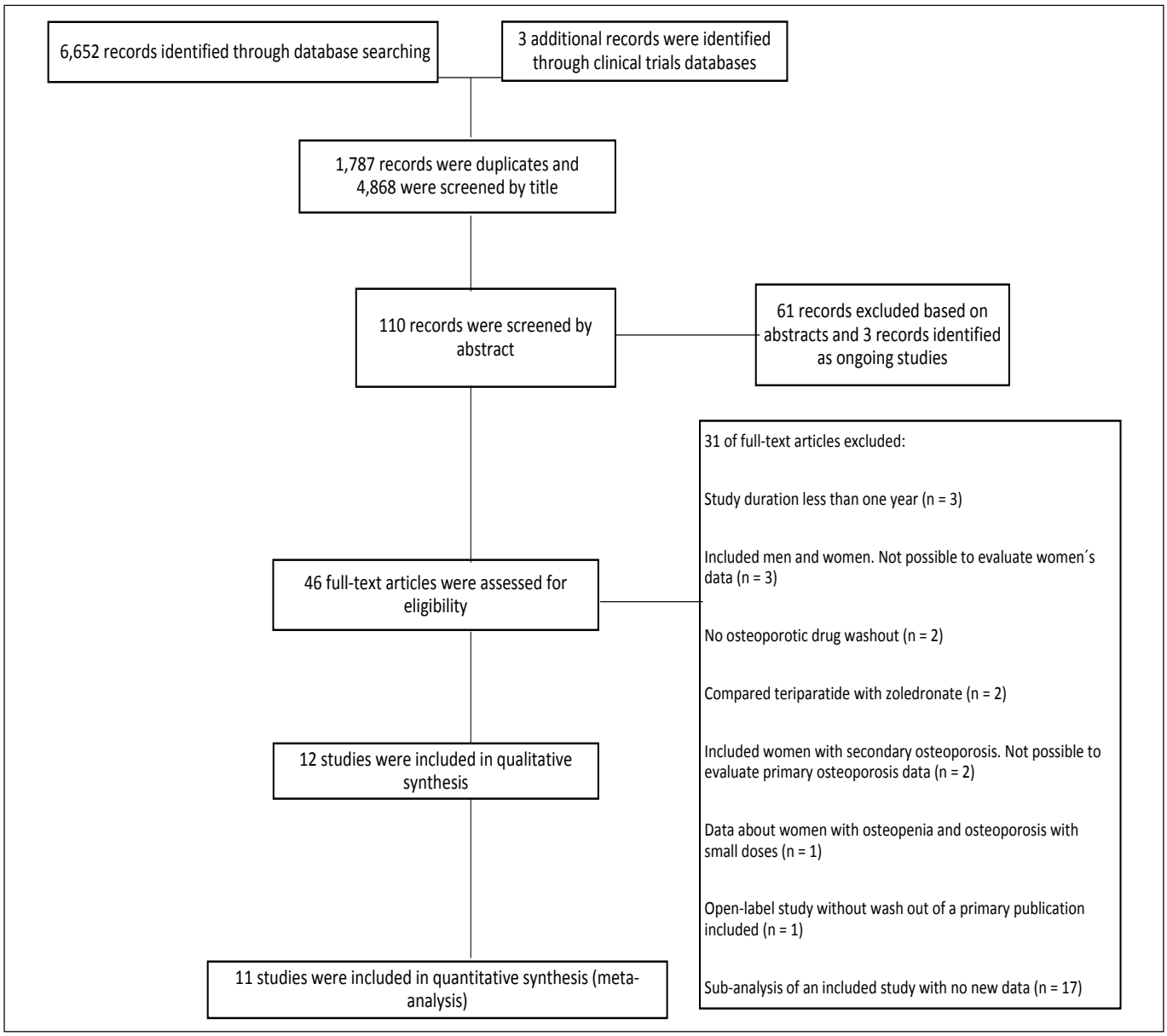


Figure 1. Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) flow diagram.

with ibandronate,[29] two RCTs studied a single dose,[24,25] and one RCT investigated each 18-month period over six years.[26] The characteristics of the included studies are summarized in **Table 1**[17,19-22,27-29] for osteoporosis and **Table 2**[23-26] for osteopenia.

Risk of bias in included studies

The risk of bias for each study and outcome is shown in **Figure 2** for osteoporosis and **Figure 3** for osteopenia, respectively.

Primary outcomes

Fractures

The incidence of fracture data was obtained from four RCTs comparing zoledronate with a placebo in women with osteoporosis and one RCT conducted on women with osteopenia. The RCTs comparing zoledronate with alendronate reported fractures as adverse events, whereas the RCT comparing ibandronate did not evaluate fractures.

Postmenopausal osteoporotic women

Upon comparing zoledronate with placebo, high-certainty evidence demonstrating that zoledronate reduces clinical and morphometric vertebral fractures since the first year was obtained (**Figure 4a** and **Figure 4b1**).

For hip fractures (**Figure 4c1**), zoledronate had no effect on reducing or increasing hip fractures after one year; however, moderate-certainty evidence (downgraded for imprecision) indicated that zoledronate probably reduces hip fractures after two years.

There was also moderate-certainty evidence (downgraded for imprecision) that zoledronate probably reduces non-vertebral fractures after two and three years (**Figure 4d1**) and high-certainty evidence that zoledronate reduces all clinical fractures after two and three years (**Figure 4e1**).

Upon comparing zoledronate with alendronate after one year, there was very low-certainty (downgraded by two points for risk of bias and one for imprecision) about the effect of zoledronate on hip fractures and clinical fractures.

Table 1. Summary of characteristics of included studies with osteoporotic women

Study ID	Study duration (years)	Comparator	Number of participants	Ethnicity	Inclusion criteria	Age (years)	Outcomes	Industry funding
Bai et al.,[20] 2013	2	0.25 mg activated vitamin D3	242 Zol X 241 Plac	Chinese	low bone mass + fracture or osteoporosis	Zol: 56.5 ± 6.83 Plac: 57.15 ± 6.3	Fractures AEs BMD	No
Black et al.,[17] 2007	3	Placebo	3,875 Zol X 3,861 Plac	More than 15 countries	low bone mass + fracture or osteoporosis	Zol: 73.0 ± 5.2 Plac: 73.1 ± 5.4	Fractures AEs BTM BMD	Yes
Chao et al.,[19] 2013	1	0.25 mg activated vitamin D3	327 Zol X 333 Plac	Chinese	low bone mass + fracture or osteoporosis	Zol: 54.6 ± 7.3 Plac: 55.3 ± 7.5	Fractures AEs	Yes
Liang et al.,[21] 2017	2	Placebo	175 Zol X 110 Plac	Chinese	only osteoporosis by DXA	Zol: 57.22 ± 2.8 Plac: 57.48 ± 3.2	Fractures BTM BMD	Yes
Yang et al.,[22] 2015	1	Placebo	50 Zol X 50 Plac	Chinese	only osteoporosis by DXA	Zol:61.4 ± 9.5 Plac: 59.7 ± 8	BTM BMD	No
Hadji et al.,[28] 2012	1	Alendronate 70 mg/week	408 Zol X 191 Aln	Germany	only osteoporosis by DXA	Zol: 67.6 ± 8.0 Aln: 68.1 ± 7.9	Fractures (AE) AEs BTM	Yes
Tan et al.,[27] 2016	3	Alendronate 70 mg/week	52 Zol X 53 Aln	Chinese	only osteoporosis by DXA	Zol: 68.1 ± 9.02 Aln: 68.0 ± 8.55	Fractures (AE) BTM BMD	No
Gonnelli et al.,[29] 2014	1	Ibandronate 3 mg/3 months	30 Zol X 30 Ibn	Italian	low bone mass + fracture or osteoporosis	Zol: 64 ± 6 Ibn: 67.0 ± 8.1	BTM BMD	No

Zol = Zoledronate; Plac = Placebo; Aln = Alendronate; Ibn = Ibandronate; DXA = dual-energy x-ray absorptiometry (DXA) or bone densitometry; AEs = adverse events; BTM = bone turnover marker; BMD = bone mineral density.

Table 2. Summary of the characteristics of included studies with osteopenic women

Study ID	Study duration (years)	Comparator	Number of participants	Ethnicity	Inclusion criteria	Age (years)	Outcomes	Industry funding
Grey et al.,[24] 2009	2	Placebo	25 Zol X 25 Plac	New Zealand	low bone mass + no fractures	Zol: 62 ± 8 Plac: 65 ± 8	Fractures (AE) AEs BTM BMD	No
Grey et al.,[25] 2012	1	Placebo	43 Zol X 43 Plac	New Zealand	low bone mass + no fractures	ZOL: 66 ± 8 Plac: 65 ± 9	Fractures (AE) AEs BTM BMD	No
McClung et al.,[23] 2009	2	Placebo	379 Zol X 202 Plac	25 centers	low bone mass + no fractures	Zol: 59 ± 8 Plac: 60 ± 8	Fractures (AE) AEs BTM BMD	Yes
Reid et al.,[26] 2018	6	Placebo	1,000 Zol X 1,000 Plac	New Zealand	low bone mass + no fractures	Zol: 71 ± 5 Plac: 71 ± 5	Fractures AEs BTM BMD	No

Zol = Zoledronate; Plac = Placebo; DXA = dual-energy x-ray absorptiometry (DXA) or bone densitometry; AEs = adverse events; BTM = bone turnover marker; BMD = bone mineral density.

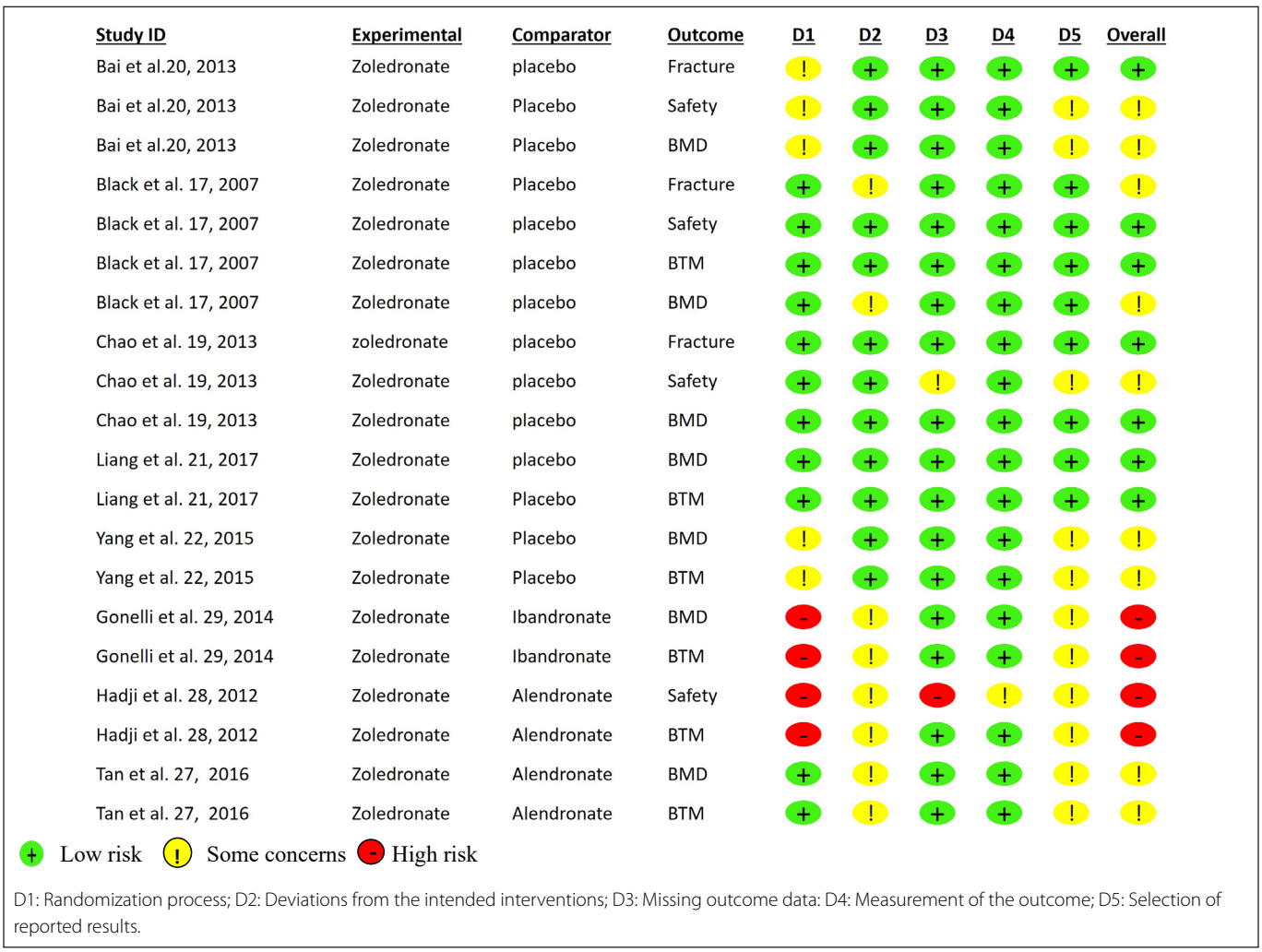


Figure 2. Risk of bias 2: Risk of bias for each outcome in all randomized controlled trials with osteoporotic women.

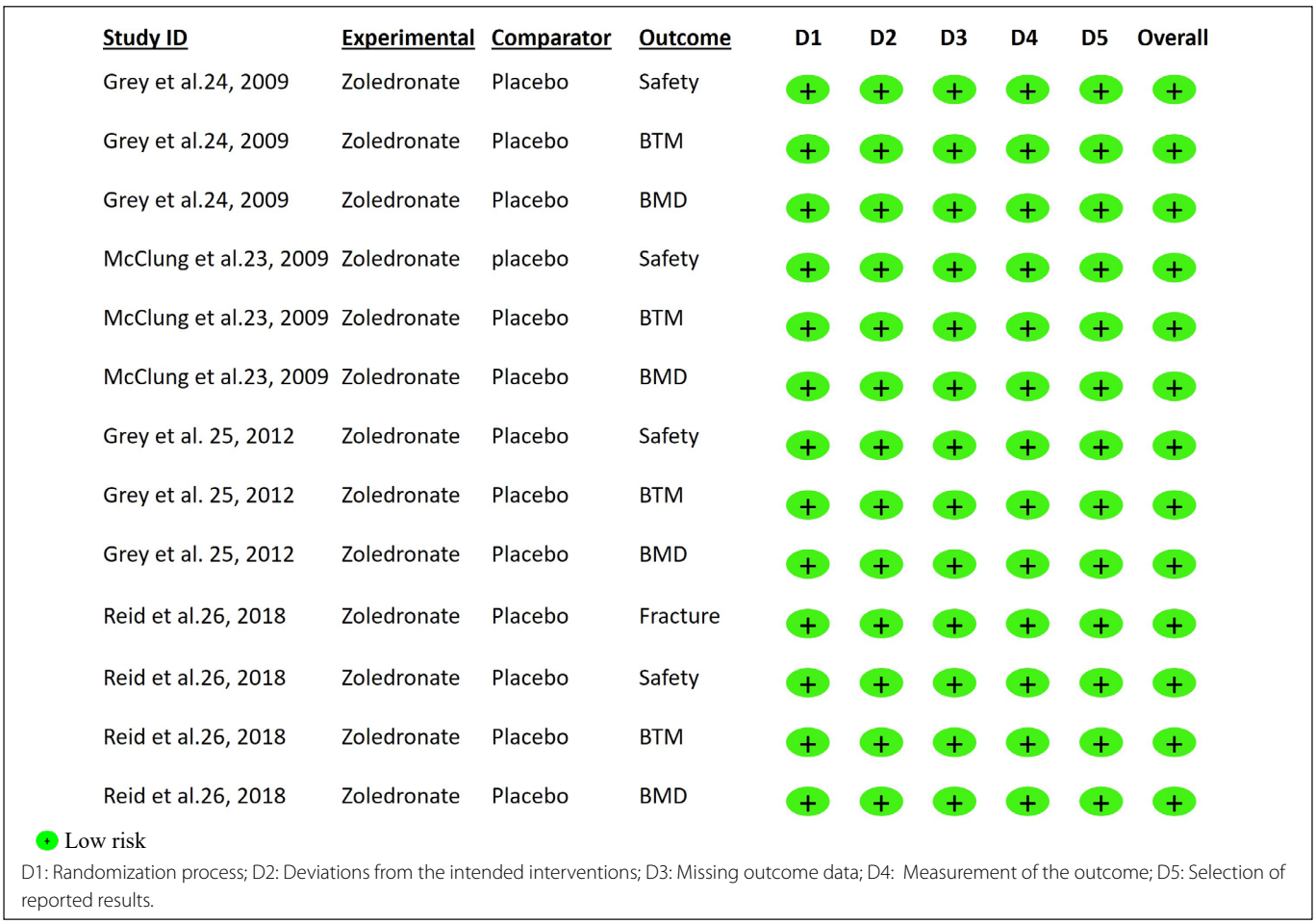


Figure 3. Risk of bias 2: risk of bias for each outcome in all randomized controlled trials with osteopenic women.

Postmenopausal osteopenic women

High-certainty evidence indicated that 5 mg of zoledronate every 18 months reduces morphometric vertebral fractures after six years (four doses) (**Figure 4b2**).

For hip fractures (**Figure 4c2**), moderate-certainty evidence (downgraded for imprecision) indicated that zoledronate probably results in little to no difference in the reduction of hip fractures after six years (four doses).

For non-vertebral fractures (**Figure 4d2**), moderate-certainty evidence (downgraded for imprecision) indicated that zoledronate likely results in little to no difference in preventing non-vertebral fractures after one year; however, after three years (2 doses), zoledronate probably reduces and after six years (4 doses), there is a high certainty that it reduces non-vertebral fractures.

For all clinical fractures, moderate-certainty evidence (downgraded for imprecision) indicated that zoledronate probably results in little to no difference in preventing clinical fractures in the first two years (**Figure 4e2**); however, after three years (2 doses), moderate-certainty evidence (downgraded for imprecision) indicated that zoledronate likely reduces clinical fractures. Additionally, after six years (4 doses), high-certainty evidence indicated that it reduces clinical fractures.

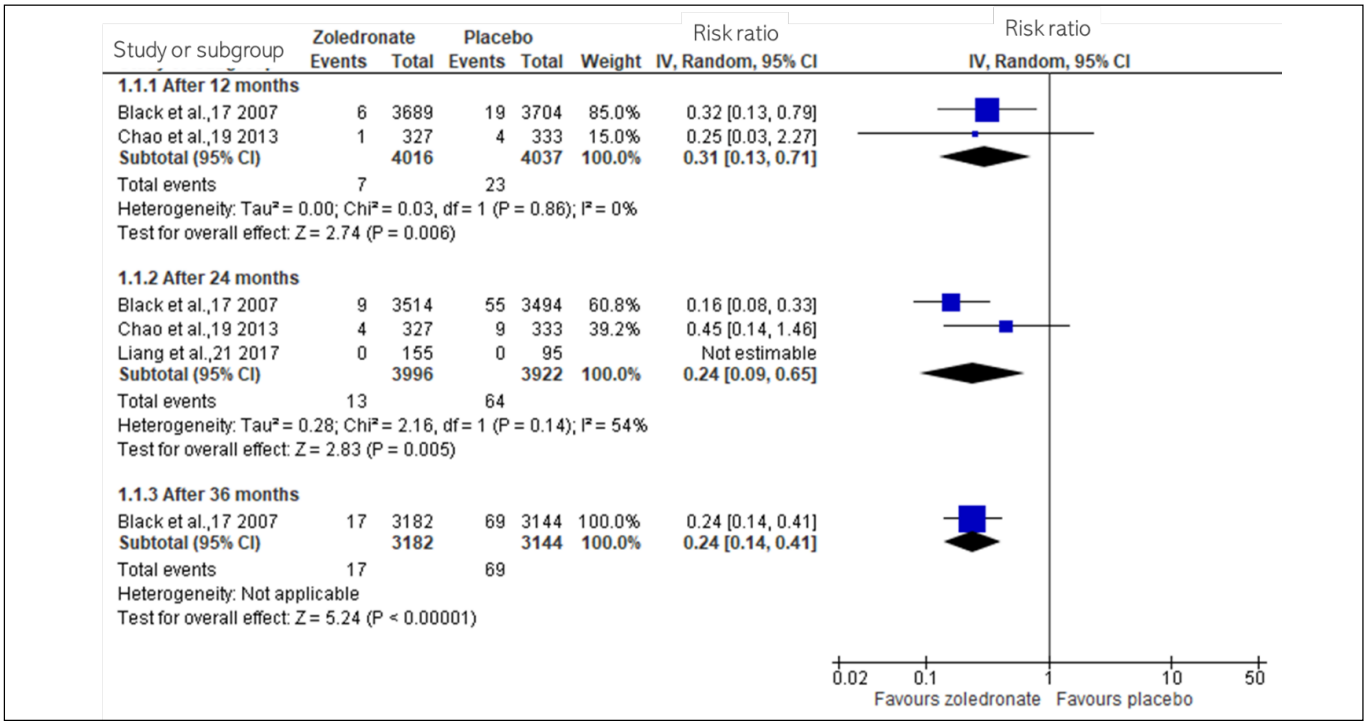
Adverse reactions

The incidence of adverse events was obtained from seven RCTs comparing zoledronate with placebo and one RCT comparing zoledronate with alendronate. An RCT of ibandronate did not evaluate any adverse events.

A comparison of zoledronate with placebo showed that moderate- to high-certainty evidence indicated that zoledronate increases the post-dose symptoms after one year (**Figure 5a**). Low-certainty evidence (downgraded for risk of bias and inconsistency) indicated that zoledronate may increase the post-dose symptoms after two years, and high-certainty evidence indicated that zoledronate may increase the post-dose symptoms after three years.

After two years, moderate-certainty evidence indicated that zoledronate may slightly increase non-serious adverse events (**Figure 5b**), and after three years, high-certainty evidence indicated that zoledronate did not increase non-serious adverse events.

4a



4b1

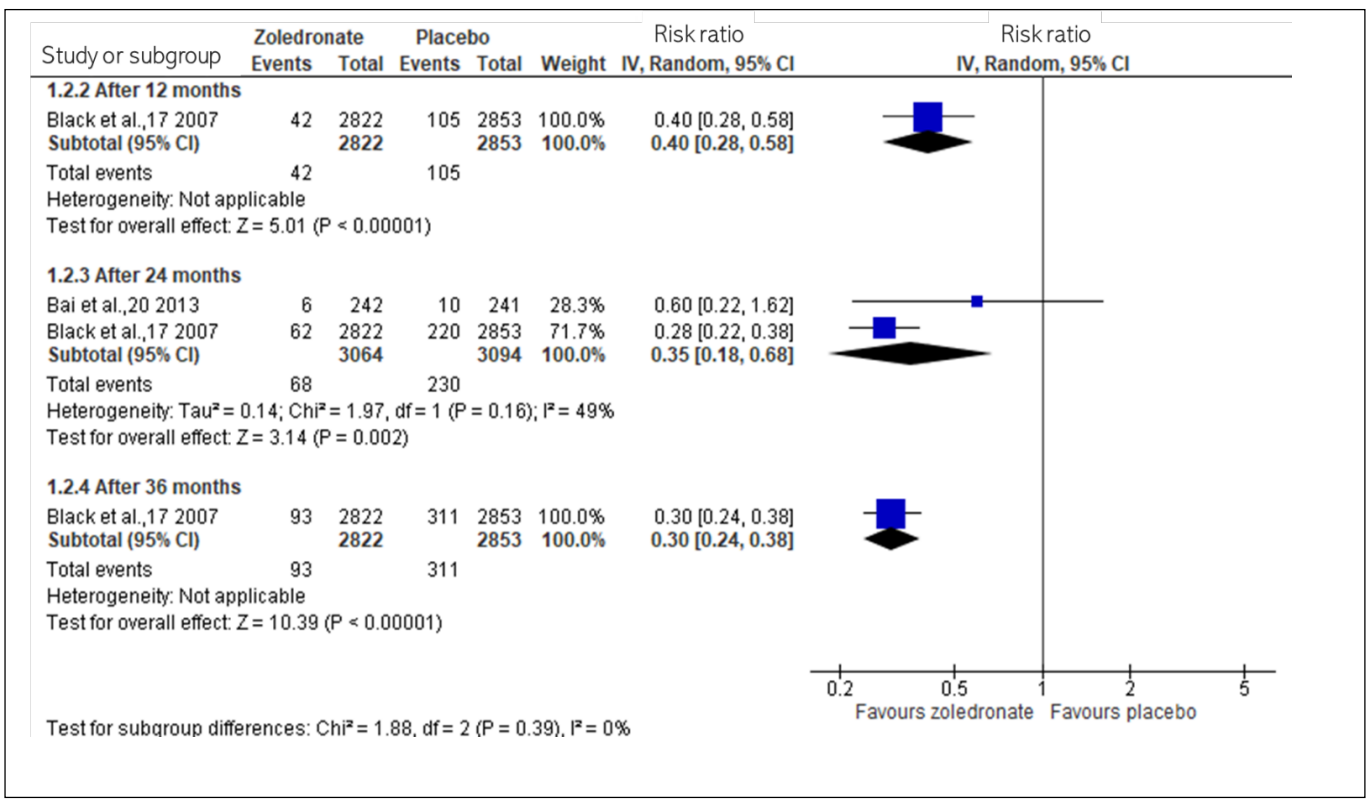
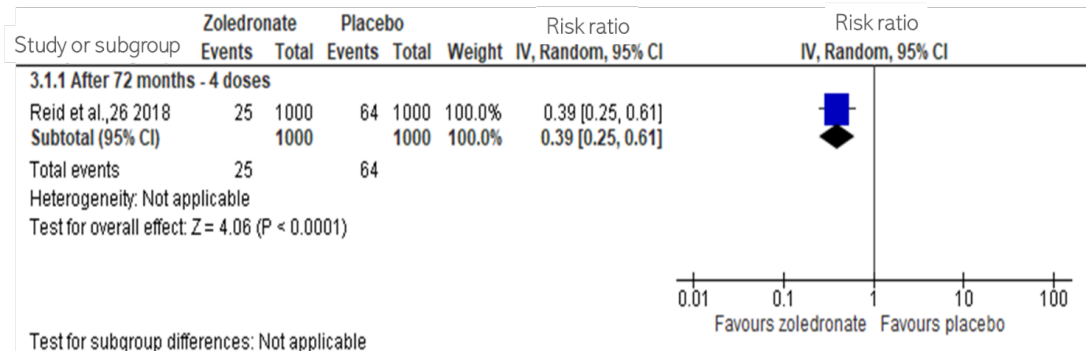


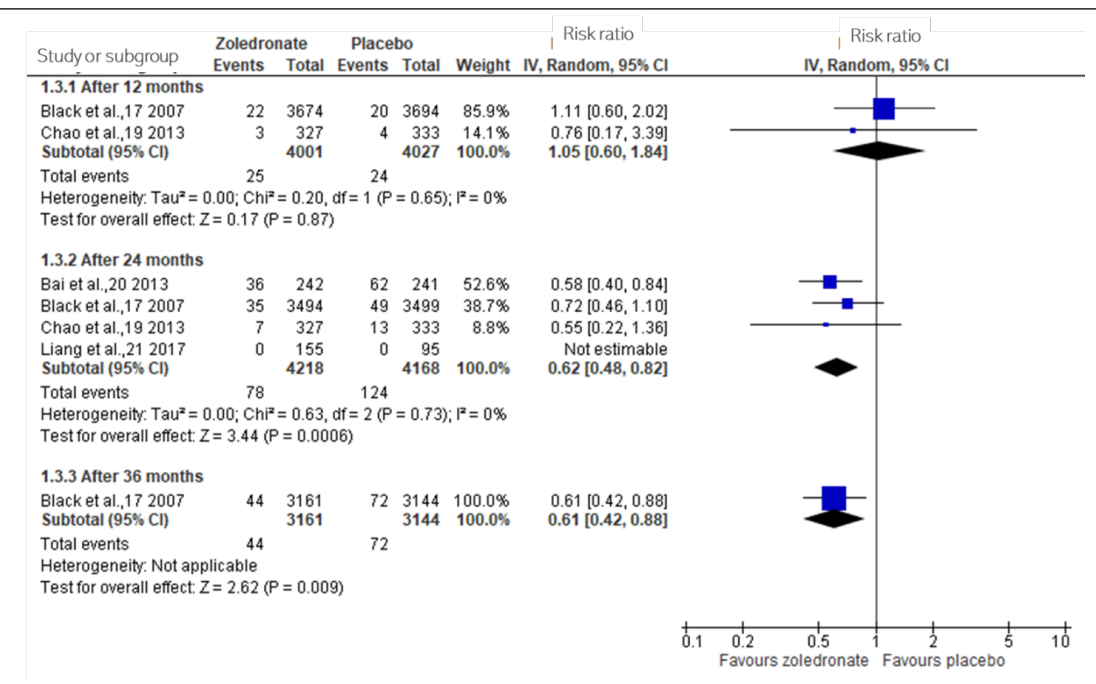
Figure 4. Incidence of fractures from 12 to 72 months in osteoporotic and osteopenic women [4a: Vertebral fractures (osteoporotic); 4b: Morphometric vertebral fractures (4b1: osteoporotic; 4b2: osteopenic), 4c: Hip fractures (4c1: osteoporotic; 4c2: osteopenic), 4d: Non-vertebral fractures (4d1: osteoporotic; 4d2: osteopenic), and 4e: All clinical fractures (4e1: osteoporotic; 4e2: osteopenic)].

Continue...

4b2



4c1



4c2

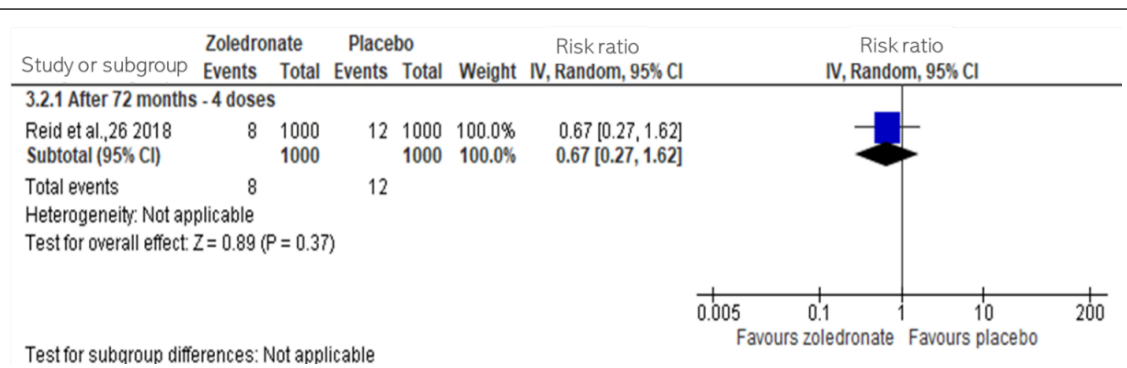
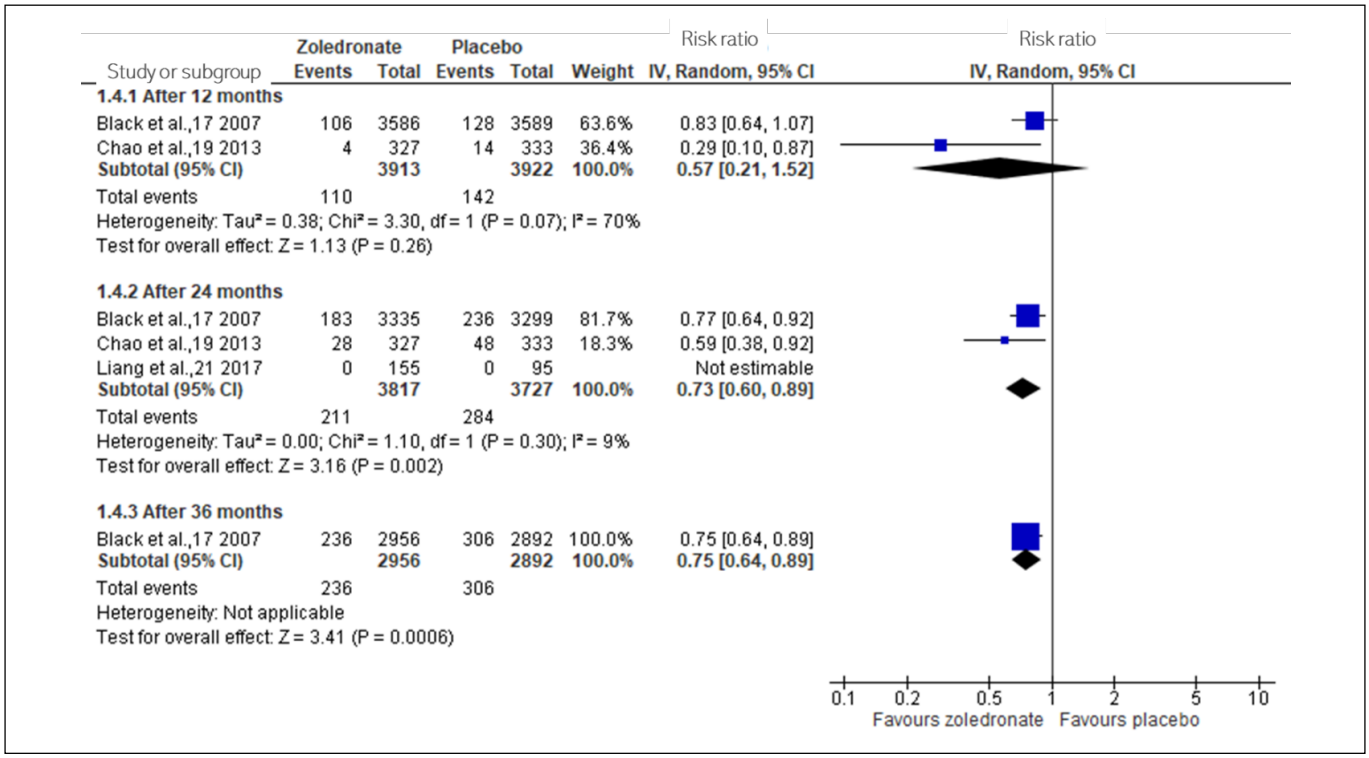


Figure 4. Incidence of fractures from 12 to 72 months in osteoporotic and osteopenic women [4a: Vertebral fractures (osteoporotic); 4b: Morphometric vertebral fractures (4b1: osteoporotic; 4b2: osteopenic), 4c: Hip fractures (4c1: osteoporotic; 4c2: osteopenic), 4d: Non-vertebral fractures (4d1: osteoporotic; 4d2: osteopenic), and 4e: All clinical fractures (4e1: osteoporotic; 4e2: osteopenic)].

Continue...

4d1



4d2

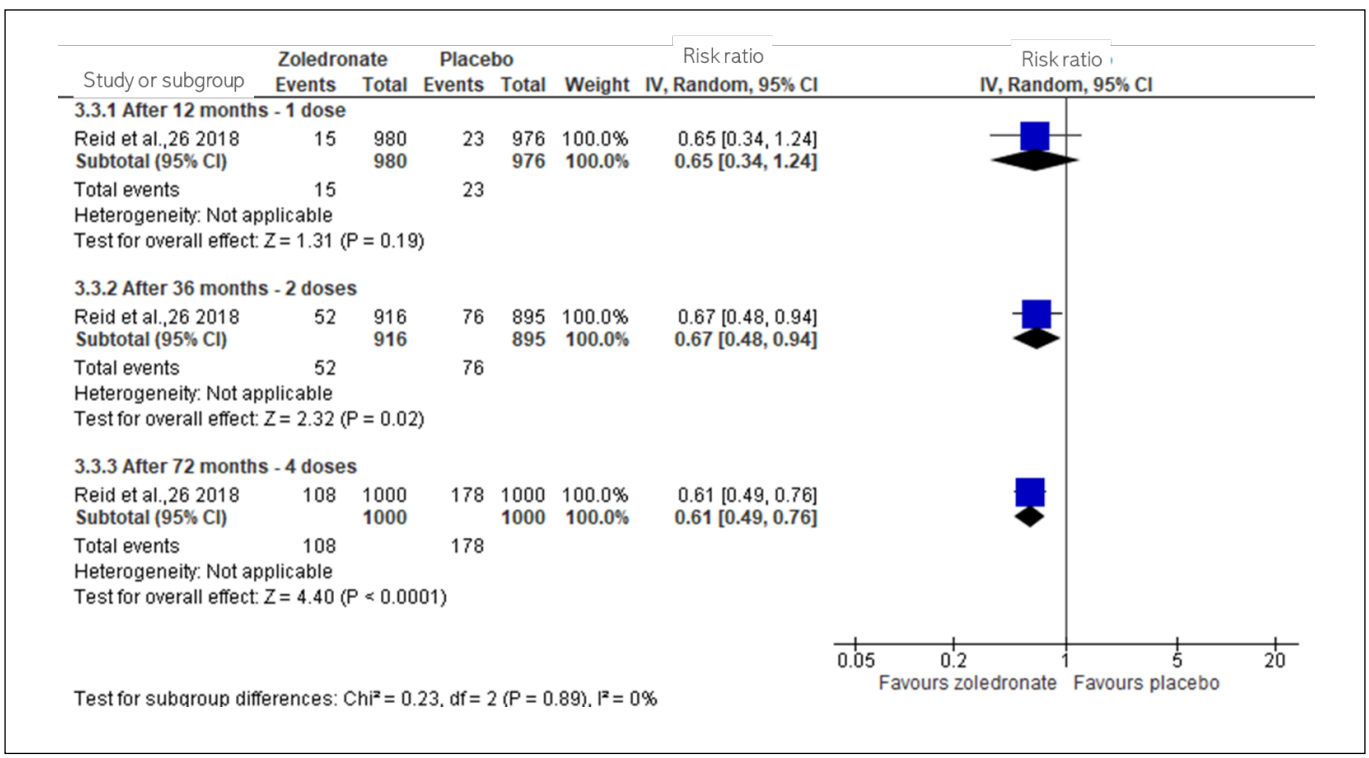
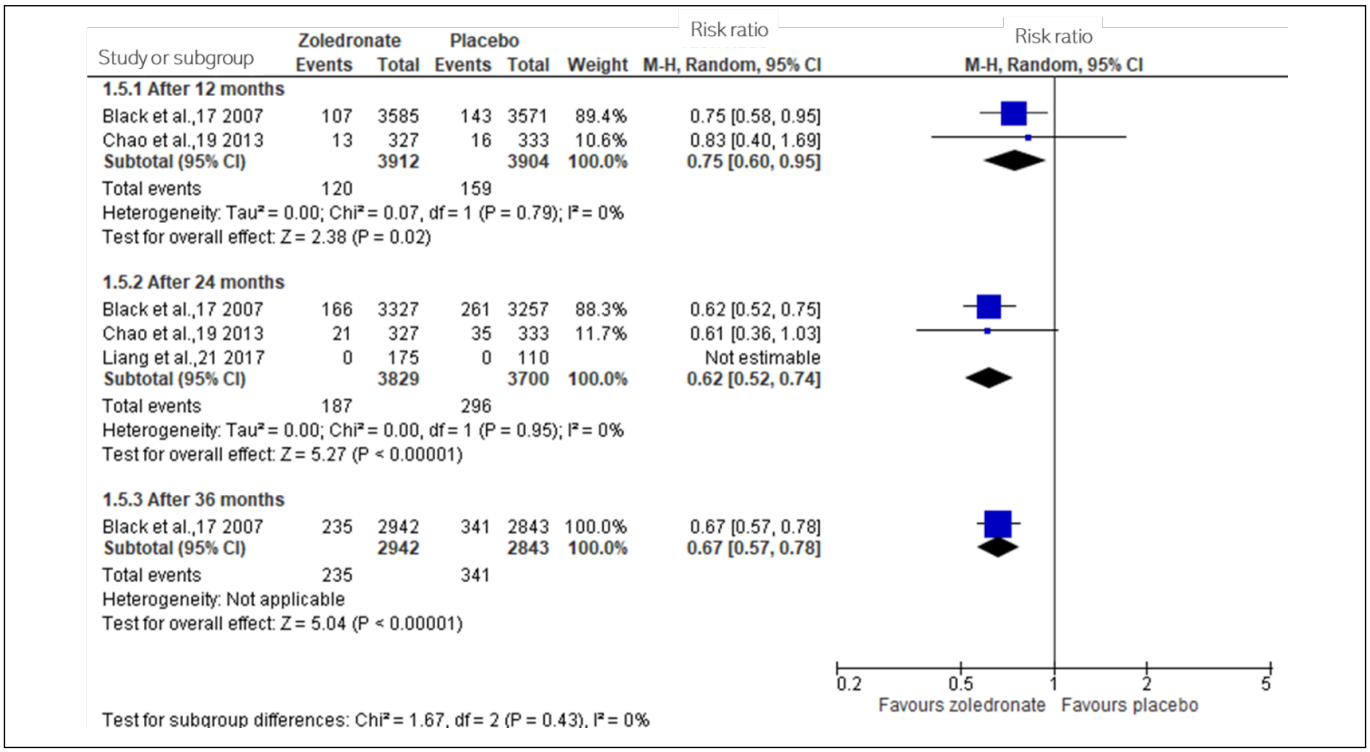


Figure 4. Incidence of fractures from 12 to 72 months in osteoporotic and osteopenic women [4a: Vertebral fractures (osteoporotic); 4b: Morphometric vertebral fractures (4b1: osteoporotic; 4b2: osteopenic), 4c: Hip fractures (4c1: osteoporotic; 4c2: osteopenic), 4d: Non-vertebral fractures (4d1: osteoporotic; 4d2: osteopenic), and 4e: All clinical fractures (4e1: osteoporotic; 4e2: osteopenic)].

Continue...

4e1



4e2

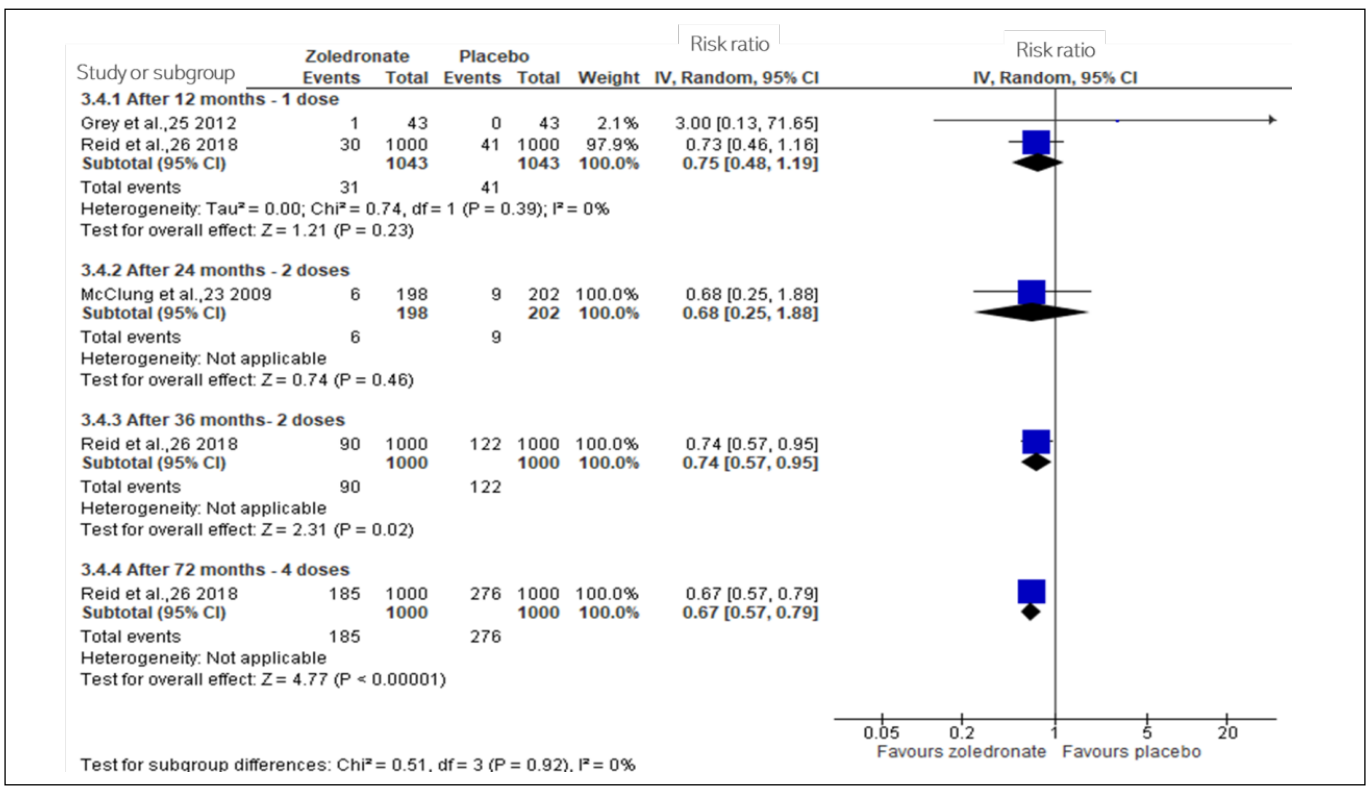
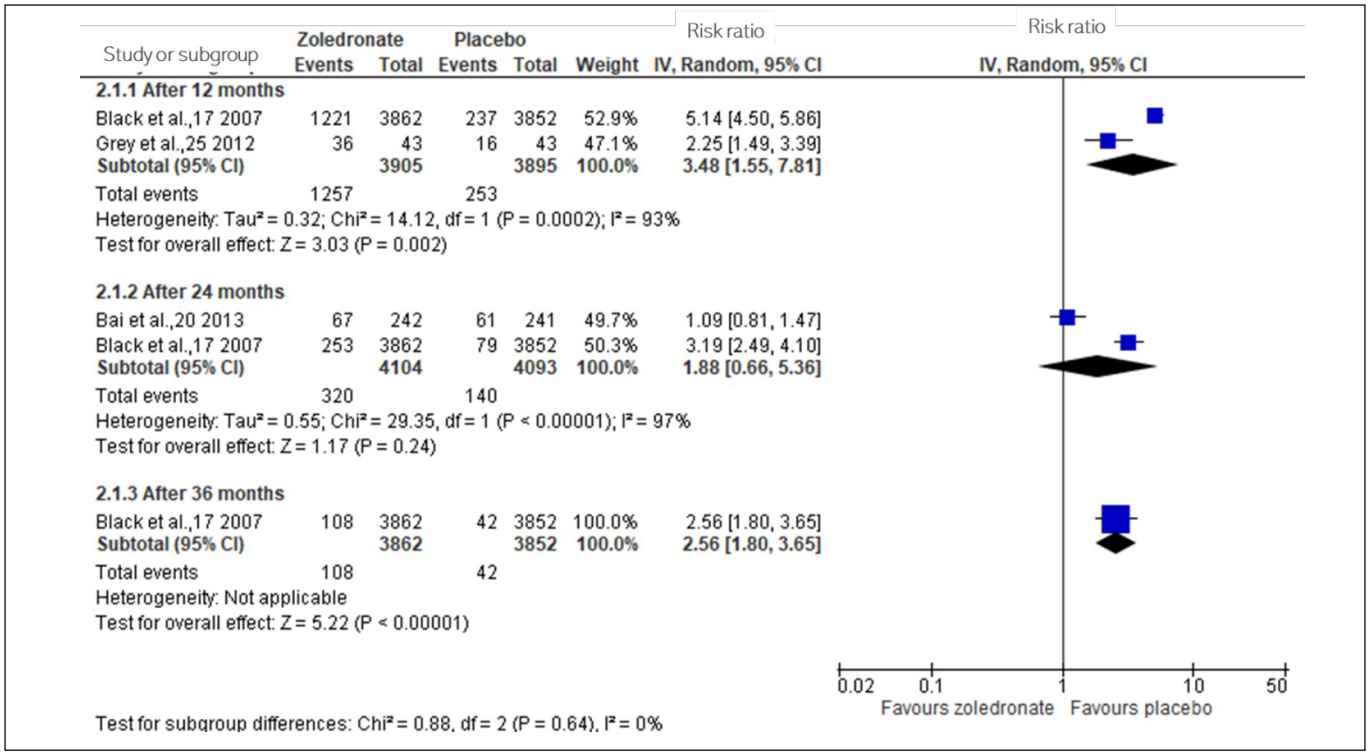


Figure 4. Incidence of fractures from 12 to 72 months in osteoporotic and osteopenic women [4a: Vertebral fractures (osteoporotic); 4b: Morphometric vertebral fractures (4b1: osteoporotic; 4b2: osteopenic), 4c: Hip fractures (4c1: osteoporotic; 4c2: osteopenic), 4d: Non-vertebral fractures (4d1: osteoporotic; 4d2: osteopenic), and 4e: All clinical fractures (4e1: osteoporotic; 4e2: osteopenic)].

Moderate-certainty evidence (downgraded for imprecision) indicated that zoledronate probably results in no difference in the SAE or death after two years (**Figure 5c**). After three years, moderate-certainty (downgraded for imprecision) indicated that it probably does not reduce or increase the SAE or death, and after six years (four doses), moderate-certainty evidence (downgraded for imprecision) indicated that zoledronate probably results in no difference in death.

5a



5b

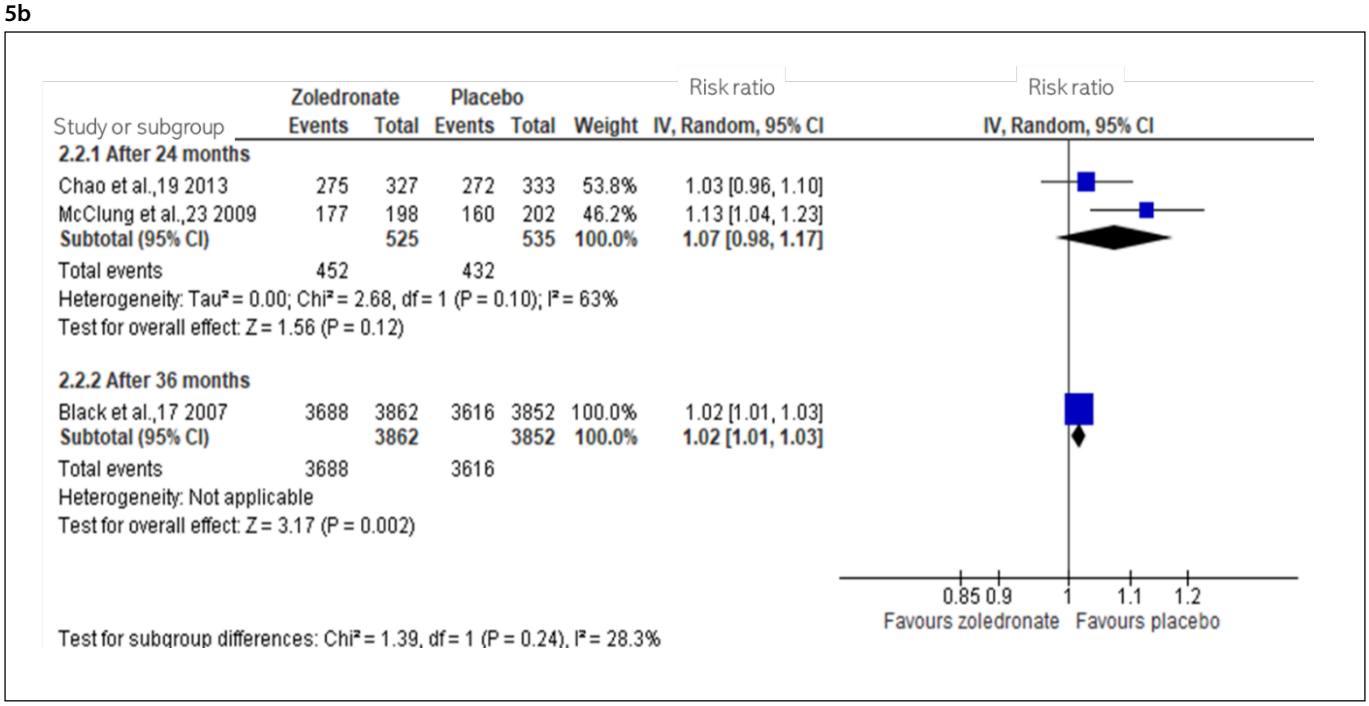
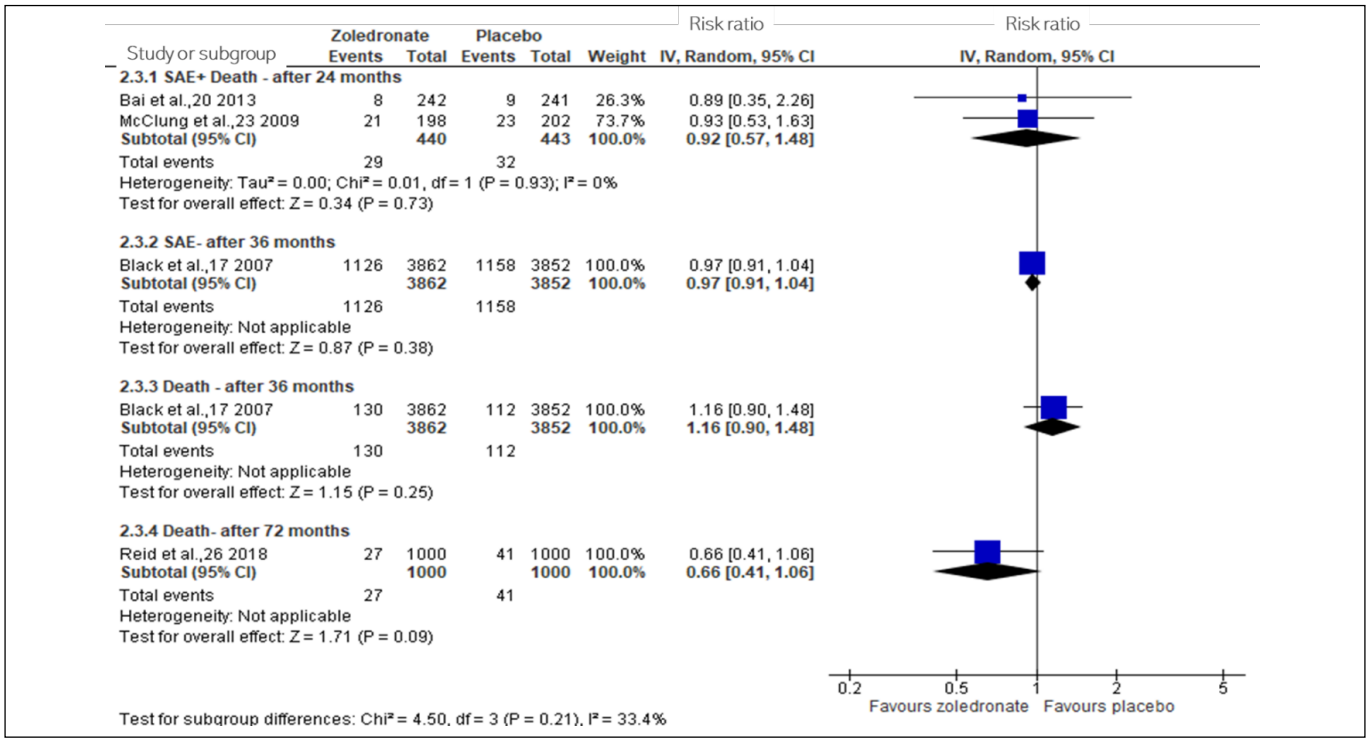


Figure 5. Incidence of adverse events from 12 to 72 months in osteoporotic and osteopenic women (5a: Any symptom of post-dose acute-phase reactions, 5b: Non-serious adverse events, 5c: Serious adverse event or death, and 5d: Atrial fibrillation).
Continue...

5c



5d

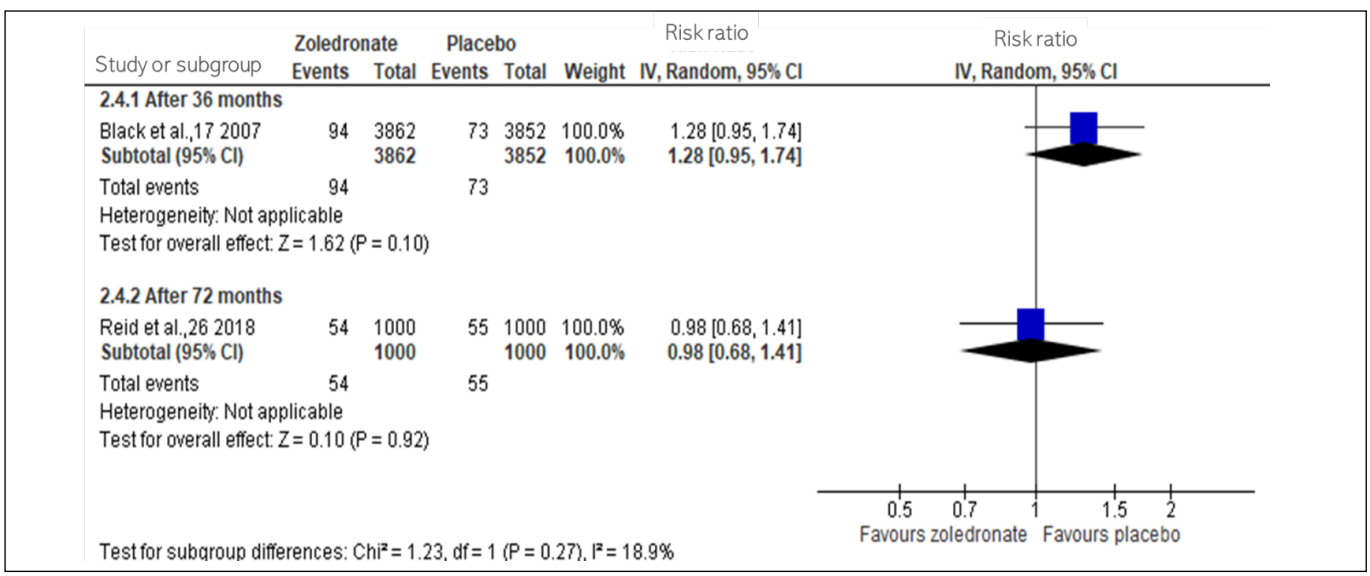


Figure 5. Incidence of adverse events from 12 to 72 months in osteoporotic and osteopenic women (5a: Any symptom of post-dose acute-phase reactions, 5b: Non-serious adverse events, 5c: Serious adverse event or death, and 5d: Atrial fibrillation).

After three years, moderate-certainty evidence (downgraded for imprecision) indicated that zoledronate may slightly increase the atrial fibrillation; but after six years (four doses), zoledronate probably does not increase atrial fibrillation (**Figure 5d**).

Moderate-certainty evidence (downgraded for imprecision) indicated that zoledronate probably results in little to no difference in eye disorders after one year, and after three years, it probably does not increase jaw osteonecrosis. After three years, high-certainty evidence indicated that the serum creatinine levels has increased.

In a study comparing zoledronate with alendronate, low-certainty evidence (downgraded for risk of bias and imprecision) indicated that zoledronate increases adverse events and influenza-like

symptoms, results in little to no difference in serious adverse events or death, and does not increase or reduce atrial fibrillation or eye disorders after one year.

Secondary outcomes

Percent change in bone turnover markers (BTM)

The percent change in BTM was obtained from six RCTs that compared zoledronate with a placebo. Yang et al. also analyzed the BTM; however, the data from this RCT were not used in the review because the baseline values were different when compared to others.[22]

Postmenopausal osteoporotic women

After six months, moderate-certainty evidence (downgraded for imprecision) indicated that zoledronate probably reduces P1NP. After one and two years, the certainty was low (downgraded for inconsistency and imprecision), and after three years, high-certainty evidence indicated that zoledronate reduces P1NP (**Figure 6a1**).

After six months and one year, high-certainty evidence indicated that zoledronate reduces the CTX levels. After two and three years, the evidence was moderate (downgraded for imprecision) (**Figure 6b1**).

Low-certainty evidence (downgraded for the risk of bias and imprecision) indicated that zoledronate results in little to no difference in P1NP and that it probably reduces the CTX compared to alendronate. For zoledronate versus ibandronate, very low-certainty evidence (downgraded by one point for risk of bias and two points for imprecision) indicated that zoledronate has no effect on CTX.

Postmenopausal osteopenic women

After six months, high-certainty evidence indicated zoledronate reduces P1NP, and after one year, low-certainty evidence (downgraded for inconsistency and imprecision). After two years (two doses) and six years (four doses), high-certainty evidence indicated that zoledronate reduces P1NP (**Figure 6a2**).

After six months and one year, moderate-certainty evidence (downgraded for inconsistency) indicated that zoledronate reduces the CTX. High-certainty evidence was observed after two years (two doses) and six years (four doses) (**Figure 6b2**).

6a1

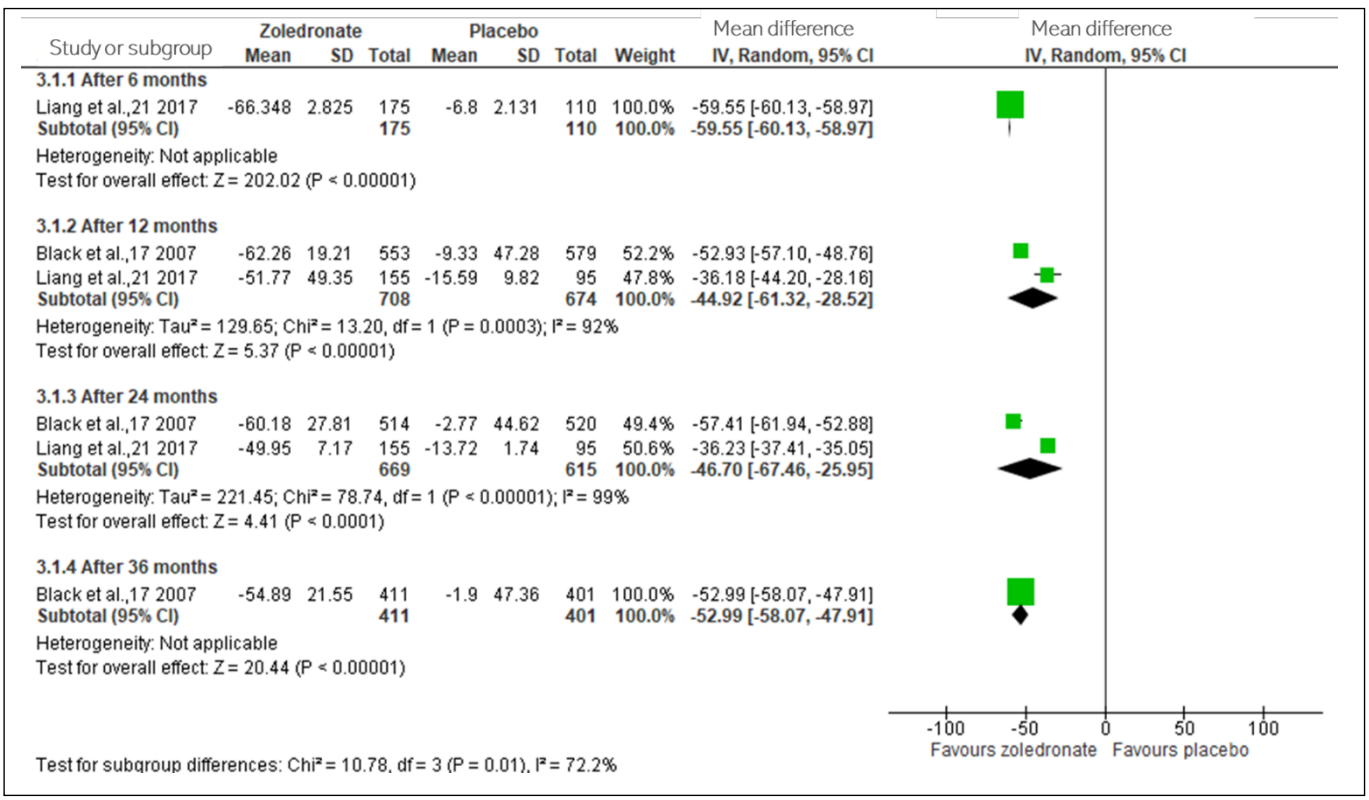


Figure 6. Percent change in bone turnover markers from 6 to 72 months in osteoporotic and osteopenic women [6a- Procollagen type 1 N propeptide (6a1- osteoporotic; 6a2- osteopenic), and 6b- C-terminal telopeptide of type 1 collagen (6b1- osteoporotic; 6b2- osteopenic)].

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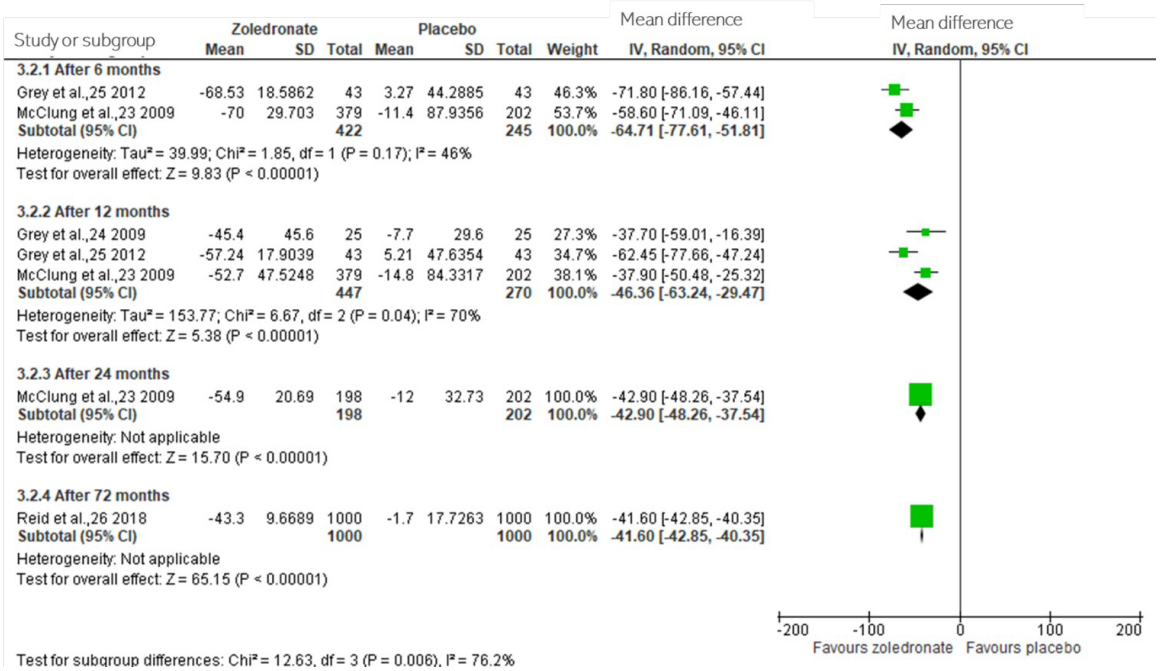
6a2



6b1

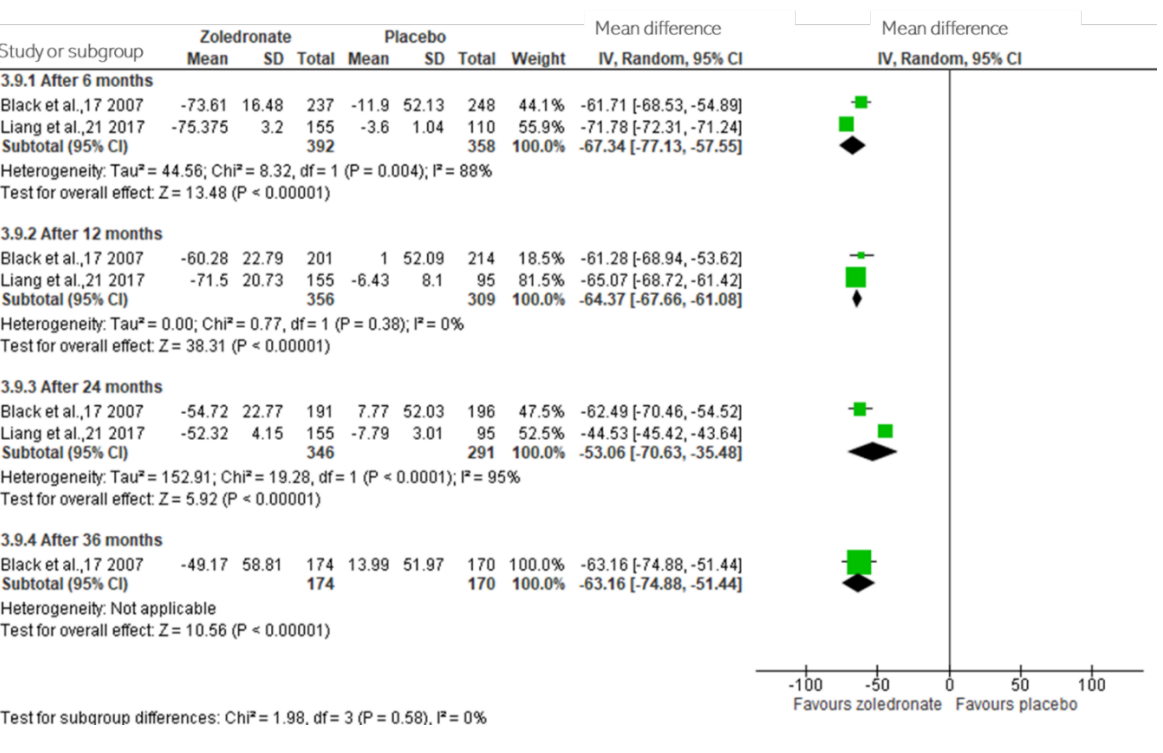


Figure 6. Percent change in bone turnover markers from 6 to 72 months in osteoporotic and osteopenic women [6a- Procollagen type 1 N propeptide (6a1- osteoporotic; 6a2- osteopenic), and 6b- C-terminal telopeptide of type 1 collagen (6b1- osteoporotic; 6b2- osteopenic)].

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6b2

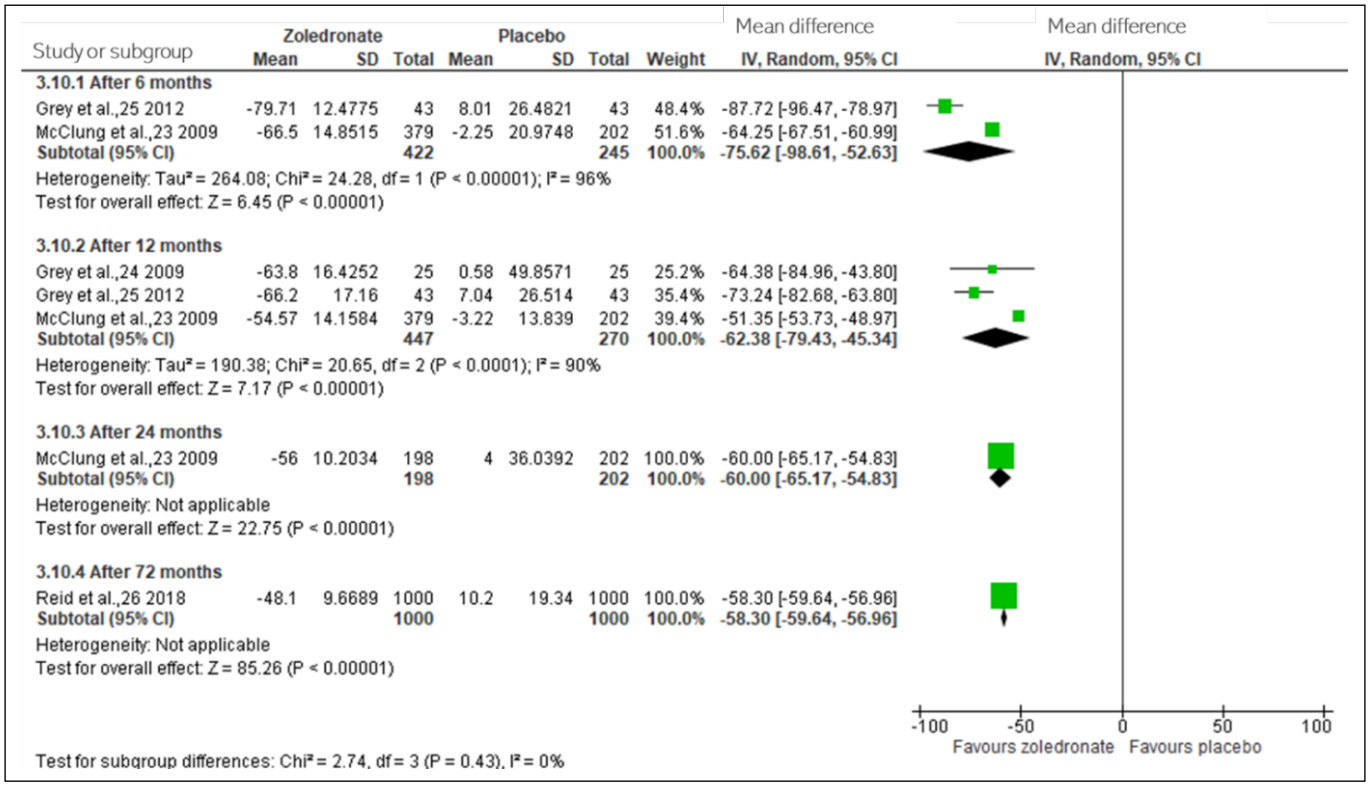


Figure 6. Percent change in bone turnover markers from 6 to 72 months in osteoporotic and osteopenic women [6a- Procollagen type 1 N propeptide (6a1- osteoporotic; 6a2- osteopenic), and 6b- C-terminal telopeptide of type 1 collagen (6b1- osteoporotic; 6b2- osteopenic)].

Percent change in BMD

The MD in BMD was obtained from eight RCTs that compared zoledronate with placebo, one with alendronate, and one with ibandronate.

Postmenopausal osteoporotic women

Moderate-certainty evidence (downgraded for risk of bias) indicated that zoledronate probably does not increase the lumbar spine BMD after one year; however, it was observed to probably increase after two years and increase after three years (**Figure 7a1**).

Moderate-certainty evidence (downgraded for risk of bias) indicated that zoledronate probably does not increase the femoral neck BMD after one year and three years, and low-certainty evidence (downgraded for inconsistency and imprecision) probably results in little increase after two years (**Figure 7b1**).

Moderate-certainty evidence (downgraded for risk of bias) indicated that zoledronate probably does not increase the total hip BMD after one year, may increase after two years, and that it increases after three years (**Figure 7c1**).

For zoledronate versus alendronate, low-certainty evidence (downgraded for risk of bias and imprecision) indicated that zoledronate increases lumbar spine, femoral neck, and total hip BMD.

For zoledronate versus ibandronate, very low-certainty evidence (downgraded by one point for risk of bias and two points for imprecision) indicated uncertainty about the presence of an effect on the lumbar spine and total hip BMD.

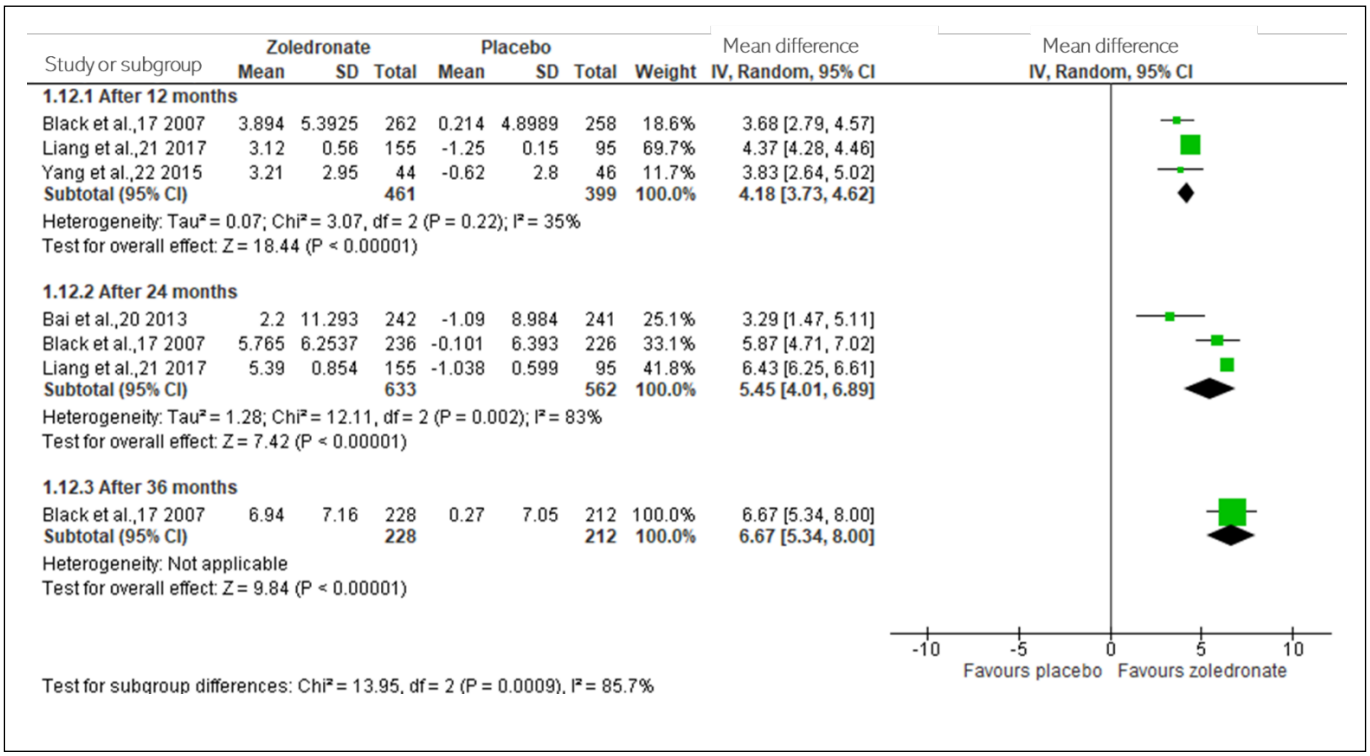
Postmenopausal osteopenic women

Moderate-certainty evidence (downgraded for inconsistency) indicated that zoledronate probably does not increase the lumbar spine BMD after one year. After two years (two doses), three years (two doses), and six years (four doses), there was high-certainty evidence that zoledronate increases the lumbar spine BMD (**Figure 7a2**).

High-certainty evidence indicated that zoledronate does not increase the femoral neck BMD after one year, and moderate-certainty evidence (downgraded for imprecision) indicated that it results in little to no difference in increasing the femoral neck BMD after two years (**Figure 7b2**).

High-certainty evidence indicated that zoledronate does not increase the total hip BMD after one year, and moderate-certainty (downgraded for imprecision) indicated that it may increase the total hip BMD after two years; however, after three years (two doses) and six years (four doses), high-certainty evidence indicated that it increases total hip BMD (**Figure 7c2**).

7a1



7a2

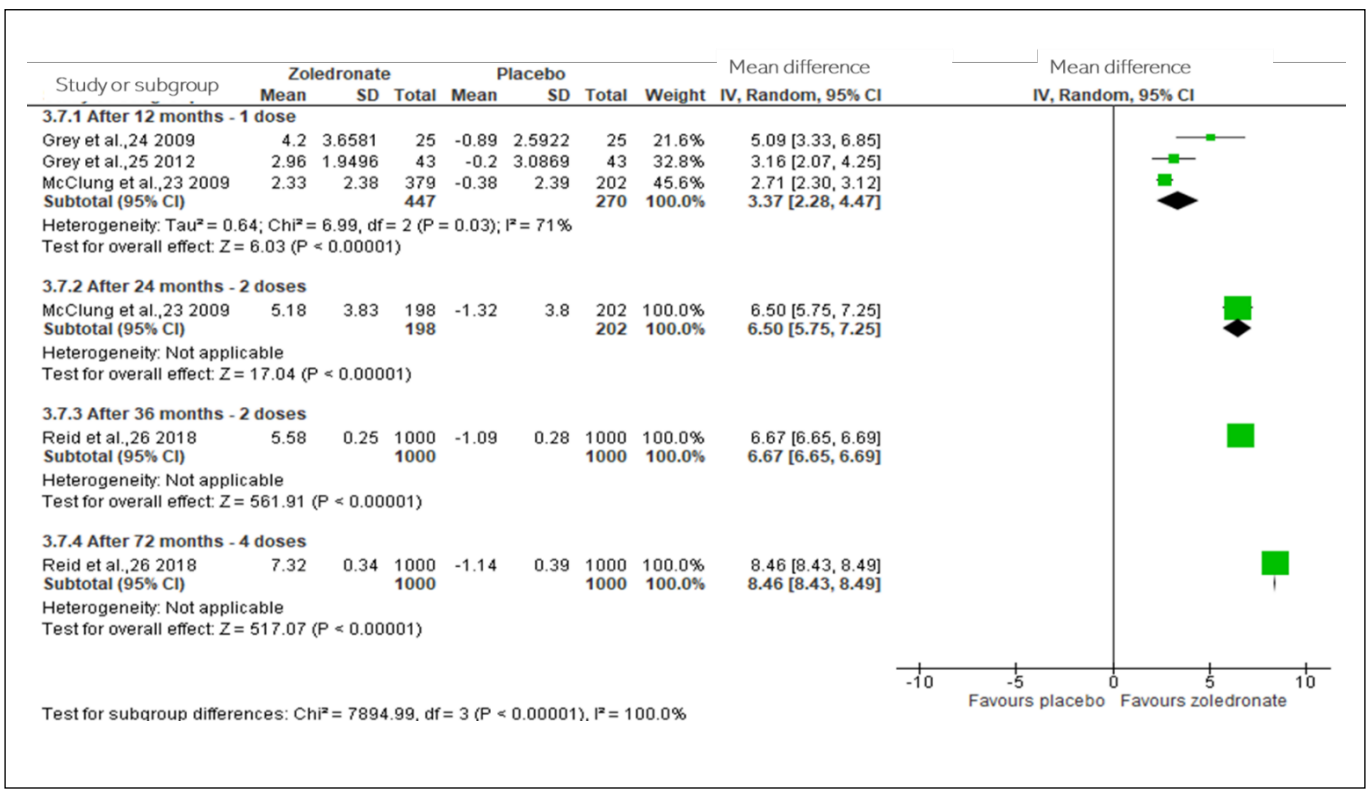


Figure 7. Percent change in bone mineral density from 12 to 72 months in osteoporotic and osteopenic women [7a- lumbar spine (7a1- osteoporotic; 7a2- osteopenic), 7b- femoral neck (7b1- osteoporotic; 7b2- osteopenic), and 7c- total hip (7c1- osteoporotic; 7c2- osteopenic)].

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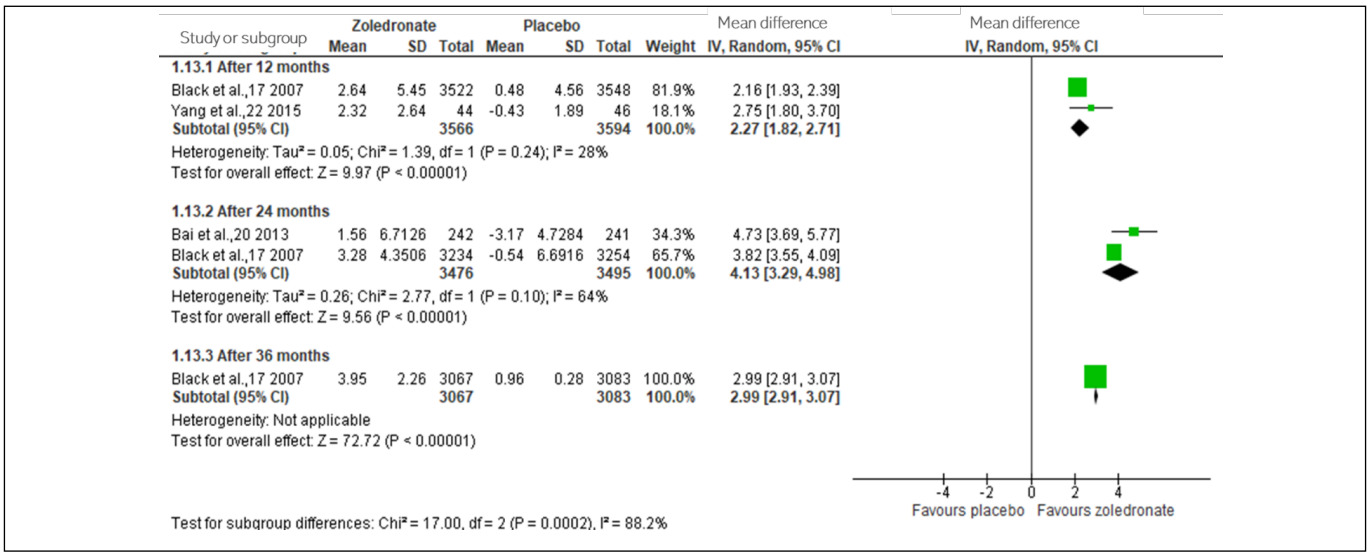
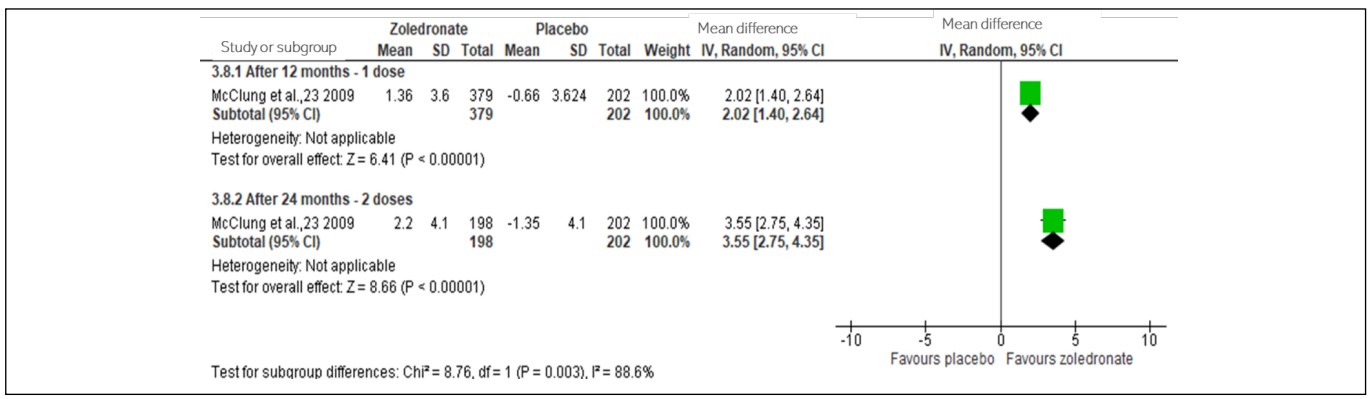
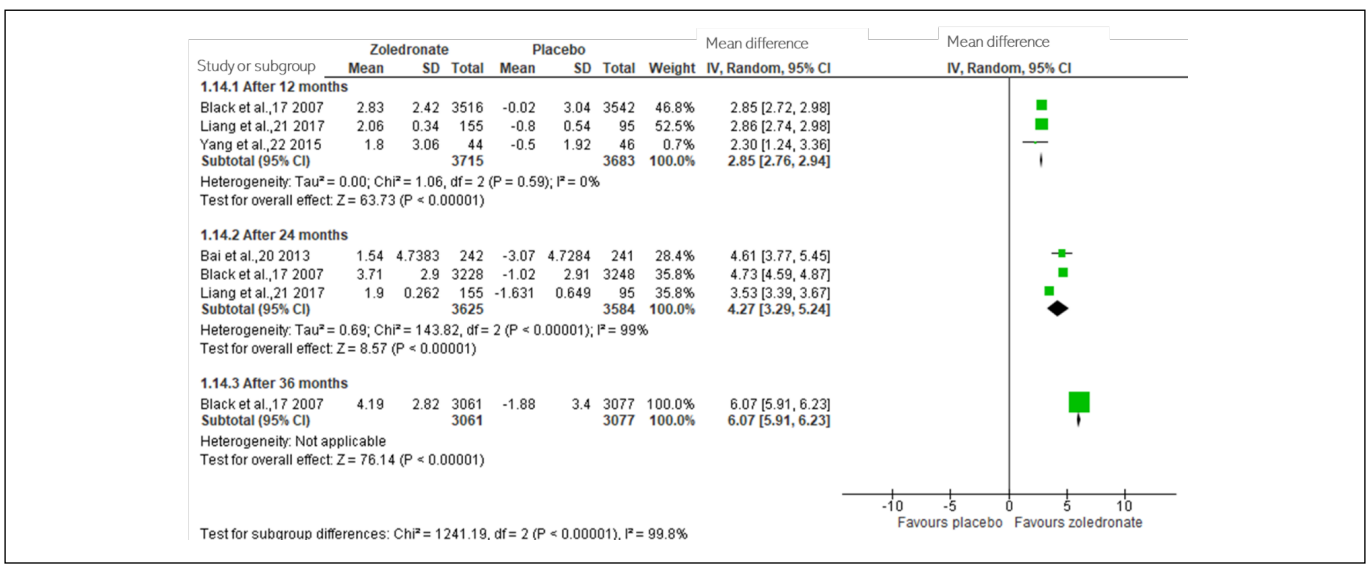
7b1



7b2



7c1



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Continue...

7c2

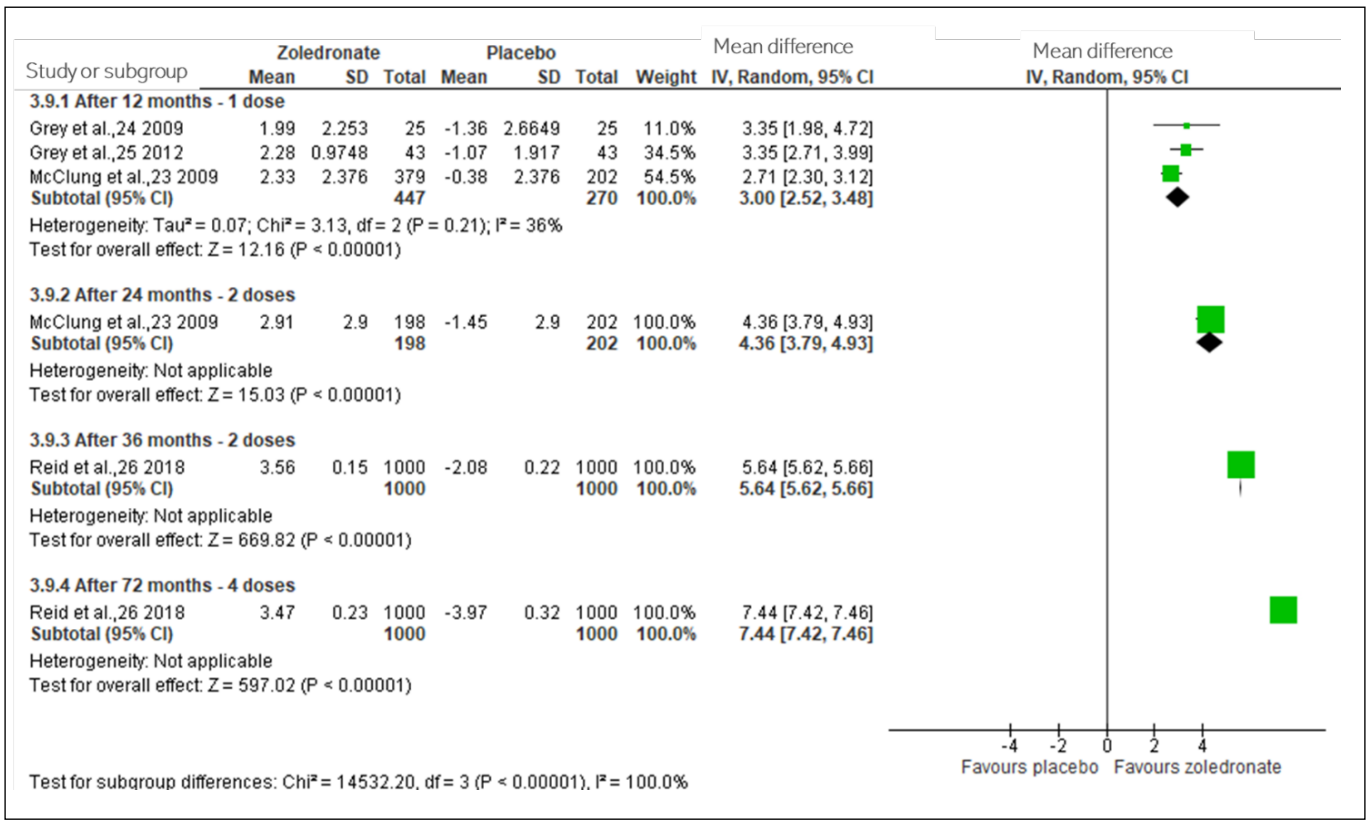

Figure 7. Percent change in bone mineral density from 12 to 72 months in osteoporotic and osteopenic women [7a- lumbar spine (7a1- osteoporotic; 7a2- osteopenic), 7b- femoral neck (7b1- osteoporotic; 7b2- osteopenic), and 7c- total hip (7c1- osteoporotic; 7c2- osteopenic)].

DISCUSSION

In this systematic review, 12 RCTs on the use of zoledronate in postmenopausal women were included: eight RCTs for osteoporosis and four RCTs for osteopenia. To assess whether there is an effective and safe response to zoledronate, thresholds of statistical significance were established according to published data found in the scientific literature.

The main objective for preventing and treating osteoporosis is to reduce the incidence of fractures, although it does not eliminate them. In this review, a minimal significant reduction of 30% was established for vertebral and hip fractures, and a 15% reduction was established for other fractures (non-vertebral and clinical). This decision was based on the thresholds for therapeutic failure published by Diez-Perez et al.[16] They considered a reduced risk of fractures ranging from 30% to 70% for vertebral fractures, 40% to 50% for hip fractures, and 15% to 20% for non-vertebral fractures.[16]

The occurrence of fractures in the RCTs was evaluated as both an outcome and an adverse event, which could have influenced the results of the analyses. The evidence for fractures was moderate to high, indicating that zoledronate reduces clinical and morphometric vertebral fractures since the first year of use, increasing its benefits each year during 3 years of treatment for osteoporotic women and for six years (5 mg every 18 months) for osteopenic women. In addition, zoledronate probably reduces the number of hip fractures after two years in osteoporotic women and probably results in little difference after six years (5 mg every 18 months) in osteopenic women. Zoledronate probably reduces non-vertebral fractures after two doses in women with osteoporosis (5 mg each year) and after two doses (5 mg every 18 months) and four doses (six years) in women with osteopenia. It reduces the number of all clinical fractures after two doses in both osteoporotic (after two years) and osteopenic (after three years) women and after six years (four doses) for osteopenic women.

No data were available regarding ibandronate-related fractures. Compared to alendronate, the results were based on fractures reported as adverse events, and the evidence was of very low certainty.

Post-dose symptoms were reported mainly after the first infusion but also after the third dose. This was expected because, according to a literature review, acute-phase reactions can occur in up to 30% of patients.[30]

There were no statistically significant differences with respect to serious adverse events, death, atrial fibrillation, osteonecrosis of the jaw, or eye disorders between the zoledronate and placebo groups. Osteonecrosis of the jaw has been described in cancer patients receiving high doses of intravenous zoledronate; however, its incidence in osteoporotic patients treated with zoledronate is considered very low.[31] Additionally, concerns have been raised regarding the possible association between bisphosphonate therapy and atrial fibrillation. A meta-analysis of RCTs and observational studies with women and men treated with bisphosphonates for any indication demonstrated an increased risk of atrial fibrillation with bisphosphonates (slightly higher with intravenous bisphosphonates).[32] Eye disorders, although rare, were associated with all bisphosphonate treatments.[33] Patel et al. reported an incidence of uveitis and episcleritis of 1.1% (95% CI 0.5–2.1). [34]

None of the RCTs included in this review reported atypical femoral fractures. Atypical femoral fractures of the subtrochanteric region are considered rare events; however, bisphosphonate treatment for more than five years increases the risk of such fractures.[35]

One RCT found a risk of increasing serum creatinine after zoledronate infusion.[17] This effect was noted by the U.S. Food and Drug Administration in 2011, advising no use in patients with creatinine clearance less than 35 mL/min or with acute renal impairment and monitoring of renal function in patients receiving zoledronic acid.[36]

A position paper endorsed by the International Osteoporosis Foundation published that a significant response to antiresorptive treatments occurs when there is a decline from baseline of at least 25% for CTX and P1NP.[16] Delmas et al. reported that a decrease in the BTM could range from 30 to 50% after starting treatment with bisphosphonates.[37] A reduction of at least 30% in BTM was also found in the data presented in this review.

The same study reported that the least significant change in BMD should be approximately 5% in the lumbar spine and 4% in the femoral neck.[16] A meta-regression analysis reported that a 4% increase in BMD of the femoral neck and total hip reduced vertebral fractures by 50% and hip fractures by 30%, and an increase in the lumbar spine BMD of 2% and 8% reduced vertebral fractures by 30% and 60%, and hip fractures by 20% and 40%, respectively.[38] Therefore, the present review considered a least significant change of a 5% increase in the lumbar spine and 4% in the femoral neck and total hip. Based on these thresholds and the presented data, the effect of zoledronate on BMD was similar in both osteopenic and osteoporotic women over the years, being statistically significant from the second year for the lumbar spine and from the third year for the femoral neck and total hip. After three years, a dose of 5 mg of zoledronate every 18 months (two doses) in osteopenic women and a dose of 5 mg yearly (three doses) in osteoporotic women increased the BMD similarly; in osteopenic women, a dose of 5 mg of zoledronate every 18 months also increased lumbar spine BMD and total hip BMD after six years (four doses). Evidence comparing zoledronate with alendronate and ibandronate has shown low to very low certainty.

When comparing the present review with others, the findings related to the efficacy were similar to those reported by Sanderson et al., Zhou et al., and He et al.[39,40,41] The main difference was that the target population included was men, corticosteroid users, and frail women with secondary osteoporosis. Despite these findings, they reported similar results regarding a reduction in fractures and an increase in BMD.

Zoledronate is a well-established option for treating osteoporosis, as recommended in various publications, and the present review highlights its benefits. Although the main evidence for osteopenic women is based on one study, the use of zoledronate (5 mg every 18 months) should be considered in this population.

The AACE recommends alendronate, risedronate, zoledronate, and denosumab as initial therapies for patients at high risk of fracture and teriparatide, abaloparatide, denosumab, romozosumab, or zoledronate for patients at very high risk of fracture and those unable to undergo oral therapy.[4]

The EULAR/EFORT recommends that alendronate and risedronate should be the first-choice agents after fragility fractures in patients older than 50 years and for the prevention of subsequent fractures because of their low cost. It is also recommended that zoledronate or denosumab should be indicated when patients have oral intolerance to bisphosphonates, dementia, malabsorption, and show non-compliance, and anabolic agents are recommended for patients with very severe osteoporosis.[42]

CONCLUSION

Moderate- to high-certainty evidence supports the use of zoledronate (5 mg) annually for three years in postmenopausal women with osteoporosis and 5 mg every 18 months for six years in postmenopausal women with osteopenia to reduce the risk of fractures.

Zoledronate was considered safe and was associated with transient post-dose symptoms. It significantly reduced the P1NP and CTX levels from the sixth month until the third year in osteoporotic women and the sixth year in osteopenic women. In addition, it increased the BMD in all bone segments analyzed after the second dose in osteopenic and osteoporotic women.

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INTRAVENOUS ZOLEDRONATE FOR POSTMENOPAUSAL WOMEN WITH OSTEOPENIA AND OSTEOPOROSIS: A SYSTEMATIC REVIEW AND METANALYSIS

Peer review information

The São Paulo Medical Journal thanks Cristiano Augusto de Freitas Zerbini and the other anonymous reviewer for their contribution to the peer-review process of this manuscript.

Peer review reports

Reviewer: 1 **Dr. Cristiano Augusto de Freitas Zerbini** **Instituto Sírio-Libanês de Ensino e Pesquisa Núcleo de Reumatologia**	
First evaluation	**Second evaluation**
Recommendation: Accept Comments: Congratulations for this very good article. Additional Questions: Does the manuscript contain new and significant information to justify publication? Yes Does the Abstract (Summary) clearly and accurately describe the content of the article? Yes Is the problem significant and concisely stated? Yes Are the methods described comprehensively? Yes Are the interpretations and conclusions justified by the results? Yes Is adequate reference made to other work in the field? Yes Is the language acceptable? Yes Please rate the priority for publishing this article (1 is the highest priority, 10 is the lowest priority): 2 Length of article is: Adequate Number of tables is: Adequate Number of figures is: Adequate Please state any conflict(s) of interest that you have in relation to the review of this paper (state "none" if this is not applicable): none Rating: Interest: 1. Excellent Quality: 1. Excellent Originality: 2. Good Overall: 1. Excellent	Recommendation: Accept Comments: Very good review. Additional Questions: Does the manuscript contain new and significant information to justify publication? Yes Does the Abstract (Summary) clearly and accurately describe the content of the article? Yes Is the problem significant and concisely stated? Yes Are the methods described comprehensively? Yes Are the interpretations and conclusions justified by the results? Yes Is adequate reference made to other work in the field? Yes Is the language acceptable? Yes Please rate the priority for publishing this article (1 is the highest priority, 10 is the lowest priority): 2 Length of article is: Adequate Number of tables is: Adequate Number of figures is: Adequate Please state any conflict(s) of interest that you have in relation to the review of this paper (state "none" if this is not applicable): None Rating: Interest: 2. Good Quality: 1. Excellent Originality: 2. Good Overall: 2. Good
Reviewer: 2 **Anonymous** **Did not authorize the publication of the peer review reports**	
First evaluation	**Second evaluation**
Recommendation: Major revision	Recommendation: Accept

Exposure to intimate partner violence and lack of asthma control in adults: a cross-sectional study

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ABSTRACT

BACKGROUND: Asthma is a chronic airway disease that affects 339 million people worldwide. It is a heterogeneous disease with different risks, including in family environments, where intimate partner violence occurs.

OBJECTIVE: This study aimed to investigate the possible association between psychosocial factors and asthma control in adults exposed to intimate partner violence.

DESIGN AND SETTING: This cross-sectional study was conducted at a Brazilian public higher education institution in Salvador, Bahia, Brazil.

METHODS: The study population consisted of adults clinically diagnosed with severe asthma and those with mild/moderate asthma identified at an asthma referral outpatient clinic. The sample comprised 492 participants who underwent clinical evaluation and completed questionnaires to assess asthma control, depression, stress, and resilience. The Conflict Tactics Scale, which measures tactics for managing marital conflicts, was used to estimate the level of intimate partner violence.

RESULTS: Of the 492 participants, 76.2% were women and 91% self-referenced color black/brown, 37.8% reported low family income, 87.4% reported low education level, 71.7% reported high stress, 32.5% reported low resilience, 18.5% reported moderate or severe depression, 83.3% reported resolute negotiation, 49.4% reported major psychological aggression, 19.6% reported major physical aggression, 15.5% reported major injury, and 7.3% reported major sexual coercion. Regression analysis revealed that sex was an effect modifier.

CONCLUSION: Women in situations of social vulnerability, with low income and poor education, with depression, severe asthma, and those who used aggression to resolve marital conflicts had a profile associated with a lack of asthma control.

INTRODUCTION

Asthma is a chronic disease, which is typically characterized by increased responsiveness of the airways, with consequent obstruction of the airflow.Asthma is usually reversible spontaneously or with treatment. Its main symptoms are shortness of breath, wheezing, and tightness in the chest.[1]

According to the Global Initiative for Asthma (GINA), asthma is a heterogeneous and multifactorial disease with different pathological processes that affects 1–22% of the world's population, regardless of age. Although the incidence of asthma among children has decreased in recent decades, it is estimated that 358 million individuals are affected worldwide. Furthermore, 495,000 deaths are caused by the disease annually.[2] In Brazil, it is estimated that 12.4% of adults are diagnosed with asthma.[3]

Several factors contribute to the risk of developing asthma, including genetics, obesity, diet, female sex, occupational exposure, exposure to allergens, and high levels of family stress.[2]

Environmental and social stressors can affect different health conditions.[4,5] Psychosocial stress alters the susceptibility to infectious and systemic diseases, which can increase airway inflammation in asthma, causing exacerbations.[6]

Intimate partner violence can be considered as a stressor related to asthma. There is evidence that stressful environments, wherein violent events are experienced, can significantly affect asthma control.[6,7]

There is evidence obtained through experimental and observational studies of the causal relationship between stress and poor asthma control; however, there is little evidence of causality between exposure to family, work, or community violence and asthma.[8]

The current World Health Organization definition of violence covers interpersonal violence, suicidal behavior, and armed conflict. It also encompasses a wide range of "acts," going beyond physical assaults, including coercion and intimidation. The latter studies mainly investigated the relationship between aggressors and victims within the scope, while marital conflict was also investigated.[9]

The Conflict Tactics Scales (CTS2) assess the different ways couples lead conflict, considering how both manage it.Aggressive behavior as a conflict management tactic was assessed using one of the CTS2 subscales.

Marital violence has been studied in different contexts and centered on gender relations; however, it has been poorly studied along with chronic diseases, such as asthma. Therefore, it is necessary to investigate the dimensions of conjugal violence and spousal conflict management associated with asthma control. The CTS2 was used in this study. Therefore, disease control is essential to prevent crises and hospitalization.

OBJECTIVE

Considering the relationships described in the literature between asthma and psychosocial factors, the aims of the present study were I) to describe CTS2 through the latent class analysis using the subscales of CTS2 in patients with asthma, II) assess the relationship between CTS2 and asthma control, and III) identify differences between sexes.

METHODS

Type of study

This is a cross-sectional study of data collected in the case-control study titled "Risk Factors, Biomarkers and Endophenotypes of Severe Asthma," from Program for the Control of Asthma in Bahia (Programa de Controle da Asma, ProAR) – Universidade Federal da Bahia (UFBA). The participants were evaluated between 2013 and 2015 using ProAR. ProAR is the main reference center for specialized care in the treatment of severe asthma in Salvador.

In this case-control study, 1,448 participants were included. The severe asthma, no asthma, and mild/moderate asthma groups included 544, 454, and 450 participants, respectively. In this cross-sectional study, only participants with asthma who responded to the CTS2 and performed an assessment for asthma control were analyzed.

Study population

The population considered included all participants in the case-control study. Participants with severe asthma were included from a ProAR cohort. Participants with mild/moderate asthma were recruited from the community. Posters were distributed in places of great circulation, including buses and places of primary care, where interviews were conducted in the waiting room or as indicated by the patients of the ProAR cohort.

The classification of patients with mild/moderate asthma was based on the concept of severity when the patient was evaluated in ProAR, including individuals with intermittent symptoms and without treatment or using low doses of controlling drugs upon evaluation by a specialist, following the criteria of the 2006 GINA,[10] maintaining criteria similar to those of participants with severe asthma classified according to the 2002 GINA criteria.[11]

The diagnostic criteria were based on the presence of typical symptoms, improvement of symptoms with the use of bronchodilators or inhaled corticosteroids, and an increase in forced expiratory volume in 1 second by 12% and 200 ml after bronchodilator use.

Sample, participants, and patients

A total of 492 volunteers with asthma were evaluated in multiple dimensions of their disease for possible risk factors and biomarkers, as described previously. In this study, a sample of 500 participants per group was estimated, and for a sample of 400 participants, we had at least 80% power.[12]

For the present study, the following inclusion and exclusion criteria were applied.

Inclusion Criteria: Patients aged above 18 years, residing in Salvador or in the metropolitan region, diagnosed with mild/moderate or severe asthma, who were in an intimate relationship in the last year, responded to the CTS2, and agreed to sign an informed consent form.

Exclusion Criteria: Pregnant women and patients with a history of serious illnesses, such as chronic obstructive pulmonary disease, or advanced neoplasia, that made it difficult to assess asthma control. Individuals who suffered a stroke (stroke), cardiac insufficiency, any other diseases that cause dyspnea; patients who suffered clinical complications that may interfere with the autonomy to answer questionnaires and that required a caregiver; and those who did not accept the signed informed consent form were also excluded.

The participants were aged ≥ 18 years, the diagnosis of asthma was confirmed by a specialist, and the individuals' clinical history and current pulmonary function were considered. Therefore, as part of our protocol, spirometry tests were used to evaluate variable airflow obstruction, and chest radiography was performed to exclude other lung diseases.

Individuals who had previous smoking records ≥ 10 packs/year and those with other serious conditions that could confuse or interfere in the asthma diagnosis and asthma control were not included.

Main measures, variables, and outcomes

Participants' data were collected using an extensive standard form filled out by nurses and doctors. All relevant and general

information, including sociodemographic variables, such as age, weight, height, income, education, and self-reported color, was registered.[13]

The following questionnaires validated in Brazil were applied to all individuals at baseline:1) Beck Scale for Depression;[14] 2) Waldnig and Young's scale of resilience;[15] 3) Questionnaire to assess the level of psychological stress;[16] 4) CTS2 was proposed and developed by Straus to identify different aspects of domestic violence with at least 1 year in a stable marital situation[17] and validated for Portuguese.[18]

The CTS2 evaluated the variety of tactics used in response to the conflict with the partner but did not identify the causes of damage and health problems or the meaning of violent acts.[17,19]

It consisted of 78 items related to behaviors or experiences that configure different tactics to resolve marital conflict. Half of the items must be answered according to the tactics used by the interviewee; for the other half, the respondent must answer references in the tactics used by his partner/partner for conflict resolution.

The instrument consisted of five dimensions that characterize different conflict resolution tactics: negotiation (with two subscales: cognitive and emotional), psychological aggression (minor and major), physical aggression (minor and major), injury, herein referred to as damage and health problems (minor and major), and sexual coercion (minor and major). The cognitive subscale is the way in which partners use emotion for negotiation through conversation, whereas the emotional subscale is when emotion is used in an attempt to negotiate. The smallest subscale can be considered absent or mild, and the largest as severe.[17,20,21] Notably, some of the conflict tactics characterized by the instrument corroborate the forms of violence from the perspective of current Brazilian law.[22]

Statistical analysis

Descriptive statistics were calculated for all the variables. Bivariate analyses were performed using Chi-square and Fisher's exact tests to identify associated and clinically relevant variables in relation to asthma control within the clinical context and violence between partners. The Mann–Whitney U test was used to verify the differences in body mass index (BMI) between the controlled and uncontrolled asthma groups. Latent class analysis (LCA) was used to describe the CTS2 of individuals on each CTS2 subscale to prevent participant overlap. Thus, the same participant was avoided from being allocated simultaneously to the subscales of the same dimension.

Questions 47, 48, 75, and 76, corresponding to the sexual coercion dimension of CTS2, were excluded from the LCA because there wasn't at least one positive answer. The number of latent classes was determined using the Akaike information criterion, Bayesian information criterion, and entropy statistics for models with two, three, and four classes, respectively. However, the better results were those closer to 1.[23] The best model was selected based on a combination of statistical criteria, parsimony, and interpretability of the latent classes. The assumption of local independence was assessed using a residual model (values < two were expected).

LCA has established itself as a useful statistical technique for grouping individuals into subtypes within a population when there is no prior knowledge about which individual belongs to which subpopulation.[23-26] LCA is a method that uses the maximum likelihood estimation to form subgroups (latent classes), internally homogeneous and externally heterogeneous.[24] The subgroups generated from LCA can be used to investigate the relationships with other characteristics, such as risk or protective factors.

Regression models were performed with dichotomized categorical predictor variables: physical aggression (minor and major), asthma severity (severe asthma and mild/moderate asthma), income (up to one salary or more than one salary), education (up to completing high school and at least not completing higher education), resilience (high and low), and depression (minimal/mild and severe/moderate). BMI was the only numerical predictor. Associations with other CTS2 dimensions were evaluated, but only the physical aggression dimension was relevant in the adjusted models.

SPSS (International Business Machines Corporation. Released 2012. IBM SPSS Statistics for Windows, Version 21.0. Armonk, New York, United States) was used to perform the descriptive analyses and hypothesis tests, and M-plus (Version 5. Computer Software. Los Angeles, California, United States: Muthén and Muthén) was used to obtain latent classes.

Ethical aspects and financial source

We received funding from the National Council for Scientific and Technological Development (Conselho Nacional de Desenvolvimento Científico e Tecnológico, CNPq) support 471057/2014-2, the State of Bahia Foundation for Research Support (Fundação de Amparo à Pesquisa do Estado da Bahia, FAPESB), and GlaxoSmilthKline (an investigator-initiated grant). Additional support was provided by the Coordination for the Improvement of Higher Education Personnel, Brazil (Coordenação de Aperfeiçoamento de Pessoal de Nível Superior CAPES; Financing Code 001). It contemplated the preservation of the ethical and bioethical rights of the research subjects in accordance with the rules recommended in Resolution 466/2012 of the Council National Health Agency for Research in Human Beings. This project was approved by the Ethics Committee of the Maternidade Climério de Oliveira under OPINION/RESOLUTION No. 099/2009 on November 11, 2009, with additive opinion No. 032/2014.

RESULTS

The participants' main characteristics are listed in **Table 1**. Individuals with uncontrolled asthma were more likely to have

Table 1. Association between sociodemographic characteristics and clinical variables with asthma control of the 492 participants included in the project "Risk factors, biomarkers and endophenotypes for severe asthma" between 2013 and 2015 who responded to conflict tactics scale (CTS2)

Variables	Controlled asthma n = 247 n (%)	Uncontrolled asthma n = 245 n (%)	Total n = 492 n (%)	P-value[&]
Severity of asthma				0.000
Moderate asthma	137 (55.5)	84 (34.3)	221 (44.9)	
Severe asthma	110 (44.5)	161 (65.7)	271 (55.1)	
Older people				0.321
No	220 (89.1)	211 (86.1)	431 (87.6)	
Yes	27 (10.9)	34 (13.9)	61 (12.4)	
Gender				0.490
Female	185 (74.9)	190 (77.6)	375 (76.2)	
Male	62 (25.1)	55 (22.4)	117 (23.8)	
Family income ≤ minimum wage n = 460[#]				0.002
No	157 (69.5)	129 (55.1)	286 (62.2)	
Yes	69 (30.5)	105 (44.9)	174 (37.8)	
Self-referenced color black / brown				0.409
No	19 (7.7)	24 (9.8)	43 (8.7)	
Yes	228 (92.3)	221 (90.2)	449 (91.3)	
Education level ≤ high school				0.016
No	40 (16.2)	22 (9.0)	62 (12.6)	
Yes	207 (83.8)	223 (91.0)	430 (87.4)	
Perception level of stress				0.213
Low	76 (30.8)	63 (25.7)	139 (28.3)	
High	171 (69.2)	182 (74.3)	353 (71.7)	
Resilience level				0.002
High	183 (74.1)	149 (60.8)	332 (67.5)	
Low	64 (25.9)	96 (39.2)	160 (32.5)	
Moderate or severe depression				0.000
No	219 (88.7)	182 (74.3)	401 (81.5)	
Yes	28 (11.3)	63 (25.7)	91 (18.5)	
Body mass index (μ±σ)*	28.0 ± 5.1	29.4 ± 5.7	28.7 ± 5.4	0.004[**]

[&]Chi-square test; [**]Mann–Whitney test; [*]Mean and standard deviation; [#]Family income.

severe asthma, a family income of up to one minimum wage, an education level of up to high school, a low level of resilience, severe or moderate depression, and a higher average BMI compared to those with controlled asthma.

Regarding the LCA, two models were chosen because models with more than two classes hindered the interpretation and concept of each subscale and the characterization of the patients' profiles according to the subscales of the CTS2 (https://documentcloud.adobe.com/link/review?uri=urn:aaid:scds:US:282ef302-057a-4291-992a-258baa9fcee0). The subscales for the dimensions of psychological aggression, physical aggression, injury, and sexual coercion were determined as described by Moraes, Paiva, and Figueiredo,[16,23] except for the negotiation dimension, where the cognitive negotiation subscale was replaced by resolutive negotiation as both the participants and their partners had a high probability of a positive answer to the cognitive negotiation and emotional negotiation questions.

Analysis of the CTS2 subscales revealed the conflicting tactics adopted for intimate partner conflict management. As shown in **Table 2**, 82.4% of participants reported resolutive negotiations, 46.4% reported major psychological aggression, 15.2% reported minor physical aggression, 10.9% reported major injury, and 11.9% reported sexual coercion. According to them, 65.1% of their partners used resolutive negotiations, 39.6% used psychological aggression, 15.9% used physical aggression, 6.2% used injury, and 7.3% used sexual coercion (https://documentcloud.adobe.com/link/review?uri=urn:aaid:scds:US:282ef302-057a-4291-992a-258baa9fcee0).

Although there was no association between the domain of negotiation and asthma control, high percentages of its use were observed regardless of sex; that is, the use of other conflict tactics jointly involves resolutive negotiation, in which the couple tries to resolve their conflicts through conversation.

According to the stratified analysis by sex, a vulnerability profile was identified for women in relation to the lack of asthma control (**Table 3**).

The use of physical assault tactics, severe asthma, low education, low income, low resilience, and moderate or severe depression determined asthma control. However, this was not observed in men, where only the severity of asthma increased the risk of having uncontrolled asthma. Several regression models were used to investigate the conflict tactic management used by partners, but no associations were found.

DISCUSSION

According to the results, 20% of the participants reported the use of physical aggression, injury, and sexual coercion to deal with conflicts within marital relationships. Although these tactics have been reported by a minority of individuals, mainly women, they still require special attention in health services because the real dimensions of women's psychological suffering and how a violent profile impacts chronic diseases, such as asthma, are unknown.

Although the results of the present study showed that women used aggression to resolve conflicts with their intimate partners, it is known that the greatest burden of violence falls on them. Women have been the main victims of men over time[27] and also those who have suffered great damage to their health.[4]

Despite the literature showing associations between risk factors for asthma and its control,[4-6] there is little evidence on the relationship between spousal violence and asthma. However, it was identified that women who suffered violence, whether in the past or recently, were at a high risk of developing asthma. In line with the present study, a stratified analysis by sex and age showed that women in the age groups below 44 years needed to use physical

Table 2. Association between the domains of the conflict tactics scale (CTS2) and the asthma control of 375 female, 117 male, and total 492 participants included in the project "Risk factors: biomarkers and endophenotypes of severe asthma" between 2013 and 2015

Domains	Controlled asthma female n = 185	Uncontrolled asthma female n = 190	P valor[&]	Controlled asthma male n = 62	Uncontrolled asthma male n = 55	P-valor[&]	Controlled asthma n = 247	Uncontrolled asthma n = 2 45	P valor[&]
Participant									
Negotiation			0.782			0.914			0.776
Resolutive	152 (82.2)	154 (81.1)		56 (90.3)	50 (90.9)		208 (84.2)	204 (83.3)	
Emotional	33 (17.8)	36 (18.9)		6 (9.7)	5 (9.1)		39 (15.8)	41 (16.7)	
Psychological aggression			0.384			0.522			0.242
Minor	94 (50.8)	88 (46.3)		44 (71.0)	36 (65.5)		138 (55.9)	124 (50.6)	
Severe	91 (49.2)	102 (53.7)		18 (29.0)	19 (34.5)		109 (44.1)	121 (49.4)	
Physical aggression			0.009			0.298[#]			0.005
Minor	163 (88.1)	148 (77.9)		58 (93.5)	49 (89.1)		221 (89.5)	197 (80.4)	
Severe	22 (11.9)	42 (22.1)		4 (6.5)	6 (10.9)		26 (10.5)	48 (19.6)	
Sexual coercion			0.502			0.189[#]			0.980
Minor	170 (91.9)	178 (93.7)		59 (95.2)	49 (89.1)		229 (92.7)	227 (92.7)	
Severe	15 (8.1)	12 (6.3)		3 (4.8)	6 (10.9)		18 (7.3)	18 (7.3)	
Injury			0.051			0.573[#]			0.053
Minor	165 (89.2)	156 (82.1)		58 (93.5)	51 (92.7)		223 (90.3)	207 (84.5)	
Severe	20 (10.8)	34 (17.9)		4 (6.5)	4 (7.3)		24 (9.7)	38 (15.5)	
Partner									
Negotiation			0.060			0.716			0.058
Resolutive	130 (70.3)	116 (61.1)		48 (77.4)	41 (74.5)		178 (72.1)	157 (64.1)	
Emotional	55 (29.7)	74 (38.9)		14 (22.6)	14 (25.5)		69 (27.9)	88 (35.9)	
Psychological aggression			0.124			0.533			0.239
Minor	111 (60.0)	99 (52.1)		43 (69.4)	41 (74.5)		154 (62.3)	140 (57.1)	
Severe	74 (40.0)	91 (47.9)		19 (30.6)	14 (25.5)		93 (37.7)	105 (42.9)	
Physical aggression			0.167			0.811			0.164
Minor	158 (85.4)	152 (80.0)		55 (88.7)	48 (87.3)		213 (86.2)	200 (81.6)	
Severe	27 (14.6)	38 (20.0)		7 (11.3)	7 (12.7)		34 (13.8)	45 (18.4)	
Sexual coercion			0.423			0.046[#]			0.809
Minor	175 (94.6)	183 (96.3)		62 (100.0)	51 (92.7)		237 (96.0)	234 (95.5)	
Severe	10 (5.4)	7 (3.7)		-	4 (7.3)		10 (4.0)	11 (4.5)	
Injury			0.588			0.721[#]			0.577
Minor	180 (97.3)	183 (96.3)		61 (98.4)	54 (98.2)		241 (97.6)	237 (96.7)	
Severe	5 (2.7)	7 (3.7)		1 (1.6)	1 (1.8)		6 (2.4)	8 (3.3)	

[&]Chi-square test; [#]Fisher's exact test.

aggression as a conflict resolution tactic and that they were also at a high risk of uncontrolled asthma.[7]

Our results reinforce the psychosocial vulnerability of this population and demonstrate its impact on marital relationships. It is noteworthy that the ability to be resilient is related to sociodemographic characteristics, such as high schooling and high income,[28] and study participants had the opposite characteristics. In addition, we believe that depression reveals psychological suffering in this population. These findings are also addressed by other authors who demonstrated the relationship between intimate partner violence and psychological stress with a lack of asthma control and psychosocial aspects.[27,29]

Another important outcome relates to negotiations as a conflict resolution tactic. Although there was no statistical relevance, the high percentages in both the controlled and uncontrolled groups indicated that both partners used this tactic to resolve marital conflict. The most frequent form was resolutive negotiation, but it was probably ineffective in dealing with conflicts if we consider the high percentages of aggression reported by women.

The use of aggression as a form of conflict may be associated with other unstudied factors, such as irritability, which may be related to depression and lack of control over asthma. The association among uncontrolled asthma, parental depression, and family chaos, including commotion, disorganization, and routine at home, should be considered.[30]

Our findings point to the need for studies, whether quantitative or qualitative, to better understand how each of these psychosocial characteristics is related to asthma control, as well

Table 3. Logistic regression analysis for association between psychosocial factors, health status, and asthma control stratified by sex

Covariates	Crude OR (CI 95%)	Adjusted OR (CI 95%)
Female		
Physical aggression	2.103 (1.199–3.687)	1.967 (1.038–3.728)
Severe asthma	2.575 (1.697–3.908)	2.647 (1.691–4.145)
Family income ≤ minimum wage	1.793 (1.169–2.752)	1.770 (1.126–2.780)
Education level ≤ high school	2.189 (1.153–4.156)	1.264 (0.613–2.607)
Body mass index	-	1.032 (0.992–1.075)
Resilience low	1.764 (1.150–2.707)	1.436 (0.870–2.371)
Moderate or severe depression	2.882 (1.711–4.856)	2.354 (1.323–4.190)
Male		
Physical assault	1.776 (0.474–6.654)	2.230 (0.533–9.334)
Severe asthma	1.964 (0.920–4.196)	2.265 (1.003–5.114)
Family income ≤ minimum wage	2.117 (0.834–5.376)	2.204 (0.804–6.044)
Education level ≤ high school	1.387 (0.460–4.181)	1.384 (0.388–4.940)
Body mass index	-	1.080 (0.979–1.191)
Resilience low	2.133 (0.874–5.208)	2.207(0.874–5.573)
Moderate or severe depression	1.542 (0.330–7.218)	1.120 (0.221–5.683)

OR = odds ratio; CI = confidence interval.
Both models were fitted using physical assault, asthma severity, family income, educational level, body mass index, resilience, and depression.

as the etiopathogenesis of the disease. Psychosocial factors play an important role in asthma, either as precipitating elements of exacerbation or disease progression, showing that a poor perception of physical control is associated with a poor quality of life in asthmatics.[31]

In contrast, asthma itself has an impact on psychosomatic responses, as it involves biological and psychological factors directly linked to interpersonal relationships and social bonds in many ways. Asthma impacts the quality of life. The disease is related to difficult experiences permeated by suffering for the patient.[31] This is supported by our results, which revealed that depression (severe or moderate), low resilience, and physical aggression were associated with a lack of asthma control.

This study has some limitations. The first relates to reverse causality. It is impossible to state the temporality of the association between depression and the lack of asthma control. However, depression may also be related to recurrent breathing difficulties. We also considered a vicious cycle in which there was bidirectional causality between asthma and depression. Second, the sample of volunteers interfered with the external validity. Therefore, the findings can only be extrapolated to parsimony.

Despite these limitations, it is important to highlight the use of LCA, which is a poorly used technique in Brazil. However, it is important to define variables that are not directly observable. The use of latent classes within the health context was also important in identifying those that would be correlated with other variables in the adjustment of the regression models.

In addition, although CTS2 is a validated questionnaire with extensive bibliographic support, the results might be influenced by interview bias, as people with depression already have a negative view of the facts, which may overestimate the use of physical aggressive tactics and underestimate such occurrences by not reporting aggression.

CONCLUSIONS

In the present study, women in situations of social vulnerability, with low income and poor education, with depression, severe asthma, and those who used aggression as a means of resolving marital conflicts had a profile associated with a lack of asthma control. Although CTS2 does not clarify the origin of violence, it is understood that its use of physical aggression tactics is in response to a conflict that occurred previously. Further studies are needed to better assess the relationship between domestic violence, mental health, and asthma and to explore its causality. Multiprofessional health teams, especially referral centers for severe asthma, should consider the importance of marital relationships and depression in asthma control and seek interventions that contribute to the development of effective and nonviolent conflict resolutions.

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Smoking among Brazilian adolescents during the COVID-19 pandemic: a cross-sectional study

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ABSTRACT

BACKGROUND: The social distancing measures during the coronavirus disease 2019 (COVID-19) pandemic resulted in mental suffering among adolescents, leading to risky consumption of psychoactive substances such as tobacco.

OBJECTIVE: To analyze the factors associated with tobacco use among adolescents during the COVID-19 social distancing period in Brazil.

DESIGN AND SETTING: Cross-sectional study used data from ConVid Adolescentes survey in Brazil.

METHODS: Tobacco use was assessed before and during social distancing. The explanatory variables investigated were sex, age, race/skin color, type of school, maternal education, region of residence, adherence to social restriction measures, number of close friends, sleep quality during the pandemic, mood, passive smoking, use of alcoholic beverages during the pandemic, sedentary behavior, and physical activity. A logistic regression model was used for the data analysis.

RESULTS: Tobacco use by adolescents did not change during the pandemic (from 2.58% to 2.41%). There was a higher chance of tobacco use among adolescents aged between 16 and 17 years, self-reported black ones, residing in the South and Southeast regions, reported feeling sad and loneliness, had sleeping problems that worsened, were using alcoholic beverages during the pandemic, and were passive smokers at home. Adolescents whose mothers had completed high school or higher, had strict social restrictions, and increased their physical activity during the pandemic had a lower chance of tobacco use.

CONCLUSION: Tobacco uses during the COVID-19 pandemic was higher in vulnerable groups, such as black adolescents and those with mental suffering.

INTRODUCTION

The coronavirus disease 2019 (COVID-19) was declared a pandemic in March 2020 by the World Health Organization. In several Brazilian states and cities, social distancing measures were decreed to reduce the spread of the disease, such as class suspension, non-essential commerce closure, and travel restriction.[1-3] Studies have described the repercussions of reduced social interaction, pointing to an increase in stress, loneliness, and sadness,[4] as well as a worsening in lifestyles.[5] Thus, studies have identified that mental suffering and feelings such as anxiety, loneliness, and sadness can lead to consumption of risky substances such as alcohol and tobacco.[5,6-9]

Tobacco use among adolescents is a global health problem. A Global Youth Tobacco Survey review conducted in 131 countries/territories between 1999 and 2005 found that 8.9% of adolescents aged 13–15 years had smoked on one or more days during the last 30 days.[10] Tobacco use can result in health damage,[11] including an increase in adult mortality among those who begin smoking in childhood and adolescence, compared to never smokers.[10]

Studies have shown that the prevalence of tobacco use is decreasing in Brazil and worldwide,[12,13] however, among adolescents, this issue remains a Public Health concern, given the high prevalence of consumption of other products such as hookah and electronic cigarettes among Brazilian students.[14,15]

The "ConVid Comportamentos" Study identified that the prevalence of adult smokers was 12% (confidence interval, CI 95%: 11.1–12.9) during the pandemic, of which 34% reported an increase in cigarette consumption. This increase in Brazilian adults was greater among women

and individuals with incomplete secondary education. The increase in cigarette consumption among Brazilian adults was associated with worse sleep quality, feeling sad or depressed, anxiety, feeling isolated from family members, having no income, and worse health status.[5] A study in Spain showed that smoking during the pandemic was used by adolescents to relieve unpleasant emotions.[16]

Among Brazilian adolescents, a study analyzing data from the ConVid Adolescentes Survey showed a decrease in tobacco consumption.[17] However, the factors associated with tobacco consumption during the pandemic have not yet been analyzed.

OBJECTIVE

This study aimed to analyze the factors associated with tobacco use among adolescents during the social distancing period in Brazil during the COVID-19 pandemic.

METHODS

A cross-sectional study that analyzed the database of "ConVid Adolescentes – Research of Behaviors" survey was conducted with Brazilian adolescents aged 12–17 years. ConVid Adolescentes is a virtual health survey aimed at evaluating changes in adolescents' lives due to the COVID-19 pandemic.

Data collection from ConVid Adolescentes was conducted via the Internet, using a self-completion questionnaire via a cell phone or computer, and took place between June 27 and October 12, 2020. The questionnaire was constructed using the Research Electronic Data Capture application and included questions about sociodemographic characteristics and changes in lifestyle, routine activities, mood, and family relationships during the social distancing period (https://convid.fiocruz.br/index.php?pag=questionario_adolescente). The information was stored on the server at the Institute of Communication and Scientific and Technological Information in Health of the Oswaldo Cruz Foundation (Instituto de Comunicação e Informação Científica e Tecnológica em Saúde, Fundação Oswaldo Cruz [ICICT/FIOCRUZ]).

Participants were invited through a chain sampling procedure, called a virtual "snowball".[18] First, the link of the research was sent to researchers from different states of Brazil, with previous experience in studies with adolescents. Theses researchers sent the link to other adults in their social network with adolescent children. These adults were then asked to invite at least three more parents or guardians of adolescent children. Thus, invitations were sent to adults and, upon receiving the invitation to participate in the research, they were asked, "Do you have children or are you responsible for young people aged between 12 and 17 years old?". Only those who answered affirmatively received the Free and Informed Consent Term with explanations about the survey, a link to contacts and clarification about the research, and a request for consent to participation of the minor under their responsibility. After obtaining the consent of the responsible adult, the adolescent received the Free and Informed Assent Term and completed the questionnaire. In addition, the research coordinator sent letters to the State Department and schools inviting them to send the link to parents and adolescents. The final sample consisted of 9,470 adolescents aged 12–17 years.

Because sampling by networking is not probabilistic, to obtain a representative sample of the population according to geographic and sociodemographic characteristics, weights were calculated using post-stratification procedures.[19] The sample was calibrated using data from the National School Health Survey,[20] and aimed to obtain the same distribution by region of residence, sex, age group (12–15 years; 16–17 years), and type of school (public or private).

Variables

In the present study, tobacco consumption before and during the pandemic was analyzed by asking the following questions: a) Before the pandemic, did you smoke cigarettes? (Yes or No); b) During the pandemic? 1- I did not smoke cigarettes; 2- I am smoking less than I used to; 3- I continued to smoke at the same frequency; 4- I am smoking more than I used to; 5- I stopped smoking but I started smoking again. Adolescents who answered "yes" to the question before the pandemic and options 2, 3, 4 or 5 during the pandemic were considered smokers.

The following explanatory variables were investigated: sex (female and male), age group (12–15 years; 16–17 years), race/skin color (white; black; brown; others), type of school (public and private), maternal education (elementary school or less; complete high school; complete higher education), region of residence (North, Northeast, Southeast, South and Midwest), adherence to social restriction measures (not very strict and very strict), number of close friends (none, 1 friend, 2 friends, 3 or more friends), sleeping quality during the pandemic (did not affect, began having sleeping problems, continued to have sleeping problems, sleeping problems got worse, reduced sleeping problems), mood [feeling sad or depressed (never/rarely, sometimes, always); feeling irritated (never/rarely, sometimes, always); feeling isolated (never/rarely, sometimes, always)], passive smoking (yes and no), consumption of alcoholic beverages during the pandemic (yes and no), sedentary behavior (maintained, increased, reduced), physical activity (maintained, increased, reduced).

Statistical analyzes

Initially, the prevalence and 95% confidence interval (CI) of cigarette consumption before and during the pandemic were calculated for the total sample according to the explanatory variables.

To verify the possible factors associated with smoking during the pandemic, crude and adjusted odds ratios (ORc and ORa, respectively) by sex, age group, and type of school logistic regression

models were used, with a significance level of 5%. All analyses were performed using the Software for Statistics and Data Science (StataCorp LP, CollegeStation, Texas, United States), version 14.0, and post-stratification weights were considered.

Ethical issues

This study was approved by the National Research Ethics Committee (opinion no.: 4,100,515, June 20, 2020). The parents or guardians of the adolescents completed a Free and Informed Consent Form, followed by their own consent. None of the adolescents were identified.

RESULTS

A total of 9,470 adolescents were evaluated, of which 50.25% (95% CI: 48.58–51.91) were female and 67.68% (95% CI: 66.28–69.05) were aged between 12–15 years. Most adolescents self-reported being of the race/color of skin brown (46.6%; 95% CI: 44.91–48.26), followed by white (40.10%; 95% CI: 38.53–41.60) and studying in public schools (85.90%; 95% CI: 85.12–86.70). The distribution of maternal education was similar, with approximately one-third of the participants in each group (**Table 1**).

Table 1. Sample characteristics. ConVid Adolescentes, 2020. (n = 9,470)

Variables	Percentage (%)	95% CI
Sex		
Male	49.75	48.09–51.42
Female	50.25	48.58–51.91
Age group		
12 to 15 years old	67.68	66.28–69.05
16 and 17 years old	32.32	30.95–33.72
Race/skin color		
White	40.09	38.53–41.66
Black	9.70	8.76–10.73
Brown	46.58	44.91–48.26
Others	3.63	3.01–4.38
Type of school		
Private	14.07	13.3–14.88
Public	85.93	85.12–86.7
Maternal education		
Elementary school or less	32.57	30.94–34.24
Complete high school	33.80	32.13–35.51
Complete higher education	33.63	32.06–35.23

CI = confidence interval.
Complete higher education: undergraduated or higher.

Cigarette consumption was reported by 2.58% (95% CI: 2.17–3.07) of adolescents before the pandemic and remained unchanged during the pandemic (2.41%; 95% CI: 2.02; 2.87). There was no statistically significant difference in the prevalence of cigarette consumption before and during the pandemic between sexes, age groups, and type of school (**Figure 1**).

When analyzing the factors associated with tobacco consumption during the pandemic, it was observed that older adolescents (ORa: 1.55; 95% CI: 1.09–2.20), who self-reported as black (ORa: 1.82; 95% CI: 1.05–3.15), who lived in the Southeast (ORa: 4.33; 95% CI: 2.55–7.36) and South (ORa: 2.33; 95% CI: 1.37–3.96), who used alcoholic beverages during the pandemic (ORa: 19.9; 95% CI: 13.10–30.20), who were passive smokers at home (ORa: 4.68; 95% CI: 3.26–6.71), who reported that sleeping problems got worse during the pandemic (ORa: 2.37; 95% CI: 1.49–3.76), who always felt sad (ORa: 1.91; 95% CI: 1.15–3.17) and who sometimes (ORa: 1.71; 95% CI: 1.05–2.80) or always (ORa: 1.65; 95% CI: 1.04–2.62) felt lonely, were more likely to consume tobacco during the pandemic. On the other hand, adolescents who study in private schools (ORa: 0.52; 95% CI: 0.34–0.78),whose mothers had completed high school (ORa: 0.33; 95% CI: 0.21–0.53) or higher (ORa: 0.45; 95% CI: 0.27–0.75), who had very strict social restrictions (ORa: 0.30;95% CI: 0.20–0.43) and that physical activity increased during de pandemic (ORa: 0.40; 95% CI: 0.16–0.98), were less likely to consume tobacco (**Table 2**).

DISCUSSION

The "Convid Adolescentes" survey evaluated the changes in the lifestyle of Brazilian adolescents during social distancing of the COVID-19 pandemic. This study shows that tobacco consumption did not change during the pandemic. Higher consumption

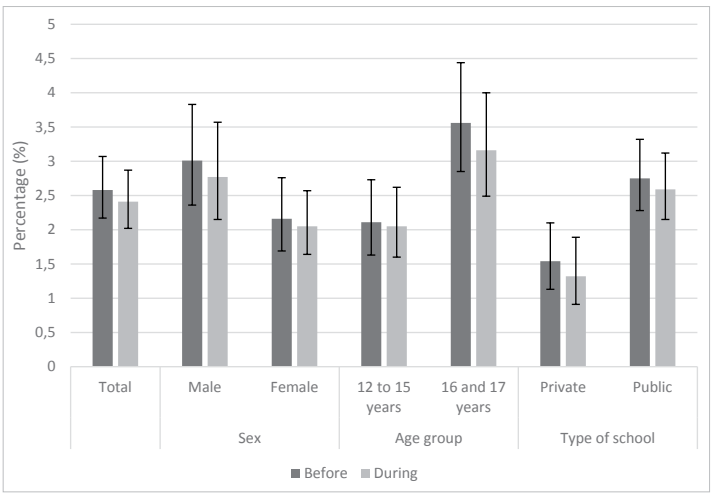

Figure 1. Prevalence and 95% confidence interval of smoking before and during the coronavirus disease 2019 (COVID-19) pandemic. ConVid Adolescentes, 2020.

Table 2. Prevalence and crude and adjusted odds ratio (OR) (95% confidence interval [CI]) of smoking by adolescents during the pandemic, according to potential associated factors. ConVid Adolescentes, 2020

Variables	During % (95% CI)	Crude OR (95% CI)	Adjusted*OR (95% CI)
Total	2.41 (2.02; 2.87)		
Sex			
Male	2.77 (2.15; 3.57)	-	-
Female	2.05 (1.64; 2.57)	0.74 (0.52; 1.04)	0.74 (0.52; 1.04)
Age group			
12 to 15 years old	2.05 (1.60; 2.62)	-	-
16 and 17 years old	3.16 (2.49; 4.00)	1.56 (1.10; 2.22)	1.55 (1.09; 2.20)
Race/Skin color			
White	2.09 (1.57; 2.77)	-	-
Black	4.09 (2.60; 6.38)	2.00 (1.15; 3.46)	1.82 (1.05; 3.15)
Brown	2.34 (1.79; 3.06)	1.12 (0.75; 1.67)	1.05 (0.70; 1.58)
Others	2.48 (1.13; 5.36)	1.19 (0.51; 2.79)	1.12 (0.48; 2.64)
Type of school			
Public	2.59 (2.15; 3.12)	-	-
Private	1.32 (0.91; 1.89)	0.50 (0.33; 0.76)	0.52 (0.34; 0.78)
Maternal Education			
Elementary school or less	4.22 (3.27; 5.42)	-	-
Complete high school	1.41 (0.96; 2.06)	0.32 (0.20; 0.52)	0.33 (0.21; 0.53)
Complete higher education	1.78 (1.25; 2.54)	0.41 (0.26; 0.64)	0.45 (0.27; 0.75)
Region of residence			
North	1.02 (0.64; 1.63)	-	-
Northeast	0.46 (0.15; 1.38)	0.45 (0.14; 1.50)	0.45 (0.13; 1.49)
Southeast	4.15 (3.34; 5.15)	4.20 (2.48;7.11)	4.33 (2.55; 7.36)
South	2.35 (1.86; 2.96)	2.34 (1.37; 3.98)	2.33 (1.37; 3.96)
Midwest	2.07 (1.12; 3.79)	2.05 (0.94; 4.49)	2.12 (0.97; 4.62)
Social restriction			
Not very strict	4.84 (3.82; 6.10)	-	-
Very strict	1.44 (0.10; 1.87)	0.29 (0.20; 0.41)	0.30 (0.20; 0.43)
Close friends			
None	1.83 (1.05; 3.18)	-	-
1 friend	2.63 (1.65; 4.16)	1.45 (0.69; 3.02)	1.49 (0.71; 3.09)
2 friends	2.59 (1.81; 3.70)	1.42 (0.73; 2.79)	1.49 (0.76; 2.92)
3 or more friends	2.36 (1.85; 3.00)	1.30 (0.70; 2.40)	1.38 (0.74; 2.57)
Sleeping			
Did not affect	1.96 (1.40; 2.57)	-	-
Started to have sleeping problems	2.66 (1.84; 3.83)	1.37 (0.86; 2.19)	1.43 (0.89; 2.31)
Continued to have sleeping problems	1.30 (0.73; 2.28)	0.66 (0.35; 1.24)	0.67 (0.36; 1.27)
Sleeping problems got worse	4.33 (3.10; 6.03)	2.27 (1.45; 3.55)	2.37 (1.49; 3.76)
Reduced sleeping problems	4.54 (2.01; 9.95)	2.38 (0.98; 5.79)	2.40 (0.99; 5.86)
Feeling sad/depressed			
Never/rarely	1.79 (1.26; 2.54)	-	-
Sometimes	2.52 (1.85; 3.42)	1.42 (0.88; 2.29)	1.53 (0.92; 2.56)
Always	2.94 (2.26; 3.83)	1.67 (1.06; 2.61)	1.91 (1.15; 3.17)

Continue...

Table 2. Continuation.

Variables	During % (95% CI)	Crude OR (95% CI)	Adjusted*OR (95% CI)
Feeling irritated			
Never/rarely	2.26 (0.49; 3.40)	-	-
Sometimes	2.46 (1.78; 3.39)	1.09 (0.64; 1.87)	1.15 (0.66; 1.98)
Always	2.45 (1.93; 3.11)	1.09 (0.67; 1.77)	1.18 (0.69; 2.01)
Feeling isolated			
Never/rarely	1.82 (1.32; 2.51)	-	-
Sometimes	2.85 (2.08; 3.90)	1.58 (1.00; 2.51)	1.71 (1.05; 2.80)
Always	2.74 (2.08; 3.61)	1.52 (0.98; 2.34)	1.65 (1.04; 2.62)
Passive smoking			
No	1.42 (1.12; 1.79)	-	
Yes	6.40 (4.96; 8.22)	4.76 (3.32; 6.82)	4.68 (3.26; 6.71)
Consumption of alcoholic beverages during the pandemic			
No	0.83 (0.60; 1.14)	-	-
Yes	13.30 (10.90; 16.12)	18.33 (12.4; 27.14)	19.90 (13.10; 30.20)
Sedentary behavior			
Maintained	2.23 (1.79; 2.78)	-	-
Increased	2.91 (2.15; 3.93)	1.31 (0.90; 1.93)	1.31 (0.89; 1.92)
Reduced	2.02 (0.75; 5.36)	0.91 (0.32; 2.55)	0.89 (0.32; 2.49)
Physical practice			
Maintained	2.36 (1.92; 2.91)	-	-
Reduced	2.82 (1.99; 3.99)	1.20 (0.79; 1.82)	1.16 (0.76; 1.76)
Increased	0.96 (0.4; 2.28)	0.40 (0.16; 0.99)	0.40 (0.16; 0.98)

*Adjusted for sex, age group, and school type.

was associated with older adolescents, black race/color of the skin, residing in the South and Southeast regions, who reported feelings of sadness and loneliness, whose sleeping problems worsened, who consumed alcoholic beverages during the pandemic, and who reported passive smoking. Tobacco consumption was lower among adolescents whose mothers had higher educational levels, who studied in private schools, who adopted stricter social distancing measures during the pandemic, and who increased their physical activity during the pandemic.

This study demonstrated the stability of smoking habits among adolescents during the pandemic. Previous studies found the same pattern.[16,21] On one hand, the stress and anxiety produced by the period of social isolation can be considered triggers for unhealthy behaviors and some adolescents could use smoking as a coping mechanism for these adverse feelings.[22] On the other hand, the decrease in income and the closure of establishments aimed at social interaction, such as bars and restaurants, may have reduced adolescents' access to cigarettes.[23,24] Thus, more studies are needed to better understand the reasons for the stability of this prevalence.

Notably, the prevalence in the current study was lower than that in Spain[16] and that in the data from the National Survey of School Health (Pesquisa Nacional de Saúde do Escolar [PeNSE]) 2019, which showed that tobacco consumption in the last 30 days was 6.8% (6.3–7.3) for students aged 13–17 years.[25] The results showed a higher prevalence of tobacco consumption in older adolescents, which is in line with other studies.[16] In PeNSE 2019, for example, it was found that adolescents aged 16–17 years consume more tobacco than those aged between 13–15 years.[25]

Adolescents who reported feelings of sadness, loneliness, and worsened sleep problems during the pandemic had higher tobacco consumption. Studies carried out during the pandemic have suggested that situations of social distancing can have negative consequences on psychological and mental health.[26-29] Therefore, some adolescents may have been involved with substance use as a way to deal with psychological discomfort and negative feelings related to the COVID-19 situation.[27,28,30,31] The increase in tobacco consumption in some groups may be a way to relieve negative emotions related to COVID-19, deal with boredom, and overcome the lack of social relationships.[27,28,30,32,33]

Lower tobacco consumption was observed among children of more educated mothers, which was also observed in a study from Spain for adolescents whose parents had a university education.[16] The COVID-19 pandemic has led to social restrictions, and adolescents spent more time with their parents at home. Higher maternal education may be related to greater access to information, not

only on the risks of tobacco but also on the possible respiratory aggravations that COVID-19 can generate in smokers.[16,30] Thus, a family attitude of disapproval of tobacco consumption by adolescents at home may have contributed to this reduction.

Smoking was higher among Black adolescents, which may reflect their greater vulnerability. In Brazil, race/skin color is associated with lower income and may also be associated with parents with less education, which would lead to less access to information.[16]

Passive smoking had the strongest association among adolescents. This finding was also identified in a previous study with data from PeNSE 2015,[14] among other studies.[34] Passive smoking at home denotes the marked influence of family members and close people, and which are highlighted by the theory of social learning.[35] Thus, adolescents frequently exposed to passive smoking naturalize the practice and end up adopting it.

The association between alcohol consumption and a greater chance of smoking during the pandemic may be explained by the fact that both habits are seen as a source of social acceptance,[36] in addition to being risky behaviors based on the same vulnerabilities, such as feelings of sadness and isolation.[37] Furthermore, a previous study showed that the consumption of alcoholic beverages increases the desire to smoke in people who already consume cigarettes.[38]

In line with this study, data from PeNSE 2019 show that the prevalence of tobacco use in the last 30 days was also higher in the South region of the country (8.0%; 95% CI: 7.1–8.7) and Southeast (7.6%; 95% CI: 6.4–8.7), compared to the North (4.7%; 95% CI: 4.3–5.2).[25]

Previous studies have suggested that the tobacco control measures implemented in the country were critical in the decline of smoking prevalence among adults[40] and adolescents.[14] Brazil has the lowest smoking prevalence among adolescents in America.[40] Law nº 12.546/2011,[41] Presidential Decree no. 8.262/2014[42] e an Interministerial Ordinance no. 2.647/2014[43] forbidden advertising at sale's point, determined the increase of prices and taxes, established closed environments completely smoke-free, and increasing images of health warnings, in addition to prohibiting the use of hookah.

However, in recent years, there have been setbacks in surveillance and regulatory policies, jeopardizing the health of children and adolescents. Data from PeNSE 2019 indicate a very high prevalence of hookah and electronic cigarette use, even though the latter is prohibited by the Brazilian Health Regulatory Agency (Agência Nacional de Vigilância Sanitária [ANVISA]).[25]

Among the limitations of the present study, it is worth mentioning that a non-random sample was selected via the Web, which may not have reached all social segments, although post-stratification weights were applied. The data obtained were based on reports by adolescents, which may have led to information bias. Furthermore, this is a cross-sectional study, which does not allow the establishment of a cause-effect relationship between the associations observed.

CONCLUSION

The results suggest that the COVID-19 pandemic has affected the social lives of young people. Although there was no change in tobacco consumption, it is necessary to remain alert, especially in older black adolescents who are subjected to passive smoking at home, have mental suffering, and have less-educated parents.

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Cognitive abilities and medical students' practice of physical exams: A quasi-experimental study

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ABSTRACT

BACKGROUND: To highlight the importance of clinical simulations and simulated laboratories for student training, especially in physical examination teaching.

OBJECTIVE: To evaluate the gains obtained by medical students in their cognitive and practical performance of physical examinations (abdominal, cardiological, and pulmonary), as well as satisfaction and self-confidence in what they have learned, after concentrated practice developed in a skills and simulation laboratory.

DESIGN AND SETTING: A quantitative and quasi-experimental study in which 48 students were evaluated at the Faculdade de Odontologia de Bauru, São Paulo, Brazil.

METHODS: A quantitative and descriptive study was conducted with regularly enrolled 2nd year medical students over 18 years of age who had content prior to data collection regarding anamnesis and physical examination remotely taught in a Moodle virtual learning environment. For data collection, the participants were subjected to a concentrated period of skill training (abdominal, cardiological, and pulmonary). Every day after the skill training session, they were subjected to a practical evaluation and completed a theoretical test before and after the practical activities. At the end of all activities, they answered the instrument to assess the simulated practices (self-confidence and satisfaction).

RESULTS: Among the 49 students evaluated, positive and significant theoretical and practical gains were identified in all three components (abdominal, cardiological, and pulmonary) (P = 0.000), as well as in the general evaluation (Theoretical 1 and Theoretical 2) (P = 0.000), satisfaction, and self-confidence (P = 0.000).

CONCLUSION: Concentrated laboratory practice resulted in positive improvements in students' physical examination skills.

INTRODUCTION

There is a progressive resumption in the discussion of the relevance of studying semiology and semiotechniques within the medical routine, and the best way and time for students to learn this content is in undergraduate courses.

The etymology and definition of the terms "semiology" and "semiotechnique" are similar and related to the study of signs. They involve technical development and interpersonal relationships, which are consolidated through clinical experience. They analyze sign systems that communicate with humans and/or other beings from various perspectives. In medicine, semiology and semiotechnics provide subsidies for the professional to identify, rank, and interpret the semiological findings and confirm the existing symptoms through a general and specific physical examination, resorting to inspection, palpation, percussion, and auscultation techniques of the different body segments, in addition to additional tests. Its teaching requires the involvement of duly prepared professors capable of developing skills that are part of routine medical work for students.[1,2]

In the most diverse areas, skills and simulation laboratories have been cited as fruitful environments to learn these skills because, in an interactive way and with creative methods such as the use of simulators and/or other technologies, they stimulate the students' experience in content that they consider difficult to understand.[3]

Physical examination has an incomparable potential in discovering problems, as it indicates diagnoses earlier in time without the need for supplementary clinical tests. In addition, verbal and non-verbal communication and also the contact between physicians and patients enhances their mutual trust and empathy.[4]

Learning the physical examination is complex, and in most medical courses in Brazil, it is taught almost entirely from the fifth semester of undergraduation,[5] assuming that students possess

enough knowledge to learn it only after this period. Scholars also report that the content has been taught in a remote learning style,[6] which characterizes the passive mode of practical learning in which the professor demonstrates and the student observes, reproducing the sequence in a repetitive manner.

The medicine courses that resort to active methodologies are based on experimental knowledge to reconstruct knowledge.[7,8] In this modality, students have contact with clinical practice and other teaching methods from the first semester, which assists them in better skill development.[7] The use of clinical simulation stands out among the various methods that resort to experimental learning.

Clinical simulation mimics clinical practice in a safe environment. It can be performed with a series of resources, for example simulators and simulated patients.[4,8-11] The difference between clinical simulation and a real practical situation is undeniable, and it is clear that reality is fundamental for training in medicine. However, several studies show that, when properly formulated and used, it can replace clinical practices by up to 50.0% without prejudice to the training quality.[11] In addition, prior skills training increases patient safety[12] and students' self-confidence, security, and ease both in the scenarios and in real practice, which minimizes the patients' unpleasant sensation of feeling like a learning object.

Skills and simulation laboratories are suitable environments for conducting physical examinations. However, some points still need to be clarified on this subject matter, such as the best resources to be used (practices with actors, role play, simulators, and other technologies) and how to distribute the activities within the curriculum of the courses (performing them sequentially, concentrated in a single block, one day after the other until they are finished, or throughout the semester and/or even the academic year, alternating between those with activities for inclusion in clinical practice).

OBJECTIVE

This study aimed to evaluate the gains obtained by medical students in their cognitive and practical performance of the physical examination (abdominal, cardiological, and pulmonary) and to examine their satisfaction and self-confidence on acquiring this knowledge following concentrated practices developed in a skills and simulation laboratory.

METHODS

Type of study

This is a quasi-experimental study. Ethical approval was obtained from the Research Ethics Committee of Hospital de Reabilitação de Anomalias Craniofaciais (HRAC) on February 26, 2021 (Opinion no. 4.562.615). This study adhered to all ethical principles.

Study locus

This study was conducted with students from a medical course at a public university in the inland of São Paulo, whose political-pedagogical project is based on an active methodology, has structured skills, and a simulation laboratory.

During the isolation period imposed by the coronavirus disease (COVID-19) pandemic in 2020, the teaching of semiology and semiotechniques underwent modifications in the course, which starts in the second semester. The theoretical contents of the anamnesis and the physical examination were taught exclusively through synchronous theoretical activities. Videos demonstrating the techniques were made available to the students in the study material of the virtual learning environment. When the students returned from the isolation period (beginning of 2021), strictly following adequate biosafety standards for their own protection,[13] the practices were performed in groups and in a concentrated manner. This was also the students' first contact with the unit, professors, facilitators, technicians, and peers of other courses.

Population and sample

The participants were students attending second year of the course. The sample included those regularly enrolled, over 18 years old, entering 2020, who had anamnesis and physical examination content taught prior to data collection exclusively remotely, and who participated in all the study activities (theoretical test before the practical activities [Theoretical 1]; practical activities of abdominal, cardiac, and respiratory physical examination; practical evaluation of the abdominal, cardiac, and respiratory physical examination; and final theoretical test [Theoretical 2]). Students who did not perform any of the proposed activities were excluded. Therefore, 49 of 56 students in this group were included in the sample.

Collection instruments

a) Instrument to characterize the subjects: An instrument with open and closed questions to characterize the students (course period, age, previous experiences with other undergraduate courses) and their behavior, as well as the resources used during the pandemic (access to the contents, interests, and availability of resources).

Knowledge assessment (Theoretical 1 and Theoretical 2): an instrument created by the researchers themselves, subdivided into the contents of the cardiac, respiratory, and abdominal physical examination (Theoretical Abdomen, Theoretical Cardiology, Theoretical Respiratory). The instrument contained 10 multiple-choice questions for each content (cardiac, respiratory, and abdominal), with four answer options, of which only one was correct. The value assigned to each correct answer was 0.1. Before the application, the instrument was peer-validated regarding the face and content and tested

a pilot stage with third-year students. No modifications were made to the instruments. The concept of cognitive knowledge used in this study arises from the theoretical perspective of the Miller pyramid. The "knowledge," which is the pyramid's base, refers to the evaluation of how the students integrate previous knowledge to the new information. In turn, practical performance corresponds to "show how to do it," applied to the evaluation of skills.[14]

b) Evaluated skills with a checklist (abdominal practice, cardiology practice, and respiratory system practice). Based on the scripts used in the training, an instrument with 10 items and a value of 0.1 were assigned to each item created by the researchers, which contained a positive answer (*performed*) and a negative answer (*not performed*) as possibilities. Before the application, the instrument was peer-validated regarding the face and content and tested on a pilot stage with five third-year students. No modifications were made to the instruments.
c) Scale of Satisfaction and Self-Confidence in Learning (SSCL):[15] a 13-item, five-point Likert-type instrument was used. It was divided into satisfaction (six items) and self-confidence in learning (seven items) dimensions, already validated and culturally adapted for Portuguese (Portuguese version: *Cronbach's Alpha* = 0.84).

Development of the study

When resuming in-person activities, the students were subjected to a concentrated skill training period for physical examinations. The training was performed for three consecutive days. The training sessions lasted for three hours and were conducted in groups of a maximum of 10 students. Before the practical activities were initiated, on day one, all students were invited to participate in the study; answer a theoretical evaluation that included content related to the abdominal, cardiac, and respiratory systems (Theoretical 1); and then participate in the practical activities.

The practical activities were divided by day into the following topics, all developed on three consecutive days: Day 1, Abdominal System; Day 2, Cardiac System; and Day 3, Respiratory System. They consisted of a demonstration for the entire group of students, followed by skill training and feedback. The demonstration was always conducted by the same facilitator, who had expertise in physical examinations. Skill training was conducted using trained and calibrated monitors under teacher supervision. Auscultation simulators and role-playing were used during the training sessions. All participants were guided by a script previously prepared and validated by the researchers.

At the end of each day of practical activity, the students were individually subjected to a practical evaluation in charge of the calibrated student monitor with the support of a checklist for skills assessment (abdominal practice, cardiology practice, and respiratory system practice). The practical evaluation followed the Objective Structured Clinical Examination model and included inspection, palpation, percussion, and auscultation techniques for all systems evaluated.

At the end of day 3 and the last practical evaluation, all students completed the knowledge evaluation (Theoretical 2) again. At the end of the evaluation, they completed the SSCL scale.[15]

Analysis and presentation of the results

The data were tabulated and analyzed with the aid of the IBM SPSS Statistics 24 (IBM Corp., Armonk, New York, United States), a software that seeks analytical and data application. Descriptive statistics, comparison of means (Student's *t*-test), reliability analysis (SSCL)[15] and correlation analyses (Pearson's test) were performed. The SSCL[15] was analyzed as proposed by the original authors, independent of satisfaction and self-confidence evaluations. The web data were tabulated and analyzed in tables and a discursive report.

RESULTS

Of the 48 students (100%), 28 (57.0%) were female and 21 (42.0%) were male. The younger student was 18 years old, the oldest was 29 years old, the average age was 21.7 years old, and the median age was 21 years. Among them, two (4.0%) had already attended another undergraduate course: one (2.0%) in Veterinary Medicine and one (2.0%) in Physical and Biomolecular Sciences.

All 48 (100.0%) students stated that they enjoyed accessing the Internet during the pandemic. Of these, nine (18.0%) reported not attending all the virtual classes. The reasons described were a lack of self-organization and readaptation to the teaching modality in five cases (10.0%) and the feeling of demotivation due to learning-at-a-distance in four cases (8.0%).

Regarding experiencing difficulties related to learning anamnesis and physical examinations through remote teaching, 48 (98.0%) reported experiencing them. The reported difficulties included a lack of practical activities (33.0%), difficulty understanding the semiotechnics (18.0%), difficulty discussing doubts remotely (18.0%), lack of correction of the skills trained at home (16.0%), lack of motivation (8.0%), and difficulty accessing the materials (4.0%).

With regard to the descriptive results of the theoretical and practical evaluations, an improvement was observed in the mean of the theoretical test after the simulated practices in the assessments of the cardiac (theoretical cardiology) and respiratory systems (theoretical respiratory), but there was no improvement in the mean of the theoretical evaluation of the abdominal system (theoretical abdomen) and in the general mean of the theoretical evaluation (Theoretical 2); however, the standard deviation for the scores of all systems and of the general evaluation was reduced. An improvement in the mean grade corresponding to practical evaluation 2 (cardiology) was also observed compared with the mean grade for practical evaluation 1 (abdomen). The mean values across practical evaluations also showed a reduction in the standard deviation.

Considering the normal distribution of the sample (Kolmogorov-Smirnov ≤ 0.05), a means comparison was also made (Student's *t*-test) between the subsequent theoretical grades and between the means of the practical evaluation and those of the final theoretical evaluation; a significant gain was observed among all the evaluations performed (**Table 1**).

The SSCL was applied to assess the students' satisfaction and self-confidence levels obtained in the simulated clinical practices during the period.[15] The scale presented good data reliability ($\alpha = 0.833$), and the comparison (Student's *t*-test) between the means obtained showed that there were significant gains when comparing satisfaction and self-confidence (**Table 2**).

Pearson's test was performed to verify whether there was any correlation between satisfaction and the evaluation results. The correlations found between the practical evaluation and scale (P = 0.218) and between the theoretical evaluation and scale (P = 0.196) were very weak.

DISCUSSION

This study was conducted with students returning from the pandemic distancing period (COVID-19), and the results showed that although they had internet access during the suspension of their academic activities, they had difficulties related to the participation and development of practical activities. In the medical field, clinical experience with patients and physical contact between students are part of the development of competent professionals and are stimulated by the Curricular Guidelines of Undergraduate Courses. However, universities have been forced to review their teaching strategies during the pandemic. Many strategies that until then were exclusively based on the face-to-face issues started to introduce online content,[16] including those related to videoconferencing, transforming face-to-face classes into synchronous ones, and others used e-learning strategies.[17] During this period, some more interactive e-learning activities were the best evaluated and accepted by the undergraduate students.[18]

With regard to the semiology and semiotechnics practices supported by e-learning, initiatives that individualize teaching and learning methods by providing feedback to the students on their limitations and possibilities through contact with real clinical cases are already in progress, have been well evaluated, and show room for improvement.[2] In the sample of this study, the physical examination was reported as the item that presented with the highest difficulty to be performed in the home environment, which can be related to the use of resources within a skill and simulation laboratory and to the constant support of a facilitator when such activities are performed in person. Supported by skills and simulation resources, physical examination has been an effective practice in both medical and other healthcare professions.[19] Some researchers emphasize the importance of clinical practice at the bedside and recommend that to balance the difficulties experienced in the post-pandemic period, activities that revisit physical examination techniques in an arduous way and individually and/or in groups should be performed with clear and precise strategies to meet the needs.[20]

In this study, to meet the requirements of the physical examination training, several sessions of the abdominal, cardiological,

Table 1. Gains obtained by the students between the theoretical and practical evaluations. Bauru, 2022

Evaluation	Fr	Min	Max	Mean	SD	*t*-test	*DoF*	P value
Theoretical								
Theoretical 1 Abdomen	49	0.3	1.9	1.3	0.375	24.018	48	0.000
Theoretical 2 Abdomen	49	0.6	1.6	1.1	0.254	49.233	48	0.000
Theoretical 1 Cardiology	49	0.3	1.7	1.0	0.322	22.361	48	0.000
Theoretical 2 Cardiology	49	0.7	1.9	1.4	0.271	36.660	48	0.000
Theoretical 1 Respiratory	49	0.0	2.0	1.1	0.412	19.223	48	0.000
Theoretical 2 Respiratory	49	1.0	2.0	2.0	0.172	79.781	48	0.000
Theoretical 1	49	0.6	1.6	1.1	0.254	31.495	48	0.000
Theoretical 2	49	0.5	1.3	1.0	0.153	45.972	48	0.000
Practical								
Practical 1 Abdomen	49	0.5	1.0	0.8	0.137	38.293	48	0.000
Practical 2 Cardiology	49	0.5	1.0	0.9	0.123	48.561	48	0.000
Practical 3 Respiratory	49	0.7	1.0	0.9	0.090	70.320	48	0.000

Fr = frequency; Min = minimum; Max = maximum; SD = standard deviation; DoF = degrees of freedom.

Table 2. Gains obtained by the students between the theoretical and practical evaluations. Bauru, 2022

SSCL	Fr	Min	Max	Mean	SD	*t*-test	*DoF*	P value
Satisfaction	49	3.3	5.0	4.3	0.518	57.706	48	0.000
Self-confidence	49	3.2	5.0	4.7	0.416	78.882	48	0.000

Fr = frequency; Min = minimum; Max = maximum; SD = standard deviation; DoF = degrees of freedom.

and respiratory examinations were performed on subsequent days. As shown in **Table 1**, the results indicate a gain in knowledge among the students after all the activities and a significant increase in practical and theoretical knowledge in the subsequent days. The practices thus exerted a positive impact both on skill training and on the students' cognitive performance.

Other studies have reported similar results regarding improvements in cognitive performance. Some time passed between practice and cognitive learning (theoretical classes were online during the COVID-19 pandemic in 2020); in this study, the association between students' theoretical and practical knowledge and experimental learning[7] demonstrated success. Although these findings need to be further explored in studies that control for other variabilities, such as online access to activities and study time, the results showed that reviewing theoretical content (cognitive learning[7]) should not be the exclusive strategy used by medical students. Students who learn by simulation learn more, and this knowledge lasts longer.[21,22] By enabling students' active participation, simulation presents itself as a strategy of greater impact for students when compared to more traditional strategies.[23]

In relation to practical performance, these findings are grounded in Kolb's theories of Experiential Learning and on David Ausubel's Theory of Meaningful Learning.[24] Experiential learning is considered a continuous process based on reflection that begins when an individual is involved in a situation. This situation can be created as in the case of clinical simulation sessions. Experience enables subjects to change their behavior or attitude; has numerous benefits for education; and promotes emotional, behavioral, and cognitive learning.[9,10,24] In addition, active experimentation can contribute to the development of competencies and skills.[24]

From the perspective of meaningful learning, knowledge is attributed to meaning when there is an interaction with previous knowledge. When interacting with new knowledge, previous knowledge modifies and enriches the previous cognitive structure. In simulations, prior knowledge is facilitated in earlier stages, such as concepts, data, information, theories, and skill practices. During a simulation session, there is a necessary interaction with previous knowledge, resulting in the attribution of meaning to knowledge and meaningful learning. Meaningful learning lasts longer.[26]

In terms of physical examination skills, there are difficulties and deficiencies in the qualifications and skills intrinsic to professionals, which makes individual training at both the undergraduate and graduate levels extremely relevant. In the cardiac physical examination, using simulators and skill and simulation laboratories have been recommended for medical education, and some studies have proven the effectiveness of skills and knowledge gained with these resources.[27] Others even report that this can be a transforming element for patient care and also for medical education.[28] In cardiology, some researchers suggest, for example, resorting to auscultation stations using deliberate practice to maximize the potential of such practice.[29]

Regarding pulmonary physical examination, this study shows good use of skill and simulation laboratories with simulators, in the sense of developing technical attributes, but also of interaction with the patient, respecting ethical and safety issues. Some researchers have moved in this direction by producing technical manuals on how to conduct such learning.[30] In turn, in abdominal physical examination, the clinical skills of inspection, palpation, percussion, and auscultation, sometimes replaced in large centers by imaging examinations, are highlighted as extremely relevant in the support of bedside diagnoses, since the beginning of the medical studies.[31]

By applying the SSCL scale[15] (**Table 2**), it was possible to identify gains in student satisfaction and self-confidence with the simulated practices. Satisfaction can be considered as a feeling of pleasure or disappointment that arises from an event and from the individual's previous perspectives on satisfaction.[32] It is an affective reaction caused by the occurrence of what is expected ahead.[33] In simulated teaching, satisfaction can be considered an important component, mainly due to the positive reinforcement in self-confidence and in the experiences that will build the profile of future professionals.[21] Satisfied students are more motivated to learn.[21,34]

Self-confidence is related to the beliefs demonstrated in the event, domains, and dexterities, and is performed with wisdom, preparation, and support.[35] In simulation, satisfaction and self-confidence seem to be related to interactivity of the resources, refinement of skills, support from facilitators, and competence.[9] A number of studies have pointed to simulation as a strategy that promotes satisfaction and self-confidence in students in the medical field.[36-40]

Limitations of the study

The study had the following limitations: non-comparison between the gains obtained after concentrated practice and other practice models, such as interleaved practices, and those distributed throughout the semester. Therefore, it is not possible to infer which model is the most suitable for teaching anamnesis and physical examinations in relation to the segments studied.

Only immediate cognitive and practical knowledge, and performance were assessed. Cognitive performance, satisfaction, and self-confidence after the online classes were not measured. Therefore, it is necessary to develop prospective and experimental studies with the objective of longitudinally monitoring performance and assimilation using different models to organize and offer skill practices in medical education.

CONCLUSION

In the cognitive performance, it was observed that the students presented positive and significant gains in all three components

(abdominal, cardiological, and pulmonary) and in the general evaluation (Theoretical 1 and Theoretical 2). Regarding the practical evaluation, there was also a positive and significant gain among all three components.

Concentrated practice provided positive and significant gains in terms of satisfaction and self-confidence among medical students. However, it was not possible to identify a strong correlation between the cognitive performance and practical evaluations.

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Authors' contributions: Yamamoto LM: methodology (equal), project administration (equal), supervision (equal), writing – original draft (equal), writing – review and editing (equal); Mazzo A: methodology (equal), project administration (equal), writing – original draft (equal), writing – review and editing (equal); Pavin ML, Souza GBD and Oliveira JLHB: methodology (equal), project administration (equal), supervision (equal); Costa RRO: writing – original draft (equal), writing – review and editing (equal); Fernandes AY: 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 for publication

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COGNITIVE ABILITIES AND MEDICAL STUDENTS' PRACTICE OF PHYSICAL EXAMS: A QUASI-EXPERIMENTAL STUDY

The São Paulo Medical Journal thanks Rodrigo Guimarães and Fernanda Miranda for their contributions to the peer review of this manuscript.

PEER REVIEW REPORTS

Reviewer 1: Rodrigo Guimarães - Universidade Federal de Mato Grosso do Sul, Instituto Integrado de Saúde

First evaluation	Second evaluation
Recommendation: Minor Revision	Recommendation: Accept
Comments: The manuscript is interesting in terms of the teaching-learning process of physical examination, but it needs some adjustments and clarifications. The title is too long and unattractive, I suggest its reduction. A suggestion would be: COGNITIVE AND PRACTICAL SKILLS OF MEDICINE STUDENTS IN PERFORMING PHYSICAL EXAMINATION: A QUASI-EXPERIMENTAL STUDY In the abstract I suggest adding between the descriptors simulation and teaching to increase the probability of reaching the article. The introduction is coherent, as well as the applied study methodology. In the results, the authors bring income as a variable of interest, but it is very loose in the manuscript. Would the idea be to associate it with internet access? I suggest establishing consistency with this variable or removing it. In Tables 2 and 3 the values of P value are all zeroed, is there the result found? I suggest reviewing. The scale used and shown in Table 3 is composed of 13 items totaling 130 points with facts of 60 and 70 points. I suggest that the authors present, in addition to the frequencies of minimum, maximum and standard deviation, such results as well as the score obtained in the general score. The manuscript presents the limitations of the study and the conclusion is adequate.	The authors accepted the proposed improvements suggestions to the manuscript. Therefore, I suggest publishing.
Additional Questions: Does the manuscript contain new and significant information to justify publication? Yes Does the Abstract (Summary) clearly and accurately describe the content of the article? Yes Is the problem significant and concisely stated? Yes Are the methods described comprehensively? Yes Are the interpretations and conclusions justified by the results? Yes Is adequate reference made to other work in the field? Yes Is the language acceptable? Yes	Additional Questions: Does the manuscript contain new and significant information to justify publication? Yes Does the Abstract (Summary) clearly and accurately describe the content of the article? Yes Is the problem significant and concisely stated? Yes Are the methods described comprehensively? Yes Are the interpretations and conclusions justified by the results? Yes Is adequate reference made to other work in the field? Yes Is the language acceptable? Yes Please rate the priority for publishing this article (1 is the highest priority, 10 is the lowest priority): 6.
Please rate the priority for publishing this article (1 is the highest priority, 10 is the lowest priority): 5.	Length of article is: Adequate. Number of tables is: Adequate. Number of figures is: Adequate.
Length of article is: Adequate. Number of tables is: Adequate. Number of figures is: Adequate.	Please state any conflict(s) of interest that you have in relation to the review of this paper (state "none" if this is not applicable): None
Please state any conflict(s) of interest that you have in relation to the review of this paper (state "none" if this is not applicable): None	Rating: Interest: 2. Good. Quality: 2. Good. Originality: 2. Good. Overall: 2. Good.
Rating: Interest: 2. Good. Quality: 2. Good. Originality: 2. Good. Overall: 2. Good.	

Reviewer 2:
Anonymous
Did not authorize the publication of the peer review reports

First evaluation	Second evaluation
Recommendation: Major Revision	Recommendation: Accept

Burial or cremation? Factors associated with preferences among patients with cancer in Brazil: a cross-sectional study

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KEYWORDS (MeSH terms):
Death.
Cremation.
Burial.

AUTHORS' KEYWORDS:
Preferences.
Burial and factors related.
End of life.
Oncology.

ABSTRACT

BACKGROUND: People living with life-limiting illnesses and their family caregivers consistently emphasize the importance of preparing for imminent death, with planned funerals being a common aspect of this preparation. Few studies have described the funeral rituals or post-mortem preferences of patients with cancer.

OBJECTIVE: To evaluate the percentage of patients with cancer who wish to be cremated and to identify the factors associated with this preference.

DESIGN AND SETTING: Cross-sectional study conducted at Barretos Cancer Hospital.

METHODS: A total of 220 patients with cancer completed a Sociodemographic and Clinical Questionnaire, the Duke University Religiosity Index, and burial or cremation preferences. Binary Logistic Regression was performed to identify independent variables associated with cremation.

RESULTS: Of the 220 patients, 25.0% preferred cremation and 71.4% preferred burial. Talks about death with family or close friends in their daily life (odds ratio, OR = 2.89; P = 0.021), patients that answered "other" (unsure, tends not be true and not true) for religious beliefs are what really lie behind my whole approach to life (OR = 20.34; P = 0.005), and education 9 to 11 years (OR = 3.15; P = 0.019) or ≥ 12 years (OR = 3.18; P = 0.024) were associated with cremation preference.

CONCLUSION: Most patients with Cancer in Brazil prefer burial after death. Discussions about death, religious beliefs and involvement, and educational level seem to influence the preference for cremation. A deeper understanding of ritual funeral preferences and their associated factors may guide policies, services, and health teams in promoting the quality of dying and death.

INTRODUCTION

People living with life-limiting illnesses and their family caregivers emphasize the importance of preparing for imminent death, and planning funeral rituals is a common aspect of this preparation. The discussion of funeral ritual preferences may be challenging in many cultures.[1,2] Funeral rituals are technical actions of dead body preparation, display, and burial or cremation, considering symbolic acts that change according to the culture of the people.[3] Cremation aims to reduce a body to ashes by burning it and these ashes are given to the family.[4-6]

Few studies have described the funeral ritual preferences of patients with cancer, including those in Brazil, and have not explored the factors that may be related to these preferences.[7] Identifying them can provide guidance to those providing care (either professionally or voluntarily) to improve the end-of-life process of patients. Such fulfilment of patients´ wishes can improve the quality of death of the patients and the grieving process of loved ones.

OBJECTIVE

This study aims to evaluate the percentage of patients with cancer who wish to undergo cremation and identify the factors associated with this preference.

METHODS

Study design and place

This cross-sectional descriptive study was performed from August/2021 to March/2022 at Barretos Cancer Hospital (Sao Paulo, Brazil).

Participants

Patients from the oncology outpatient clinic and chemotherapy infusion center were invited to participate. Eligibility criteria included ≥18-year-old, cancer diagnosis, undergoing individual or concomitant treatment of chemotherapy, surgery, radiotherapy or hormone therapy, cognitive capacity and coherent communication, no acute psychiatric illness, and no recent medical communication of bad news.

Data collection

This study was approved by the Research Ethics Committee of the Barretos Cancer Hospital (No. 4.312.986; date: October 1, 2020). Interviews were conducted *face-to-face* after the participants answered the sociodemographic and clinical information questionnaires. Participants were also invited to fill in the Duke Religion Index, a questionnaire that measures religious beliefs and involvement.[8] The patients' attitudes and beliefs regarding cremation and burial were also determined by the research team, developing a survey based on the literature to obtain information regarding funeral ritual preferences in the cultural context.[9-11] The clarity and pertinence of each item of the Burial and Cremation Preference Survey was evaluated by a committee of experts.[12] Data were recorded using Research Electronic Data Capture (REDCap).[13]

Statistic

The sample size was calculated based on prevalence estimates. For this purpose, it was considered that the cremation rates of Colombia and Argentina in 2017 ranged from 2.1% to 25.4%[14] and, in Brazil, it was approximately 10%, with a precision of 4% and a 95% confidence interval.[15] The minimum sample size was 216 participants.

Descriptive statistics were used to summarize patient characteristics. Chi-square or Fisher's exact test, t-test, or Mann-Whitney U test were used to examine the difference between patient characteristics and ritual funeral preference (cremation: yes versus no). To identify independent predictors associated with funeral ritual preference, variables ($P < 0.20$ were included in the initial Binary Logistic Regression Model. For the final model adjustment, the variables were selected using the backward method, and the model comprised variables with $P < 0.05$. Multicollinearity was verified by estimating variance inflation factors (VIF).

Data were analyzed by IBM-SPSS v.27.0 (IBM Corp., Armonk, New York, United States). Statistical significance was set at $P < 0.05$, considered significant.

RESULTS

A total of 220 (48.5%) of the 454 eligible patients were included in the study. A total of 234 patients were excluded because of recent medical communication of bad news (n = 133; 57.0%), refusal (n = 82; 35.0%), or the absence of full cognitive capacity (n = 19; 8.0%). The main reasons expressed by patients who refused to participate in the study were feeling uncomfortable talking about death (n = 48; 58.5%), absence of interest in participating in the study (n = 30; 36.6%), and the presence of uncontrolled symptoms at the time of the approach (n = 4;4.9%).

The mean age was 51.8 years; 167 (75.9%) patients were female; 114 (51.8%) were white, 146 (66.4%) were married/with partner, and 85 (38.7%) had a low educational level. The most common types of cancer were breast (n = 113; 51.4%) and gastrointestinal (n = 62; 28.2%). Overall, funeral ritual preferences were burial (n = 157; 71.4%), cremation (n = 55; 25.0%), and indifference (n = 8; 3.6%).

Univariate analysis identified the variables associated with ritual funeral preferences. These variables included the patient's age, ethnicity, education, human development index of the city of origin, self-perception of health, talking about death with one's family or close friends, talking about one's wishes regarding one's own funeral, and considering cremation as an easier alternative if there were difficulties in transporting the body and paying for this process (**Table 1**).

Table 2 reports the results of the Binary logistic regression analysis. Education 9 to 11 years (odds ratio, OR = 3.15; P = 0.019) or ≥ 12 years (OR = 3.18; P = 0.024), talks about death with family or close friends in their daily life (OR = 2.89; P = 0.021), and patients that answered "other" (unsure, tends not be true and not true) for religious beliefs are what really lie behind my whole approach to life (OR = 20.34; P = 0.005) were potential predictors associated with higher chances of cremation preference.

DISCUSSION

In our study, the vast majority (71.4%) of patients preferred to be buried. Cremation was preferred by 25.0% of the patients. The findings may provide important information for the evaluation of profiles of patients who prefer cremation, and how health care professionals may help these patients realize their desires.

Religious teachings, traditions, beliefs, and education level may have an important influence on a patient's decision making about end-of-life care.[2] The growing practice of cremation has provided many countries with a spread of locations offering this service, and made it cheaper as compared to burial.[16,17] In many Asian cities with scarce physical space, funeral planning agencies have sought to reduce space for the dead by encouraging conversion from burial to cremation over several decades.[17] In 2017, the cremation rate in Canada was 70.5%.[18] Cremation rates are low in countries where Catholicism predominates.[19] In the United

Table 1. Association between demographic and clinical characteristics and religious involvement with ritual funeral preference of cancer patients

Variables		Cremation		P value
		No n (%)	Yes n (%)	
Demographic characteristics				
Age Years, average (SD)		52.2 (13.0)	51.3 (12.4)	**0.003****
Gender	Male	37 (23.6)	14 (25.5)	0.855
	Female	120 (76.4)	41 (74.5)	
Ethnicity	White	73 (46.5)	39 (70.9)	**0.014***
	Black	17 (10.8)	4 (7.3)	
	Brown	64 (40.8)	11 (20.0)	
	Yellow	3 (1.9)	1 (1.8)	
Education	0 to 8 years	72 (45.9)	12 (21.8)	**0.006**
	9 to 11 years	47 (29.9)	21 (38.2)	
	≥ 12 years	38 (24.2)	22 (40.0)	
Family income	No income	3 (1.9)	4 (7.3)	**0.002***
	1 to 3 minimum wages	117 (74.5)	28 (50.9)	
	4 to 6 minimum wages	28 (17.8)	13 (23.6)	
	≥ 7 minimum wages	9 (5.7)	10 (18.2)	
HDI of city of origin	Low	10 (6.4)	1 (1.8)	**0.004***
	Medium	32 (20.4)	7 (12.7)	
	High	108 (68.8)	36 (65.5)	
	Very high	7 (4.5)	11 (20.0)	
Clinical characteristics				
Type of cancer	Breast	76 (48.4)	32 (58.2)	0.768*
	Gastrointestinal	46 (29.3)	14 (25.5)	
	Others	35 (22.3)	9 (16.4)	
Health self-perception	Very good	17 (10.8)	13 (23.6)	**0.081***
	Good	79 (50.3)	28 (50.9)	
	Regular	56 (35.7)	13 (23.6)	
	Poor	5 (3.2)	1 (1.8)	
Duke Religion Index				
How often do you attend church or other religious Meetings	More than once/week	99 (63.1)	32 (58.2)	0.864*
	Other frequency[1]	58 (36.9)	23 (41.8)	
How often do you spend time in private religious activities, such as prayer, meditation or bible study	More than once a day	132 (84.1)	47 (85.5)	0.936
	Other frequency[2]	25 (15.9)	8 (14.5)	
In my life, I experience the presence of the God or Holy Spirit	Totally true for me/true	157 (100.0)	53 (96.4)	**0.133***
	Other (in general not true)[3]	0 (0.0)	2 (3.6)	
My religious beliefs are what really lie behind my whole approach to life	Totally true for me/true	154 (98.1)	51 (92.7)	**0.152**
	Other (in general not true)[3]	3 (1.9)	4 (7.3)	
I try hard to carry my religion over into all other dealings in life	Totally true for me/true	149 (94.9)	51 (92.7)	0.692*
	Other (in general not true)[3]	8 (5.1)	4 (7.3)	
Burial and Cremation Preference Questionnaire				
Talks about death with your family or close friends	No	64 (40.8)	10 (18.2)	**0.003**
	Yes	93 (59.2)	45 (81.2)	

Continue...

Table 1. Continuation.

Variables		Cremation		P value
		No n (%)	Yes n (%)	
Talks about your wishes regarding own funeral	No	98 (62.4)	20 (36.4)	**0.001**
	Yes	59 (37.6)	35 (63.6)	
If you know what cremation is:				
Manifested the wish to be cremated by a loved one	No	2 (25.0)	15 (27.8)	1.000*
	Yes	6 (75.0)	39 (72.2)	
Greater difficulty for desire to be cremated not being fulfilled				
Cremation cost is very expensive	No	2 (25.0)	19 (35.2)	0.705*
	Yes	6 (75.0)	35 (64.8)	
My family not accept cremation	No	7 (87.5)	46 (85.2)	1.000*
	Yes	1 (12.5)	8 (14.8)	
My religion not approve of cremation	No	8 (100.0)	50 (92.6)	1.000*
	Yes	0 (0.0)	4 (7.4)	
There is no crematorium in the city/near homes	No	3 (37.5)	29 (53.7)	0.467*
	Yes	5 (62. 5)	25 (46.3)	
It's not common for people in my family to be cremated	No	3 (37.5)	30 (55.6)	0.456*
	Yes	5 (62.5)	24 (44.4)	
Considers cremation as an easier alternative if there were difficulties in transporting the body and paying for this process	No	62 (39.5)	6 (10.9)	**<0.001**
	Yes	95 (60.5)	49 (89.1)	

SD = standard deviation; HDI = human development index. Pearson's Chi-square test; *Fisher Exact test; **Man-Whitney test. P value 0.05. The option "yes" refers to patients who preferred to be cremated (n = 55) and the option "no" are those who preferred to be burial. Other[1]: Two to three times/month, a few times a year, once a year or less and never; Other[2]: two or more times/week, once a week, a few times/month and rarely or never; Other[3]: unsure, tends not be true and not true.

States, meanwhile, the proportion of deceased persons who were cremated increased from 3.6% in 1960 to 48.6% in 2015, with a projected 71% by 2030.[20]

In Brazil, as the practice of cremation is not widespread, the funeral process and the location where cremation takes place still make choosing this method less feasible. This could be identified in our study, in which many participants did not choose cremation, justifying that the cost is too expensive or that the place that offers cremation services is located in cities far away from where they live. On the other hand, the alternative of cremation as a way to minimize situations in which there were difficulties and costs for the transfer of the body over long distances was an option mentioned by a good part of the patients.

Since talking about death or preparing for the moment of death is not in habit,[21] it may hinder communication about terminality and opportunity for the patient to express their wishes about the funeral ceremony. In this study, not discussing the subject was motivated by the fact that the participants' families did not have a culture of this dialogue.

This study had some limitations. First, it was cross-sectional, and it was, therefore, impossible to determine cause-and-effect relationships. Second, it was conducted at a single reference center of oncology in Brazil, which provides care to patients in different regions of the country. Third, most participants were very religious; that is, it was not possible to identify a sample of nonreligious patients for comparison. Other studies have found that patients with advanced cancer express a high frequency of religiosity.[22] There was an important number of patients not agreeing to participate in the research, which may be a sampling bias. It is possible that these patients experienced greater stigma about death and preferences for more traditional funeral methods in Brazil.

CONCLUSION

Most Brazilian patients with cancer prefer burial after death. Discussions about death, religious beliefs and involvement, and educational level seem to influence the preference for cremation. A deeper understanding of ritual funeral preferences and their associated factors may guide policies, services, and health teams in promoting the quality of dying and death. Future studies should be conducted to evaluate funeral ritual preferences in countries with cultures similar to Brazil.

Table 2. Binary logistic regression analysis of the potential predictors associated with funeral ritual preference (cremation) in patients with cancer

Variable	Cremation (yes)			
	n (events)	Category	OR (IC 95%)	P value
Demographic characteristic				
Education				
0 to 8 years	84 (12)	1	-	-
9 to 11 years	68 (21)		3.15 (1.21–8.24)	0.019
≥ 12 years	60 (22)		3.18 (1.16–8.67)	0.024
HDI city of origin				
Very high	18 (11)	1	-	-
High	144 (36)		0.18 (0.05–0.63)	0.007
Medium	39 (7)		0.15 (0.03–0.67)	0.014
Low	11 (1)		0.08 (0.00–1.00)	0.051
Clinical characteristics				
Health self-perception				
Very good	30 (13)	1	-	-
Good	107 (28)		0.26 (0.09–0.75)	0.013
Regular	69 (13)		0.18 (0.05–0.59)	0.005
Poor	6 (1)		0.18 (0.01–2.61)	0.209
Duke Religion Index				
My religious beliefs are what really lie behind my whole				
Approach to life				
Totally true for me/true	205 (51)	1	-	-
Other (in general not true) [1]	7 (4)		20.34 (2.44–169.38)	0.005
Burial and Cremation Preference Questionnaire				
Talks about death with your family or close friends				
No	74 (10)	1	-	-
Yes	138 (45)		2.89 (1.17–7.13)	0.021

Binary Logistic Regression Model; P value < 0.05 Wald test. Other[1]: unsure, tends not be true and not true.
OR = odds ratio; CI = confidence interval.

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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.

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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

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LANÇAMENTO

Essência Brasileira

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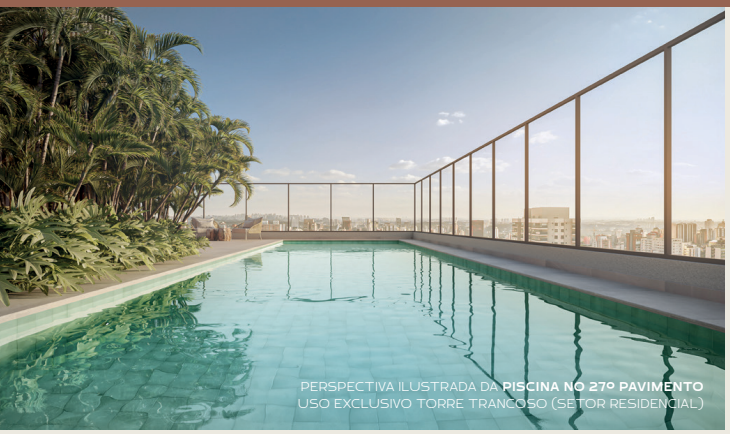

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Módulo 05 — Características das plataformas de telemedicina

Módulo 06 — Certificação digital e prescrição eletrônica

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Matricule-se já!

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