ISSN (ON-LINE): 1806-3756

JBP

Jornal Brasileiro de **Pneumologia**

PUBLICAÇÃO OFICIAL DA SOCIEDADE BRASILEIRA DE PNEUMOLOGIA E TISIOLOGIA

Volume 51, Number 2
March | April
2025

Volume 51, Number 2 March | April 2025

HIGHLIGHT

Brazilian Guidelines for the Pharmacological Treatment of Pulmonary Embolism – SBPT, GRADE-based

Depression and anxiety in adolescents with cystic fibrosis in Brazil: prevalence, stability over time, and relationship with treatment adherence

Level of agreement between two asthma control questionnaires in children and adolescents

ISSN (ON-LINE): 1806-3756

JBP Jornal Brasileiro de Pneumologia

Continuous and Bimonthly Publication, J Bras Pneumol. v. 51, n. 2 March/April 2025

Associação Brasileira de Editores Científicos

ABEC

Publicação Indexada em:
Latindex, LILACS, Scielo Brazil, Scopus, Index Copernicus, ISI Web of Knowledge, MEDLINE e PubMed Central (PMC)

Disponível eletronicamente nas versões português e inglês:
www.jornaldepneumologia.com.br e www.scielo.br/jbpneu

ISSN (ON-LINE): 1806-3756

Jornal Brasileiro de Pneumologia

Expediente

BRAZILIAN THORACIC SOCIETY

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The Brazilian Journal of Pulmonology (ISSN 1806-3756) is published once every two months by the Brazilian Thoracic Society (BTS). The statements and opinions contained in the editorials and articles in this Journal are solely those of the authors thereof and not of the Journal's Editor-in-Chief, peer reviewers, the BTS, its officers, regents, members, or employees. Permission is granted to reproduce any figure, table, or other material published in the Journal provided that the source for any of these is credited.

ADMINISTRATIVE SECRETARIAT OF THE BRAZILIAN JOURNAL OF PULMONOLOGY
Address: SCS Quadra 01, Bloco K, Asa Sul, salas 203/204. Edifício Denasa, CEP 70398-900, Brasília, DF, Brazil. Tel. +55 61 3245-1030/+55 08000 616218.
Editorial Manager: Luana Maria Bernardes Campos.
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Distribution: Free to members of the BTS and libraries

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ISSN (ON-LINE): 1806-3756

Jornal Brasileiro de Pneumologia

Continuous and Bimonthly Publication, J Bras Pneumol. v. 51, n. 2 March/April 2025

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Jornal Brasileiro de Pneumologia

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https://dx.doi.org/10.36416/1806-3756/e20250086

COPD and bronchiectasis; more than mere enemies

Grace Oscullo[1,2], Amina Bekki[1,2], Miguel Ángel Martinez-García[1,2]

COPD, asthma, and bronchiectasis are currently the three most common chronic inflammatory diseases of the airways.[1-3] However, it has not always been this way. COPD and asthma have been known for decades, but bronchiectasis began to be clearly visible in the 1980s when Naidich et al.[4] defined it based on CT images and later on its high-resolution forms. Until then, no one suspected that there could be any relationship between bronchiectasis, COPD, and asthma. The first paper that found a relationship between bronchiectasis and COPD dates back to 2003, when a group in London observed that 50% of patients with severe COPD presented with radiological bronchiectasis, longer exacerbations, and greater bronchial inflammation, as well as a greater quantity of bronchial pathogens.[5] We are therefore faced with a story that began about 20 years ago. This development attracted a lot of attention from the scientific community, since the first questions that appeared to require an answer were, obviously, as follows. Is "this" bronchiectasis caused by COPD itself or by other etiologies? And, most importantly, does the presence of bronchiectasis alter the prognosis and treatment of patients with COPD?

A search in PubMed for studies that have addressed this issue about the relationship between bronchiectasis and COPD shows that the research on this relationship has skyrocketed significantly in the past 8 years. All of this has led, nowadays, to the main international regulations on COPD[6,7] and bronchiectasis[8,9] considering this combination as a special phenotype, given the high prevalence of bronchiectasis in COPD and the negative prognosis it produces. This conclusion is based on dozens of studies and two meta-analyses,[10,11] which show that the prevalence of bronchiectasis in COPD is between 6% and 57% and that it increases with greater severity of COPD in terms of airflow obstruction, just as the presence of pathogenic microorganisms, the clearest cause of the onset of bronchiectasis, is also greater in severe forms of COPD.

Of all these studies, we might highlight four. The first, published in 2013 and one of the oldest, a multicenter study, was the first to demonstrate that bronchiectasis not only caused greater severity of COPD, but also doubled the probability of death by 2.5, after adjustments.[12]

Two subsequent meta-analyses published in 2015 and 2016, respectively,[10,11] delved deeper into these conclusions. Ni et al.[10] observed, in a group of 881 patients with COPD, that the mean prevalence of bronchiectasis was 54% (95% CI: 25-69%), similarly to previous studies; this was higher in those with greater severity of COPD, especially in men with a longer history of smoking and a greater quantity of and purulence in sputum, greater purulence in expectoration, worse lung function, greater systemic inflammation, and greater chronic infection by pathogenic microorganisms, especially *Pseudomonas aeruginosa*. For their part, Du et al.,[11] in addition to confirming these results, went further and confirmed the previously observed results of the doubling of the adjusted mortality in these patients with COPD. Therefore, the high prevalence of bronchiectasis in COPD, the impact on the prognosis, and the different treatments that bronchiectasis require for these patients—it is necessary to remember that the treatment of bronchiectasis, unlike that of COPD, is based on antibiotics, and there is a relative contraindication of inhaled corticosteroids—meant that this type of patient could be identified as having the COPD-bronchiectasis phenotype, as it appears in the guidelines for both diseases.[8,13] Moreover, this phenotype was supported by a particular endotype, since these patients presented with a greater amount of mucins, greater neutrophilic inflammation, and gram-negative infection in the airways.[14,15]

However, the last question remained unresolved. Is COPD *per se* the cause of bronchiectasis? Or, in other words, is bronchiectasis a normal part of the natural history of COPD? Although the general recommendation is that the appearance of bronchiectasis in patients with COPD should not always be sought for a cause other than COPD, it was observed, in a well-designed study,[16] that 19.5% of patients with COPD without bronchiectasis had radiological bronchiectasis and compatible symptoms after 8.5 years of follow-up, and "this" bronchiectasis could not be attributed to other etiologies (Figure 1). For the first time, a causal relationship was established between the two diseases.[16]

Finally, with regard to treatment, the guidelines[8,13] recommend that both diseases should be treated, but there is a double dilemma that has yet to be resolved. On the one hand, treatment with inhaled corticosteroids in patients with COPD and bronchiectasis can increase the risk of pneumonia; so, if they have to be used, minimal doses are recommended or should be replaced with macrolides when possible. On the other hand, there is a long-term treatment with inhaled antibiotics for COPD patients with chronic bronchial infection without bronchiectasis to prevent the onset of the latter, although this remains under study.

We can also think the other way around. What percentage of patients with a major diagnosis of bronchiectasis has COPD? According to an analysis of several bronchiectasis registries around the world, this

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ISSN 1806-3756

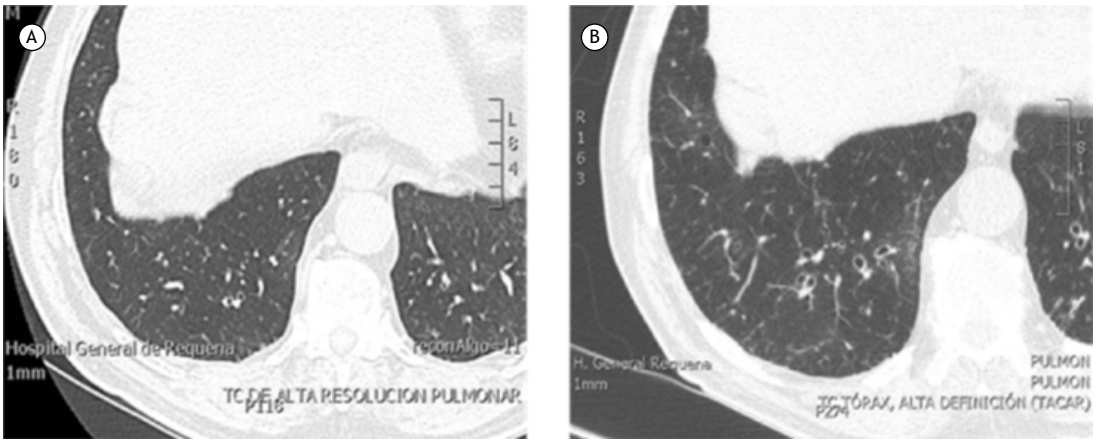

Figure 1. CT scans of a patient without bronchiectasis (A) and showing the development of bronchiectasis seven years later (B). With permission of the Journal of Clinical Infectious Disease.

is between 3.4% and 20%, with little information on how COPD can affect the prognosis of bronchiectasis, although a study by a Spanish bronchiectasis group shows that the diagnosis of COPD in these patients has increased significantly, from 7% to 12% overtime.[9]

Therefore, it is currently recommended that in COPD patients with multiple exacerbations, repeated isolation of pathogenic microorganisms in respiratory samples, especially *P. aeruginosa*, a too rapid decline in lung function, poor clinical evolution, or severe COPD, a CT scan should be performed in search of bronchiectasis[7,8,13] regardless of whether this is due to COPD itself or not; both the prognosis and the evolution/treatment of the patients might change, and bronchiectasis can therefore become another treatable trait in these patients.

AUTHOR CONTRIBUTIONS

The authors equally contributed to this editorial.

CONFLICTS OF INTEREST

None declared.

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Comprehensive care in cystic fibrosis: mental health assessments

Paulo Camargos[1,2]

People with chronic conditions, such as cystic fibrosis (CF), often experience mental health challenges. Effectively managing these complex diseases requires a comprehensive approach and a dedicated multidisciplinary care team, considering the correlation between distress levels and the severity of the condition.

CF is a chronic and potentially life-threatening condition that affects thousands of people in Brazil. Alongside its "organic" features, it is connected to various biopsychosocial issues that increase the risk of anxiety and depression for patients, as well as for their families and caregivers. Consequently, effective management of CF relies on a multidisciplinary team to promote overall wellness and address the challenges of managing this complex chronic condition. To support people with CF (pwCF) and their families, the team must be aware of, understand, and explore the multiple manifestations of the disease, including various clinical targets, to foster the best possible well-being for patients and their loved ones.

According to the Brazilian CF Patient Registry, the median survival age was 43 years between 1999 and 2017.[1,2] In comparison, recent estimates indicate that North American CF patients born between 2019 and 2023 might have a median survival age of approximately 60 years.[3] This suggests that as life expectancy for CF patients increases, caregivers and parents still face significant challenges. Effectively managing CF throughout life will improve the mental health of patients as their conditions evolve.

PwCF experience anxiety and depression based on validated assessments. These findings highlight the clinical relevance of the study by Rozov et al.[4] published in this issue of the *Jornal Brasileiro de Pneumologia*: as survival rate increases, it becomes essential to incorporate mental health evaluations routinely—such as those proposed by the authors—into care protocols that have yet to be implemented in accordance with the recommendations of the Brazilian CF guidelines.[1] Through the *Patient Health Questionnaire and Generalized Anxiety Scale,* the authors[4] noted that their results demonstrate "*the importance of annual screening and suggest that tools for assessing depression and anxiety can be enormously useful for early detection, intervention, as well as for reducing stigma.*"

As we move into the era of CF transmembrane conductance regulator (CFTR) modulators, the significance of this care component increases. Integrating CFTR modulator drugs into clinical practice has yielded remarkable therapeutic results. These modulators have improved numerous patient outcomes by providing substantial benefits to those who qualify and can utilize them, decelerating disease progression and improving quality of life. Despite these positive outcomes, several side effects have been noted, such as a rise in psychiatric reactions following the start of using CFTR modulators in combination, transforming the psychosocial landscape of pwCF and including new challenges and psychosocial needs.

Many patients and their parents have reported experiencing negative neuropsychiatric side effects after starting combination therapy with CFTR modulators, adversely affecting their mental and psychosocial well-being. Commonly reported concerns include anxiety, depression, mood swings, and sleep disturbances, 60% of which classified as adverse events. Nonetheless, these effects remain poorly understood.[5] Therefore, it is essential to include mental health assessments in routine care, regardless of the use of this medication class, and to integrate these assessments into the care protocol for patients undergoing these treatments. Thus, addressing psychiatric effects through proper evaluation, counseling, and ongoing monitoring are crucial. In other words, the findings establish assumptions for identifying future research priorities, guiding policy efforts, and enhancing communication in areas that promote the well-being of pwCF.

Caregivers and family members often devote countless hours to their caregiving roles and frequently report experiencing poor health. Consequently, enhancing dyadic coping could be beneficial. Interventions aimed at caregivers of pwCF could also improve home care management, bolster caregiver health, and foster better dyadic coping between caregivers and patients, ultimately alleviating the burden on caregivers. Therefore, developing a similar strategy to address the mental health needs of these individuals would be advantageous.

Additional regional or national studies utilizing the same tools reported and assessed by Rosov et al.,[4] especially those with a sufficiently large and representative random sample, would deepen our understanding of the impact of CFTR modulators on the nervous system and CF itself by identifying opportunities and strategies to optimize psychosocial care.

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J Bras Pneumol. 2025;51(2):e20250145
https://dx.doi.org/10.36416/1806-3756/e20250145

The pitfalls of evaluating asthma control in children and adolescents

Regina Maria de Carvalho-Pinto[1], Magali Santos Lumertz[2,3], Débora Carla Chong-Silva[4]

Asthma is one of the most common chronic diseases in childhood and adolescence. The Global Asthma Report indicates a global asthma prevalence of 9.1% among children, 11.0% among adolescents, and 6.6% among adults.[1,2] Furthermore, according to the GINA , these numbers appear to be increasing in many countries, especially among children.[3] Childhood asthma is also a reflection of social inequality, as the greatest burden is often associated with low-income families, even among school-aged children.[4] In Brazil, a study based on data from the Global Burden of Disease estimated the prevalence of asthma in the pediatric population to be 12.1%.[5] Brazilian studies have shown a progressive decline in asthma-related hospitalization rates.[6,7] These improvements are at least partially attributed to a program for the distribution of asthma medications for free, which has been in place for approximately fifteen years, via the Brazilian *Sistema Único de Saúde* (SUS, Unified Health Care System).[6-8] A study published in 2020 described trends of hospital admissions due to asthma between 2008 and 2015 and evaluated their relationship with trends of inhaled corticosteroids (ICS) provision by the government in Brazil. Although the decrease in hospital admissions per 100,000 population was the greatest in those with an age range of 15-39 years (from 59.9 to 32.3), a notable reduction was also observed among children and adolescents aged 5-14 years (from 148.3 to 110.9). These results reinforce that the provision of ICS free of charge by the Brazilian government was associated with a decrease in asthma-related admissions at both municipal and national levels during that period. The reduction in hospital admissions was also associated with the increase in the number of physicians and in the number of subjects who received ICS. Although asthma control using specific tools—GINA, Asthma Control Test (ACT) or Childhood ACT (cACT)—was not directly assessed, it can be inferred that the reduction in hospitalizations was due to improved care and asthma control.[9]

Assessing control is one of the main pillars of asthma treatment. It is widely recognized that effective asthma control leads to better outcomes—not only for the individual and his/her family but also for social impact. In addition to access to appropriate follow-up and treatment, one significant barrier to asthma control is the persistence of misconceptions regarding the diagnosis and management of the disease, especially in the pediatric population. In clinical practice, asthma treatment is guided by severity and adjusted on the basis of the level of control.[3] According to a study published in 2016, caregivers of children and adolescents with asthma often show less concern about the use of systemic corticosteroids (which are typically used in exacerbations) than about aerosolized medications, particularly pressurized inhalers.[10] This perception contributes to poor adherence to treatment and, consequently, lack of disease control.[10,11] Moreover, it is well documented that both patients/caregivers and health care professionals tend to overestimate asthma control.[12,13] So, determining asthma control is still a challenge on a daily basis of pediatric practice.

The Global Asthma Network Phase I, a cross-sectional study, evaluated asthma management and control in children, adolescents, and adults across 25 countries. The sample included 101,777 children and 157,784 adolescents. Among these, 6,445 (6.3%) children and 12,532 (7.9%) adolescents had physician-diagnosed asthma. For children and adolescents, asthma was assessed using written questionnaires distributed in schools. Adolescents (13-14 years old) completed self-administered questionnaires, while children (6-7 years old) questionnaires were completed by their parents. Asthma control was defined by two questions: unscheduled visits to a doctor or to the emergency department due to asthma, and hospital admissions due to asthma. Three categories were used to define asthma control: poorly controlled, partially controlled, and well-controlled asthma. Among children and adolescents, well-controlled asthma, according to the study definition, was achieved in only 44.1% of children and 55.4% of adolescents.[14]

A real-world cross-sectional study evaluating children and adolescents showed that the asthma control questionnaire (cACT/ACT) revealed that about 30% of patients perceived uncontrolled asthma. On the other hand, GINA asthma control level was considerably lower (12.6%), highlighting the difference between scores used in the assessment of asthma control.[15] One could argue that these disparities are partly due to the self-administered nature of the cACT/ACT questionnaires, which may not always be well understood by patients.

Therefore, it is crucial to use validated tools designed to assess asthma control in the pediatric population, such as the GINA questionnaire and specific instruments such as the cACT for younger children and the ACT for adolescents ≥ 12 years of age. This was the objective of the study by Amorim et al. published in this issue

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◄ Voltar ao sumário

of the *Jornal Brasileiro de Pneumologia*: to compare two validated instruments capable of measuring pediatric asthma control and to verify the agreement between them, as well as the agreement with clinical, laboratory, and spirometric variables.[16]

As discussed, asthma control is the central pillar in preventing exacerbations, hospitalizations, and long-term loss of lung function.[11] The lack of comparison between the GINA and the cACT/ACT questionnaires, both widely used in outpatient settings and clinical studies, still represents a gap in the national literature.

The study stands out for demonstrating, in a representative sample of patients treated at the SUS, that the GINA questionnaire is more sensitive in identifying pediatric patients with uncontrolled asthma than are the cACT/ACT. Despite showing moderate agreement between the instruments (Kappa = 0.505), the study highlights that only GINA was able to detect significant differences in clinical (smoke exposure, disease severity, and IC dosage) and spirometric variables (FEV_1, FVC, $FEF_{25-75\%}$) between groups classified as having controlled and uncontrolled asthma. This finding adds strength to the results and suggests that the cutoff value used by the cACT/ACT leads to an overestimation of asthma control—a fact already noted in previous international studies,[15] but until now, little explored in the Brazilian pediatric population. Moreover, the article explores relevant contextual factors, such as the choice of inhaler device (aerosol versus dry powder), treatment adherence, and the reality of the SUS, which add not only robustness to the analysis but also practical applicability that goes beyond a simple comparison between scales.

From a practical standpoint, the findings have a direct impact on clinical management by pediatric pulmonologists, allergists, and primary care physicians. The demonstration that GINA has greater discriminatory power suggests that, in various contexts, this instrument may be more effective in guiding therapeutic decisions, optimizing drug prescriptions, and adjusting monitoring and follow-up strategies. Additionally, the association between lack of control and factors such as passive smoking exposure reinforces the need for multidisciplinary and educational approaches in the care of children with asthma.

The information provided by the study by Amorim et al.,[16] which highlights the superiority of GINA as a screening tool for uncontrolled asthma in children, serves as a guide for public and private outpatient services and provides a basis for the construction of clearer and more efficient clinical flowcharts.

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Why we should rethink military metaphors in cancer

Gustavo Faibischew Prado[1,2], Thais Azzi Gonçalves[3]

There is something both seductive and treacherous about military metaphors when we talk about diseases. From the moment of diagnosis, the patient is often enlisted—without choice—into a personal war. We tell them they must be strong, that they need to fight, that giving up is not an option. If the disease progresses, "the enemy was relentless"; if they pass away, "they lost the battle." These expressions are so deeply embedded in our medical, journalistic, and everyday language that we rarely stop to question them. But we should.

"*It took me years to understand why it bothered me to be called a 'warrior,' especially when, in moments of vulnerability, comments reinforced this 'battle.' This metaphor imposes an unnecessary burden and fuels guilt that ignores the complexity of the illness experience.*"

War is a setting of cruelty and sacrifice; and our perceptions of these harrowing events, especially those from the early 20th century to today, show us unequivocally that there is nothing romantic about them.

These metaphors rely on two premises: there is an enemy (the disease) and a clear objective—victory. However, diseases are not adversaries that can be vanquished through willpower or a positive attitude, and patients are not soldiers who fail when treatment does not yield the desired effect.

"*During treatment, I wasn't fighting against something; I was simply living one day at a time. Talking about a fight gives the impression that sheer willpower is enough to win, but disease doesn't work that way.*"

Cancer treatment is frequently described as a battle in news reports and social media. For example: "On December 5, 2015 (...) Marília Pêra lost her battle against lung cancer, which she had been fighting for two years."[1]

This illustrates how the disease is portrayed as an invading army. However, unlike this well-intentioned depiction, cancer is a complex phenomenon that arises from our own bodies, the result of biological processes that are sometimes beyond modification. Its progression is far more influenced by factors beyond our control than by the patient's emotional resilience.

THE BURDEN OF BLAME

The problem with these metaphors is not merely theoretical. In my daily interactions with patients, I see how they impose an immense emotional burden. They reduce and hijack our discourse, which should be compassionate and understanding, into a motivational speech straight out of a self-help seminar. This distances us from patients, deafens our listening, and invalidates their suffering. Worse still, it shifts the unfathomable weight of illness onto the shoulders of this so-called "soldier." If treatment is not well-tolerated, if it fails to halt disease progression, if symptoms become unbearable—what does that imply? That the patient was not strong enough? That they lacked courage? That they were not a true warrior? This narrative subtly suggests that the outcome of the disease is proportional to individual effort, leading patients to feel like failures in a situation that was never under their control.

This is particularly cruel for cancer patients. For many families, seeing a loved one as a warrior may be a way to make sense of immeasurable suffering, to name the unnamable, to impose order on chaos. But this very metaphor can place an unbearable weight on the patient. What if they can't take it anymore? What if they cry in pain? What if they no longer want to be "strong"? The idea that "giving up" equates to surrender creates a cycle of anguish for both patients and their loved ones.

ILLNESS IS NOT A BATTLE, AND THE PATIENT IS NOT A SOLDIER

The way we talk about health shapes how we approach it. The concept of a "war on cancer" is not just a linguistic phenomenon—it influences public policy, directs campaigns, and affects medical decision-making. Since Nixon declared his "war on cancer" in the 1970s,[2] investment in oncology research has grown significantly, and the military vocabulary has persisted. The unintended consequence is that cancer has come to be seen as something to be "eradicated," and the patient as someone who must resist at all costs.

"*When facing my second recurrence, the inevitable question arose: had I not fought hard enough? This sense of guilt, the suggestion that something more could have changed the outcome, only deepened the pain of difficult moments.*"

But romanticizing war, idealizing death, and glorifying the fallen hero are nothing new.[3] These themes are present in Homeric verses, such as Hector's death in Troy. The Greek epic tradition exalted heroic death in war as the pinnacle of existence—a sacrifice worthy of eternal honor and glory. Yet even within the *Iliad* and the *Odyssey*, this ideal was challenged. Achilles, centuries later, in the underworld, shatters this romanticized vision, declaring that he would rather be a living farmer than a king among the dead.[4] This cult of war and

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sacrifice still echoes in the military metaphors we use to describe illness. But does a patient need to be a warrior? Does illness have to be a battle? Among the pain, the fears, and the many uncertainties, perhaps what we need is not a call to arms but a more sensitive approach and a discourse that embraces rather than imposes struggle.

And what happens when we acknowledge that some diseases cannot be defeated—only managed? That living with a chronic condition is not a failure? That accepting the limits of treatment is not surrender but a legitimate form of care?

METAPHORS MATTER

This does not mean we must eliminate all metaphors—they are part of how we make sense of the world. But perhaps we can choose better ones.

If we insist on comparing illness to war, we will always seek winners and losers. Instead, we could view this challenge as a *journey*—with difficult and lighter moments, with uncertain and unexpected paths, but without a single finish line or a predetermined outcome. The experience of illness is already a difficult road; it does not need to be a battlefield. The journey of treatment should allow suffering to be expressed, validated, and acknowledged. It should enable the patient to find support in care and grant them permission not to be always positive or upbeat.

"*If we compare illness to war, cancer does not play fair. There is no guaranteed strategy, and often it is an endless battle that demands adaptation, coexistence, and management. Living with disease does not mean losing—not every day requires us to be soldiers or heroes.*"

And all of us, as participants in a care network, can take on other roles: supporters, partners, and friends.

Because yes, we fall ill; and yes, one day, we will die. But life, death, and everything beautiful—and challenging—that happens in between can (and should) be lighter.

After all, no one should die thinking they lost.

AUTHOR CONTRIBUTIONS

GFP: conception, writing and reviewing the manuscript, approval of the final version of the manuscript. TAG: conception, compilation of quotes, reviewing the manuscript, approval of the final version of the manuscript.

CONFLICTS OF INTEREST

None declared.

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Centrilobular nodules with central calcifications

Edson Marchiori[1], Bruno Hochhegger[2], Gláucia Zanetti[1]

A 67-year-old man complained of chronic cough and dyspnea on exertion. He had undergone renal transplantation for chronic renal failure many years ago. CT scans showed centrilobular nodular ground-glass opacities, predominantly in the upper lobes, some of which showed a central focus of calcification (Figure 1).

The nodules presented with a typical centrilobular distribution, sparing the pleural surfaces. The main diseases that present with this pattern are silicosis, hypersensitivity pneumonitis, some forms of bronchiolitis and metastatic pulmonary calcification (MPC). In most cases, the nodules of hypersensitivity pneumonitis and bronchiolitis have ground-glass attenuation. In hypersensitivity pneumonitis, a history of exposure to certain antigens generally aids in the diagnosis. In bronchiolitis, the nodules are often associated with the tree-in-bud pattern, which corresponds to the presence of centrilobular branching opacities, more evident in the lung periphery, resembling the budding appearance of some plants. The centrilobular nodules of this patient had unique characteristics that differentiated them from other diseases: they had ground-glass attenuation, imprecise contours, and central foci of calcification, making them practically pathognomonic of MPC.

CPM is a metabolic lung disease characterized by calcium deposition in normal lung tissue under conditions that directly or indirectly result in hypercalcemia. It most commonly arises as a long-term complication of chronic renal failure, especially seen in patients undergoing dialysis. Other causes include primary hyperparathyroidism, excessive exogenous administration of calcium and vitamin D, massive osteolysis due to metastases or multiple myeloma, orthotopic liver transplantation, and cardiac surgery, among others.[1,2]

Clinical manifestations of MPC are usually minimal; when present, symptoms are nonspecific and include dyspnea and nonproductive cough. Acute respiratory failure has been described, although it is rare. Therefore, the diagnosis is often initially suspected based on imaging findings. The relative stability of pulmonary infiltrates and their persistence despite treatment, in the presence of hypercalcemia, are important diagnostic clues. The main pattern observed on chest CT is nodular ground-glass opacities in the centrilobular airspace, with or without intervening foci of calcification. Other findings include high-attenuation consolidations (dense consolidation), calcification in vessels of the chest wall, and pleural effusion. The changes are usually bilateral.[1,2] The patient underwent lung biopsy, which showed thickening of the alveolar septa due to fibrosis, in addition to calcium deposits in their walls, confirming the diagnosis of MPC.

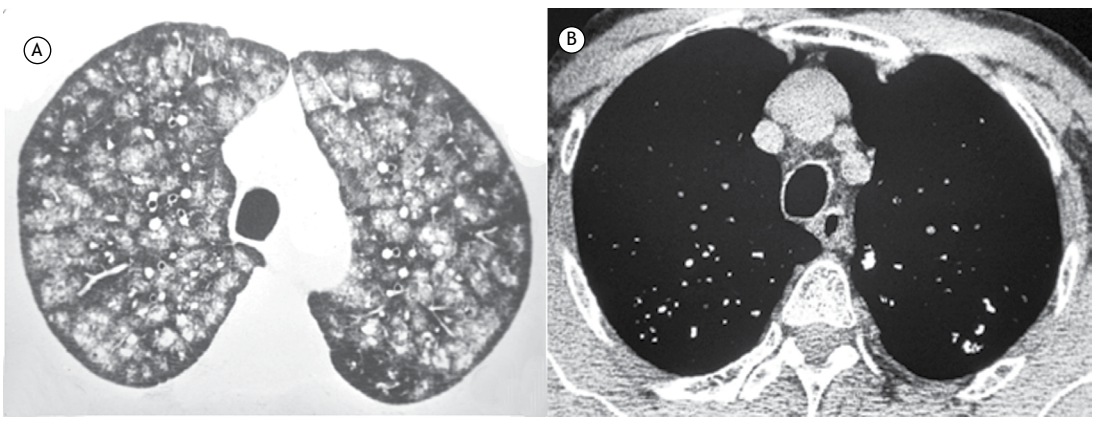

Figure 1. In A, axial CT scan of the chest with lung window setting at the level of the upper lobes shows nodular ground-glass opacities in a predominantly centrilobular distribution. In B, mediastinal window setting demonstrating small foci of calcification, corresponding to the ground-glass nodules.

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Beyond the average: why data spread matters in clinical studies

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PRACTICAL SCENARIO

A pulmonologist is conducting a quality improvement study to evaluate whether lung function, measured by FVC, differs across two outpatient asthma centers within the same health care system. Her research question is: "Do patients from Center A have better lung function than those from Center B?"

Since spirometry values are strongly influenced by patient age, she first checks whether the two groups are comparable in terms of age distribution. The mean age in Centers A and B, respectively, is 39.2 years 38.9 years. At first glance, the groups appear similar, and she assumes that age is unlikely to affect the comparison of spirometry outcomes between the centers. However, upon further examination of the age histograms for each center, she finds that the age dispersion varies markedly between the groups (Figure 1). Should she reconsider her conclusion?

LIMITATIONS OF THE MEAN AS A CENTRAL TENDENCY MEASURE

When summarizing clinical data that are continuous, we typically report a measure of central tendency—mean or median— and a measure of spread—standard deviation (SD) or interquartile range (IQR). These measures of spread are not just statistical formalities; they inform how we accurately interpret patient data that inform clinical decisions.

The mean is the average of a continuous variable (e.g., age), and is calculated by dividing the sum of all values in a dataset by the total number of observations.[1] It serves as a measure of central tendency by summarizing the distribution using a single value. However, the mean is sensitive to extreme values, which can distort its true value in study samples (accuracy) and make it misleading, especially when the distribution of the data is skewed or when outliers are present. For this reason, the mean is typically reported when data is normally distributed, where values are symmetrically spread around the mean, and outliers are less likely to impact the interpretation of results.

The median, on the other hand, is the middle value of a continuous variable in a dataset arranged in rank order. It divides the data into two halves: 50% of values fall below or equal to it, and 50% above or equal to it, placing it at the 50th percentile.[1] When the number of observations is odd, the median is the value positioned exactly in the middle of the ordered dataset. If the number of observations is even, it is calculated by averaging the two central values. Unlike the mean, the median is a more robust measure because it is less influenced by extreme values, since it depends only on central data points rather than the entire distribution of the data. As such, the median is preferred for non-normally distributed data, where skewness or outliers of the data may make the mean less representative of the "typical" observation.[1]

Choosing between the mean and the median is more than a statistical decision, because it can influence the clinical interpretation of the data. If a small number of patients have very high or very low values on a variable, the median might reflect the "typical" patient more accurately.[2]

SD: MEASURING SPREAD AROUND THE MEAN

The SD measures how much individual data points differ from the mean. It reflects the average distance of each value from the mean of the dataset.[2] When data points are tightly spread around the mean, the SD is small; when they are more widely spread, the SD increases. In the extreme case when all values are identical, the SD is zero. Because it shares the same units as the mean, the SD is straightforward to interpret.[1] In our practical scenario, the SD of age was 5.8 years for Center A and 13.0 years for Center B. This wide discrepancy suggests that while the mean ages are very similar, the two groups are not truly comparable. A broader spread in Center B may reflect greater patient diversity, requiring additional stratification in analysis.[1]

IQR: CAPTURING THE MIDDLE 50%

The IQR complements the median and is commonly used for non-normally distributed data.[2] It is calculated as the difference between the 25th and 75th percentiles, representing the range within which the central 50% of values lie. By excluding the lowest and highest quartiles, the IQR is resistant to the influence of outliers.[2] In our example, the IQR regarding age was [36.3-42.8 years] and [30.5-49.0 years] for Centers A and B, respectively. Similarly to the SD, the IQR uses the same units as the original data, which enhances its interpretability.[1]

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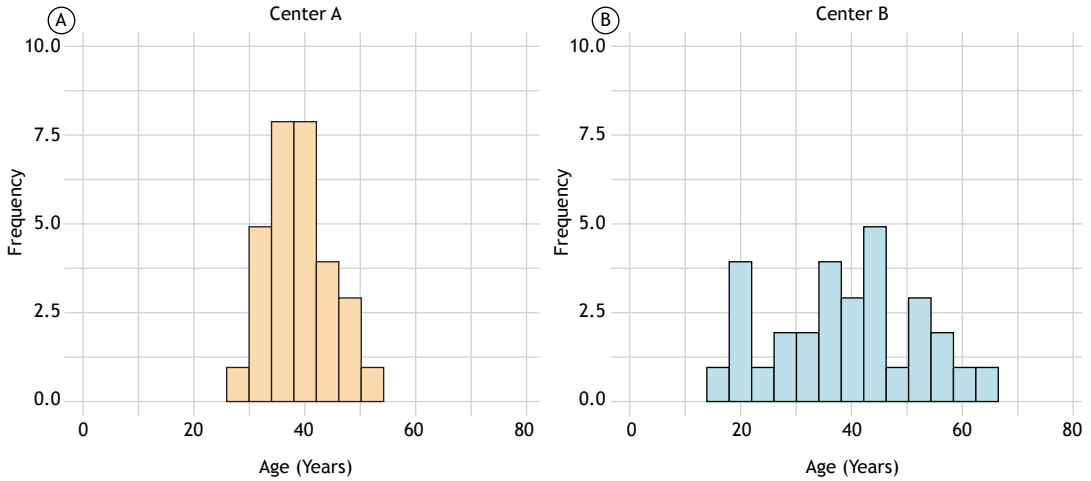

Figure 1. Age distribution of adult outpatients from respiratory consultations. In A, Center A, characterized by a narrow age dispersion. In B, Center B, characterized by a wide age dispersion. N = 30 patients per group.

In our practical scenario, differences in age dispersion suggest that comparing spirometry values without adjusting for age distribution could be misleading. By adjusting for age, the pulmonologist accounts for the variability in the data to draw more accurate conclusions, reinforcing the importance of dispersion measures in clinical research.

TAKE-HOME MESSAGES FOR CLINICIANS

Never report means or medians alone without a measure of spread.

Use the median and IQR for variables with skewed data or that include outliers.

Use the mean and SD for variables with symmetric, normally distributed data.

Using statistics to assess both central tendency and variability provides a more complete and clinically relevant picture.

In clinical research, knowing where the average lies is helpful, but knowing how far the rest of the data stray from it is what truly makes comparisons meaningful.

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The lung function laboratory to assist in the management of chronic kidney disease

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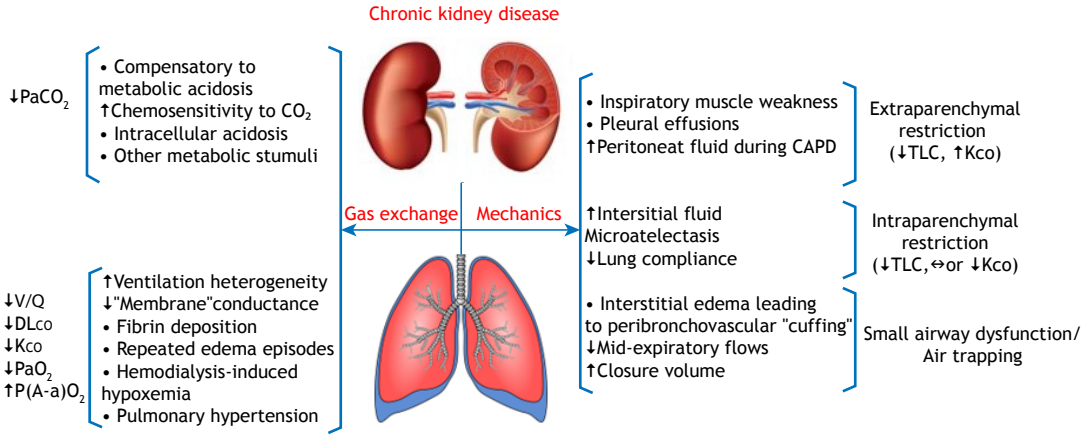
BACKGROUND

The kidneys and lungs share the mutual task of maintaining acid-base homeostasis. Abnormalities in fluid balance, blood electrolytes, hemoglobin concentration (Hb), and vascular tone in chronic kidney disease (CKD) may have profound effects on respiratory function. Chronic lung disease and CKD frequently coexist,[1] creating further challenges to pulmonary function tests (PFTs) interpretation.

OVERVIEW

A 68-year-old man under long-term hemodialysis (HD) and progressive exertional dyspnea underwent PFTs as part of the workup pre-kidney transplant. Spirometry suggested, and body plethysmography confirmed, mild restriction. Hb-corrected DL_{CO} and K_{CO} were severely reduced; further workup confirmed mixed pre- and post-capillary pulmonary hypertension (PH). Despite comprehensive treatment, the patient died before transplantation (**patient A**). A 77-year-old woman with "mild" COPD on spirometry presented with severe hypoxemia (↓PaO_2) but only mild-moderate decrements in SpO_2 ~two hours within the HD sessions. Detailed assessment of gas exchange in a subsequent session showed similar decrements in the alveolar pressure for O_2 (PAO_2) and a measured respiratory exchange ratio (RER; CO_2 output/O_2 consumption) of only 0.63 (0.85 pre-HD). She was diagnosed with HD-induced hypoxemia (**patient B**).

CKD patients often develop a mild restrictive spirometry pattern, which has been traditionally ascribed to chronic fluid overload. They show an exquisite sensitivity to develop "flash" interstitial edema over time, causing repeated episodes of acute-on-chronic restriction. However, lung volumes may decrease without overt edema, likely reflecting interstitial structural abnormalities and low compliance.[2] When the glomerular filtration



CKD Stage	eGFR (mL/min/1.73m²)	Lung Volumes	[Hb]-corrected DLco
I	≥90	↔	↔
II	60-89	↔	↔/↓
III	30-59	↔/↓	↓
IV	15-29	↓	↓↓
V	<15	↓↓↓	↓↓↓

Figure 1. A simplified overview of the main respiratory consequences of chronic renal failure and their impact on common pulmonary function tests. The table depicts the relationship between chronic kidney disease (CKD) progression towards failure and the most relevant respiratory functional findings in stable patients. Abbreviations: $PaCO_2$: partial arterial pressure of carbon dioxide; V/Q: (alveolar) ventilation/perfusion ratio; K_{CO}: carbon monoxide transfer coefficient; PaO_2: partial arterial pressure of oxygen; $P(A\text{-}a)O_2$: alveolar-arterial oxygen pressure difference; CAPD: continuous ambulatory peritoneal dialysis; eGFR: estimated glomerular filtration rate; ↓: decreased; ↑: increased; and ↔: preserved.

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rate decreases further, pulmonary edema, pleural effusion, and respiratory muscle dysfunction are more common. Electrolyte disturbance may also contribute to skeletal (including respiratory) muscle weakness. In some patients, apparent restriction on spirometry is not due to low TLC but higher residual volume, likely due to early closure of the dependent small airways (Figure 1).[3]

Anemia is a major determinant of low DL_{CO} (and K_{CO}) in CKD. Interestingly, both may remain low after Hb correction. This has been ascribed to lower "membrane" conductance rather than impaired capillary blood flow.[4] It remains present after dialysis and may not completely reverse after kidney transplantation.[2] The underlying mechanisms are unclear, but akin to heart failure, it may result from the deposition of fibrin following repeated episodes of clinical or sub-clinical edema. Low DL_{CO} may also signal PH, a comorbidity closely associated with poor prognosis (**patient A**).

Some patients—particularly those with underlying lung disease—may develop significant hypoxemia as the HD session progresses. Several mechanisms have been put forward; most evidence points out the loss of CO_2 into the dialysis fluid. The non-respiratory loss of CO_2 causes a lower CO_2 output at the mouth, leading to hypoventilation and a lower RER. Since $PAO_2 = PiO_2 - (PACO_2/RER)$, a low RER implies lower PAO_2 and, consequently, lower PaO_2.[5] A shift in the O_2 dissociation curve due to the increasing pH explains why SpO_2 may underestimate the severity of hypoxemia (**patient B**).

CLINICAL MESSAGE

Most centers recommend "full" PFTs pre-kidney transplantation for higher-risk patients, i.e., dialysis for an extended period, diagnosis of COPD, history of tobacco exposure, obstructive sleep apnea, previous pulmonary embolism, and/or suspected PH.[6] Close interaction between nephrologists and pulmonologists is paramount, given the bidirectional nature of the observed abnormalities in a population that may present with preexisting, frequently underrecognized lung dysfunction.

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An overview of electronic cigarette use and consequences among adolescents.

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INTRODUCTION

Electronic nicotine delivery systems (ENDS), commonly referred to as electronic cigarettes or "e-cigarettes," function by delivering aerosolized particles containing nicotine or other substances to the user.[1] First introduced to the U.S. market around 2007, these devices emerged as an alternative for individuals attempting to quit traditional cigarettes.[2] However, they have been shown to be equally harmful—if not more so—as they deliver higher levels of nicotine along with other potentially toxic chemicals, such as dichloromethane, acetaldehyde, acrolein, nitrosamines, and various agents that remain insufficiently characterized in the scientific literature.[3] Consequently, another significant concern is the limited research on these devices and their long-term effects, particularly given their relatively recent introduction to the Brazilian market.[2] Therefore, understanding the factors contributing to their increased use among adolescents, the short- and long-term effects of such use, and the broader context of the issue in Brazil warrants further investigation.

ARE ENDS BETTER THAN CONVENTIONAL CIGARETTES?

E-cigarettes are often marketed as a safer alternative to traditional cigarettes. Unlike conventional tobacco products, ENDS operate without combustion, thereby reducing the release of numerous toxic substances associated with smoking-related health issues.[1] For instance, emissions from e-cigarettes typically contain lower levels of particulates and carcinogenic compounds compared to traditional cigarette smoke. However, the perception that ENDS are significantly safer remains a topic of ongoing debate. As relatively recent innovations, their long-term health effects are not yet fully understood, resulting in an incomplete and evolving body of evidence.[2] Moreover, inconsistencies in product labeling and wide variability in nicotine and chemical content across different brands and models further complicate efforts to assess their safety. While ENDS may produce fewer harmful emissions than traditional cigarettes, they still expose users to nicotine—a highly addictive substance—and other potentially hazardous chemicals, raising concerns about their overall impact on health.[1]

WHY ARE ENDS DANGEROUS?

ENDS are associated with several significant health risks. One of the primary concerns is their efficient delivery of nicotine, which can lead to rapid dependence and adverse health effects, such as increased heart rate and blood pressure. In extreme cases, nicotine toxicity may result in seizures, respiratory failure, or even death. The vapor produced by ENDS contains various harmful chemicals, including ultrafine particles, volatile organic compounds, and carbonyl compounds—some of which have been detected at levels comparable to those found in conventional tobacco smoke.[1] These substances can irritate the respiratory tract, induce oxidative stress, and trigger inflammation. Moreover, flavoring agents commonly used in ENDS liquids, such as cinnamon, have demonstrated cytotoxic effects, raising concerns about the long-term consequences of inhaling such additives.[3] Although ENDS emit fewer harmful substances than traditional cigarettes, secondhand vapor still exposes non-users to potentially dangerous chemicals, the full extent of which remains unclear. Furthermore, the appealing packaging and flavors of ENDS liquids present a serious hazard, particularly to children, as accidental ingestion can lead to severe health complications.[1]

ADOLESCENTS AS MAIN USERS OF ENDS

With the rise in e-cigarette use, one population of particular concern is adolescents. A recent systematic review involving individuals aged 8 to 20 years from 69 countries and territories reported a pooled prevalence of 17.2% for ever-use (any lifetime use) of ENDS and 7.8% for current use (use within the past 30 days).[4] ENDS are as addictive as conventional cigarettes and can cause neurocognitive effects, including impaired reflexes, deficits in attention and reasoning, and mood disorders. Furthermore, nicotine exposure at a young age can result in permanent brain damage, increase the risk of addiction, and contribute to sustained tobacco use into adulthood.

CONSEQUENCES OF ENDS USE

ENDS pose significant health risks due to their chemical composition and the interactions these substances have within the human body. For example, e-cigarettes contain propylene glycol and vegetable glycerin—compounds that are highly toxic to lung cells. Generally, the greater the number of ingredients, the higher the potential harm to health.[1] The consequences of ENDS use can be broadly categorized into five main areas: respiratory problems,

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◄ Voltar ao sumário
ISSN 1806-3756

Table 1. Health risks and management strategies related to e-cigarette use.

CONSEQUENCE	DESCRIPTION	HOW TO MANAGE
RESPIRATORY PROBLEMS	On usage, one inhales an aerosol laden with chemicals that can be harmful to the lungs. These agents travel deep within the lungs, causing irritation and inflammation. With time, this may lead to breathing disorders, including cough, wheezing, and asthma.	Discontinuing the use of all vaping products to prevent more damage is the main goal in management. Besides that, doctors are able to treat acute respiratory symptoms through prescribing medications such as bronchodilators, corticosteroids, or antibiotics. If breathing is severely compromised, the doctor may recommend hospitalization and oxygen therapy.
CARDIOVASCULAR PROBLEMS	Nicotine has a deleterious effect on cardiovascular health: it makes the heart beat faster and raises blood pressure. Long-term use of e-cigarettes with nicotine may be a risk factor for cardiovascular disease, which results from plaque build-up in arteries.	Other than stop vaping, treating acute cardiovascular symptoms associated with 'vaping' using beta-blockers, anti platelet agents, statines and ACE inhibitors is one of the most important ways to manage. Also, adopting a healthier lifestyle with regular exercise and stress reduction.
NICOTINE ADDICTION	It is able to quickly produce a great feeling of pleasure in the brain, thus carrying with it the sense of reward and reinforcement. The potential for strong nicotine dependence makes quitting electronic cigarettes very difficult for many individuals.	Treatment for mental health issues, nicotine addiction and vaping-related substance abuse requires an integrated approach starting with banning the use of any vape with nicotine replacement therapy, approved cessation programs and supporting therapy.
MENTAL HEALTH ISSUES	When it comes to emotional well-being, teenagers who vape may have a much more challenging time fending off anxiety and depression. Heads up, nicotine from e-cigarettes also plays a role in regulating neurotransmitters in the brain that control mood and increase the risk of anxiety and mood disorders.	In this context, emotional problems related to e-cigarettes need to be approached through therapies, like Cognitive behavioral therapy (CBT), relaxation techniques or if needed medication prescribed by a medical expert, such as psychiatrists.
RISK OF SUBSTANCE ABUSE	Research findings show that adolescents who engage in e-cigarette usage are more likely to use other tobacco products and illicit drugs. This increased likelihood of substance use is often attributable to the social and environmental factors that usually the use of e-cigarettes, such as exposure to peers who smoke other illicit substances and a tendentious propensity for risk-taking.	Expert counselling, support groups and for the more serious cases rehabilitation programmes can reduce risk for substance abuse. Healthy lifestyle, balanced diet, quality sleep and exercise also play a role in overall wellness and recovery. Consult with emergency help in case of acute mental health symptoms.

cardiovascular damage, nicotine addiction, mental health issues, and substance abuse.

WHAT IS THE CONTEXT OF ENDS IN BRAZIL?

The sale, importation, storage, transportation, and advertisement of e-cigarettes in Brazil have been prohibited by the National Health Surveillance Agency (ANVISA) since Collegiate Board Resolution (RDC) No. 46 of 2009. In 2024, the regulation was reviewed and reaffirmed by the Brazilian government with even stricter measures, including a ban on the manufacture and distribution of ENDS within the national territory.[5] It is also important to note that electronic cigarettes are subject to Decree-Law No. 8.262 of 2014, which prohibits the use of any smoking device in enclosed public or private collective spaces.[6]

In 2022, the Covitel study was conducted in Brazil to estimate the prevalence of e-cigarette use among Brazilian adults. The study found that among 1,800 individuals, the prevalence of current commercial cigarette smoking was 12.2%. Furthermore, young adults aged 18 to 24 had the highest rates of e-cigarette experimentation, with usage being more common in the Central-West region and among individuals with higher levels of education.[6]

CONCLUSION

In summary, while often considered a healthier alternative to traditional cigarettes, ENDS are, in fact, equally harmful—or potentially more so. In addition to causing nicotine dependence, they are associated with respiratory issues, cardiovascular problems, and negative impacts on mental health. Although the sale of these devices is prohibited in Brazil by ANVISA, their growing popularity among adolescents underscores the urgent need for both educational initiatives and strengthened regulatory measures.

AUTHOR CONTRIBUTIONS

MAULC, LMP, GABS, and MPCH: searching and writing. LAP and DCCS: writing, reviewing, and editing.

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J Bras Pneumol. 2025;51(2):e20240407
https://dx.doi.org/10.36416/1806-3756/e20240407

ORIGINAL ARTICLE

Level of agreement between two asthma control questionnaires in children and adolescents

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Submitted: 12 December 2024.
Accepted: 17 February 2025.

Study carried out at the Ambulatório de Pneumologia Pediátrica da Universidade Estadual de Londrina, Londrina (PR) Brasil.

ABSTRACT

Objective: To investigate the level of agreement between the GINA questionnaire and the Asthma Control Test (ACT) in children and adolescents with asthma, as well as to compare the clinical, laboratory, and spirometric characteristics of patients with controlled and uncontrolled asthma as assessed by the two questionnaires. **Methods:** Children and adolescents with asthma had their level of asthma control cross-sectionally assessed by the GINA questionnaire and the ACT, the Childhood ACT (C-ACT) being used for the children in the sample. The participating patients also underwent spirometry, clinical assessment (for passive smoking, asthma severity, medication use, and type of inhaler device used), and laboratory measurements of vitamin D levels, blood eosinophils, and total IgE. **Results:** A total of 76 patients were assessed. Of those, 62% were male, and the mean age was 10 [9-12] years. In addition, 42% and 20% were classified as having uncontrolled asthma by the GINA questionnaire and the C-ACT/ACT, respectively. There was moderate agreement between the two questionnaires regarding identification of controlled and uncontrolled asthma (κ = 0.505; p < 0,0001). The patients classified as having uncontrolled asthma by the GINA questionnaire had worse results in terms of daily inhaled corticosteroid dose, asthma severity, passive smoking, and spirometric parameters (FVC, FEV_1, and $FEF_{25-75\%}$). However, there was no significant difference between patients classified as having controlled or uncontrolled asthma by the C-ACT/ACT. **Conclusions:** In children and adolescents with asthma, the level of agreement between the GINA questionnaire and the C-ACT/ACT appears to be moderate. The GINA questionnaire appears to have a stronger association with functional parameters, indicating better clinical assessment with less underreporting of uncontrolled asthma.

Keywords: Asthma; Pediatrics; Surveys and questionnaires; Therapeutics.

INTRODUCTION

Asthma is a chronic, heterogeneous disease characterized by airway inflammation. It is the most common chronic disease among children and adolescents,[1] and remains a public health issue despite efforts to reduce hospitalizations and mortality. In children and adolescents, the prevalence of asthma is increasing, posing a burden for patients and their parents.[2]

The diagnosis of asthma is based on identification of a recurring pattern of wheezing, dyspnea, chest tightness, and/or cough that may improve with the use of bronchodilators, as well as on documentation of airflow limitation, whenever possible.[2] There is a wide range of therapeutic medications, particularly inhaled corticosteroids (ICSs), which may be combined with long-acting β_2 agonists (LABAs).[2]

Once asthma medication treatment begins, patient symptoms must be periodically reassessed in order to maintain symptom control, thereby reducing the risk of exacerbations and mortality. To achieve this goal, clinical questionnaires are used in order to evaluate asthma control and adjust asthma medication therapy.[2] Among the questionnaires assessing asthma control, the most well-known are the GINA questionnaire[2] and the Asthma Control Test (ACT), with the Childhood Asthma Control Test (C-ACT) being used for children[1,3] and the ACT being used for adolescents.[4,5] Each questionnaire is applied differently. The GINA questionnaire is easy to apply, being administered verbally by the physician to the patient or their legal guardian and addressing aspects such as symptom frequency, medication use, and limitations in daily activities through four yes or no questions.[6] The C-ACT/ACT are printed questionnaires answered by the patient and their legal guardian (in the case of the C-ACT)[3] or by the patient only (in the case of the ACT),[5] with each question being assigned a score that is summed up (the maximum being 27 for the C-ACT and 25 for the ACT).

These questionnaires for assessing asthma control are widely used and of great importance because patients and physicians tend to overestimate the level of disease control and the improvement achieved with treatment.[6] However, neither questionnaire includes lung function

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Financial support: None.

parameters. Although this simplifies their application, it also means that they fail to provide a functional evaluation of patients with asthma by failing to identify changes in lung function.[7]

Although the GINA questionnaire and the C-ACT/ACT are widely used, it is yet unknown whether their results are consistent or even interchangeable. Therefore, the objective of the present study was to assess the level of agreement between the GINA questionnaire and the C-ACT/ACT in children and adolescents with asthma, as well as to compare the clinical, laboratory, and spirometric characteristics of patients with controlled and uncontrolled asthma as assessed by the two questionnaires.

METHODS

The present study was conducted at the Pediatric Pulmonology Outpatient Clinic of the University Hospital of the State University at Londrina, located in the city of Londrina, Brazil. This was a primary study in which an analytical cross-sectional design was used.

A convenience sample of patients treated at the outpatient clinic between May of 2019 and August of 2023 were consecutively recruited to participate in the study. All participants were assessed at a single time point, undergoing clinical, laboratory, and spirometric evaluations. All of the patients who met the inclusion criteria and agreed to participate in the study were consecutively included and evaluated. The legal guardians of all participating patients gave written informed consent. The study was approved by the Human Research Ethics Committee of State University at Londrina (Protocol no. 3.093.047/2018).

The inclusion criteria were as follows: being in the 6- to 14-year age bracket; being followed at the Pediatric Pulmonology Outpatient Clinic of the University Hospital of the State University at Londrina; having received a clinical diagnosis of asthma in accordance with the GINA criteria[2]; currently using an ICS (beclomethasone, budesonide, or fluticasone), with or without a LABA, with no restrictions on the duration of use; being clinically stable, without the need for oral corticosteroids in the last month because of asthma exacerbation; having no other lung diseases (e.g., chronic lung disease of prematurity, obliterative bronchiolitis, bronchiectasis, and cystic fibrosis); having no signs or symptoms of gastroesophageal reflux disease or dysphagia; and having used an antiparasitic drug in the last 12 months. The exclusion criteria were as follows: having taken vitamin D supplementation (because vitamin D has an impact on modulation of inflammation and, consequently, on asthma control); and having experienced asthma exacerbations requiring hospitalization for more than one day and/or the use of oral corticosteroids in the last month.

The participating patients underwent assessment of asthma severity and control level with the GINA questionnaire[2] and the C-ACT/ACT.[1,3-5] They also underwent spirometry and laboratory measurements of blood eosinophils and total IgE.

The GINA asthma control questionnaire consists of 4 yes or no questions regarding the past four weeks. The questions are as follows: 1) Asthma-like symptoms during the day for more than a few minutes, more than once a week?; 2) Any activity limitation due to asthma?; 3) Need for reliever medication more than once a week?; and 4) Any nighttime awakening or cough due to asthma? If all responses are "no," the patient is classified as having controlled asthma; if 1 or 2 questions have an affirmative response, the classification is partially controlled; if 3 or 4 responses are affirmative, the disease is classified as uncontrolled.[2] The questions on the GINA questionnaire were asked directly to the patients, who were however assisted by their parents/legal guardians/companions whenever needed; they could intervene in case there were any questions or difficulties. For analysis purposes, the patients in the present study were classified as having controlled or uncontrolled asthma, with the latter group including patients with partially controlled and uncontrolled asthma.

The C-ACT and the ACT were applied in accordance with patient age. For children < 12 years of age, the C-ACT was used. The C-ACT consists of seven questions, four of which are answered by the patients themselves and three of which are answered by their parents or legal guardians, with a minimum score of 0 and a maximum score of 27. A higher score translates to a better asthma control. Scores between 20 and 27 classify patients as having controlled asthma; scores between 15 and 19 classify patients as having partially controlled asthma; and scores between 0 and 14 classify patients as having uncontrolled asthma.[3] Children ≥ 12 years of age completed the ACT, which consists of five questions. Each question is scored on a scale of 1 to 5 points; therefore, the minimum total score is 5, and the maximum total score is 25. A higher score translates to a better asthma control. Scores between 20 and 25 classify patients as having controlled asthma; scores between 16 and 19 classify patients as having partially controlled asthma; and scores between 5 and 15 classify patients as having uncontrolled asthma.[2] For analysis purposes, children and adolescents were classified as having controlled or uncontrolled asthma, with the latter group including patients with partially controlled and uncontrolled asthma. In summary, the patients in the present study were divided into two groups based on asthma control (controlled or uncontrolled) as assessed by the GINA questionnaire and the C-ACT/ACT. For the GINA questionnaire, patients in the controlled asthma group (the GINA controlled asthma group) were characterized by answering "no" to all four questions, whereas those in the uncontrolled asthma group (the GINA uncontrolled asthma group) had at least one affirmative response.[2] For the C-ACT/ACT, controlled asthma (the ACT controlled asthma group) was characterized by a score of 20 or higher, whereas

uncontrolled asthma (the ACT uncontrolled asthma group) had a score of 19 or lower.[3,4]

All participating patients underwent spirometry with a MiniSpir spirometer (MIR, Rome, Italy) and the WinspiroPRO software, version 5.9, the technique recommended by the American Thoracic Society being used.[8] Reference values for the Brazilian population[9] were used. All analyses utilized pre-bronchodilator spirometry results and the pre- and post-bronchodilator variation. Obstructive ventilatory disorder was defined by a reduction in the FEV_1/FVC ratio below the 5th percentile of the predicted value (lower limit).[10]

With regard to the laboratory tests for sample characterization, immunoturbidimetry (Architect c8000; Abbott Laboratories, Abbott Park, IL, USA) was used for IgE analysis and quantification. An automated method was used for serum eosinophils, as described elsewhere.[11]

The inhalers and medications used by the participating patients were also recorded. Inhaler devices included metered dose inhalers and dry powder inhalers such as Turbuhaler® and Aerolizer®. Additionally, the sample included patients using beclomethasone and budesonide. For dose analysis, the corresponding budesonide dose was used, as recommended by GINA,[2] varying according to patient age (6-11 years of age and > 12 years of age). ICS doses were based on budesonide and were categorized as low, medium, or high.[2] For the age group of 6-11 years, a budesonide dose of 100-200 µg/day was defined as low; a budesonide dose > 200 ≤ 400 µg/day was defined as medium; and a budesonide dose > 400 µg/per day was defined as high.[2] For patients > 12 years of age, a dose of 200-400 µg/day was defined as low; a dose > 400 ≤ 800 µg/day was defined as medium; and a dose > 800 µg/day was defined as high.[2] Formoterol was the only LABA used in association with budesonide. Asthma severity was classified as mild, moderate, or severe on the basis of the GINA stepwise system, as follows: mild (for patients receiving GINA step 1 or 2 treatment); moderate (for patients receiving GINA step 3 treatment); and severe (for patients receiving GINA step 4 or 5 treatment).[2]

In the statistical analysis, the Shapiro-Wilk test was used in order to analyze the normality of data distribution. Normally distributed data were described as mean and standard deviation, and non-normally distributed data were described as median and interquartile range. Comparisons of continuous variables were performed with the unpaired Student's t-test (for parametric variables) or the Mann-Whitney test (for nonparametric variables), whereas categorical variables were analyzed with the chi-square test and reported as absolute and relative values (proportions). The level of agreement between the controlled and uncontrolled asthma groups as assessed by the GINA questionnaire or the C-ACT/ACT was determined by calculating the kappa statistic, as follows: < 0, no agreement; 0-0.2, very low agreement; 0.2-0.4, fair agreement; 0.4-0.6, moderate agreement; 0.6-0.8, substantial agreement; and 0.8-1, excellent agreement.[12] The Fisher's exact test was used to identify statistically significant difference between the proportion of individuals classified as having controlled asthma according to the two classifications. The strength of association between the GINA questionnaire and the C-ACT/ACT was determined by calculating Cramér's V, as follows: 0-0.10, negligible association; 0.11-0.20, weak association; 0.21-0.40, moderate association; 0.41-0.60, relatively strong association; 0.61-0.80, strong association; 0.81-0.99, very strong association; and 1, perfect association.[13] All statistical analyses were performed with the IBM SPSS Statistics software package, version 25.0 (IBM Corporation, Armonk, NY, USA), and the level of significance was set at $p < 0.05$.

RESULTS

Seventy-six patients were included in the present study, with no exclusions. The baseline characteristics of the participating patients are detailed in Table 1. The median age of the patients was 10 [9-12] years, and the median BMI was 18 [15-22] kg/m^2. The C-ACT/ACT scores were significantly lower in the GINA uncontrolled asthma group than in the GINA controlled asthma group (20 [15-22] points vs. 24 [23-25] points; Figure 1).

There was moderate agreement ($\kappa = 0.505$; $p < 0.0001$) between the controlled and uncontrolled asthma groups as assessed by the GINA questionnaire and the C-ACT/ACT, with good sensitivity (0.72) and excellent specificity (1.00). All patients classified as having controlled asthma by the GINA questionnaire were also classified as having controlled asthma by the C-ACT/ACT; however, not all patients classified as having uncontrolled asthma by the GINA questionnaire were also classified as having uncontrolled asthma by the C-ACT/ACT, with a discrepancy of 22% of the sample. Additionally, 58% of the sample was categorized as having controlled asthma by the GINA questionnaire, whereas 80% were categorized as having controlled asthma by the C-ACT/ACT, with a significant difference between the two evaluation methods (Fisher's exact test, $p < 0.0001$). Nevertheless, there was a relatively strong association between the GINA and C-ACT/ACT classifications (Cramér's $V = 0.581$; $p < 0.0001$; Figure 2).

All comparisons between individuals with controlled and uncontrolled asthma as assessed by the GINA questionnaire and the C-ACT/ACT are shown in Table 2. When we compared the GINA controlled asthma and uncontrolled asthma groups, we found a significant difference in variables such as type of inhaler device, daily ICS dose, GINA treatment step, asthma severity, passive smoking, and spirometric parameters (FVC, FEV_1, and $FEF_{25-75\%}$). However, we found no significant differences between the ACT controlled asthma and uncontrolled asthma groups.

Table 1. Clinical, spirometric, and laboratory characteristics of the study sample (N = 76).[a]

Variable	
Sex, male/female	47/29 (62/38)
Age, years	10 [9-12]
Race, White/Black	61/15 (80/20)
BMI, kg/m^2	18 [15-22]
GINA, uncontrolled asthma	32 (42)
C-ACT/ACT, uncontrolled asthma	15 (20)
Inhaler device	
Metered dose inhaler	29 (38)
Turbuhaler®	14 (19)
Aerolizer®	33 (43)
Medication	
Beclomethasone	1 (1)
Budesonide	25 (33)
Formoterol + budesonide	50 (66)
Daily dose, µg	405 ± 148
Dose load	
Low	20 (26)
Medium	49 (65)
High	7 (9)
GINA treatment classification	
Step 1 (mild asthma)	0 (0)
Step 2 (mild asthma)	9 (12)
Step 3 (moderate asthma)	25 (33)
Step 4 (severe asthma)	38 (50)
Step 5 (severe asthma)	4 (5)
Asthma severity	
Mild	9 (12)
Moderate	25 (33)
Severe	42 (55)
Passive smoking	35 (46)
Spirometry	
FVC, L	2.45 ± 0.68
FVC, % predicted	97 ± 14
ΔFVC (pre- and post-BD), %	3.32 [−0.57 to 8.43]
FEV_1, L	2.01 ± 0.59
FEV_1, % predicted	90 ± 18
ΔFEV_1 (pre- and post-BD), %	6.61 [3.05-14.22]
FEV_1/FVC	83 [78-88]
FEV_1/FVC, % predicted	95 [88-99]
ΔFEV_1/FVC (pre- and post-BD), %	3.24 [0.89-7.43]
$FEF_{25-75\%}$, L/s	2.12 ± 0.87
$FEF_{25-75\%}$, % predicted	79 ± 29
Δ$FEF_{25-75\%}$ (pre- and post-BD), %	16 [5-33]
Laboratory test results	
IgE, IU/mL*	519 [250-1,281]
Eosinophils, cells/µL*	588 [340-814]

C-ACT: Childhood Asthma Control Test; ACT: Asthma Control Test; and BD: bronchodilator. [a]Data presented as n (%), mean ± SD, or median [IQR]. *n = 68.

DISCUSSION

The present study identified significant differences in the proportions of children classified as having controlled or uncontrolled asthma by two different questionnaires assessing disease severity. Specifically, the C-ACT/ACT identified a smaller proportion of children with uncontrolled asthma than did the GINA questionnaire, despite a strong association and moderate agreement between the two questionnaires. Additionally, among the children with uncontrolled asthma as assessed by the GINA questionnaire, metered dose inhalers were the most commonly used inhaler devices; GINA treatment step 4 (severe asthma)[2] was the most commonly given treatment; passive smoking was highly prevalent; and spirometric values were worse than those observed in the GINA controlled asthma group. These findings may indicate the need for a more personalized management of patients with uncontrolled asthma, including intensification of counseling on the importance of smoking cessation—smoking being a modifiable risk factor and a factor contributing to the worsening of respiratory conditions—aggressive therapy for disease control; and close monitoring (allowing earlier intervention to minimize exacerbations and hospitalizations). On the other hand, these differences were not observed when the children were classified as having controlled or uncontrolled asthma by the C-ACT/ACT. Therefore, regarding disease control, the results of the present study suggest some superiority of the GINA questionnaire over the C-ACT/ACT.

Regarding the level of asthma control as assessed by the GINA questionnaire and the C-ACT/ACT, Koolen et al.[6] reported results that are similar to ours, although only 17% of the patients in their sample had controlled asthma as assessed by the GINA questionnaire and 40% had controlled asthma as assessed by the C-ACT/ACT. By comparing the results of the present study with those of that by Koolen et al.,[6] we find similar sensitivity (72% vs. 66%, respectively) and specificity (100% in both studies). This suggests an overestimation of asthma control by caregivers and/or patients, an observation that has been reported elsewhere.[14-17] With regard to the levels of asthma control as defined by the two questionnaires, we hypothesize that the cutoff for uncontrolled asthma on the C-ACT/ACT (i.e., 19 points) underestimates the proportion of children with uncontrolled asthma as assessed by the GINA questionnaire.[6] Thus, the GINA questionnaire might be superior to the C-ACT/ACT for identifying obstructive ventilatory disorder, which has important clinical implications in the therapeutic management of these children.

The GINA questionnaire assesses a broader range of factors using dichotomous questions regarding daytime and nighttime symptoms, as well as limitations in daily activities and use of relief medications, providing a more comprehensive view of asthma control.[18,19] Despite having been validated and praised for its simplicity and ease of use, the ACT, through 4-5 possible answers to each question, one of which is subjective (question 5, which considers the judgment of control), focuses primarily on symptoms and activity limitations, giving less attention to other important points of asthma control assessment, such as exacerbations.[20]

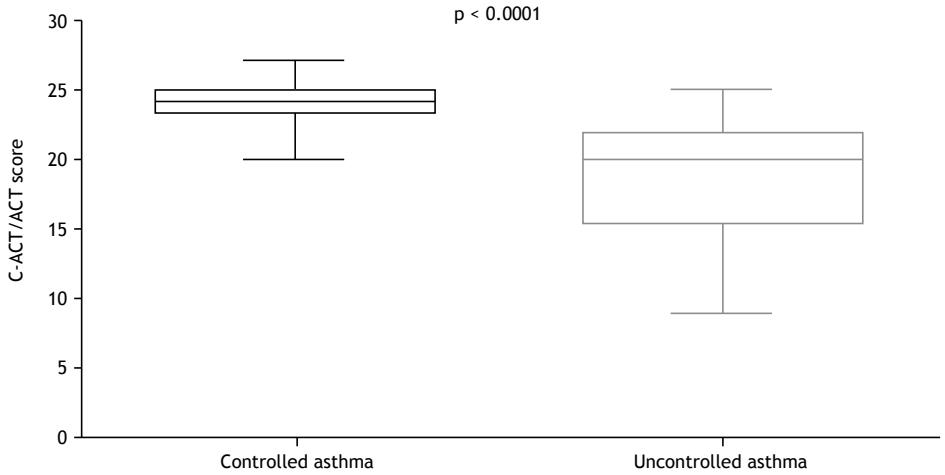

Figure 1. Comparison of Childhood Asthma Control Test/Asthma Control Test (C-ACT/ACT) scores for controlled and uncontrolled asthma as assessed by the GINA questionnaire.

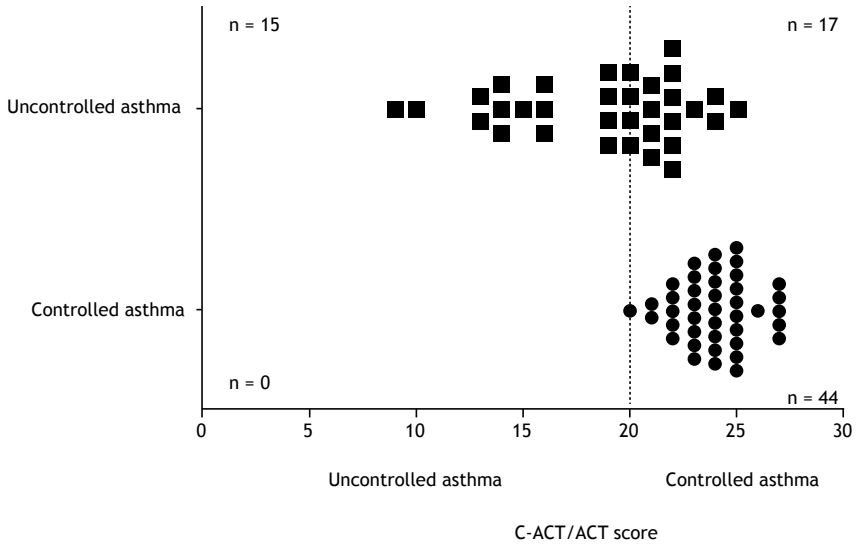

Figure 2. Controlled and uncontrolled asthma groups as assessed by the Childhood Asthma Control Test/Asthma Control Test (C-ACT/ACT) and the GINA questionnaire.

One point to highlight is that the GINA questionnaire may be associated with spirometric parameters and may provide important information on asthma severity,[21] especially $FEF_{25-75\%}$. Cottini et al.[21] found no association between $FEF_{25-75\%}$ and the ACT, a finding that is consistent with those of the present study. Yi et al.[22] found that children with poorer asthma control as assessed by the GINA questionnaire had worse FEV_1 and $FEF_{25-75\%}$, a finding that is also consistent with those of the present study.

It is known that higher doses of medications are needed to control asthma in patients with worse clinical severity.[2] However, ours is the first study to show the superiority of the GINA questionnaire over the C-ACT/ACT in terms of ICS doses and disease severity in relation to the level of disease control. Nevertheless, previous studies[23,24] highlighted some of the positive aspects of the GINA questionnaire used in combination with spirometric data for the management of pediatric asthma in terms of dose adjustment and assessment of asthma severity.

The results of the present study show that the patients in the GINA controlled asthma group mainly used dry powder inhalers, whereas those in the GINA uncontrolled asthma group mainly used metered dose inhalers. Choosing an inhaler device is challenging because the choice must be based on patient preference and their ability to use the device, incorrect inhaler use resulting in poor lung deposition of the drug.[25,26] Lavorini et al.[27] found that patients had a greater preference for dry powder inhalers and that dry powder inhalers generally provide better pulmonary deposition of the drug than do other types of inhaler devices, a finding that might explain those of the present study.

Table 2. Comparisons between children and adolescents with controlled and uncontrolled asthma as assessed by the GINA questionnaire and the Childhood Asthma Control Test/Asthma Control Test.[a]

Variable	GINA questionnaire N = 76			C-ACT/ACT N = 76		
	Controlled asthma (n = 44)	Uncontrolled asthma (n = 32)	p	Controlled asthma (n = 61)	Uncontrolled asthma (n = 15)	p
Sex, M/F	30 (68)/14 (32)	17 (53)/15 (47)	0.182	39 (64)/22 (36)	8 (53)/7 (47)	0.645
Age, years	10.2 ± 2.3	10 ± 2.1	0.773	10.2 ± 2.2	9.7 ± 2.1	0.457
BMI, kg/m^2	18 [16-23]	18 [15-21]	0.388	18 [16-22]	20 [14-21]	0.700
Inhaler device			0.013			0.376
Metered dose inhaler	12 (27)	17 (53)		23 (38)	6 (40)	
Turbuhaler®	8 (18)	6 (19)		9 (15)	5 (33)	
Aerolizer®	24 (55)	9 (28)		29 (48)	4 (27)	
Medication			0.124			0.187
Beclomethasone	1 (2)	0 (0)		1 (2)	0 (0)	
Budesonide	17 (39)	8 (25)		22 (36)	3 (20)	
Budesonide + formoterol	26 (59)	24 (75)		38 (62)	12 (80)	
Daily dose, µg	372 ± 104	445 ± 173	0.049	386 ± 123	470 ± 191	0.075
Dose load			0.071			0.198
Low	14 (32)	6 (19)		17 (28)	3 (20)	
Medium	28 (63)	21 (65)		40 (65)	9 (60)	
High	2 (5)	5 (16)		4 (7)	3 (20)	
GINA treatment classification			0.026			0.080
Step 1 (mild asthma)	0 (0)	0 (0)		0 (0)	0 (0)	
Step 2 (mild asthma)	6 (14)	3 (9)		8 (13)	1 (7)	
Step 3 (moderate asthma)	19 (43)	6 (19)		22 (36)	3 (20)	
Step 4 (severe asthma)	18 (41)	20 (63)		29 (48)	9 (60)	
Step 5 (severe asthma)	1 (2)	3 (9)		2 (3)	2 (13)	
Asthma severity			0.043	3 [2-3]	3 [2-3]	0.128
Mild	6 (14)	3 (9)		8 (13)	1 (7)	
Moderate	19 (43)	6 (19)		22 (36)	3 (20)	
Severe	19 (43)	23 (72)		31 (51)	11 (7)	
Passive smoking			0.025			0.314
No	33 (75)	16 (50)		41 (67)	8 (53)	
Yes	11 (25)	16 (50)		20 (33)	7 (47)	
Spirometry						
FVC, L	2.53 ± 0.65	2.33 ± 0.71	0.214	2.49 ± 0.64	2.26 ± 0.80	0.259
FVC, % predicted	100 ± 14	93 ± 14	0.047	97 ± 14	95 ± 16	0.639
ΔFVC (pre- and post-BD), %	2 [−1 to 8]	5 [0-9]	0.391	3 [−1 to 8]	4 [0-9]	0.845
FEV_1, L	2.09 ± 0.58	1.88 ± 0.59	0.127	2.04 ± 0.56	1.83 ± 0.67	0.218
FEV_1, % predicted	94 ± 18	85 ± 17	0.040	91 ± 17	87 ± 21	0.500
ΔFEV_1 (pre- and post-BD), %	6 [3-11]	8 [2-16]	0.288	7 [4-15]	6 [1-14]	0.422
FEV_1/FVC	84 [78-89]	82 [76-87]	0.374	81 [78-88]	82 [74-92]	0.615
FEV_1/FVC, % predicted	95 [89-100]	93 [86-98]	0.333	95 [89-100]	94 [81-100]	0.485
ΔFEV_1/FVC (pre- and post-BD), %	3 [1-8]	5 [2-7]	0.222	3 [1-7]	2 [−1 to 10]	0.980
$FEF_{25-75\%}$, L/s	2.20 [1.64-2.92]	2.02 [1.43-2.42]	0.092	2.17 [1.5-72.74]	2.16 [0.87-2.46]	0.285
$FEF_{25-75\%}$, % predicted	89 [61-112]	71 [55-86]	0.028	82 [63-103]	78 [41-99]	0.312
Δ$FEF_{25-75\%}$ (pre- and post-BD), %	16 [1-29]	16 (8-40]	0.446	17 [7-32]	9 [2-69]	0.382

C-ACT: Childhood Asthma Control Test; ACT: Asthma Control Test; and BD: bronchodilator. [a]Data presented as n (%), mean ± SD, or median [IQR].

In addition to personal preference, the use of metered dose inhalers in children requires spacers (with or without a mask), which are not needed when dry powder inhalers are used. This can be a limiting factor because the inhaler device can be misplaced or inadequately cleaned, contributing to medication deposition on the spacer wall and having less medication available for pulmonary deposition.[28,29] It is also

important to consider the availability of medications in the Brazilian public health system. The medications may not always be the most suitable for patients, and the range of medications available in the public health system is not as wide as that available in the private health system. The patients in the present study were all recruited from among those followed at a public outpatient clinic, and the formoterol-budesonide combination (LABA+ICS) is often available only in inhaled capsule form. However, not all patients know how to use it correctly; therefore, treatment must be individualized with medications delivered in spray form, such as beclomethasone, which do not have the same bronchoprotective effect as do those in the LABA-ICS combination.[30,31]

In the present study, passive smoking showed a significant difference between the GINA controlled asthma and uncontrolled asthma groups, with a higher proportion of uncontrolled asthma among those exposed to passive smoking. Tobacco exposure is known to have a variety of harmful effects on children; it aggravates asthma symptoms, worsens asthma control, reduces lung capacity, and directly impacts quality of life.[32,33] The literature corroborates our findings regarding loss of lung function in children exposed to smoking. Moshammer et al.[34] showed an association between maternal smoking, reduced FEV_1, and small airway obstruction, as evidenced by reduced $FEF_{25-75\%}$. McEvoy et al.[35] demonstrated persistent deficits in lung function in children whose mothers smoked during pregnancy, including increased airway smooth muscle, collagen deposition, airway hyperresponsiveness, and reductions in forced expiratory flows persisting up to the age of 21 years.

One of the limitations of the present study is that recruitment was carried out in a single center in Brazil among children with a specific socioeconomic profile (i.e., users of the public health system). Further studies investigating children with controlled and uncontrolled asthma should add a longitudinal follow-up to identify other factors related to the questionnaires used in the present study, as well as to study their responsiveness.

In conclusion, although the GINA questionnaire and the C-ACT/ACT are universally accepted as tools for assessing asthma control, the GINA questionnaire proved to be more suitable for the children in the present study and showed a stronger association with functional parameters, indicating better clinical assessment with less underreporting of uncontrolled asthma. It is worth emphasizing the importance of health care professionals exercising caution when interpreting patient symptoms to avoid overestimating the clinical control of the disease. This ensures that the necessary therapeutic adjustments, including medication adjustments, are made for each patient.

AUTHOR CONTRIBUTIONS

CLCGA: study design, data collection, data analysis, and manuscript writing; KCF: study design, data collection, data analysis, and manuscript revision; TC: study design, data analysis, and manuscript revision; FP: study design, data collection, data analysis, manuscript revision, and study supervision.

CONFLICTS OF INTEREST

None declared.

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J Bras Pneumol. 2025;51(2):e20240406
https://dx.doi.org/10.36416/1806-3756/e20240406

Impact of elexacaftor/tezacaftor/ivacaftor on the small airways in cystic fibrosis

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Submitted: 12 December 2024.
Accepted: 12 February 2025.

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ABSTRACT

Objective: To evaluate the impact of the elexacaftor/tezacaftor/ivacaftor (ELX/TEZ/IVA) combination on the small airways in adults with cystic fibrosis (CF), a genetic disorder that primarily affects the respiratory system, leading to progressive lung disease. In CF, the small airways play a critical role, contributing to chronic symptoms such as cough, sputum production, and dyspnea. **Methods:** This was a single-center, retrospective observational study of adults with CF treated with ELX/TEZ/IVA for 12 months. We compared the patients who were homozygous for the F508del mutation of the CF transmembrane conductance regulator (*CFTR*) gene with those who were heterozygous for that mutation, in terms of lung function outcomes (FEV_1, $FEF_{25-75\%}$, and the RV/TLC ratio) and the extent of non-homogeneous ground-glass opacity. Among the patients within the cohort, the same parameters were evaluated separately in those who had advanced lung disease and in those who had previously undergone CFTR modulator therapy. **Results:** There was a significant post-treatment improvement in lung function, with a median increase of 0.42 L/s in the $FEF_{25-75\%}$ ($p < 0.001$) and a 5% reduction in the mean RV/TLC ratio ($p < 0.001$). There was a trend toward a higher improvement the F508del homozygous patients. A significant reduction in non-homogeneous ground-glass opacity was observed in 79.5% of the patients. Among the patients with advanced lung disease, there were notable post-treatment improvements in all of the parameters assessed. **Conclusions:** Our results highlight the positive impact that ELX/TEZ/IVA treatment can have on small airway function in patients with CF, with potential benefits even for those with advanced lung disease. Further research is needed in order to evaluate the long-term effects of this treatment and its relationship with patient-reported outcomes.

Keywords: Cystic fibrosis/diagnostic imaging; Lung/physiopathology; Respiratory function tests; Lung/drug effects; Lung/diagnostic imaging; Cystic fibrosis/drug therapy.

INTRODUCTION

Cystic fibrosis (CF) is a rare genetic disease with autosomal recessive inheritance, caused by variants in the CF transmembrane conductance regulator (*CFTR*) gene, that affects approximately 100,000 people worldwide.[1] Dysfunction of the CFTR protein leads to the development of multiple manifestations across various organ systems, with the respiratory system being the most prominent. Pulmonary involvement typically causes the most severe, progressive form of CF, ultimately leading to death. Over 2,000 variants have been described, the most common being F508del, which is found in nearly 90% of CF patients, of whom approximately 50% are homozygous for this mutation.[2]

The importance of the small airways in the pathophysiology of lung disease in CF is well known, because CFTR dysfunction causes viscous secretions and failure of mucociliary clearance due to respiratory mucin adherence to the airway epithelium. This leads to the production and accumulation of viscous bronchial secretions, air trapping, and increased respiratory muscle workload. Together, these factors contribute to chronic symptoms such as cough, sputum production, dyspnea, and reduced exercise capacity.[3]

In July of 2021, the CFTR modulator combination elexacaftor/tezacaftor/ivacaftor (ELX/TEZ/IVA) was approved for use in Portugal for patients who are homozygous for the F508del mutation and F508del heterozygous patients carrying a second minimal function mutation; in February of 2022, it was approved for those carrying at least one F508del allele.[4]

The safety and tolerability profile of ELX/TEZ/IVA have been well established, as have its benefits, including improvements in FEV_1, a reduction in the number of pulmonary exacerbations, and a reduction in the need for inhaled antibiotics,[5] as well as enhanced quality of life, nutritional status, and survival.[6,7] However, there is still limited knowledge regarding the impact of this combination on the small airways.

In this study, we aimed to identify the functional and imaging outcomes of patients who initiated treatment with the ELX/TEZ/IVA combination, in order to assess its impact on small airways disease. We also aimed to compare the outcomes of ELX/TEZ/IVA treatment

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Financial support: None.

ISSN 1806-3756

between F508del homozygous patients and F508del heterozygous patients.

METHODS

This was a retrospective, observational, single-center study of adult CF patients followed at the Cystic Fibrosis Referral Center of the Hospital de Santa Maria, in the city of Lisbon, Portugal, who started treatment with ELX/TEZ/IVA and continued it for at least one year. Patient recruitment was conducted between September and November of 2024.

The collected data included age; sex; *CFTR* genotype; date of treatment initiation; prior treatment with other CFTR modulators; lung function, at baseline and after one year of treatment; and imaging findings on chest CT performed prior to the initiation of ELX/TEZ/IVA and after at least one year of treatment. Relevant medical histories were evaluated by reviewing patient medical records.

Lung function parameters were obtained through spirometry and plethysmography. Small airways function was assessed by measuring $FEF_{25-75\%}$, expressed in liters/second and as a percentage of the predicted value, calculating the RV/TLC ratio, and looking for a non-homogeneous ground-glass opacity pattern on chest CT. Improvement in the non-homogeneous ground-glass opacity pattern was subjectively assessed by a thoracic radiologist, who evaluated chest CT scans (performed during inspiration and expiration) and compared them to the previous scans. The impact that treatment with ELX/TEZ/IVA had on obstruction of the larger airways was also assessed by measuring FEV_1, expressed in liters.

Because the study period overlapped with the transition to new Global Lung Function Initiative equations, some pulmonary function tests (PFTs) were conducted using the old equations and more recent PFTs were conducted using the new equations. Therefore, the analysis of the results focused on the comparison of absolute values, given that the use of different equations for predicting reference values could introduce bias. Advanced lung disease was defined as an FEV_1 < 40% of the predicted value.

Lung function data were collected as close as possible to (before) the initiation of ELX/TEZ/IVA therapy (often on the same day). However, due to the constraints imposed by the COVID-19 pandemic, the median time from the pre-treatment lung function evaluation to the initiation of therapy was 82.55 days (IQR: 17.75-102.0 days). For the post-treatment evaluation, the PFT conducted soonest after at least 12 months of therapy was selected. The median time from the initiation of therapy to the follow-up PFT was 439.0 days (IQR: 385.3-491.8 days).

For descriptive statistics, continuous variables with normal distribution are presented as mean ± standard deviation, whereas the remaining data are expressed as median and interquartile range. Categorical variables are reported as absolute and relative frequencies. The mean differences between subgroups were analyzed by t-test for independent samples if the data had a normal distribution and by Mann-Whitney U test if the data had a non-normal distribution. Pre- and post-treatment comparisons of data with normal and non-normal data distribution were made with t-test for paired samples and the Wilcoxon test, respectively. Categorical variables were analyzed by using the chi-square test for independent comparisons and McNemar's test for paired comparisons. Values of $p < 0.05$ were considered statistically significant. Statistical analysis was performed with the IBM SPSS Statistics software package, version 28.0 (IBM Corp., Armonk, NY, USA).

RESULTS

During the study period, a total of 74 adult patients were followed at our referral center for CF. Of those, 55 were eligible for ELX/TEZ/IVA therapy, in agreement with national recommendations. Nine patients were excluded because they had been on the therapy for less than 12 months and 2 because they were on a clinical trial of another CFTR modulator.

Patient recruitment, enrollment, and follow-up are depicted in Figure 1. Table 1 summarizes the demographic and clinical features of the study cohort at baseline. The mean age at the diagnosis of CF was 13.4 ± 12.5 years. The mean age at initiation of ELX/TEZ/IVA therapy was 31.9 ± 12.5 years. Advanced lung disease was seen in 8 (18.2%) of the 44 patients.

After 12 months of ELX/TEZ/IVA therapy, there was a median increase of 0.42 L/s in the $FEF_{25-75\%}$ ($p < 0.001$) and a 5% reduction in the mean RV/TLC ratio ($p < 0.001$). A post-treatment improvement in the non-homogeneous ground-glass opacity pattern was observed in 35 (79.5%) of the 44 patients evaluated. The median time from the initiation of therapy to the follow-up chest CT was 623.0 days (IQR: 424.3-795.0 days). Of the 17 patients in the F508del homozygous group, 14 (82.4%) showed improvement in that pattern, compared with 77.8% of the 27 patients in the heterozygous group. Even among the 8 patients with advanced lung disease, 7 (87.5%) exhibited radiological improvement in the pattern. Among the 11 patients previously treated with other CFTR modulators, 8 (72.7%) showed radiological improvement in the non-homogeneous ground-glass opacity pattern.

The degree of improvement in FEV_1, as an absolute value and as a percentage of the predicted value, was similar between the F508del homozygous patients and the F508del heterozygous patients (Table 2). As shown in Figure 2, the improvements in the small airways, as assessed by measuring the $FEF_{25-75\%}$ (in L/s) and the RV/TLC ratio, were greater in the F508del homozygous patients, although the differences in comparison with the F508del heterozygous patients were not statistically significant ($p = 0.947$ and $p = 0.723$, respectively).

DISCUSSION

The benefits of highly effective CFTR modulator therapy for lung function, particularly for improving FEV_1, are well-established in the literature.[7-10] To our knowledge, data on the impact of such therapies on the small airways are sparse. In this real-world study, we have provided clear evidence of the positive impact that 12 months of treatment with ELX/TEZ/IVA has on the small airways, observing a median improvement of 0.42 L/s in the $FEF_{25-75\%}$ and a 5% reduction in the mean RV/TLC ratio. When evaluating the impact on patients with advanced lung disease, we observed statistically significant improvements across all parameters assessed. The greatest improvement was seen in the RV/TLC ratio, whereas the improvement in the $FEF_{25-75\%}$, albeit statistically significant, was more modest.

Although trends in improvement in the small airways were observed in patients previously treated with other CFTR modulators, those changes were not statistically significant. That might reflect a gain achieved with previous treatment, rendering further improvement more challenging to assess.

We also observed improvements in the non-homogeneous ground-glass opacity pattern on chest CT, in homozygous and heterozygous patients, as well as in those previously treated with other CFTR modulators, and even in patients with advanced lung disease.

These results highlight the potential of ELX/TEZ/IVA therapy to target small airway dysfunction, which is critical in the management of CF. Further studies are needed in order to assess the long-term effects of this therapy on the small airways, as well as its relationship with patient-reported outcomes.

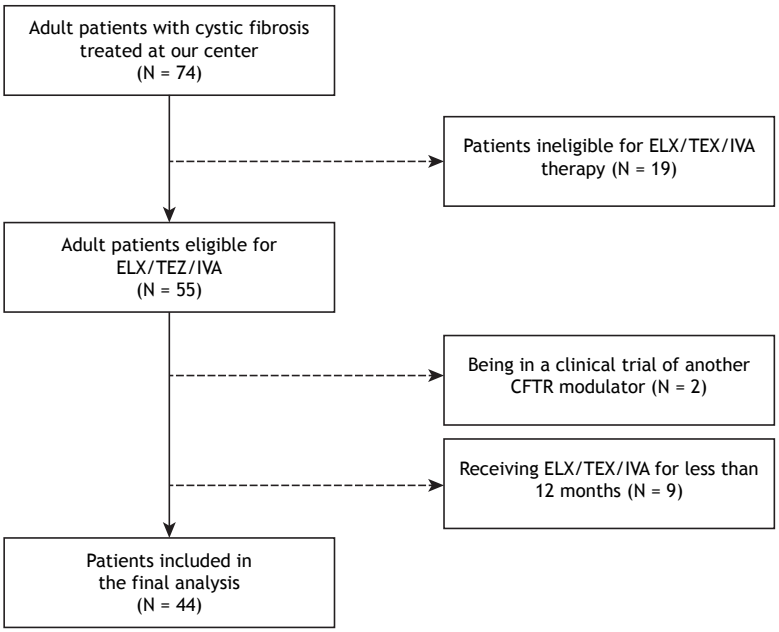

Figure 1. Flow chart of patient recruitment and enrollment. ELX/TEZ/IVA: elexacaftor/tezacaftor/ivacaftor; and CFTR: cystic fibrosis transmembrane conductance regulator.

Table 1. Clinical and demographic characteristics of the patients included in the study.

Variable	(N = 44)
Sex, n (%)	
Female	22 (50.0)
Male	22 (50.0)
Age (years) at CF diagnosis, mean ± SD	13.4 ± 12.5
Age (years) at ELX/TEZ/IVA initiation, mean ± SD	31.9 ± 12.5
CFTR genotype, n (%)	
Homozygous F508del	17 (38.6)
F508del/R334W	7 (15.9)
F508del/P205S	4 (9.1)
F508del/R1066C	2 (4.5)
Other heterozygous F508del	14 (31.8)
Prior CFTR modulator therapy[a], n (%)	11 (25.0)
Advanced lung disease, n (%)	8 (18.2)

ELX/TEZ/IVA: elexacaftor/tezacaftor/ivacaftor; and CFTR: cystic fibrosis transmembrane conductance regulator. [a]Two patients were previously treated with TEZ/IVA, and nine were previously treated with lumacaftor/IVA.

Table 2. Effects of elexacaftor/tezacaftor/ivacaftor treatment on FEV_1, $FEF_{25-75\%}$, and the RV/TLC ratio in patients with cystic fibrosis (N = 44).

Group	Outcome measure	Baseline Value [95% CI]	Follow-up Value [95% CI]	Difference Value [95% CI]	p
Overall	FEV_1 (L), mean	2.06 [1.80 to 2.33]	2.49 [2.18 to 2.76]	0.42 [0.28 to 0.57]	< 0.001
	FEV_1 (% pred.), mean	60.11 [53.92 to 66.30]	73.36 [66.46 to 80.26]	13.25 [9.25 to 17.25]	< 0.001
	$FEF_{25-75\%}$ (L/s), median	0.98 [0.91 to 1.42]	1.22 [1.33 to 2.11]	0.42 [0.22 to 0.70]	< 0.001
	$FEF_{25-75\%}$ (% pred.), median	24.00 [21.88 to 34.51]	31.00 [32.22 to 49.33]	10.0 [6.50 to 15.50]	< 0.001
	RV/TLC ratio, mean	44.80 [41.06 to 49.29]	39.80 [35.53 to 42.31]	−5.0 [−7.55 to −2.44]	< 0.001
F508del homozygous	FEV_1 (L), mean	2.19 [1.57 to 2.54]	2.61 [1.94 to 2.92]	0.42 [0.22 to 0.63]	0.01
	FEV_1 (% pred.), mean	64.76 [48.73 to 73.74]	76.88 [61.22 to 84.01]	12.12 [6.90 to 17.40]	< 0.001
	$FEF_{25-75\%}$ (L/s), median	1.42 [0.98 to 1.83]	1.45 [1.33 to 2.47]	0.46 [0.10 to 0.81]	0.010
	$FEF_{25-75\%}$ (% pred.), median	35.50 [22.92 to 45.58]	39.00 [31.49 to 58.15]	10.00 [0.30 to 17.00]	0.009
	RV/TLC ratio, mean	43.37 [36.82 to 49.85]	37.72 [31.09 to 44.35]	−5.62 [−8.66 to −2.58]	0.002
F508del heterozygous	FEV_1 (L), mean	1.99 [1.60 to 2.37]	2.41 [1.97 to 2.87]	0.42 [0.22 to 0.63]	< 0.001
	FEV_1 (% pred.), mean	57.19 [49.51 to 67.24]	71.15 [62.03 to 83.30]	13.96 [8.09 to 19.84]	< 0.001
	$FEF_{25-75\%}$ (L/s), median	0.73 [0.68 to 1.34]	1.11 [1.06 to 2.15]	0.37 [0.13 to 1.25]	0.001
	$FEF_{25-75\%}$ (% pred.), median	18.60 [16.65 to 31.91]	27.00 [26.49 to 49.95]	10.00 [5.5 to 20.5]	< 0.001
	RV/TLC ratio, mean	45.60 [39.92 to 51.27]	40.93 [36.38 to 45.48]	−4.67 [−8.40 to −0.93]	0.017
Advanced lung disease	FEV_1 (L), mean	1.00 [0.82 to 1.10]	1.34 [1.03 to 1.51]	0.34 [0.17 to 0.52]	0.019
	FEV_1 (% pred.), mean	33.38 [28.76 to 36.37]	45.63 [34.27 to 53.73]	12.25 [5.49 to 19.01]	0.036
	$FEF_{25-75\%}$ (L/s), median	0.43 [0.31 to 0.59]	0.54 [0.38 to 0.90]	0.16 [0.02 to 0.36]	0.028
	$FEF_{25-75\%}$ (% pred.), median	10.50 [9.0 to 14.00]	14.00 [11.00 to 23.00]	4.50 [5.00 to 9.00]	0.034
	RV/TLC ratio, mean	62.23 [55.05 to 69.42]	54.73 [45.10 to 64.36]	−7.51 [−11.37 to −3.64]	0.002
Prior CFTR modulator therapy	FEV_1 (L), mean	2.36 [1.55 to 2.88]	2.71 [1.76 to 3.08]	0.35 [0.08 to 0.61]	0.016
	FEV_1 (% pred.), mean	71.36 [51.98 to 85.17]	81.27 [59.10 to 92.62]	9.91 [3.02 to 16.80]	0.009
	$FEF_{25-75\%}$ (L/s), median	1.35 [1.14 to 3.12]	1.46 [1.07 to 2.31]	0.38 [0.14 to 0.82]	0.139
	$FEF_{25-75\%}$ (% pred.), median	37.00 [27.00 to 49.96]	39.00 [29.00 to 64.50]	8.00 [2.0 to 17.0]	0.109
	RV/TLC ratio, mean	39.26 [33.26 to 45.25]	34.51 [29.39 to 39.64]	−4.74 [−10.17 to −0.68]	0.076

% pred.: percentage of the predicted value.

AUTHOR CONTRIBUTIONS

SCS and EF: patient follow-up; data collection; statistical analysis; and drafting of the manuscript. AB and MC: patient follow-up; and data collection. PA: study conception and design; and patient follow-up. All the authors revised the manuscript, approved the final version as submitted, and agree to be accountable for all aspects of the work.

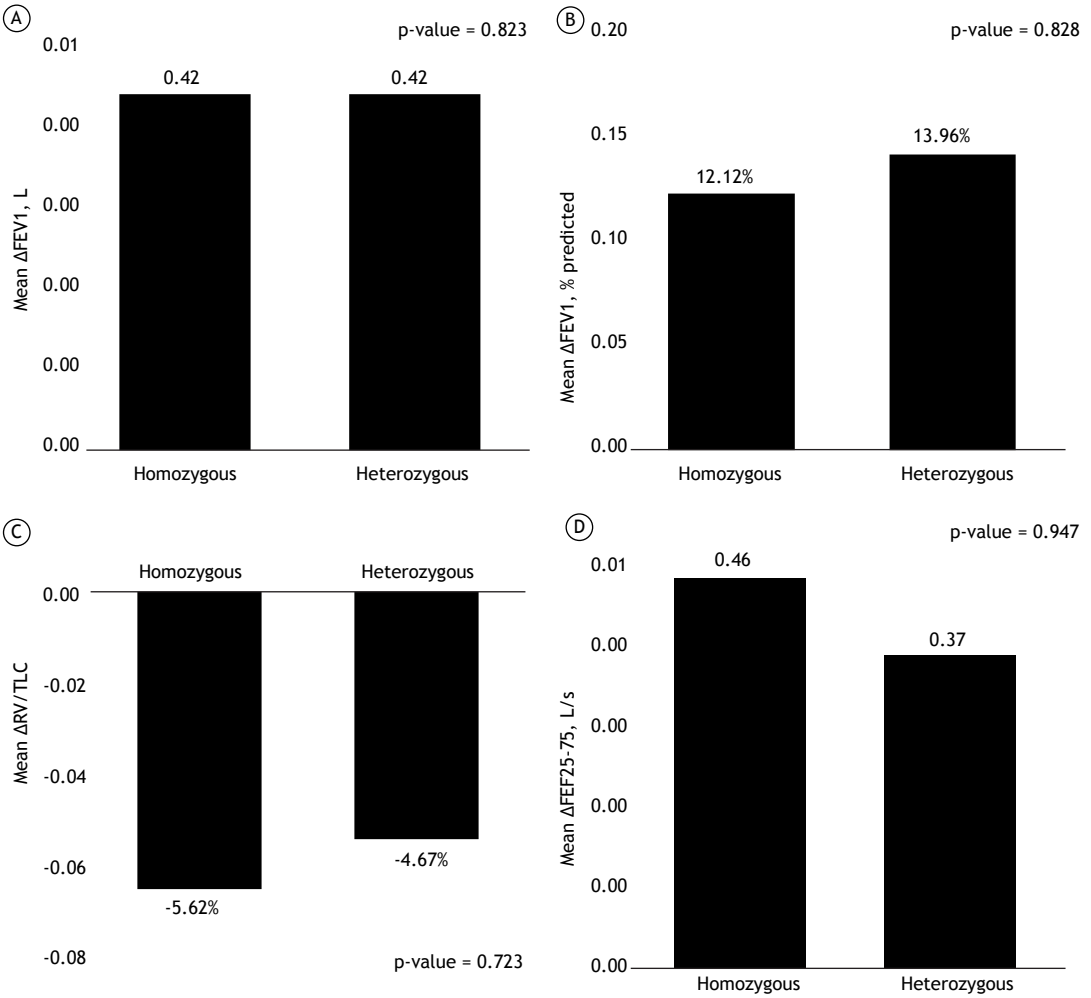

Figure 2. Differences in outcomes between F508del homozygous and F508del heterozygous patients.

CONFLICTS OF INTEREST

EF receives speaking and lecture fees from Vertex Pharmaceuticals, Inc. PA receives consulting or advisory fees, as well as speaking and lecture fees, from Vertex Pharmaceuticals, Inc.

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J Bras Pneumol. 2025;51(2):e20240416
https://dx.doi.org/10.36416/1806-3756/e20240416

Depression and anxiety in adolescents with cystic fibrosis in Brazil: prevalence, stability over time, and relationship with treatment adherence

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Submitted: 9 January 2015.
Accepted: 18 February 2025.

ABSTRACT

Objective: Depression and anxiety have been documented in people with cystic fibrosis (CF), jeopardizing treatment adherence. To date, no studies have assessed the prevalence of psychosocial issues in adolescents with CF in Brazil. We sought to assess the prevalence of depression and anxiety in adolescents with CF in Brazil, as well as the impact of depression and anxiety on treatment adherence. **Methods:** This was a multicenter, prospective, observational, longitudinal study conducted between 2017 and 2019 at 14 CF referral centers in Brazil. We used standardized tools such as the nine-item Patient Health Questionnaire (for depression), the seven-item Generalized Anxiety Disorder scale (for anxiety), and the eight-item Morisky Medication Adherence Scale (for treatment adherence) in order to collect data on 218 CF patients at two different time points. **Results:** The prevalence of depression was 19.1% at time point 1 and 15.4% at time point 2. The prevalence of anxiety was 19.1% at time point 1 and 18.0% at time point 2. Depression and anxiety were significantly higher in female patients and lower in those who underwent home physiotherapy or had psychological support. Significant correlations were found between depression and anxiety at both time points, the associations being strongest at time point 1 ($r = 0.68$; $p < 0.001$). Most (66.7%) of the study participants reported low adherence to treatment, and the remainder reported either average adherence (in 28%) or high adherence (in 5.3%). Depression and anxiety showed inverse correlations with treatment adherence. **Conclusions:** The prevalence of depression and anxiety in adolescents with CF in Brazil appears to be similar to that reported in other countries, being higher in females and lower in those undergoing home physiotherapy or receiving psychological care. Depression and anxiety appear to correlate with lower treatment adherence. Treating psychosocial issues may effectively improve rates of treatment adherence in adolescents with CF.

Keywords: Cystic fibrosis; Anxiety; Depression; Treatment adherence and compliance; Adolescent.

INTRODUCTION

In a recent systematic review and meta-analysis including 26 studies conducted across European and North American countries, the mean prevalence of depression in people with cystic fibrosis (CF) was found to be 18.7% in North America and 13.3% in Europe, and the mean prevalence of anxiety was found to be 23.6% in North America and 26.8% in Europe.[1] Additionally, studies have shown that depression and anxiety are associated with a higher number of pulmonary exacerbations, worse

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◄ Voltar ao sumário
ISSN 1806-3756

adherence to prescribed treatments, missed clinic visits, and worse health-related quality of life (HRQoL).[2] The objective of the aforementioned systematic review and meta-analysis was to determine the level of anxiety and depression among people with CF worldwide.[1] However, data from Latin American countries such as Brazil were not included in that study.[3-5] There are approximately 5,128 CF patients registered with the *Grupo Brasileiro de Estudos de Fibrose Cística* (Brazilian Cystic Fibrosis Study Group); of those, 1,590 (31%) are adolescents.[6]

CF is a progressive lung disease that affects multiple organ systems and leads to frequent pulmonary exacerbations; worse energy and physical functioning; difficulty gaining and maintaining weight; and an increased number of days in hospital. Disease progression increases limitations in daily activities, treatment burden, and uncertainty about the future. These stressors are associated with increased symptoms of depression and anxiety, as well as with medical traumatic stress and worsening HRQoL.[3,7-11] There are currently no data on the prevalence of depression and anxiety in CF patients or the impact of depression and anxiety on CF management in Brazil or other Latin American countries.

Most of the CF patients followed at referral centers in Brazil have class I or II mutations in the cystic fibrosis transmembrane conductance regulator (*CFTR*) gene, all of which are associated with severe forms of CF that lead to multisystem involvement.[6] Disease severity has been correlated with an increased prevalence of depression and anxiety in some studies. Graziano et al.[5] found a high prevalence of depression as reported by patients with CF and their parents (adolescents, 37%; adults, 45%; and parents, 49%). Symptoms of anxiety were also highly prevalent (adolescents, 48%; adults, 46%; and parents, 66%). In a landmark study including more than 6,000 adolescents and adults with CF and over 4,200 caregivers across nine countries, symptoms of depression and anxiety were found to be 2-3 times more common in CF patients than in community samples.[3]

Quittner et al.[11] found that 19% of adolescents with CF, 29% of adults with CF, 34% of mothers of patients with CF, and 25% of fathers of patients with CF were above the clinical cutoff for the Center for Epidemiological Studies Scale for Depression, and 22% of adolescents with CF, 32% of adults with CF, 48% of mothers of patients with CF, and 36% of fathers of patients with CF were above the clinical cutoff for the Hospital Anxiety and Depression Scale. Although a number of studies have been published on rates of depression and anxiety in Europe and North America, studies of mental health in countries with higher rates of economic and cultural inequality, such as Brazil, are scarce, the exception being a study performed in Turkey and reporting higher prevalences of depression and anxiety in children and adolescents with CF in comparison with a control group.[12]

Following the publication of the aforementioned landmark study,[3] the European Cystic Fibrosis Society and the Cystic Fibrosis Foundation developed international guidelines on mental health screening and treatment, recommending close patient monitoring; annual screening of depression and anxiety; and adoption of appropriate prevention and intervention strategies.[3,11,13] New CF-specific cognitive behavioral therapy interventions have been developed in the USA and are being disseminated in Europe and Australia.[14-17]

The objectives of the present epidemiological study were as follows: to assess the prevalence of depression and anxiety in adolescents with CF followed at referral centers in Brazil; to examine the stability of depression and anxiety scores over time; to assess self-reported adherence to CF treatments; and to evaluate the relationship of depression and anxiety with sociodemographic variables and rates of treatment adherence.

METHODS

Study design and setting

This was a multicenter, prospective, observational, longitudinal study conducted at 14 CF referral centers in Brazil, with data collection occurring between 2017 and 2019. All of the patients followed at the 14 participating centers were invited to participate in the study, as were their caregivers. The inclusion criteria were being in the 10- to 19-year age bracket and having a diagnosis of CF confirmed by two or more sweat chloride measurements ≥ 60 mEq/L and/or two disease-causing mutations in the *CFTR* gene. A total of 218 patients were enrolled in the study, corresponding to 13.7% of 1,590 adolescents included in the Brazilian Cystic Fibrosis Registry. All participating patients were asked if they were undergoing psychological/psychiatric treatment and if they were taking any psychoactive drugs.

Procedures

During a routine outpatient visit, the study participants completed questionnaires assessing depression, anxiety, and treatment adherence, as well as completing a sociodemographic form. The stability of scores over time was assessed at two different time points, at least three months apart.

The study was approved by the institutional review boards of all participating centers including the coordinating center (Protocol no. 1.851.482). The study was conducted in accordance with the ethical standards established in Brazilian National Health Council Resolution no. 466/2012.

Written informed consent was obtained from all the participants. In the case of participants < 18 years of age, consent was obtained from their caregivers.

Measures

Demographic and medical variables

We collected data on the following demographic variables: sex; age; age at diagnosis of CF; and level

of education. In addition, we collected data on the following anthropometric and medical variables: height for age; BMI; Shwachman-Kulczycki scores; FEV_1; FVC; FEV_1/FVC; $FEF_{25-75\%}$; use of oxygen therapy; home physiotherapy; bacterial colonization of the airways; chronic use of azithromycin; pancreatic insufficiency; liver disease; CF-related diabetes; and newborn screening for CF. Furthermore, we collected data on the following psychosocial variables: a diagnosis of anxiety, depression, or both; prior referral for psychological or psychiatric treatment; and use of psychoactive drugs.

The following patient-reported outcome measures were administered: the nine-item Patient Health Questionnaire (PHQ-9),[18,19] the seven-item Generalized Anxiety Disorder (GAD-7) scale,[19] and the eight-item Morisky Medication Adherence Scale (MMAS-8),[20] all of which were used after permission was granted from the original authors.

The PHQ-9

The PHQ-9[18,19] is a self-report measure of depressive symptoms mapping on to the diagnostic criteria for depression. The PHQ-9 was developed by Spitzer et al.[18] and validated for use by Kroenke et al.[18] It has extensive evidence of reliability (Cronbach's alpha = 0.86-0.89), validity, sensitivity, and specificity. Each symptom is rated on a four-point scale ranging from 0 (not at all) to 3 (nearly every day) over the past two weeks; one question asks about suicidal ideation. Depression is categorized as no symptoms (0-4), mild (5-9), moderate (10-14), or severe (> 15). We used a Brazilian Portuguese version of the PHQ-9, validated for use in Brazil by Osório et al.[21]

The GAD-7 scale

The GAD-7 scale[19] is a self-report measure assessing generalized anxiety, with extensive evidence of reliability (Cronbach's alpha = 0.92) and validity. Each symptom is rated on a four-point scale from 0 (not at all) to 3 (nearly every day) over the past two weeks. Anxiety is categorized as no symptoms (0-4), mild (5-9), moderate (10-14), or severe (> 15). The GAD-7 scale was developed by Spitzer et al.[19] and validated for use by Kroenke et al.[18] on the basis of Diagnostic and Statistical Manual of Mental Disorders, fourth edition criteria. It was translated into Portuguese and validated for use in Brazil by the Mapi Research Trust in 2006.

The MMAS-8

The MMAS-8 was administered to assess adherence to prescribed medications and treatments. It is a brief, self-report scale developed by Morisky et al.[21] and validated for use in Brazil by Oliveira-Filho et al.[22] Scores range from 0-8, as follows: 8, high adherence; 6-7, average adherence; and < 6, low adherence. MMAS-8 scores were collapsed into two categories: low adherence and average/high adherence.

Statistical analysis

Data were collected and entered into a database created with the IBM SPSS Statistics software package, version 26.0 for Windows (IBM Corporation, Armonk, NY, USA). Normality was assessed by the Kolmogorov-Smirnov test. For analysis of associations between continuous and categorical variables, the Mann-Whitney test was used. Associations between categorical variables were assessed by the chi-square test.

Associations between two continuous variables were evaluated by Pearson's correlation coefficients. For assessment of agreement between depression and anxiety at two different time points, intraclass correlation coefficients were computed. The level of significance was set at $p \leq 0.05$.

RESULTS

A total of 218 adolescents with CF followed at any of 14 CF referral centers in Brazil participated in the study. Figure 1 shows the numbers and proportions of patients from each center.

Characteristics of the study population

A nationally representative sample was recruited for the present epidemiological study. Overall, girls were significantly older; had significantly lower FEV_1, FEV_1/FVC, and $FEF_{25-75\%}$; and had been using azithromycin for longer. No significant differences between boys and girls were found for the remaining variables (Table 1).

Prevalence of depression and anxiety; stability of anxiety and depression scores over time; and adherence to treatment

PHQ-9 scores showed that 19.1% of the study participants were depressed at time point 1. The prevalence of depression decreased slightly at time point 2, to 15.4%. PHQ-9 scores ranged from 0 to 23 at time point 1 (with a median score of 4) and from 0 to 24 at time point 2 (with a median score of 3). GAD-7 scale scores showed that 19.1% of the study participants suffered from anxiety at time point 1, with a similar proportion (18%) at time point 2. GAD-7 scale scores ranged from 0 to 20 at both time points, with a median score of 4. Girls reported a higher prevalence of depression and anxiety at both time points than did boys.

With regard to the stability of anxiety and depression scores over time, intraclass correlation coefficients showed a high degree of stability. The level of agreement between depression scores at the two time points was high (intraclass correlation coefficient = 0.81; $p < 0.001$), with similarly high rates of stability for anxiety (intraclass correlation coefficient = 0.78; $p < 0.001$).

With regard to the rates of treatment adherence, most (66.7%) of the study participants had low adherence as assessed by the MMAS-8, with 28% reporting moderate adherence and only 5.3% reporting high adherence (Table 2). Treatments were prescribed in

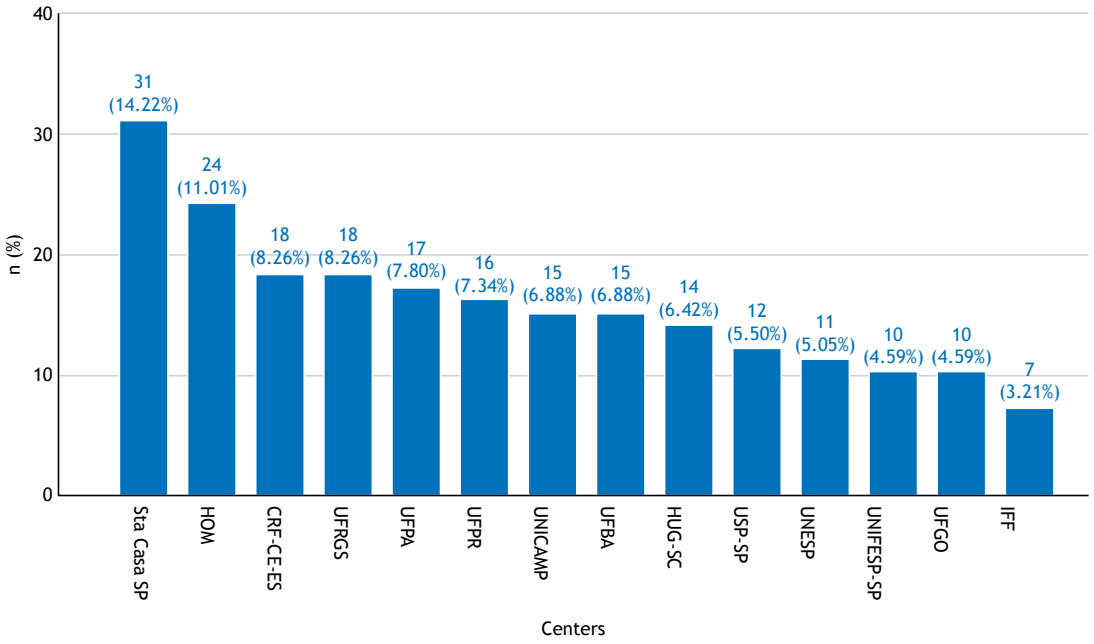

Figure 1. Numbers and proportions of patients from the 14 cystic fibrosis referral centers participating in the present study. Sta Casa SP: *Irmandade da Santa Casa de Misericórdia de São Paulo* (located in the city of São Paulo, Brazil); HOM: *Hospital Otavio Mangabeira* (located in the city of Salvador, Brazil); UFRGS: *Universidade Federal do Rio Grande do Sul* (located in the city of Porto Alegre, Brazil); CRFC-ES: *Centro de Referência em Fibrose Cística do Espírito Santo* (located in the city of Vitória, Brazil); UFPA: *Universidade Federal do Pará* (located in the city of Belém, Brazil); UFPR: *Universidade Federal do Paraná* (located in the city of Curitiba, Brazil); UFBA: *Universidade Federal da Bahia* (located in the city of Salvador, Brazil); UNICAMP: *Universidade Estadual de Campinas* (located in the city of Campinas, Brazil); HJG-SC: *Hospital Joana de Gusmão – Santa Catarina* (located in the city of Florianópolis, Brazil); USP: *Universidade de São Paulo* (located in the city of São Paulo, Brazil); UNESP: *Universidade Estadual Paulista* (located in the city of Botucatu, Brazil); UFGO: *Universidade Federal de Goiás* (located in the city of Goiânia, Brazil); UNIFESP: *Universidade Federal de São Paulo* (located in the city of São Paulo, Brazil); and IFF: *Instituto Fernandes Figueira* (located in the city of Rio de Janeiro, Brazil).

accordance with Brazilian guidelines for the diagnosis and treatment of CF.[23] Primary treatments were provided by the Brazilian Unified Health Care System and included pancreatic enzyme replacement therapy for pancreatic insufficiency; dornase alfa for recurrent pulmonary symptoms; and inhaled tobramycin or colistin for gram-negative bacteria in sputum culture. The triple combination of elexacaftor, tezacaftor, and ivacaftor has yet to be approved for use in Brazil. Scores for depression, anxiety, and treatment adherence are summarized in Table 2.

Some of the independent variables showed an association with psychosocial outcomes. Patients with depression were significantly older at both time points. The age at diagnosis of CF was significantly higher in the patients with anxiety and depression at both time points. Patients undergoing home physiotherapy had lower prevalences of depression and anxiety at both time points, as well as higher treatment adherence rates. Patients without depression (at both time points) or anxiety (at time point 2) had significantly higher Shwachman-Kulczycki general activity domain scores. Patients with high or medium treatment adherence rates had significantly higher Shwachman-Kulczycki radiological findings domain scores (Table 3).

Symptoms of depression were positively correlated with symptoms of anxiety at both time points. As predicted, depression and anxiety were negatively correlated with rates of treatment adherence (Table 4).

DISCUSSION

This is the first study in Latin America to assess mental health in adolescents with CF, measuring the prevalence of depression and anxiety at 14 CF referral centers across Brazil. Using patient-reported outcome measures recommended by the International Committee on Mental Health in Cystic Fibrosis,[11] we found that 15.4-19.1% of the adolescents with CF in the present study reported elevated symptoms of depression, and 18-19.1% reported elevated symptoms of anxiety. Although the rates of depression in the present study were higher than those reported elsewhere,[3] they were similar to those reported in other studies using the same screening tools.[1,5,15] These results show that one of five adolescents with CF is struggling with mental health challenges. Routine, standardized mental health screening is likely to improve the quality of care for individuals with CF.

The prevalence of depression in the present study was 19.1% at time point 1 and 15.4% at time point

Table 1. General characteristics of the study population, by sex.[a]

	Total sample (N = 218)	Males (n = 101)	Females (n = 117)	p
Age, years	14.86 [9.90-20.83]	14.16 [10.15-20.77]	15.52 [9.90-20.83]	0.03*
Age at diagnosis of CF, years	1.67 [0.02-19.36]	1.09 [0.04-15.86]	2.70 [0.02 - 19.36]	0.14*
Completed high school	40 (18.9%); 95% CI, 14.2-24.7	18 (17.8%); 95% CI, 11.6-26.4	22 (19.6%); 95% CI, 13.3-27.9	0.71**
Short stature	28 (13.3%); 95% CI, 9.3-18.5	13 (13.3%); 95% CI, 7.9-21.4	15 (13.3%); 95% CI, 8.2-20.7	0.99**
Malnutrition	40 (19.0%); 95% CI, 14.2-24.8	20 (20.4%); 95% CI, 13.6-29.4	20 (17.7%); 95% CI, 11.8-25.8	0.62**
Shwachman-Kulczycki score	80 [40-100]	80 [45-100]	75 [40-100]	0.17*
FEV_1, % predicted	78 [17-143]	84 [17-143]	66.75 [17-121]	0.02*
FVC, % predicted	87 [26.80-141.00]	91 [32-147]	85 [26.8-129]	0.07*
FEV_1/FVC	84.77 [13.82-114.76]	87.88 [43.82-114.76]	83.11 [54.72-111.96]	0.01*
$FEF_{25-75\%}$	56 [6-210]	66 [6-210]	42.5 [6-135]	0.01*
Pancreatic insufficiency	174 (80.9%); 95% CI, 77.1-85.6	80 (79.2%); 95% CI, 70.3-86.0	94 (82.5%); 95% CI, 74.4-88.3	0.54**
Liver disease	44 (21.9%); 95% CI, 16.7-28.1	21 (21.9%); 95% CI, 14.8-31.1	23 (21.9%); 95% CI, 15.1-30.7	0.99**
Diabetes	22 (10.7%); 95% CI, 7.2-15.7	8 (8.2%); 95% CI, 4.2-15.4	14 (12.9%); 95% CI, 7.9-20.6	0.28**
Chronic airway colonization	142 (71.4%); 95% CI, 64.7-77.2	64 (67.4%); 95% CI, 57.4-76.0	78 (75.0%); 95% CI, 65.9-82.3	0.23**
Chronic airway colonization with *Pseudomonas aeruginosa*	101 (53.2%); 95% CI, 46.1-60.1	49 (59.8%); 95% CI, 48.9-69.7	52 (48.1%); 95% CI, 38.9-57.0	0.15**
Home physiotherapy	158 (75.6%); 95% CI, 69.3-80.9	71 (74.0%); 95% CI, 64.4-81.7	87 (77.0%); 95% CI, 68.4-83.8	0.61**
Home oxygen therapy	12 (5.7%); 95% CI, 3.3-9.7	4 (4.0%); 95% CI, 1.6-9.9	8 (7.2%); 95% CI, 3.7-13.6	0.32**
Azithromycin use	109 (55.9%); 95% CI, 48.9-62.7	41 (46.1%); 95% CI, 36.1-56.4	68 (64.1%); 95% CI, 54.7-72.6	0.01**
Previous psychological evaluation	40 (47.6%); 95% CI, 37.3-58.2	18 (46.1%); 95% CI, 31.7-61.4	22 (48.9%); 95% CI, 35.0-63.0	0.23**
Psychotropic drug use	11 (11.3%); 95% CI, 6.4-19.2	3 (6.8%); 95% CI, 2.3-18.2	8 (1.5%); 95% CI, 7.8-27.0	0.20**

[a]Data expressed as n (%) or median [IQR]. *Mann-Whitney test ($p < 0.05$). **Chi-square test ($p < 0.05$).

2. Elevated rates of anxiety were found in 19.1% at time point 1 and in 18% at time point 2. Importantly, these rates are 2-3 times higher than those found in community samples.[23] These results are similar to those reported in a recent systematic review and meta-analysis of people with CF, with an overall prevalence of 12.7% for depression and 26.2% for anxiety varying across countries.[1,2,10] The authors of the aforementioned systematic review and meta-analysis concluded that there is an urgent need for systematic screening and a multidisciplinary approach to addressing mental health concerns in people with CF to reduce complications and the negative impact of depression and anxiety on HRQoL.[3]

A document from the WHO states that Brazil is one of the countries in the world with the highest prevalence of anxiety and depression in the general population (9.3% and 5.8%, respectively).[24] Graziano et al.[5] showed that almost half of adolescents with CF reported elevated (mostly mild) depression, although 30% were found to have moderate to severe depression.

In the present study, depression and anxiety were both significantly correlated with worse treatment adherence. Self-reported adherence was low in the present study, with most of the study participants falling into the poor adherence group (67%). Although CF medications are provided free of charge in the Brazilian Unified Health Care System, the prevalence of poor adherence to treatment was similar to that reported in other studies of CF, as well as in studies of other chronic diseases, in the absence of specific intervention.[23,25]

Table 2. Psychosocial outcomes in the study population, by sex.[a]

	Total sample (N = 218)	Males (n = 101)	Females (n = 117)	p
Depression at T1, PHQ-9	19.1%; 95% CI, 14.4-24.8	11.0%; 95% CI, 6.2-18.6	26.1%; 95% CI, 18.9-34.8	0.005*
Depression at T1, PHQ-9	4 [0-23]	3 [0-22]	5 [0-21]	0.03**
Depression at T2, PHQ-9	15.4%; 95% CI, 11.1-20.9	9.3%; 95% CI, 5.0-16.7	20.7%; 95% CI, 14.2-29.2	0.02*
Depression at T2, PHQ-9	3 [0-24]	3 [0-24]	3 [0-24]	0.46**
Anxiety at T1, GAD-7 scale	19.1%; 95% CI, 14.4-24.8	12.0%; 95% CI, 7.0-19.8	25.2%; 95% CI, 18.2-33.9	0.014*
Anxiety at T1, GAD-7 scale	4 [0-20]	3 [0-20]	6 [0-20]	0.005**
Anxiety at T2, GAD-7 scale	18.0%; 95% CI, 13.4-23.7	10.2%; 95% CI, 5.6-17.8	24.8%; 95% CI, 17.7-33.5	0.006*
Anxiety at T2, GAD-7 scale	4 [0-20]	3 [0-19]	5 [0-20]	0.06**
Treatment adherence, MMAS-8				0.54*
High	5.3%; 95% CI, 2.6-10.5	6.8%; 95% CI, 2.7-16.2	4.1%; 95% CI, 1.4-11.4	
Average	28.0%; 95% CI, 21.2-36.2	28.8%; 95% CI, 18.6-41.4	27.4%; 95% CI, 1.5-38.6	
Low	66.7%; 95% CI, 58.2-74.1	64.4%; 95% CI, 51.7-75.4	68.5; 95% CI, 57.1-78	
Treatment adherence, MMAS-8	5 [0-8]	5 [1-8]	5 [0-8]	0.93**

T1: time point 1; T2: time point 2; PHQ-9: nine-item Patient Health Questionnaire; GAD-7: seven-item Generalized Anxiety Disorder; and MMAS-8: eight-item Morisky Medication Adherence Scale. [a]Data expressed as % or median [IQR]. *Chi-square test ($p < 0.05$). **Mann-Whitney test ($p < 0.05$).

Table 3. Significant associations of depression, anxiety, and treatment adherence with independent variables.[a]

	Depression at T1 (prevalence - %)	Depression at T2 (prevalence - %)	Anxiety at T1 (prevalence - %)	Anxiety at T2 (prevalence - %)	Treatment adherence (prevalence - %) (High/Average vs. Low)
Age, years (median)	15.95 vs. 14.52 p = 0.04**	16.09 vs. 14.53 p = 0.02**	15.87 vs. 14.52 p = 0.10**	15.75 vs. 14.64 p = 0.11**	15.12 vs. 13.85 p = 0.08**
Age at CF diagnosis, years (median)	5.10 vs. 1.24 p = 0.003**	5.10 vs. 1.37 p = 0.02**	4.07 vs. 1.24 p = 0.007**	4.86 vs. 1.24 p = 0.004**	2.19 vs. 1.04 p = 0.34**
Home physiotherapy (Y vs. N)	15.8%; 95% CI, 10.9-22.3 vs. 28.0%; 95% CI, 17.5-41.7 p = 0.05*	12.3%; 95% CI, 8.0-18.5 vs. 25.5%; 95% CI, 15.2-39.5 p = 0.03*	14.6%; 95% CI, 10.0-21.0 vs. 29.4%; 95% CI, 18.7-43.0 p = 0.02*	14.6%; 95% CI, 10.0-21.0 vs. 29.8%; 95% CI, 18.6-44.0 p = 0.02*	39.3%; 95% CI, 29.8-49.7 vs. 20.5%; 95% CI, 10.8-35.5 p = 0.04*
Use of flutter or shaker (Y vs. N)	12.7%; 95% CI, 7.6-20.6 vs. 29.6%; 95% CI, 19.1-42.8 p = 0.01*	10.1%; 95% CI, 5.6-17.6 vs. 23.1%; 95% CI, (12.5-36.8) p = 0.03*	14.9%; 95% CI, 9.2-23.1 vs. 27.3%; 95% CI, 17.3-40.2 p = 0.06	15.8%; 95% CI, 10.0-24.2 vs. 24.5%; 95% CI, 14.9-37.6 p = 0.19	43.9%; 95% CI, 31.8-56.7 vs. 24.4%; 95% CI, 14.2-38.7 p = 0.04*
Liver disease (Y vs. N)	9.1%; 95% CI, 3.6-21.2 vs. 21.8%; 95% CI, 16.0-28.9 p = 0.08	4.7%; 95% CI, 1.3-15.5 vs. 17.9%; 95% CI, 12.6-24.8 p = 0.03*	11.4%; 95% CI, 4.9-24.0 vs. 22.4%; 95% CI, 11.6-29.6 p = 0.10	9.1%; 95% CI, 3.6-21.2 vs. 20.9%; 95% CI, 15.3-28.2 p = 0.08	56.5%; 95% CI, 36.8-74.4 vs. 29.2%; 95% CI, 21.0-38.9 p = 0.01*
Psychological referral (Y vs. N)	14.6%; 95% CI, 6.9-28.4 vs. 27.6%; 95% CI, 17.7-40.2 p = 0.13	17.1%; 95% CI, 8.5-31.3 vs. 18.5%; 95% CI, 10.4-30.8 p = 0.86	07.5%; 95% CI, 2.6-19.9 vs. 25.9%; 95% CI, 16.3-38.4 p = 0.02*	22.0%; 95% CI, 12.0-36.7 vs. 19.6%; 95% CI, 11.3-31.8 p = 0.78	31.7%; 95% CI, 19.6-46.7 vs. 36.2%; 95% CI, 25.1-49.1 p = 0.64
Shwachman-Kulczycki score, general activity (median)	20 vs. 25 p = 0.007**	20 vs. 25 p = 0.01**	25 vs. 25 p = 0.09	22 vs. 25 p = 0.04**	25 vs. 25 p = 0.50
Shwachman score, radiological findings (median)	15 vs. 15 p = 0.62	16.50 vs. 15 p = 0.91	19 vs. 15 p = 0.15	15 vs. 15 p = 0.88	15 vs. 10 p = 0.03**

T1: time point 1; T2; time point 2; CF: cystic fibrosis; N: no; and Y: yes. [a]Data expressed as % and 95% CI, except where otherwise indicated. *Chi-square test ($p < 0.05$). **Mann-Whitney test ($p < 0.05$).

Table 4. Correlations between treatment adherence and psychosocial outcomes.

	Adherence (MMAS-8)	Depression at T1 (PHQ-9)	Depression at T2 (PHQ-9)	Anxiety at T1 (GAD-7)	Anxiety at T2 (GAD-7)
Adherence (MMAS-8)					
Depression at T1(PHQ-9)	−0.42**				
Depression at T2 (PHQ-9)	−0.33**	0.69**			
Anxiety at T1 (GAD-7)	−0.34**	0.69**	0.55**		
Anxiety at T2 (GAD-7)	−0.22*	0.56**	0.72**	0.65**	

T1: time point 1; T2: time point 2; PHQ-9: nine-item Patient Health Questionnaire; GAD-7: seven-item Generalized Anxiety Disorder scale; and MMAS-8: eight-item Morisky Medication Adherence Scale. *Pearson's correlation coefficient ($p < 0.05$). **Pearson's correlation coefficient ($p < 0.01$).

Notably, other barriers affect treatment adherence, including symptoms of depression and anxiety.[26]

Several studies have found associations of depression and anxiety with worse health outcomes. Waters et al.[27] found that patients with elevated depression and anxiety had worse treatment adherence, lower lung function, lower BMI, more frequent hospitalizations, and worse HRQoL.

Modi et al.[28] assessed depression and anxiety in adolescents and young adults with CF and found that 32% reported elevated symptoms; females reported higher levels of anxiety than did males, and mental health scores were positively associated with age (r = 0.28-0.36). In a study comparing CF patients and controls in the 8- to 16-year age bracket in Turkey,[4] at least one psychiatric comorbidity was found in the group of patients with CF (in 68%, with 46% related to anxiety). Depression was three times more common in people with CF than in controls and was associated with worse disease severity, longer periods of hospitalization, and higher anxiety. In a follow-up study of participants in a landmark epidemiological study,[3] a single elevated depression screen was associated with a doubling of mortality over five years. Thus, elevated symptoms of depression and anxiety have profound consequences for disease management and health outcomes. These findings reinforce the need for adequate screening, diagnostic confirmation, and mental health care for people with CF.[29,30]

Given the high rates of depression and anxiety in adolescents with CF in Brazil, it is critical to note that mental health symptoms were lower in those receiving in-home physiotherapy (a form of support) and psychological referrals and interventions. In the USA, where screening for depression and anxiety is universal across CF centers, educational materials, training courses, and new evidence-based and psychological interventions have been developed. Implementation of mental health screening and treatment have been highly successful, with over 85% of CF centers reporting annual screening of all people with CF ≥ 12 years of age. Assessing mental health in people with CF has also gained greater importance in the context of new, highly effective modulators, which have been shown to have side effects that include worsening mental health, insomnia, and cognitive fogging.[31-36]

Our results in Brazil show the importance of annual screening and suggest that tools for evaluating depression, anxiety, and treatment adherence can be enormously useful for early detection and intervention, as well as for reducing stigma. The present study was conducted before the COVID-19 pandemic. Therefore, the rates of depression and anxiety were not a result of the pandemic. In fact, Smith et al. showed that mental health symptoms worsened in adolescents during the COVID-19 pandemic.[37]

The main limitation of our study is the fact that we used a convenience sample rather than collecting data using a randomized sampling strategy. However, given the high number of participating centers, we estimate that our sample size of 218 reflects an accurate profile of adolescents with CF in Brazil, corresponding to 23.1% of the 943 patients included in the Brazilian Cystic Fibrosis Registry in the same age range. It is noteworthy that our sample was larger than those of most of the studies included in a recent systematic review and meta-analysis.[2]

Identifying people with CF at a higher risk of poor treatment adherence and poor disease management is critically important as new medications, such as CFTR modulators, are released. Although CFTR modulators have dramatically improved clinical outcomes, quality of life, and life span, identifying CF patients with mental health challenges will be critical for sustaining adherence in this different era of CF care. To date, studies evaluating mental health outcomes after the introduction of the triple combination of elexacaftor, tezacaftor, and ivacaftor have failed to identify significant changes in the prevalence of depression in treated patients.[38,39] However, the possibility of confounding factors should be highlighted, given the multifactorial aspects of the pathogenesis of mental disorders.

Mental health screening is a brief, reliable way to assess patient well-being and can easily be incorporated into in-person (e.g., the medical assistant gives out

the screening forms once in the clinic room; they can also be given when patients are checked in) or telehealth visits. In a recent survey of people with CF and their families in Europe and the USA, mental health screening was viewed as a positive, supportive intervention on its own. It signaled to patients and families that the CF team was caring and concerned, and it opened the door to a discussion of various brief intervention strategies.[40] Future directions include conducting a prevalence study of depression, anxiety, and behavior problems in children > 12 years of age and developing a brief checklist of other mental health comorbidities (e.g., substance misuse and procedural anxiety/distress).

The adolescent patients with CF in the present study showed low rates of treatment adherence, similar to those observed in other cohorts of CF and other chronic diseases, in the absence of specific intervention; an inverse correlation between adherence, depression, and anxiety; an inverse correlation between adherence and age; a positive association between adherence and commitment to care (home physiotherapy and exacerbations treated at home); a direct correlation between depression and anxiety across two time periods; a direct correlation between age, depression, and anxiety; a higher prevalence of depression and anxiety in girls; a lower prevalence of depression and anxiety in patients undergoing home physiotherapy; and a lower prevalence of anxiety in patients receiving psychological care.

It is well known that anxiety and depression are multifaceted conditions that are not exclusively related to CF. Patients with CF may have other conditions leading to anxiety and depression (e.g., comorbidities and adolescence-related psychosocial factors). Future studies could employ a longitudinal design, including comparison with healthy controls, to allow multivariate analysis in the CF group. These aspects highlight the importance of systematic assessment of psychosocial factors in the life course of individuals with chronic diseases such as CF.

This is the first multicenter study on mental health in children and adolescents with CF in Brazil. We emphasize the importance of identifying high-risk groups with low treatment adherence, such as those with depression and anxiety. This can contribute to improving the standards of care for CF.

AUTHOR CONTRIBUTIONS

TR, JDR, ALQ: study design, manuscript writing, general coordination, and final review. MAGOR: database setup, local center coordination, data collection, manuscript writing, and final review. MTNS: data analysis, manuscript writing, and final review. ND, MAPS, PJCM, RCNCM, VCM, CAR, ELSS, NLN, RAA, FWY, LDCC, SMC, and IS: local center coordination, data collection, and manuscript review. BADAS: data collection and manuscript review. TR, MTNS, and MAGOR contributed equally to this study. JDR and ALQ contributed equally as senior authors.

CONFLICTS OF INTEREST

None declared.

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J Bras Pneumol. 2025;51(2):e20240167
https://dx.doi.org/10.36416/1806-3756/e20240167

Early discharge, inpatient treatment, or ICU management for patients with acute pulmonary embolism: is the guideline-recommended practice being followed?

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Submitted: 23 May 2024.
Accepted: 12 February 2025.

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ABSTRACT

Objective: To describe the rates of adherence to the 2019 European Society of Cardiology guideline recommendations on the setting of care for patients with acute pulmonary embolism (PE) of varying severity. **Methods:** This was a retrospective cohort study of PE patients treated in a referral hospital in Colombia between 2019 and 2022. **Results:** We analyzed 506 patients with acute PE (median age, 67 years). Of those, 58% were women, and 33% had a history of cancer. In-hospital mortality was 9.2%, and 30-day mortality was 17.9%. Of the total of patients, 8.3% were classified as low-risk patients, 77.6% were classified as intermediate–low-risk patients, 11.2% were classified as intermediate–high-risk patients, and 2.7% were classified as high-risk patients. Of the total of low-risk patients, 9.5% were discharged early in accordance with the guideline recommendations. Of the total of intermediate–high-risk patients, 43.8% were treated in the general ward instead of being transferred to the ICU for monitoring. Of the total of high-risk patients, 92.8% were treated in the ICU. No cancer patients were discharged early. **Conclusions:** These results suggest that clinical practice guideline recommendations regarding the setting of care for patients with acute PE are not being followed. This is particularly true for low-risk PE patients who may be candidates for early discharge. Further studies are needed to investigate the reasons why low-risk patients are not being discharged early.

Keywords: Pulmonary embolism; Practice guidelines as topic; Mortality; Patient care; Anticoagulants.

INTRODUCTION

Venous thromboembolism, represented by pulmonary embolism (PE) and deep vein thrombosis, is the third most common cause of cardiovascular disease worldwide after acute myocardial infarction and stroke, affecting more than 300,000 people annually in the United States,[1,2] with an all-cause hospital mortality of 14.8% in Colombia.[3] This leads to high hospitalization rates and an approximate cost of $8,764 per patient, representing more than $2 billion in annual expenditures for its care in the United States between 2003 and 2010.[1] Over the past 15 years, the mortality rate for PE has decreased as a result of advances in management strategies and early diagnosis, although the annual incidence continues to increase. In the general population, the incidence is estimated to be approximately 39-115 per 100,000 population per year, and it can be up to eight times higher in people > 80 years of age.

There are several PE risk classification tools based on patient hemodynamic status and comorbidities. The Pulmonary Embolism Severity Index (PESI) and its simplified version (sPESI) are two of the most widely used scales predicting 30-day mortality. A combination of the clinical parameters assessed by the PESI/sPESI and the presence or absence of right ventricular dysfunction or positive biomarkers determines the final classification of patients as high-risk, intermediate–high-risk, intermediate–low-risk, or low-risk patients in accordance with the 2019 European Society of Cardiology (ESC) guidelines for the diagnosis and management of acute PE.[4] The risk-adapted management strategies proposed in the guidelines include the setting of care, which may be inpatient treatment (in the general ward or ICU) or outpatient home treatment.[1,4]

Although a patient with PE can be correctly stratified on the basis of the PESI and sPESI, the current literature suggests that the recommendations of clinical practice guidelines regarding the setting of care for patients with acute PE are not always followed. For example, 80-90% of low-risk patients remain in hospital 24 h after admission, although 30-55% would be candidates for early discharge.[5,6] In an observational study conducted in Italy between 2006 and 2013, the PESI did not significantly affect the rate or duration of hospitalization in low-risk patients.[7] Given that there is a gap in knowledge regarding adherence to guideline recommendations for PE management in Latin America, the objective of the present study is to describe the rates of adherence

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Financial support: None.

ISSN 1806-3756

to the 2019 ESC guideline recommendations on the setting of care for patients diagnosed with acute PE in a referral hospital in Colombia between 2019 and 2022.

METHODS

We performed a retrospective cohort study evaluating all patients with a diagnosis of acute PE admitted to the emergency department of the *Hospital Universitario San Ignacio*, in Bogotá, Colombia, between September of 2019 and July of 2022. Patients > 18 years of age with a diagnosis of acute PE based on CT pulmonary angiography or ventilation/perfusion scan findings were included. Patients with a diagnosis of acute PE related to SARS-CoV-2 infection were excluded because it has been documented that the PESI underestimates mortality in COVID-19 patients.[8] Informed consent was waived for the present study, which was approved by the local research ethics committee (Protocol no. FM-CIE-0354-23).

Patients were identified through the *Hospital Universitario San Ignacio* Anticoagulation Registry. This institutional registry includes all patients starting anticoagulant therapy for any diagnosis in the hospital. For the present study, patients with a diagnosis of acute PE were selected. Sociodemographic data and data on comorbidities, diagnostic test reports, anticoagulation use, and the sPESI were retrieved from the registry, where information is systematically collected at the point of care using standardized instruments. The *Hospital Universitario San Ignacio* Research Electronic Data Capture (REDCap; Vanderbilt University, Nashville, TN, USA) database and tools were used in order to collect and manage the data.[9,10] Regular audits of the data collection process were performed to identify areas for improvement and ensure data quality. Missing information was supplemented with data from the institutional electronic medical records, which were retrospectively reviewed.

The 2019 ESC guidelines for the diagnosis and management of acute PE were used for PE risk stratification,[4] as follows. Low-risk patients were defined as having no hemodynamic instability at presentation, an sPESI of 0, no right ventricular dysfunction, and negative biomarkers. Intermediate–low-risk patients were defined as having no hemodynamic instability at presentation, an sPESI ≥ 1, no right ventricular dysfunction, and negative biomarkers (or positivity for only one of two parameters). Intermediate–high-risk patients were defined as having no hemodynamic instability at presentation, an sPESI ≥ 1, right ventricular dysfunction, and positive biomarkers. High-risk patients were defined as having hemodynamic instability at presentation or meeting any other criteria defined in the 2019 ESC guidelines.[4] Right ventricular dysfunction was defined on the basis of the echocardiographic or imaging criteria in the 2019 ESC guidelines.[4] Data on 30-day mortality were obtained from the Colombian *Administradora de los Recursos del Sistema General de Seguridad Social en Salud* (Social Security Administration) database, which systematically records the date of death of patients in the social security system in Colombia.[11]

Adherence to the 2019 ESC guideline recommendations on the setting of care for patients with acute PE of varying severity[4] was evaluated. Adherence to the recommendations was considered high if low-risk patients were discharged within 24 h of admission; if intermediate–low-risk patients were admitted to the general ward; if intermediate–high-risk patients were closely monitored in the ICU; and if high-risk patients were monitored in the ICU. In addition, information on treatment, type of anticoagulation, and thrombolysis was collected.

Absolute and relative frequencies were used in order to describe qualitative variables. Measures of central tendency and dispersion were calculated for quantitative variables (mean and standard deviation for variables with normal distribution and median and interquartile range for variables with non-normal distribution). The Shapiro-Wilk test was used in order to assess the normality assumption. Categorical variables are presented as absolute numbers and percentages. Adherence to the 2019 ESC guideline recommendations is presented as percentages and absolute numbers for each risk group. Statistical analysis was performed with Stata software, version 16 (StataCorp LLC, College Station, TX, USA).

RESULTS

A total of 506 patients were included in the present study. Their clinical and demographic characteristics are described in Table 1. All patients with acute PE diagnosed in our hospital and meeting the eligibility criteria were included. There were no missing data issues. The median age of the patients was 67 years, with hypertension being the most common comorbidity. Of the 506 patients included in the present study, 31.4% had concomitant deep vein thrombosis, 33.4% had a history of cancer, and the vast majority (85%) had active cancer at the time of diagnosis of PE. The most common cancer subtypes were gastrointestinal cancer (in 23.6%), genitourinary cancer (in 21.8%), breast cancer (in 12.4%), and hematologic cancer (in 10.6%). Most (77.6%) of the patients were classified as being intermediate–low-risk patients.

Table 2 shows clinical and paraclinical characteristics of interest, by PE severity. The frequency of anemia and thrombocytopenia increased with PE severity. All high-risk patients and 3.9% of the intermediate–high-risk patients met the 2019 ESC guideline definition of hemodynamic instability. Eighteen patients (4.5%) in the intermediate–low-risk group had hemodynamic instability for other causes, including septic shock (in 12) and hypovolemic shock (in 2). In addition, 57% of the high-risk patients received systemic thrombolysis. For the remaining patients, other reperfusion methods were used, such as thrombectomy and thrombolysis,

Table 1. Sociodemographic and clinical characteristics of patients with pulmonary embolism.[a]

Variable	n = 506
Female sex	294 (58.1)
Age, years	67 [54-76]
Comorbidities	
Diabetes mellitus	61 (12.0)
Uncontrolled hypertension	192 (37.9)
Kidney failure	15 (2.9)
GFR (mL/min)[b]	
< 30	22 (4.4)
30-60	129 (26.2)
> 60	340 (69.2)
Drugs	
Aspirin	62 (12.2)
P2Y12 inhibitors	5 (0.9)
NSAIDs	22 (4.3)
Cancer	169 (33.4)
Active cancer[c]	145 (85.2)
Cancer subtype[c]	
Gastrointestinal	40 (23.6)
Genitourinary	37 (21.8)
Breast	21 (12.4)
Hematologic	18 (10.6)
Lung	16 (9.4)
Head and neck	14 (8.2)
Skin	13 (7.6)
Other[d]	9 (5.3)
Central nervous system	1 (0.5)
Previous VTE	7 (1.3)
Concomitant DVT	159 (31.4)
Proximal DVT[e]	75 (47.1)
Distal DVT[e]	84 (52.8)
In-hospital mortality	47 (9.3)
30-day mortality	91 (17.9)
sPESI classification	
0 points	43 (8.5)
1 point	122 (24.1)
2 points	239 (47.2)
3 points	93 (18.3)
4 points	9 (1.7)
ESC classification	
Low risk	42 (8.3)
Intermediate-low risk	393 (77.6)
Intermediate-high risk	57 (11.2)
High risk	14 (2.7)

GFR: glomerular filtration rate; NSAIDs: nonsteroidal anti-inflammatory drugs; VTE: venous thromboembolism; DVT: deep vein thrombosis; sPESI: simplified Pulmonary Embolism Severity Index; and ESC: European Society of Cardiology. [a]Data expressed as n (%) or median [IQR]. [b]Creatinine clearance measured with the Cockcroft-Gault formula. [c]Among all cancer patients. [d]Including sarcomas, neuroendocrine tumors, undifferentiated tumors, and metastatic disease with unknown primary. [e]Among all deep vein thrombosis cases.

because of the high risk of bleeding. All high-risk patients and some of the intermediate–high-risk patients were discussed with our PE response team. This led to two cases being reclassified because of echocardiographic evidence of chronic right ventricular dysfunction and because the hemodynamic instability was unlikely to be secondary to PE. None of the patients in other risk groups received reperfusion therapy. Biomarker positivity was not assessed in all high-risk patients, because they met the criteria for hemodynamic instability and right ventricular dysfunction.

In-hospital and 30-day mortality, length of hospital stay (in days), and bleeding complications increased with the risk of PE severity (Table 3). Notably, there was no 30-day mortality or bleeding complications in the low-risk group. Of those who died in hospital, 46% had a history of cancer, as did 57% of those who died at 30 days.

Adherence to the 2019 ESC guideline recommendations regarding the setting of care is shown in Table 4. Only 4 patients (9.5%) in the low-risk category were discharged early. The remaining patients were treated in the general ward. Only 56% of the intermediate–high-risk patients were monitored in the ICU, as were more than 90% of the high-risk patients. It is of note that 11.9% of the intermediate–low-risk patients were monitored in the ICU, most of them for reasons other than PE.

A subgroup analysis was performed to evaluate adherence to recommendations on setting of care in cancer patients (Table 5). Of the total of patients with a history of cancer, 88.1% were classified as intermediate–low-risk patients, 9.4% were classified as intermediate–high-risk patients, and 2.3% were classified as high-risk patients, with no low-risk cases documented. None of the cancer patients were discharged early, the majority was managed in the general ward, and 50% of the intermediate–high-risk cases were monitored in the ICU.

Regarding anticoagulation therapy, all of the patients in the present study received initial anticoagulation with low-molecular-weight heparin. At the time of discharge, 203 (40.1%) of the patients were sent home on low-molecular-weight heparin, 34 (6.7%) were sent home on a vitamin K antagonist, and 213 (42.1%) were sent home on direct oral anticoagulants. Of the remaining 56 patients, 47 (9.3%) died in hospital and 9 (1.8%) were discharged without anticoagulation, because of bleeding complications.

DISCUSSION

The present study shows the rates of adherence to the 2019 ESC guideline recommendations on the setting of care for patients with acute PE of varying severity in a referral hospital in Colombia. Inadequate adherence was observed in the group of low-risk patients, most of whom were not discharged early as recommended. Similarly, in the intermediate–high-risk group, there was inadequate adherence to recommendations for monitoring in the ICU.

The patients included in the present study had demographic characteristics and comorbidities that

Table 2. Clinical and paraclinical characteristics of patients with pulmonary embolism of varying severity, as assessed by the European Society of Cardiology classification.

ESC classification	n	%	Cancer, n (%)*	Anemia[a], n (%)*	Thrombocytopenia[b], n (%)*	Positive troponin, n (%)*	Hemodynamic instability due to PE, n (%)*	Thrombolysis, n (%)*
Low risk	42	8.3	0 (0)	6 (14.2)	3 (7.1)	0 (0)	0 (0)	0 (0)
Intermediate-low risk	393	77.6	149 (37.9)	197 (50.1)	24 (6.1)	55 (13.9)	0 (0)	0 (0)
Intermediate-high risk	57	11.2	16 (28.0)	30 (52.6)	6 (10.5)	56 (98.2)	7 (3.9)	0 (0)
High risk	14	2.7	4 (28.5)	9 (64.2)	5 (35.7)	10 (71.4)	14 (100.0)	8 (57)
Total	506	100	169 (33.4)	242 (47.8)	38 (7.5)	121 (23.9)	21 (4.1)	8 (1.5)

ESC: European Society of Cardiology; and PE: pulmonary embolism. [a]Defined as hemoglobin < 13 g/dL in men and < 12 g/dL in women. [b]Defined as a platelet count < 150,000 per microliter. *The proportions refer to the total number of patients in each category.

Table 3. Outcomes in patients with pulmonary embolism of varying severity, as assessed by the European Society of Cardiology classification.

ESC classification	n	%	In-hospital mortality, n (%)*	30-day mortality, n (%)*	Hospital LOS, days Median [IQR]	Bleeding complications, n (%)*
Low risk	42	8.3	0 (0)	0 (0)	2 [2-7]	0 (0)
Intermediate-low risk	393	77.6	34 (8.6)	72 (18.3)	7 [4-13]	22 (5.6)
Intermediate-high risk	57	11.2	8 (14.0)	13 (22.8)	9 [6-15]	2 (3.5)
High risk	14	2.7	5 (35.7)	6 (42.8)	10.5 [3-15]	3 (21.4)
Total	506	100	47 (9.2)	91 (17.9)	7 [3-12]	27 (5.3)

ESC: European Society of Cardiology; and LOS: length of stay. *The proportions refer to the total number of patients in each category.

Table 4. Adherence to the European Society of Cardiology-recommended setting of care for patients with acute pulmonary embolism of varying severity.

ESC classification	n	%	Setting of care		
			Early discharge, n (%)*	Hospitalization in the general ward, n (%)*	ICU, n (%)*
Low risk	42	8.3	4 (9.5)	37 (88.1)	1 (2.3)
Intermediate-low risk	393	77.6	0 (0)	346 (88.0)	47 (11.9)
Intermediate-high risk	57	11.2	0 (0)	25 (43.8)	32 (56.1)
High risk	14	2.7	0 (0)	1 (7.1)	13 (92.8)
Total	506	100	4 (0.7)	409 (80.3)	94 (18.3)

ESC: European Society of Cardiology. *The proportions refer to the total number of patients in each category. Note: Patients who were managed as recommended by the 2019 ESC guidelines are highlighted in gray.

Table 5. Adherence to the European Society of Cardiology-recommended setting of care for cancer patients with acute pulmonary embolism of varying severity.

ESC classification	n	%	Setting of care		
			Early discharge, n (%)*	Hospitalization in the general ward, n (%)*	ICU, n (%)*
Low risk	0	0	0 (0)	0 (0)	0 (0)
Intermediate-low risk	149	88.1	0 (0)	137 (91.9)	12 (8.0)
Intermediate-high risk	16	9.4	0 (0)	8 (50.0)	8 (50.0)
High risk	4	2.3	0 (0)	0 (0)	4 (100)
Total	169	100	0 (0)	145 (85.8)	24 (14.2)

ESC: European Society of Cardiology. *The proportions refer to the total number of patients in each category.

were similar to those reported in previous studies of populations diagnosed with PE,[12] although the incidence of cancer was higher than the approximately 20% reported elsewhere.[13-15] The distribution of cancer types in our study sample was similar to that in the general population, with gastrointestinal cancer being

the most common.[16] We used the sPESI because it is a widely validated tool for PE risk stratification, especially to identify low-risk patients.[17,18] Regarding the frequency of risk groups, we found a lower proportion of low-risk patients.[17] This might be due to a higher incidence of cancer in our sample, with most patients having an sPESI > 1.

Our mortality rate was significantly higher than that reported in the literature. In the high-risk group, we found an in-hospital mortality of 35% in comparison with the 25% described in the general population; on the other hand, the in-hospital mortality in the intermediate-risk group was 8-14% in comparison with the 2-6% reported in previous studies.[19] Thirty-day mortality was also higher in the present study: 42% in the high-risk group vs. 20% in previous studies; 22% in the intermediate–high-risk group vs. 8% in previous studies; and 18% in the intermediate–low-risk group vs. 6% in previous studies.[17] These findings might be due to a higher incidence of cancer in our study population, especially given that more than half of the patients had a history of cancer at the time of death, with 94.2% having active cancer.

In terms of adherence to recommendations for the setting of care for PE, it is noteworthy that only 9.5% of the patients classified as low-risk patients were discharged early, with a median hospital stay of 2 days, staying as long as 7 days in 25% of cases. Similar results have been observed in other studies, in which approximately 30-55% of low-risk patients are candidates for early discharge but in actual clinical practice 80-90% receive inpatient care.[5,6] Outpatient treatment rates may vary across countries, being as low as 2% in Italy and 4% in France,[20] both of which are even lower than those reported in the present study. These findings could be explained by differences across health care systems, as well as the perception of each physician regarding the management of low-risk PE and a possible lack of knowledge of the literature supporting the safety of early discharge in these cases.[21] There are several risk prediction models such as the PESI, the sPESI, and the Hestia criteria to help clinicians stratify patients into appropriate risk groups. Nevertheless, an international survey of different European scientific societies found that the most commonly used prognostic tool for PE was clinical judgment, with prognostic models such as the PESI/sPESI used in only 30% of cases.[22] In addition, other clinical and/or sociodemographic factors, such as social support network and access to health services, may have influenced the decision for early discharge. We do not have sufficient data on socioeconomic conditions, access to health care, or the possibility of post-discharge monitoring; therefore, we cannot be certain as to why inpatient management was decided on. The guidelines state that the decision for early discharge depends on social aspects such as access to anticoagulants, access to health care, and treatment monitoring after discharge. Thus, the decision for in-hospital management is correct in cases in which the conditions for early discharge are not met, a recommendation that also appears in the clinical practice guideline.

In the present study, the recommendation to monitor intermediate–high-risk patients was found to be poorly adhered to, with approximately half of the cases being managed in the general ward rather than in the ICU as recommended.[23] These results could also be explained by a lack of knowledge of the recommendations of the guidelines and the current evidence. Another explanation could be the presence of active cancer in most of the intermediate–high-risk patients admitted to the general ward. The prognosis of cancer may have been a contraindication to ICU admission or even the use of systemic thrombolysis. In addition, the availability of resources in the Colombian health care system, where access to an ICU is not immediate, may have been another reason why 40% of the patients in the present study did not receive close monitoring despite the indication.

The results of the present study show that despite robust evidence for risk-adjusted management strategies for PE, including recommendations for setting of care, there is inadequate adherence to these recommendations, particularly for low-risk and intermediate-risk patients. This suggests that there are physician-related, clinical, sociodemographic, and health system-related factors that are barriers to adequate adherence to these recommendations. The objective of the present study was not to determine the factors influencing decisions regarding the setting of care, particularly outpatient management. Our results describe the setting of care in which patients with PE were treated, but further studies are needed to assess factors associated with this decision so that we can propose different strategies to promote adherence to guideline recommendations on the setting of care.

The main limitation of the present study is its retrospective nature. However, missing data were minimal and did not significantly affect the results. Nevertheless, although the results of this study suggest a lack of adherence to recommendations regarding the setting of care for PE treatment, we did not identify the factors that influenced this decision or the reasons for not choosing the expected setting of care. We used an objective and validated prognostic score (the sPESI) in conjunction with other criteria in the risk model included in the 2019 ESC guidelines for the diagnosis and management of acute PE. However, there are other risk models to identify low-risk patients, such as the Hestia criteria, which include not only objective measures of risk but also other reasons for hospitalization, clinical situations that may require closer monitoring, and medical or social reasons for admission. We decided to use the sPESI because it is easier to retrieve data from electronic medical records, and studies have shown that the strategies based on the Hestia criteria and those based on the sPESI have similar safety and efficacy.[18] Nevertheless, both tools need to be complemented by the judgment of

the attending physician, given that in approximately 12% of patients eligible for outpatient management in accordance with the sPESI, the decision is overruled by the attending physician for other reasons. Future studies should focus on assessing the factors that influence the decision for outpatient or inpatient treatment, as well as the decision of whether or not to monitor patients in the ICU.

In conclusion, the results of the present study suggest that clinical practice guideline recommendations regarding the setting of care for patients with acute PE are not being followed. This is particularly true for low-risk PE patients who may be candidates for early discharge. Further studies are needed to investigate the reasons why low-risk patients are not being discharged early.

AUTHOR CONTRIBUTIONS

PRT, OMM, and SMS designed the study and collected, analyzed, and interpreted patient data. All authors read and approved the final manuscript.

CONFLICTS OF INTEREST

None declared.

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J Bras Pneumol. 2025;51(2):e20240384
https://dx.doi.org/10.36416/1806-3756/e20240384

Characteristics of nicotine product use, perceptions of dependence, and passive exposure among first-year university students in Brazil

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Submitted: 21 November 2024.
Accepted: 2 March 2025.

Study carried out in the Disciplina de Pneumologia, Departamento de Clínica Médica, Faculdade de Medicina de Botucatu, Universidade Estadual Paulista, Botucatu (SP) Brasil.

ABSTRACT

Objective: To assess nicotine product use among incoming students at public and private universities in Brazil. **Methods:** This was a multicenter cross-sectional study including a convenience sample of incoming university students (≥ 18 years of age). Current use of conventional cigarettes, electronic cigarettes, and other nicotine products, as well as indicators of dependence and knowledge of the consequences of active use of or passive exposure to nicotine products were investigated with the use of a 38-item questionnaire. Descriptive statistics were used to analyze the data. **Results:** A total of 863 students completed the questionnaire. Of those, most (61%) were female, and most (76.6%) identified themselves as White. In addition, most (86%) were in the 18- to 24-year age bracket, and most (88.6%) attended a public university. In the past 30 days, 20.7% reported using electronic cigarettes, 23.2% reported using conventional cigarettes, and more than 50% reported using other nicotine products. More than 80% agreed that electronic cigarettes are harmful to health and are as damaging as other types of smoking. Over half of the respondents reported using the product shortly after waking up, and, paradoxically, 81% stated that they would quit whenever they wanted. Passive exposure was reported by 21.6%, occurring at home (in 33.6%), in other indoor environments (in 41.7%), and in open environments (in 87.5%). **Conclusions:** Experimentation and current use of nicotine products are high among incoming students at public and private universities in Brazil. Passive exposure to nicotine products is commonplace. Advanced communication tools are needed, particularly to emphasize the dangers of nicotine dependence. Being a legal drug, nicotine is often perceived as harmless, reinforcing the misconception that it can be used without consequences.

Keywords: Cigarette smoking; Electronic nicotine delivery systems; Tobacco use disorder; Tobacco smoke pollution.

INTRODUCTION

Smoking has been considered the world's greatest public health issue for decades. In the 20th century, 100 million premature deaths occurred as a result of tobacco use.[1] The WHO estimates that more than 8 million people die prematurely each year from tobacco-related diseases.[2] In fact, approximately 50% of smokers who do not quit die from tobacco-related diseases.[3,4]

A 2024 WHO report showed that smoking has been declining worldwide, with Brazil standing out globally with a 35% reduction since 2010.[5] However, progress in tobacco control is under threat of regression because the tobacco industry has introduced new, noncombustible products, particularly electronic nicotine delivery systems (ENDS).

Nicotine is the component of tobacco smoke that leads to addiction, and the nicotine content of ENDS has increased in more recent models, being as high as 60 mg/ml. When used in salt form or as analogs, it accelerates and enhances drug delivery to the brain at levels comparable to conventional cigarettes.[6] In 2022, over 2.5 million young people, including 14.1% of U.S. high school students, were electronic cigarette users.[7] Data from the National Youth Tobacco Survey show that prevalence was 3.1% and rose to 9.4% in 2022.[8] National Youth Tobacco Survey data from students in the 11- to 17-year age bracket across 17 European cities revealed that the prevalence of electronic cigarette users doubled in some countries between 2014 and 2018, with rates ranging from 7.6% to 18.5%.[9]

In Brazil, ENDS have been banned since 2009. However, the COVITEL study—a telephone survey including 1,800 individuals from the five regions of the country—showed a lifetime prevalence of electronic cigarette use at 7.3% (95% CI, 6.0-8.9), being higher in men than in women, particularly among those in the 18- to 24-year age bracket and those with higher levels of education.[10]

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Financial support: None.

ISSN 1806-3756

Martins et al. assessed 711 medical students from the five regions of Brazil, reporting electronic cigarette experimentation and current use rates of 13.2% and 2.3%, respectively. The risk of experimentation was higher among those with higher socioeconomic status and those who had smokers in their social group.[11]

Although the tobacco industry claims that electronic cigarettes are 95% safer than conventional cigarettes, this statement is unsupported.[12] An umbrella review that included data from 17 systematic reviews indicated a potential risk of cardiovascular effects of electronic cigarette use in smokers and nonsmokers. Short-term use has been linked to failure of pulmonary defense mechanisms, impacts on lung function, and increased airway resistance in smokers and nonsmokers.[13] Users of flavored electronic cigarettes containing sugars, mint, menthol, or fruity flavors show the highest levels of DNA damage.[12,14] Additional concerns include potential negative effects on brain development in young people using ENDS.[12]

In addition to the problems related to smoking any type of cigarette, nonsmokers who inhale the smoke released from the lit end of a cigarette or exhaled by smokers, as well as aerosols from ENDS, are subject to the same risks as active smokers. Passive or secondhand smokers are often unaware that there is no safe level of passive exposure and that even brief exposures can cause immediate harm. Passive exposure in adults leads to various life-threatening diseases, such as lung cancer, stroke, chronic obstructive pulmonary disease, and ischemic heart disease.[15] In children, exposure is associated with an increased risk of sudden infant death syndrome, acute respiratory infections, otitis media, more severe asthma, long-term developmental issues, and reduced lung function, among others.[16]

WHO data estimate that 1.3 million nonsmokers exposed to secondhand smoke die prematurely each year.[2] In a study evaluating the global prevalence of passive exposure among adolescents in the 12- to 16-year age bracket in 142 countries, it was reported that 62.9% were exposed on one or more days of the week; the exposure occurred at home, in public places, or other locations.[17] In a study conducted across 18 countries in Latin America and the Caribbean, a passive exposure prevalence of 60.9% was reported, with no difference between boys and girls.[18] Home is the primary location where children are exposed to cigarette smoke. In Australia, larger households, rural living, lower socioeconomic status, and single-parent households were risk factors for children's exposure.[19]

In children, several factors are associated with greater susceptibility to tobacco smoke exposure, including a higher respiratory rate, a larger lung area, and the ongoing development process. In addition, they are generally unable to control their environment and, therefore, cannot avoid exposure to tobacco. Their lower ability to eliminate the chemicals in smoke that cause cancer makes them more susceptible to the effects of secondhand exposure.[20] Although data on passive exposure to electronic cigarette aerosols is scarce, studies have provided evidence of respiratory changes[21] and heavy metals in breast milk and umbilical cord blood, as well as in the urine and hair of children living with electronic cigarette smokers.[22]

Considering the severity of the consequences of active or passive exposure to any form of tobacco-derived products or nicotine-containing products, as well as the need to prevent addiction, we sought to characterize the use of and passive exposure to those products in students entering university, thus developing awareness, prevention, and treatment measures. In the present study we present results regarding nicotine product use and perceptions of dependence and passive exposure among first-year university students in Brazil.

METHODS

Participants and procedures

We investigated nicotine product use in first-year students at the *Universidade Estadual Paulista* (Unesp, São Paulo State University), a public multicampus university in Brazil, and the *Centro Universitário Claretiano* School of Medicine, a private college located in the city of Rio Claro, Brazil, during the 2023-2024 academic years. We used a 38-item electronic questionnaire based on the Global Youth Tobacco Survey questionnaire.[23] The questionnaire used in the present study is available in the supplementary material. We also investigated indicators of dependence; how the nicotine products were purchased or obtained; and participant knowledge of the consequences of active use of or passive exposure to nicotine products. The present study was conducted in strict accordance with the Declaration of Helsinki and was approved by the Unesp School of Medicine at Botucatu Research Ethics Committee (Reference no. 56582322.7.0000.5504).

Undergraduate students ≥ 18 years of age attending Unesp or the *Centro Universitário Claretiano* School of Medicine were sent the questionnaire via email by the Unesp Office of the Dean for Undergraduate Studies, in compliance with the Brazilian National General Personal Data Protection Law (Law no. 13.709/2018). All participating patients gave written informed consent before completing the questionnaire. All responses were considered in the analysis.

For statistical analysis, the proportions of each outcome were calculated for the sample as a whole and for each outcome separately in the public and private sectors, in accordance with the characteristics of the sample.

RESULTS

Although 1,155 students gave written informed consent, only 863 (74.7%) completed the questionnaire. Of those, most (61%) were female, and most (76.6%)

identified themselves as White. In addition, most (86%) were in the 18- to 24-year age bracket, and most (88.6%) attended a public university. Undergraduate students in the humanities accounted for 40.5% of the study sample, the remaining 59.5% being in the sciences (biological sciences, 32%; and exact sciences, 27.5%). Nearly half (47%) of the respondents reported having less than 1,000 Brazilian reals per month for personal expenses, and the majority (> 75%) of parents or legal guardians had completed at least high school. Almost all participants (99.8%) had heard of electronic cigarettes. For any product, users were defined as those who reported using it at least once in the past 30 days. Experimentation of other tobacco products was assessed by the following question: Have you ever tried tobacco-derived products or tobacco products other than cigarettes (such as hookahs and hand-rolled cigarettes)? The proportions and characteristics of electronic cigarette users are presented in Table 1. Although most of the study participants recognized that electronic cigarettes are harmful, the prevalence of electronic cigarette use was found to be high, particularly at social events, and nearly 30% reported using electronic cigarettes on 10 or more days each month. Electronic cigarettes are widely available, with 30% of users reporting difficulty in avoiding smoking. Additionally, the use of hookahs or hand-rolled cigarettes was found to be common.

Regarding the use of conventional cigarettes, most (51.1%) reported that they had already tried them. The characteristics of conventional cigarette users and their use of other nicotine products, as well as dependence indicators and opinions on the potential harm caused by nicotine product use, are presented in Table 2. Conventional cigarettes remain very popular, their prevalence being higher than that of electronic cigarettes; more than half of users reported smoking conventional cigarettes on more than 10 days each month. The use of other tobacco products is also highly prevalent, and the majority reported that they consider electronic cigarettes harmful to health.

The combined use of ENDS and conventional cigarettes was reported by 53.5% of the conventional cigarette users and 59% of the ENDS users. Concurrent use of conventional cigarettes, electronic cigarettes, and other tobacco products (such as hookahs and roll-your-own cigarettes) in the last 30 days is shown in Figure 1. In this group of participants, the use of different tobacco products and combinations of different forms of smoking was very common.

Of the total of ENDS users in the present study, 36.3% reported that they always or sometimes smoke

Table 1. Characteristics of electronic cigarette users, as well as dependence indicators, opinions on potential harm, and concurrent use of conventional cigarettes.[a]

Variable	All	Public school students	Private school students
Prevalence	179 (20.7)	161 (21.0)	18 (18.4)
Place of use			
Home	30 (16.7)	27(16.8)	3 (16.7)
Social events	104 (58.1)	96(59.6)	8 (44.4)
Other	45 (25.2)	38(23.6)	7 (38.9)
Use in the last 30 days, no. of days			
1-2	81 (45.3)	75(46.6)	6 (33.3)
3-9	45 (25.1)	39 (24.2)	6 (33.3)
> 10	53 (29.6)	47(29.2)	6 (33.4)
Place of purchase			
Tobacco shops	68 (38.0)	61(37.9)	7 (38.9)
Websites	71 (39.7)	55(34.2)	6 (33.3)
Other	40 (22.3)	45 (27.9)	5 (27.8)
Difficulty staying a week without using			
Easy/very easy	146 (81.6)	131(81.4)	15 (83.3)
Difficult/very difficult	33 (18.4)	30(18.6)	3 (16.7)
Difficulty quitting			
Easy/very easy	122 (68.2)	107(66.5)	13 (72.2)
Difficult/very difficult	57 (31.8)	54(33.5)	5 (27.8)
Experimentation with other forms of tobacco*	157 (87.7)	142 (88.2)	83.3 (85.7)
Use of other forms of tobacco in the last 30 days	95 (53.1)	90 (55.9)	6 (33.3)
ENDS are harmful to health			
Maybe yes/Maybe no/No	25(14.0)	20(12.3)	5 (27.8)
Yes	154 (86.0)	141(87.0)	13 (72.2)
ENDS are as harmful as other forms of nicotine use			
Yes	155 (86.5)	141(87.5)	14 (77.8)
No	24 (13.4)	20(12.5)	4 (22.2)

ENDS: electronic nicotine delivery systems. [a]Data expressed as n (%). *Experimentation of other tobacco products was assessed by the following question: Have you ever tried tobacco-derived products or tobacco products other than cigarettes (such as hookahs and hand-rolled cigarettes)?

Table 2. Characteristics of conventional cigarette users and their use of other nicotine products, as well as dependence indicators, opinions on potential harm, and concurrent use of electronic nicotine delivery systems.[a]

Variable	All	Public school students	Private school students
Prevalence	200 (23.2)	179 (23.4)	21 (21.4)
Use in the last 30 days, no. of days			
1-2	49 (24.5)	43 (24.0)	6 (28.6)
3-9	45 (22.5)	41 (22.9)	4 (19.0)
>10	94 (53.0)	95 (53.1)	11 (52.4)
Age at initiation, years			
> 11	4 (2.0)	3 (16.7)	1 (4.8)
11-14	40 (20.0)	39 (21.8)	1 (4.8)
15-18	121 (60.5)	107 (59.8)	16 (76.2)
> 18	35 (17.5)	30 (16.8)	3 (14.2)
Experimentation with other forms of tobacco*	179 (89.5)	161 (89.9)	18 (85.7)
Use of other forms of tobacco in the last 30 days	111 (55.5)	105 (58.7)	6 (28.6)
ENDS are as harmful as other forms of nicotine use			
Yes	169 (84.5)	155 (86.6)	15 (71.4)
No	31 (15.5)	24 (13.4)	6 (28.6)

ENDS: electronic nicotine delivery systems. [a]Data expressed as n (%). *Experimentation of other tobacco products was assessed by the following question: Have you ever tried tobacco-derived products or tobacco products other than cigarettes (such as hookahs and hand-rolled cigarettes)?

Figure 1. Venn diagram showing the numbers and proportions of users of electronic cigarettes, conventional cigarettes, and other tobacco products among first-year students at the São Paulo State University and the *Centro Universitário Claretiano* School of Medicine, both of which are located in the state of São Paulo, Brazil.

shortly after waking up, as did 53.5% of conventional cigarette smokers. Nearly half of ENDS users (47.2%) and conventional cigarette smokers (48.2%) expressed an interest in quitting. Of the total of conventional cigarette smokers, 58% had been advised to quit, 50.5% had attempted to quit in the last 12 months, and 81% believed that they could quit if they wanted to. Of the total of ENDS users, 52.5% had been advised to quit, 46.3% had attempted to quit in the last 12 months, and 84.4% believed that they could quit if they wanted to.

Of the 863 respondents, 21.6% reported to be unsure whether passive exposure to cigarette smoke or electronic cigarette aerosols causes harm, 33.6% reported passive exposure at home, 41.7% reported passive exposure in other indoor environments, and 85.7% reported passive exposure in open environments. Additionally, 89.9% had seen people smoking on the school/campus premises. Nearly half (42.5%) of the respondents reported that they support a ban on the use of nicotine products in open public spaces.

DISCUSSION

The main findings of the present study are a high proportion of nicotine product users among students entering university in Brazil; a high proportion of users of more than one product; a high rate of passive exposure in indoor environments; and a lack of awareness of nicotine dependence. Although a significant number of students show signs of dependence, the vast majority believe that they can quit tobacco whenever they choose.

The proportions of nicotine product users reporting conventional cigarette or ENDS use at least once in the past 30 days were much higher in our study than in other studies conducted in Brazil,[10,11,24] being 20.7% for ENDS and 22.3% for conventional cigarettes, with 30% of ENDS users and 53% of conventional cigarette users using them on more than 10 days in the past month. Additionally, over 50% of the public school students and approximately 30% of the private school students using ENDS or conventional cigarettes reported using other forms of tobacco in the past 30 days. In a study evaluating 711 medical students across the five regions of Brazil, the rates of current use were found to be 7.9% for conventional cigarettes, 11.4% for hookahs, and 2.3% for electronic cigarettes.[11] In the COVITEL study,[10] which evaluated 9,004 Brazilians ≥ 18 years of age, with 84.3% being > 24 years of age, the prevalence of conventional cigarette smoking was found to be 12.2%. The prevalence of daily or occasional ENDS use was 3.2% among men and 1.9% among women, whereas, for hookah use, it was 3.5% among men and 1.2% among women.[10] Data from the 2019 Brazilian National Health Survey show that most electronic cigarette users (70%) are in the 15- to 24-year age bracket and approximately 90% are nonsmokers of conventional cigarettes.[24] More than half of the nicotine product users in our study reported a combined use of conventional cigarettes and electronic cigarettes, with a high use in both groups. In the past 30 days, use of other nicotine products was above 50%, which is well above the rate reported in the COVITEL study.[10]

Data from the latest edition of the *Vigilância de Fatores de Risco e Proteção para Doenças Crônicas por Inquérito Telefônico* (VIGITEL, Telephone-based System for the Surveillance of Risk and Protective Factors for Chronic Diseases) show that, in individuals in the 18- to 24-year age bracket, the prevalence of active smoking is 6.7%, with 6.1% using electronic cigarettes.[25] Analysis of data from the 2015 and 2019 Brazilian National School-Based Adolescent Health Surveys, which assessed students in the 13- to 17-year age bracket, shows that the proportion of students in Brazil who smoked in the 30 days prior to the survey was 6.8%, and the rate of experimentation with electronic cigarettes was 16.8%. The highest prevalence of (daily or occasional) electronic cigarette use was found among adult males, young adults in the 18- to 24-year age bracket, and individuals who had had ≥ 12 years of schooling.[26]

Possible explanations for the differences in the proportions of users of different nicotine products between the aforementioned studies and our study include the timing of data collection (between 2016 and early 2022), the characteristics of the sample, and the age groups included. Moreover, students usually undergo a period of significant stress before entering university and are therefore more susceptible to risk behaviors.

In the present study, a substantial proportion of students reported passive exposure to nicotine products at home (33.6%), in other enclosed spaces (41.7%), and in open spaces (87.5%), with the vast majority (89.9%) witnessing people smoking on the school/campus premises. Additionally, a significant number are uncertain whether passive exposure causes health damage. Data from the 2023 VIGITEL show passive smoking at home at 9.9% and in the workplace at 8.9% among individuals in the 18- to 24-year age bracket.[25] Among adolescents in the 12- to 16-year age bracket, the global prevalence in 142 countries was 62%, being 60.9% in Latin America.[18,27] Therefore, the issue of passive exposure remains serious and widespread, and spreading awareness of the risks of passive smoking should be the subject of ongoing national campaigns. Although Brazilian Federal Law no. 12,546, issued on December 14, 2011, prohibits the use of cigarettes, cigars, cigarillos, pipes, or any other smoking product, whether tobacco-derived or not, in closed collective spaces, private or public, tobacco smoking of any kind and, consequently, exposure to smoke in private and public spaces is still prevalent and represents a significant public health problem.

The perception of nicotine dependence is an interesting and concerning finding of the present

study. The study population is familiar with electronic cigarettes (99.8%) and has tried them (51.5%), as well as knowing that they are harmful to health and as damaging as other forms of nicotine use (> 70%), with most parents having at least a high school education (> 75%). Signs of dependence (evidenced by smoking soon after waking) were present in 53.5%, yet interest in quitting tobacco is low (approximately 47%). The vast majority (84.4%) believe that they can quit whenever they want, indicating a misconception about the severity of nicotine dependence. Therefore, addressing aspects related to dependence is very important in this population.

Our study has some limitations. We used the electronic platform of the Unesp School of Medicine at Botucatu, and the questionnaire was sent by email through the Unesp Office of the Dean for Undergraduate Studies. The email was sent three times at intervals of 2-3 weeks in 2023 and 2024. However, students rarely check their emails and are frequently invited to participate in studies, which may have affected adherence. Another possibility is that the respondents were primarily nonsmokers; nonetheless, the proportion of users was still very high. Additionally, Unesp has campuses in 24 cities, all of which are located in the state of São Paulo, and the *Centro Universitário Claretiano* School of Medicine is also located in the state of São Paulo; therefore, caution is required in generalizing the results.

We conclude that rates of experimentation with and current use of electronic cigarettes and other nicotine products are high among incoming students at public and private universities in Brazil. Additionally, passive exposure to nicotine products in various settings is commonplace. Although knowledge gaps remain, awareness of the harms associated with nicotine dependence is widespread. However, merely knowing the risks does not prevent active or passive exposure. The use of nicotine products raises societal concerns, ongoing and tailored awareness initiatives being required for different social segments. More advanced communication tools are urgently needed, particularly to emphasize the dangers of nicotine dependence. Being a legal drug, nicotine is often perceived as harmless, reinforcing the misconception that it can be used without consequences. In response to these findings, the Unesp for a Nicotine-Free Generation program is being implemented across all university campuses, with full participation of students and professors, as well as official support from the university health office.

ACKNOWLEDGMENTS

The authors wish to express their gratitude to the Unesp Office of the Dean for Undergraduate Studies for emailing the questionnaire to the students. We also extend our thanks to Pedro Fernandes Abadde for designing the Venn diagram shown in Figure 1.

AUTHOR CONTRIBUTIONS

IG participated in the study conception and design; the acquisition, analysis, and interpretation of data; the statistical analysis; and the drafting and revision of the manuscript. MMS and LCB participated in the study conception and design, as well as in the revision of the manuscript. SET participated in the study conception and design. IG participated in the study conception and design; the acquisition, analysis, and interpretation of data; and the drafting and revision of the manuscript. SSM participated in the acquisition of data. All authors read and approved the final manuscript.

CONFLICTS OF INTEREST

None declared.

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J Bras Pneumol. 2025;51(2):e20240327
https://dx.doi.org/10.36416/1806-3756/e20240327

A polymorphism in the *FAM13A* gene confers protection against tuberculosis in Brazilian workers exposed to silica

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Submitted: 11 February 2025.
Accepted: 12 February 2025.

Study carried out at the Universidade Federal Fluminense (UFF), Niterói (RJ), Brasil; Universidade do Estado do Rio de Janeiro (UERJ), Rio de Janeiro (RJ), Brasil; Fundação Oswaldo Cruz, Rio de Janeiro (RJ), Brasil.

ABSTRACT

Objective: Tuberculosis (TB) is an infectious disease caused by the bacillus *Mycobacterium tuberculosis*, which was recognized by the World Health Organization (WHO) as a global epidemic in 1993. TB is the leading infectious disease associated with silicosis, with studies showing an increased risk when compared to healthy individuals. We conducted an association study to evaluate the influence of polymorphisms in the *ACE*, *FAM13A*, *FAS*, *FASLG*, *IL1RN*, *NOS2*, *TGFB1*, and *TNF* genes on TB susceptibility. **Methods:** Nine polymorphisms were genotyped using Polymerase Chain Reaction (PCR) in a sample of 143 patients with silicosis in Rio de Janeiro (RJ), Brazil. **Results:** Seventy (49%) patients had a confirmed prior diagnosis of TB, of whom 25 (35.7%) had simple silicosis and 45 (64.3%) had complicated silicosis. The TG genotype of rs2609255 in *FAM13A* showed a protective effect against TB (OR=0.46; 95% CI: 0.22–0.98; p=0.040) compared to the GG genotype, and also when compared to the two combined homozygous genotypes (TT+GG) (OR=0.43; 95% CI: 0.20–0.90; p=0.024). Logistic regression analysis, including independent clinical variables, confirmed the protective effect of the TG genotype. **Conclusion:** This study suggests that the rs2609255 polymorphism in *FAM13A* may play a role in TB risk among patients with silicosis. Given the limited research on genetic polymorphisms and TB susceptibility in silicosis patients, further studies are needed to validate these findings.

Keywords: silicosis, tuberculosis, genetic polymorphisms, genetic association studies, cytokines.

INTRODUCTION

Tuberculosis (TB) is an infectious disease caused by the bacillus *Mycobacterium tuberculosis* (*M. tuberculosis*). Despite significant progress, it remains one of the most lethal infectious diseases worldwide.[1] Several conditions increase the risk of TB, including malnutrition, alcohol abuse, smoking, anemia, diabetes, anti-TNF drugs, HIV infection, and silicosis.[2–5]

Silicosis is a fibrotic lung disease caused by the inhalation of crystalline silica particles, and TB is its most commonly associated infectious disease. Studies have shown that individuals with silicosis have a higher risk of developing TB when compared to healthy individuals.[6] A recent meta-analysis by Ehrlich et al. (2021) further demonstrated that the severity of radiological manifestations of silicosis significantly increases the risk of TB.[6]

Tuberculosis is primarily transmitted through the air, but the mucociliary clearance mechanism plays a role in containing the bacillus.[7] Bacilli that evade this physical barrier reach the alveolar space, triggering the intense production of reactive oxygen species (ROS) and reactive nitrogen species (RNS), which cause direct damage to invading agents.[8] This oxidative stress environment results from increased levels of nitric oxide synthase (NOS2).[8,9] Additionally, it stimulates the release of several interleukins, including interleukin-1 (IL-1α, IL-1β), which promote fibroblast activation and collagen fiber deposition in the alveolar space, while the IL-1 receptor antagonist (IL-1Ra) inhibits their action.[10]

Bacilli that survive this intense oxidative environment are phagocytosed by alveolar macrophages (AM), triggering various inflammatory and anti-inflammatory pathways mediated by cells and multiple cytokines.[7] Several molecules are involved in these pathways, including tumor necrosis factor-alpha (TNFα), which is produced by activated AM and stimulates fibroblast recruitment and proliferation, in addition to serving as a ligand for apoptosis receptors.[9] TNFα also plays a crucial role in granuloma formation, a fundamental mechanism for containing *M. tuberculosis*. Activated AM also release anti-inflammatory cytokines, such as transforming growth factor beta-1 (TGFβ1), which downregulates proinflammatory cytokines and inhibits T-cell proliferation and activation, balancing the response

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◄ Voltar ao sumário
ISSN 1806-3756

between bacterial eradication and host survival.[11] Angiotensin-converting enzyme (ACE), released by epithelial cells and macrophages, is a biomarker of lung injury, and a gene polymorphism has recently been identified as a risk factor for TB.[12,13] AM apoptosis also contributes to the pathogenesis of TB and silicosis, with increased expression of cellular apoptosis receptors (FAS) and their ligands (FASLG and TNFα), promoting the recruitment of inflammatory cells.[9] Additionally, the interaction between AM and silica crystals elevates NOS2 levels, leading to increased nitric oxide production by macrophages and the generation of ROS and RNS, which cause extensive damage to cell membranes.[9,14]

The ability of macrophages and lymphocytes to migrate within interstitial compartments is essential for tissue surveillance and pathogen elimination. The Rho-GTPase family, a group of enzymes that bind and hydrolyze GTP, plays a fundamental role in cytoskeletal regulation and cell migration.[15] Several pathogenic bacteria secrete proteins into host cells, acting as activators or inhibitors of Rho-GTPases, thereby facilitating their pathogenesis.[16] *M. tuberculosis* also interferes with macrophage signaling pathways through GTP-binding proteins on Rho-GTPases, which are crucial for phagocytosis signal transduction.[16] The FAM13A isoform 1 protein contains a Rho GTPase-activating protein (RhoGAP) domain, suggesting its involvement in modulating Rho-GTPase activity.[17]

Despite the high risk of TB, some patients with silicosis do not develop this infectious complication, suggesting that genetic polymorphisms may influence susceptibility.[8,18,19] It is important to emphasize that silicosis is an irreversible and incurable disease, and that TB accelerates the progression of fibrosis in the lung parenchyma.[20]

Identifying biomarkers associated with a higher risk of TB in patients with silicosis is a valuable tool for disease management and follow-up. Therefore, the aim of the present study was to evaluate the influence of genetic polymorphisms in *ACE* (Ins/Del), *FAM13A* (rs2609255), *FAS* (rs2234767), *FASLG* (rs763110), *IL1RN* (rs419598 and rs2234663), *NOS2* (rs2297518), *TGFB1* (rs1800469), and *TNF* (rs1800629) on TB susceptibility in 143 Brazilian patients with silicosis. This is the first and largest Brazilian association study on genetic polymorphisms and tuberculosis in patients with silicosis.

METHODS

Subjects

This study included a total of 143 patients with silicosis, who were treated at the Antônio Pedro Hospital of the Federal Fluminense University, the Pedro Ernesto Hospital of the State University of Rio de Janeiro, and the National School of Public Health of the Oswaldo Cruz Foundation, all located in the State of Rio de Janeiro, Brazil. The study was approved by the Ethics Committees of these three institutions, and informed consent was obtained from all patients.

The diagnosis of silicosis was based on the occupational history of exposure to silica particles, in combination with radiological findings consistent with the disease, according to the International Classification of Radiographs of Pneumoconiosis (ILO). All chest radiographs were evaluated independently by three ILO-certified readers and classified as simple silicosis (opacities < 1.0 cm) or complicated silicosis (at least one opacity > 1.0 cm), following ILO criteria. The degree of agreement, measured using the Kappa coefficient, was 0.86. In cases of disagreement between readers regarding the classification of small and large opacities, the final result was determined by consensus among the three readers. The chest radiographs were obtained using Siemens AG equipment (model LX30; Erlangen, Germany) and a second device from VMI *Tecnologias* (LDM206-VM, MG, Brazil), applying the same radiological technique. At the time of diagnosis, all patients were removed from their workplaces. The patients included in this study were diagnosed with silicosis between 1969 and 2019, with a median diagnosis year of 2004.

The diagnosis of TB was confirmed through the association of clinical characteristics of the infectious disease with new radiological findings, in addition to confirmatory laboratory tests, such as a positive culture for *M. tuberculosis*, adenosine deaminase (ADA) levels, polymerase chain reaction (PCR), or histopathological findings of granulomatous disease with caseous necrosis. The diagnosis of TB occurred between 1975 and 2023, with a median diagnosis year of 2005.

Clinical characteristics

The following social, clinical, and functional characteristics were evaluated: age (years), confirmed prior diagnosis of TB, occupational activity, silica exposure (SE; years), weekly working hours (WW; hours), total exposure time (TET; hours), exposure withdrawal (EW; years), smoking level (SL; pack-years), and use of personal protective equipment (PPE). The individual TET (in hours) was calculated by adjusting WW hours for each worked month (11/12; one-month vacation), which was then multiplied by the total number of working years. The EW (in years) was determined by subtracting the year of silicosis diagnosis (and work removal) from the year of sample collection

Laboratory procedures

Genetic material was collected from cell samples obtained by mouthwash with 5 mL of saline solution (NaCl 0.5%) for 60 seconds. Individual samples were identified, and genomic DNA extraction was performed as previously described.[21]

Genotyping was carried out by PCR. *IL1RN* 2018T/C (rs419598), 86 bp variable number of tandem repeats (VNTR) (rs2234663), and *ACE* Ins/Del (rs4646994) were evaluated by standard PCR, as previously

described.[13,22,23] For *ACE* rs4646994, the D allele, consisting of a 190-bp fragment, and the I allele, of a 490-bp fragment, were detected by electrophoresis of PCR products in a 2% agarose gel.

Genotypes of *IL1RN* rs2234663 (VNTR) were detected according to the PCR product sizes in a 2.5% agarose gel, which consisted of: *IL1RN**1 (four repeats), 410 bp; *IL1RN**2 (two repeats), 240 bp; *IL1RN**3 (five repeats), 500 bp; *IL1RN**4 (three repeats), 325 bp; and *IL1RN**5 (six repeats), 595 bp. Restriction fragment length polymorphism (RFLP), using 1U of *Msp I* in a reaction following the manufacturer's instructions (New England Biolabs), was used for genotyping *IL1RN* rs419598. Alleles were detected by electrophoresis in a 3% agarose gel, based on the following fragment sizes: 123 and 233 bp (C allele) and 356 bp (T allele).

Real-time polymerase chain reaction was performed using predesigned and validated TaqMan® assays (Thermo Fisher Scientific, Brazil) for genotyping *FAM13A* rs2609255 (C_15906608_10), *FAS* rs2234767 (-1377G/A; C_12123966_10), *FASLG* rs763110 (-844C/T; C_3175437_10), *NOS2* rs2297518 (Ser608Leu; C_11889257_10), *TGFB1* rs1800469 (-509C/T; C_8708473_10), and *TNF* rs1800629 (-308G/A; C_7514879_10). The samples were processed using the CFX96 real-time PCR system (Bio-Rad Laboratories, CA, USA), following the manufacturer's instructions (Thermo Fisher Scientific, Brazil).

Statistical analyses

Gene counting was performed to analyze allele frequencies. Deviations from Hardy-Weinberg equilibrium were evaluated using the χ^2 test. The χ^2 test or Fisher's exact test was also used to perform association analyses between gene polymorphisms and TB. The t-test and Mann-Whitney test were used to analyze quantitative clinical characteristics with normal distribution and those with deviations from normal distribution, respectively, as determined by the Kolmogorov-Smirnov test. Values were presented as mean ± standard deviation (SD).

The odds ratio (OR) and 95% confidence interval (95% CI) for independent predictors of TB susceptibility were evaluated using multivariate logistic regression analysis. The logistic regression model included the following independent variables: polymorphisms significantly associated with TB, TET > 44,229 hours, EW in years, and silicosis severity (complicated silicosis). Statistical tests were performed using SPSS version 20.0 software (SPSS Inc., Chicago, IL, USA). A p-value < 0.05 was considered significant.

RESULTS

Clinical and radiological characteristics

Among the 143 patients, 66 (46%) worked in sandblasting, the most prevalent occupation in our sample. Other occupations included marble working (21 patients, 15%), hammer drilling (18 patients, 12%), civil construction (17 patients, 12%), and various other activities (tilemaker, sandblasting manager, welder, painter, ceramicist), which accounted for 21 patients (15%).

Seventy patients (49%) had a confirmed prior diagnosis of TB, including 25 (35.7%) with simple silicosis and 45 (64.3%) with complicated silicosis (p=0.321). Among these 70 TB cases, 57 (81%) had pulmonary tuberculosis, 11 (16%) had pleural tuberculosis, and 2 (3%) had lymph node tuberculosis. The clinical parameters and diagnostic procedures are shown in Table 1.

Regarding the radiographic classification of patients without a confirmed prior diagnosis of TB according to the ILO 2022 criteria, 28 patients were categorized as having simple chronic silicosis, with categories 1 (1/1 and 1/2) and 2 (2/1 and 2/2) being the most prevalent in this group, accounting for 68% of cases. In this group, 37 patients presented with large opacities and were classified as follows: 13 (35%) as category A, 17 (46%) as category B, and 7 (19%) as category C. Among patients with a confirmed prior diagnosis of TB, as classified by the ILO 2022, 25 were categorized as having simple chronic silicosis, with categories 2 (2/1 and 2/2) and 3 (3/2 to 3/3) being the most prevalent, together comprising 73% of cases. In this group, 42 patients presented with large opacities and were classified as follows: 11 (26%) as category A, 19 (45%) as category B, and 12 (29%) as category C. Other clinical and demographic characteristics are presented in Tables 2 and 3.

No statistically significant differences were observed in silica exposure (SE) (p=0.865), weekly working hours (WW) (p=0.759), total exposure time (TET, hours) (p=0.741), exposure withdrawal (EW) (p=0.880), or smoking level (SL) (p=0.404) between patients with and without a confirmed prior diagnosis of TB.

Association analyses

The genotype distribution of *ACE* (Ins/Del), *FAM13A* (rs2609255), *FAS* (rs2234767), *FASLG* (rs763110), *IL1RN* (rs419598 and rs2234663), *NOS2* (rs2297518), *TGFB1* (rs1800469), and *TNF* (rs1800629) polymorphisms was in equilibrium according to the Hardy-Weinberg principle.

A summary of genotype and allele distribution in the total sample and among individuals with a confirmed prior diagnosis of TB is provided in Table 4. A statistically significant association was observed between rs2609255 in *FAM13A* and TB. The TG genotype exhibited a protective effect against TB (OR=0.46; 95% CI: 0.22–0.98; p=0.040). Additionally, the analysis revealed that the *FAM13A* TG genotype was also a predictor of protection against TB (OR=0.43; 95% CI: 0.20–0.90; p=0.024) when

Table 1. Procedures and methods for the diagnosis of tuberculosis.

TUBERCULOSIS	PULMONARY 57 (81%)	PLEURAL 11 (16%)	LYMPH NODE 2 (3%)	TOTAL 70
DIAGNOSTIC PROCEDURE				
SPONTANEOUS SPUTUM	38	0	0	38
INDUCED SPUTUM	03	0	0	03
BRONCHOSCOPY / BAL	16	0	0	16
THORACOCENTESIS (WITH PLEURAL BIOPSY)	0	11	0	11
LYMPH NODE BIOPSY	0	0	02	02
TOTAL				70
DIAGNOSTIC METHOD				
ACID-FAST BACILLI (AFB) TEST	39	0	0	39
MYCOBACTERIAL CULTURE (WITH OR WITHOUT POSITIVE AFB)	45	0	02	47
MOLECULAR TESTING - PCR (*M. tuberculosis*)	12	0	0	12
ADA (ADENOSINE DEAMINASE)	0	11	0	11
HISTOPATHOLOGY (GRANULOMA WITH CASEOUS NECROSIS)	2	9	02	13

BAL, bronchoalveolar lavage; PCR: polymerase chain reaction.

Table 2. Distribution of sociodemographic and clinical characteristics between patients with and without a confirmed prior diagnosis of tuberculosis.

Variables	Total (143)	No tuberculosis (73)	Tuberculosis (70)	p
Age (years)	59.98±8.81	60.60±8.99	59.34±8.63	0.395[a]
SE (years)	21.55±9.31	21.49±10.02	21.61±8.58	0.865[b]
WW (hours)	47.06±9.37	47.53±9.32	46.57±9.46	0.759[b]
TET (hours)	44,229±19,939	44,771±21,100	43,663±18,788	0.741[a]
EW (years)	14.00±10.19	13.75±9.88	14.23±10.55	0.880[b]
SL (pack-years)	36.15±30.52	36.05±25.69	36.26±34.62	0.404[b]

SE, silica exposure in years; WW, weekly working hours; TET, total exposure time (in hours); EW, exposure withdrawal (in years); SL, smoking level (in pack-years). Values expressed as mean ± standard deviation. [a]t-test, Kolmogorov-Smirnov: p>0.05; bMann-Whitney test, Kolmogorov-Smirnov: p<0.05

Table 3. Silicosis – clinical classification.

CLINICAL CLASSIFICATION	WITHOUT TUBERCULOSIS	WITH TUBERCULOSIS	TOTAL
ACUTE	0 (%)	0 (%)	0 (0%)
SUBACUTE PROGRESSIVE (ACCELERATED SILICOSIS)	8 (73%)	3 (27%)	11 (8%)
CHRONIC	65 (49%)	67 (51%)	132 (92%)
CLASSIFICATION: CHRONIC SILICOSIS			
CHRONIC SIMPLE	28 (53%)	25 (47%)	53 (40%)
CHRONIC COMPLICATED	37 (47%)	42 (53%)	79 (60%)

compared to the combined homozygous genotypes (TT+GG) (Table 4). No significant associations were found for the remaining polymorphisms.

The multiple logistic regression model, including the potential independent risk variables for TB susceptibility, is presented in Table 5. After adjusting for other risk factors, rs2609255 in *FAM13A* was the only independent variable significantly associated with TB. The *FAM13A* TG genotype exhibited a protective effect against TB susceptibility (OR=0.32; 95% CI: 0.13–0.75; p=0.009), while no effect was observed for EW, TET, or silicosis severity (complicated silicosis).

DISCUSSION

The respiratory system has mechanisms that prevent the entry of various agents, such as particulate inorganic material, viruses, bacteria, and mycobacteria. Additionally, several leukocytes that compose the immune system contribute to the defense process, with AM being the most important.[24,25]

Macrophages phagocytose bacilli and, after breaking them down, present their main antigens to lymphocytes. This antigen presentation triggers a cascade of biological events in lymphocytes, including activation, clonal expansion, and cytokine secretion, which in turn activate other macrophages. AM also serve as a reservoir for harboring bacilli, allowing intracellular multiplication. The bacilli are ultimately eliminated from the AM interior through apoptosis.[26]

The ability of leukocytes to migrate through interstitial compartments is essential for tissue surveillance and pathogen elimination. Each stage of this migration

Table 4. Genotype and allele distribution in patients with and without a history of tuberculosis.

Polymorphism	Total	No tuberculosis	Tuberculosis	p	OR (95%CI)
ACE rs4646994	121	61	60		
DD	72	37 (0.61)	35 (0.58)		1.00
DI	45	22 (0.36)	23 (0.38)	0.942	1.11 (0.52-2.33)
II	4	2 (0.03)	2 (0.03)		1.06 (0.07-15.31)
D	189	96 (0.79)	93 (0.78)	0.823	1.00
I	53	26 (0.21)	27 (0.23)		1.07 (0.58-1.97)
FAM13A rs2609255	132	67	65		
TT	79	36 (0.54)	43 (0.66)		1.00
TG	45	29 (0.43)	16 (0.25)	0.040	0.46 (0.22-0.98)
GG	8	2 (0.03)	6 (0.09)		2.51 (0.41-26.67)
T	203	101 (0.75)	102 (0.78)	0.552	1.00
G	61	33 (0.25)	28 (0.22)		0.84 (0.47-1.49)
TT+GG	87	38 (0.57)	49 (0.75)	0.024	1.00
TG	45	29 (0.43)	16 (0.25)		0.43 (0.20-0.90)
FAS rs2234767	129	67	62		
GG	97	52 (0.78)	45 (0.73)	0.709	1.00
GA	32	15 (0.22)	17 (0.27)		1.17 (0.51-2.66)
G	226	119 (0.89)	107 (0.86)	0.540	1.00
A	32	15 (0.11)	17 (0.14)		1.26 (0.60-2.65)
FASLG rs763110	97	52	45		
CC	30	18 (0.35)	12 (0.27)		1.00
CT	39	21 (0.40)	18 (0.40)	0.584	1.29 (0.49-3.37)
TT	28	13 (0.25)	15 (0.33)		1.73 (0.61-4.91)
C	99	57 (0.55)	42 (0.47)	0.258	1.00
T	95	47 (0.45)	48 (0.53)		1.39 (0.79-2.44)
IL1RN rs419598	143	73	70		
TT	92	45 (0.62)	47 (0.67)		1.00
TC	49	26 (0.36)	23 (0.33)	0.498	0.85 (0.42-1.70)
CC	2	2 (0.03)	0 (0.00)		0.00 (0.00-5.31)
T	233	116 (0.79)	117 (0.84)	0.370	1.00
C	53	30 (0.21)	23 (0.16)		0.76 (0.42-1.39)
IL1RN rs2234663	141	72	69		
11	107	55 (0.76)	52 (0.75)		1.00
12	26	12 (0.17)	14 (0.20)	0.844	1.23 (0.52-2.91)
13	4	3 (0.04)	1 (0.01)		0.35 (0.01-4.59)
22	4	2 (0.04)	2 (0.04)		1.06 (0.07-15.08)
1	244	125 (0.87)	119 (0.86)		1.00
2	34	16 (0.11)	18 (0.13)	0.679	1.18 (0.58-2.42)
3	4	2 (0.01)	1 (0.00)		0.35 (0.01-4.45)
NOS2 rs2297518	132	54	78		
GG	94	50 (0.70)	44 (0.72)		1.00
GA	35	21 (0.30)	14 (0.23)	0.144	0.76 (0.34-1.67)
AA	3	0 (0)	3 (0.05)		
G	223	121 (0.85)	102 (0.84)	0.720	1.00
A	41	21 (0.15)	20 (0.16)		1.13 (0.58-2.20)
TGFB1 rs1800469	139	71	68		
CC	63	32 (0.45)	31 (0.46)		1.00
CT	55	28 (0.39)	27 (0.40)	0.992	1.00 (0.49-2.07)
TT	21	11 (0.15)	10 (0.15)		0.94 (0.35-2.52)
C	181	92 (0.65)	89 (0.65)	0.909	1.00
T	97	50 (0.35)	47 (0.35)		0.97 (0.59-1.59)
TNF rs1800629	140	72	68		
GG	120	62 (0.86)	58 (0.85)	0.890	1.00
GA	20	10 (0.14)	10 (0.15)		1.07 (0.41-2.64)
G	260	134 (0.93)	126 (0.93)	0.894	1.00
A	20	10 (0.07)	10 (0.07)		1.06 (0.43-2.64)

Table 5. Multivariate logistic regression model for independent predictors of tuberculosis susceptibility.

Variables	B	SE	Wald	df	p	OR	95% CI
FAM13A (TG)	-1.15	0.44	6.84	1	0.009	0.32	0.13-0.75
TET > 44,229 (hours)	0.16	0.42	0.14	1	0.704	1.17	0.51-2.68
Complicated silicosis	0.04	0.42	0.01	1	0.920	1.04	0.46-2.37
Exposure withdrawal (years)	0.001	0.02	0.001	1	0.948	1.00	0.96-1.04

Legend: B, estimated coefficient; SE, standard error; Wald, test for the statistical significance of each coefficient (B) in the model (*Z* statistic); df, degree of freedom; OR, odds ratio; CI, confidence interval.

relies on the dynamic regulation of the cytoskeleton. The Rho-GTPase families play a fundamental role in cytoskeleton regulation, thereby ensuring adequate cell migration.[15] Rho-GTPases transmit signals from cell surface receptors and regulate the actin cytoskeleton and microtubules, controlling cell shape, polarity, mobility, and adhesion.[17]

Changes in Rho-GTPases have been described in lung diseases such as asthma, COPD, and acute lung injury,[17] and are also associated with infectious diseases.[16] *Salmonella typhimurium*, for example, secretes the SptP protein, which functions as a GTPase-activating protein (GAP) on Rho-GTPases, influencing the host cell.[27]

Tuberculosis is also associated with Rho-GTPases.[16] Sun et al. (2010) described how the mycobacterial nucleoside diphosphate kinase protein (Ndk) exhibited activity on the GTPase-activating protein, inhibiting phagosome maturation and thereby promoting the survival of mycobacteria within macrophages.[28] The same authors also demonstrated that the NdK protein was associated with a reduction in nitric oxide production mediated by NOS2, interfering with apoptosis dependent on reactive oxygen species and affecting the activity of Rho-GTPases.[29]

The FAM13A isoform 1 protein contains a RhoGAP domain, suggesting its involvement in modulating the activity of Rho-GTPases.[17] The FAM13A (family with sequence similarity 13, member A) is expressed in the airways, particularly in type II epithelial cells and macrophages of human lungs, and its coding gene is located on chromosome 4q22.[17,30,31] Two variants of *FAM13A* have been identified in human lung tissue, with 24 exons and 17 exons, respectively.[17] Corvol et al. (2014) described how genetic variation in *FAM13A* affects Rho-GTPase activation and is associated with cellular pathways, though its exact biological function remains poorly understood.[17]

In this study, we observed an association between the rs2609255 polymorphism of the *FAM13A* gene and TB in patients with silicosis. The TG genotype showed a protective effect against TB susceptibility in these patients. Since the *FAM13A* protein contains a RhoGAP domain, the rs2609255 polymorphism in *FAM13A* could act as a modulator of Rho-GTPase activity, thereby promoting host protection mechanisms against *Mycobacterium tuberculosis* bacilli. However, no functional study of this polymorphism has been conducted to date. Other studies have also shown associations between polymorphisms in *FAM13A* and various lung diseases, such as idiopathic pulmonary fibrosis,[31,32] asthma,[33] chronic obstructive pulmonary disease (COPD),[34] cystic fibrosis,[35] and also increased susceptibility to silicosis.[30] This increased susceptibility to silicosis could be explained by other mechanisms. A recent study revealed that *FAM13A* can activate the Wnt pathway, a network of protein interactions that regulates several cellular functions, including cell differentiation, migration, and proliferation, and controls the protein stability of β-catenin.[36] The Wnt/β-catenin pathway has been reported to play a role in the development and progression of silicosis, with β-catenin acting as a key regulator of this process.[37,38] Moreover, the Wnt/β-catenin pathway has been shown to be significantly activated in lung tissue from patients with lung fibrosis, and the aberrant activation of this pathway may induce increased fibroblast migration.[39] In addition, the pharmacological and genetic inhibition of the Wnt /β-catenin pathway may attenuate, or even reverse, lung fibrosis.[40]

No associations were observed with the other polymorphisms evaluated in this study. This lack of association may be attributed to certain study limitations, such as the inability to analyze all pathways of TB pathogenesis and the small sample size. Further studies are needed to investigate the associations between genetic polymorphisms and the pathophysiological mechanisms of TB in patients with silicosis. Given the limited number of studies correlating genetic polymorphisms with TB susceptibility in patients with silicosis, additional research is required to confirm our findings.

ACKNOWLEDGMENTS

Financial support was provided by the National Council for Scientific and Technological Development (CNPq, Brazil; No. 402244/2016-8 and 310147/2023-9), the Rio de Janeiro State Research Support Foundation (FAPERJ, Brazil; No. E-26/210.293/2024), and the Pro-Rectorate of Research, Graduate Studies, and Innovation of the Federal Fluminense University (Proppi/PDI/UFF).

AUTHOR CONTRIBUTIONS

Study conception or design: FBK and ASFN; sample collection: MCSC, ASFN, KCRS, VMB, HC, PC, WC, and FBK; data acquisition, analysis, and interpretation: MCSC, KCRS, VMB, CBMN, and FBK; drafting the manuscript or revising it critically for important intellectual content: MCSC, JMR, and FBK; final approval of the manuscript: MCSC, ASFN, KCRS, VBM, JMR, HC, PC, WC, CBMN, and FBK.

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J Bras Pneumol. 2025;51(2):e20240426
https://dx.doi.org/10.36416/1806-3756/e20240426

Knowledge of, Attitude towards, and Preventive Behavior towards Tuberculosis questionnaire: translation and cross-cultural adaptation for use in Brazil

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Submitted: 2 January 2025.
Accepted: 13 March 2025.

Study carried out at the Faculdade de Medicina, Universidade Estadual Paulista Júlio de Mesquita Filho – UNESP – Botucatu (SP) Brasil.

ABSTRACT

Objective: To translate the Knowledge of, Attitude towards, and Preventive Behavior towards Tuberculosis questionnaire into Brazilian Portuguese and adapt it for use in Brazil. **Methods:** This methodological study followed internationally recommended guidelines for translation and cross-cultural adaptation. After permission was obtained from the original authors, the process of translation and cross-cultural adaptation began, including translation into Brazilian Portuguese by bilingual translators, synthesis of the translations, back-translation for similarity analysis, revision, and preparation of the final version. A pretest was conducted on 68 medical students. **Results:** Most of the questionnaire items showed strong content similarity, with minor semantic differences. The content validity index for the questionnaire was 0.882, and Cronbach's alpha coefficients were 0.682, 0.809, and 0.613 for knowledge of tuberculosis, attitudes toward tuberculosis, and preventive behavior toward tuberculosis, respectively. Cronbach's alpha and omega coefficients were $\alpha = 0.717$, $\omega1 = 0.673$, $\omega2 = 0.673$, and $\omega3 = 0.520$. **Conclusions:** The process of translation and cross-cultural adaptation of the Knowledge of, Attitude towards, and Preventive Behavior towards Tuberculosis questionnaire was successful, making the Brazilian Portuguese version of the questionnaire reliable for reproducibility. It can be used in order to collect tuberculosis-related data and support changes in health education curricula.

Keywords: Tuberculosis; Cross-cultural comparison; Attitude; Behavior.

INTRODUCTION

Despite efforts by the WHO and many countries to eliminate tuberculosis, incidence and mortality rates have declined slowly, tuberculosis remaining a major global health concern. This situation has been worsened by COVID-19 and recent armed conflicts, creating a pressing global tuberculosis crisis. Well-structured, effective, and multisectoral responses are essential in order to meet eradication targets.[1]

In Brazil, the National Plan to End Tuberculosis as a Public Health Problem, issued in 2017, has not been able to prevent more than 80,000 new cases and approximately 5,000 deaths annually. Brazil ranks alongside nations such as Bangladesh and Zambia,[2] reflecting gaps in tuberculosis prevention, diagnosis, treatment, and research investments.[3]

Between 2015 and 2023, tuberculosis cases increased, particularly among vulnerable groups. From 2022 to 2023, tuberculosis cases among health care workers also rose.[2] Recognizing and preventing tuberculosis is crucial not only for patient care but also for health care professionals.

Assessing knowledge, attitudes, and behaviors regarding tuberculosis among health students can enhance disease recognition, improve patient care, and foster empathy toward infected individuals. Findings can inform policy decisions and curriculum enhancements in health education, which remains an area requiring further research.[4-7]

The WHO developed the Knowledge, Attitudes, and Practices (KAP) questionnaire in the 1950s to assess various health issues. The tuberculosis-specific version, available since 2008, provides guidance on adapting the questionnaire to different social contexts.[8] However, although the KAP questionnaire is effective for general knowledge assessment, it has limitations in evaluating tuberculosis-related practices and attitudes.[9]

The Knowledge of, Attitude towards, and Preventive Behavior towards Tuberculosis questionnaire, developed by Yun Choi and Geum Hee Jeong and published in English in 2018,[10] was initially designed to assess knowledge of, attitudes toward, and preventive behaviors toward tuberculosis among Korean army soldiers. The questionnaire integrates KAP questionnaire components, features clear and concise statements, and is suitable

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Financial support: None.

ISSN 1806-3756

for international studies. However, it has yet to be translated and adapted for use in Brazil.

The objective of the present study was to translate the Knowledge of, Attitude towards, and Preventive Behavior towards Tuberculosis questionnaire into Brazilian Portuguese and adapt it for use among health students in Brazil.

METHODS

This study is a methodological investigation of translating the Knowledge of, Attitude towards, and Preventive Behavior towards Tuberculosis questionnaire into Brazilian Portuguese and adapting it for use in health students in Brazil. The study followed methodological guidelines from Beaton et al. and Fortes & Araújo, who proposed that self-report measures be cross-culturally adapted in accordance with international recommendations, following the steps of preparation, translation, reconciliation of translations, back-translation, revision, and pretesting.[11,12]

The original scale was based on an examination tool by the Korean Centers for Disease Control and Prevention[10] and is multidimensional, measuring knowledge, attitudes, and preventive behavior related to tuberculosis, with original Cronbach's alpha coefficients of 0.87, 0.83, and 0.82, respectively.[12] To measure tuberculosis knowledge, 20 items (six of which are formulated in reverse) offer three response options (yes, no, and I don't know)[10] with binomial correction (correct/incorrect). The sections measuring attitudes and behavior each contain 15 items with positive statements scored on four-point Likert scales, higher scores translating to better attitudes and more appropriate behaviors toward tuberculosis. The tool offers the advantage of being evaluated by items or subcategories for each section.

The adaptation process began with permission from the original authors. Ethical considerations were adhered to, and approval was obtained from the Research Ethics Committee of the São Paulo State University School of Medicine at Botucatu (Ruling nos. 5.278.736 and 5.453.561), in accordance with Brazilian National Health Council Resolution nos. 510/2016 and 466/2012.

The original questionnaire was independently translated into Brazilian Portuguese by two Brazilians who were fluent in English, one of whom is in the field of health sciences and one of whom is in the field of biological sciences. The translators were identified as translator 1 and translator 2, producing two independent translations (T1 and T2). For the synthesis of the translations, a review committee was formed, including medical and nursing professionals, as well as a researcher experienced in translating and culturally adapting self-report measures. All committee members have a doctoral degree and knowledge of English and Brazilian Portuguese. The committee held meetings to compare translations and discuss until a consensus version was agreed upon (T3).

The evaluation considered semantic equivalence, idiomatic equivalence, cultural equivalence, and conceptual equivalence. The resulting version was then back-translated into English by an independent professional who is fluent in Portuguese and English, and who had no medical training, being unaware of the original English-language version of the questionnaire. This process resulted in a back-translation (T4), which was compared with the original for similarity analysis.

To better assess the internal consistency of the questionnaire, the committee expanded the four-point Likert scales to six points in the attitudes and behavior domains, with a minimum score of 15 and a maximum score of 90.

For calculation of the content validity index, each item was scored on a Likert scale from 1 to 4 on the basis of the feasibility of translation to the Brazilian context.[13] The content validity index for the entire questionnaire was calculated as the arithmetic mean of the item scores, with 100% as the approval parameter.[14]

A pilot test was conducted on 68 medical students at a public university in Brazil. After completing the questionnaire, student judges evaluated clarity, comprehension, and possible uncertainties regarding the items, being given an opportunity to suggest improvements. On the basis of the mean of positive scores, the minimum acceptable value was set at 0.80. The entire process of translation and cross-cultural adaptation is shown in Figure 1.

To assess internal consistency, the Kuder-Richardson formula 20 was used for knowledge-related items, whereas Cronbach's alpha and Omega coefficients were applied with values between 0.60 and 0.95 being considered acceptable.[15-17] Additionally, item-total correlation was analyzed, with correlations greater than 0.20 suggesting good correlation.[18,19]

RESULTS

The process of translation and adaptation of the Knowledge of, Attitude towards, and Preventive Behavior towards Tuberculosis questionnaire occurred between May of 2023 and March of 2024. Of the 50 questionnaire items, 49 showed strong content similarity, with only minor semantic differences.

In the process of translating the 50 items that constitute the questionnaire, similarities prevailed in 49 (98%) of the items regarding content, with few semantic differences. Only one item had exact similarity.

For the consensus version (T3), T1 and T2 were adapted to the Brazilian culture and context, in accordance with the WHO KAP guidelines.[8] The review committee standardized the items by using the first-person pronoun "I". The committee opted for terms that are more commonly used by patients ("phlegm," "tiredness," and "fever" instead of "expectoration/sputum," "fatigue," and "sweating"),

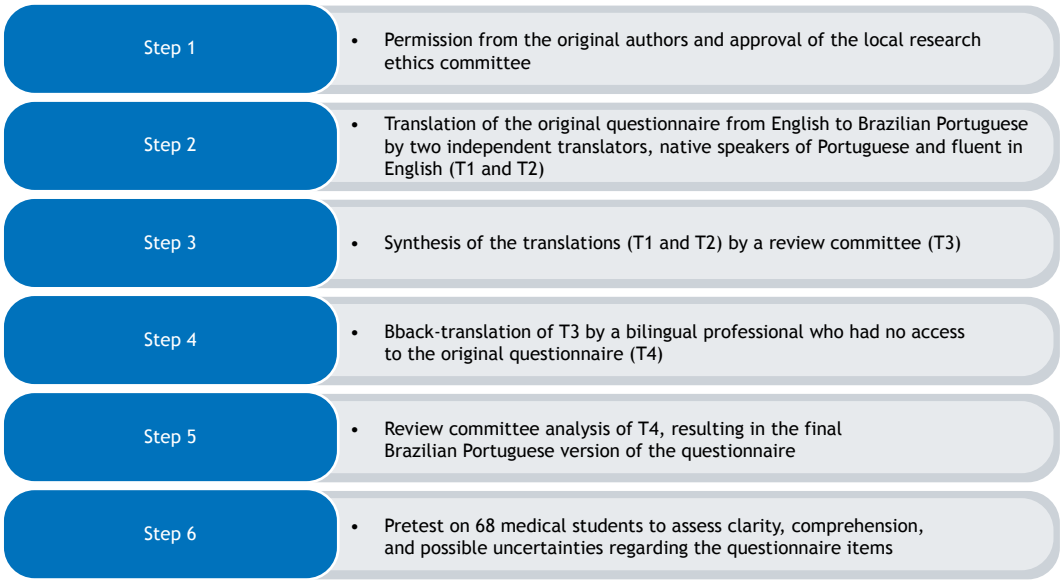

Figure 1. Flowchart of the process of translation and cross-cultural adaptation of the Knowledge of, Attitude towards, and Preventive Behavior towards Tuberculosis questionnaire for use in Brazil.

as well as culturally appropriate terms ("glasses and cutlery" instead of "bowls").

Adjustments related to the medical context were necessary because, according to the current literature, smoking is a relevant factor for greater susceptibility to tuberculosis, regardless of frequency (item 7). For the item referring to nocturnal fever, the committee opted for "nocturnal period" rather than "at dusk," considering that patients do not always correctly identify specific times (item 11).

To ensure clarity, the committee maintained the term "medicines" in some items to avoid repetition while preserving comprehension. Adjustments for terms commonly accepted in Brazil were necessary, such as in items 23, 24, 25, and 28 ("I think" and "I believe").

In the back-translation (T4), there were differences from the original because of the need to make adjustments; however, there were no conceptual errors or inconsistencies detrimental to the evaluation. The back-translation reproduced the same ideas as did the items in the original version, passing the validity checks and having no potential errors. The content validity index for the questionnaire was 0.95 in the first evaluation and 1.00 in the second, expert consensus being achieved for all items.

A pretest was conducted in March of 2024. Most of the students to whom the questionnaire was administered were < 25 years of age (80.9%), female (57.4%), single (98.5%), and nonsmokers (91.2%). Only 7.4% of the respondents reported tuberculosis cases in their families. The mean knowledge score was 10.51, with 79% (n = 54) failing to answer 70% of questions correctly. In the attitudes domain, the mean total score was 72.3 [IQR, 20-90], being = 4.82 per item, with the mean score being lowest (2.34) for item 26. For the behavior domain, the mean total score was 61.1 [IQR, 38-87], being 4.08 per item, with the mean scores being lowest (1.57, 1.56, and 1.46) for items 42, 43, and 44, respectively.

In the evaluation of the questionnaire, the mean coefficient calculated for clarity, comprehension, and uncertainty was 0.882. In the analysis of the internal consistency of the questionnaire, Cronbach's alpha coefficients were 0.682 for knowledge of tuberculosis, 0.809 for attitudes toward tuberculosis, and 0.613 for preventive behavior toward tuberculosis (Table 1). With regard to Cronbach's alpha and McDonald's omega coefficients, the results were as follows: α = 0.717 and ω1 = 0.673; ω2 = 0.673; and ω3 = 0.520 for knowledge of tuberculosis, attitudes toward tuberculosis, and preventive behavior toward tuberculosis, respectively. The highest item-total correlations were obtained in the attitudes domain (Table 1). Chart 1 shows the original English-language version of the Knowledge of, Attitude towards, and Preventive Behavior towards Tuberculosis questionnaire and the Brazilian Portuguese version of the questionnaire.

DISCUSSION

The present study described the process of developing a Brazilian Portuguese version of the Knowledge of, Attitude towards, and Preventive Behavior towards Tuberculosis questionnaire for undergraduate health students, following the methodological steps recommended in the literature. The translated questionnaire achieved semantic, idiomatic, conceptual, and cultural equivalence, with adequate comprehension by the target population and good internal consistency.

Table 1. Cronbach's alpha coefficient for evaluation of a Brazilian Portuguese version of the Knowledge of, Attitude towards, and Preventive Behavior towards Tuberculosis questionnaire.

Item	Scale mean if item deleted	Scale variance if item deleted	Corrected item-total correlation	Cronbach's alpha if item deleted
1	10.37	10.177	0.233	0.674
2	9.58	10.095	0.323	0.668
3	9.93	9.797	0.231	0.674
4	9.79	9.289	0.451	0.649
5	9.96	9.559	0.308	0.665
6	10.37	10.419	0.115	0.683
7	9.97	10.393	0.038	0.697
8	9.60	10.517	0.079	0.685
9	10.06	9.784	0.235	0.674
10	10.21	9.380	0.425	0.652
11	10.24	9.700	0.321	0.664
12	10.19	9.644	0.319	0.664
13	9.75	10.313	0.093	0.688
14	10.06	9.905	0.195	0.678
15	9.78	9.661	0.319	0.664
16	10.16	9.533	0.346	0.661
17	10.07	9.464	0.346	0.661
18	10.06	9.875	0.205	0.677
19	9.61	10.180	0.231	0.674
20	9.60	9.941	0.377	0.663
21	67.85	105.142	0.005	0.838
22	66.84	92.197	0.587	0.787
23	67.56	96.698	0.363	0.803
24	67.59	96.962	0.347	0.804
25	67.16	94.645	0.585	0.789
26	69.97	105.372	0.019	0.832
27	68.19	94.605	0.329	0.808
28	67.18	91.342	0.642	0.783
29	68.25	94.668	0.392	0.801
30	66.65	93.008	0.777	0.781
31	66.78	92.980	0.648	0.785
32	66.57	94.666	0.709	0.785
33	66.91	96.440	0.506	0.794
34	68.22	94.772	0.423	0.798
35	66.60	93.736	0.787	0.782
36	57.78	53.843	0.357	0.574
37	57.04	50.013	0.476	0.546
38	55.67	62.133	0.127	0.610
39	56.01	60.803	0.173	0.606
40	57.37	59.571	0.077	0.629
41	56.49	60.314	0.130	0.612
42	59.87	59.936	0.145	0.610
43	59.88	61.379	0.097	0.615
44	59.99	60.591	0.159	0.607
45	57.01	59.833	0.088	0.624
46	56.51	55.436	0.201	0.607
47	56.46	54.707	0.430	0.566
48	57.12	52.198	0.483	0.552
49	56.76	54.700	0.359	0.575
50	56.30	56.910	0.293	0.588

Chart 1. Original and translated versions of the Knowledge of, Attitude towards, and Preventive Behavior towards Tuberculosis questionnaire.

Original version (in English) Knowledge of, Attitude towards, and Preventive Behavior towards Tuberculosis questionnaire		Translated version (in Brazilian Portuguese) Instrumento de avaliação de conhecimento, atitudes e comportamento sobre tuberculose	
Knowledge of tuberculosis		**Conhecimento sobre tuberculose**	
Infection route	1-Tuberculosis can break out anywhere in the human body.	Transmissão	1-A tuberculose pode se manifestar em qualquer parte do corpo humano.
	2-Tuberculosis can be transferred through coughing and sneezing.		2-A tuberculose pode ser transmitida pela tosse e espirros.
	3-Tuberculosis may be transmitted by physical contact such as shaking hands or hugging.*		3-A tuberculose pode ser transmitida por contato físico, como aperto de mão ou abraço.
	4-Everyone infected with *Mycobacterium tuberculosis* becomes ill.*		4-Toda pessoa infectada com *Mycobacterium tuberculosis* adoece.
	5-If infected with tuberculosis once, lifelong immunity is formed.*		5-Uma vez infectado com tuberculose, se cria imunidade para o resto da vida.
	6-Tuberculosis is not transmitted through towels, plates, or bowls.		6-A tuberculose não é transmitida através de toalhas, pratos, copos ou talheres.
	7-Tuberculosis is more frequent in people who smoke a lot.		7-A tuberculose é mais frequente em pessoas que fumam.
	8-Tuberculosis is inherited by children from parents.*		8-A tuberculose é uma doença hereditária, transmitida dos pais para os filhos.
	9-Tuberculosis bacillus exists in the air.		9-O bacilo da tuberculose existe no ar.
Symptoms	10-No specific symptoms are present in the early stages of tuberculosis infection.	Sintomas	10-Não há sintomas específicos nos estágios iniciais da infecção pela tuberculose.
	11-If infected with tuberculosis, a slight fever occurs in the afternoon.		11-Quando infectado pela tuberculose, ocorre uma leve febre no período noturno.
	12-If a mild fever persists, accompanied by weight loss, tuberculosis is suspected.		12-Caso uma febre leve persistir, acompanhada de perda de peso, suspeita-se de tuberculose.
Preventive examinations	13-Chest X-rays are one way to diagnose tuberculosis.	Exames preventivos	13-O raio-X de tórax é uma forma de diagnosticar a tuberculose.
	14-Only one vaccination with BCG can provide lifelong immunity.*		14-Apenas uma vacinação com BCG pode gerar imunidade para o resto da vida.
	15-One should be examined if a prolonged cough with sputum persists for more than 2 weeks.		15-Deve-se examinar se a tosse prolongada com catarro persistir por mais de 2 semanas.
	16-Even if no special symptoms of coughing or sputum are present, I should be examined for tuberculosis if I have weight loss, fatigue, and so on.		16-Mesmo que não haja sintomas como tosse ou catarro, eu deveria ser examinado para a tuberculose se tiver perda de peso, cansaço, etc.
Treatment	17-Tuberculosis cannot be treated in the absence of overt symptom.*	Tratamento	17-A tuberculose não pode ser tratada na ausência de sintomas evidentes.
	18-Tuberculosis is treated by taking medicine every day for at least 6 months.		18-A tuberculose é tratada tomando remédios todos os dias por pelo menos 6 meses.
	19-One can recover from tuberculosis if medical treatment is followed, but if not, death can result.		19-Pode-se recuperar da tuberculose se o tratamento médico for seguido, mas, se não for, pode resultar em morte.
	20-Treatment is difficult, and if anti-tuberculosis drugs are not taken regularly, drug resistance can occur.		20-O tratamento é difícil e, se os remédios não forem tomados regularmente, pode ocorrer resistência da bactéria aos medicamentos.

Continue...▶

Original version (in English) Knowledge of, Attitude towards, and Preventive Behavior towards Tuberculosis questionnaire		Translated version (in Brazilian Portuguese) Instrumento de avaliação de conhecimento, atitudes e comportamento sobre tuberculose	
Attitudes towards tuberculosis		**Atitudes em relação à tuberculose**	
Recognition of tuberculosis	21-I do not mind if friends or people close to me know about my tuberculosis infection.	Reconhecimento da tuberculose	21-Não me importo se amigos ou pessoas próximas a mim souberem da minha infecção por tuberculose.
	22-If I get tuberculosis diagnosis, I should immediately inform the army.		22-Se eu receber o diagnóstico de tuberculose, devo informar imediatamente as pessoas com quem trabalho e convivo.
	23-I think that tuberculosis can be caught without even realizing it.		23-Eu acredito que a tuberculose pode ser contraída sem perceber nada.
	24-I think that I may experience obstacles in my familial and professional life if I am infected with tuberculosis.		24-Eu acho que posso enfrentar problemas na minha vida familiar e profissional se estiver contaminado com tuberculose.
	25-I think that tuberculosis is a very serious disease.		25-Eu acho que a tuberculose é uma doença muito grave.
	26-I have a higher than usual likelihood of tuberculosis infection.		26-Tenho uma probabilidade maior do que o normal de contrair tuberculose.
Preventive examinations	27-I think that it helps to prevent tuberculosis if I get a tuberculosis medical examination regularly every year.	Exames preventivos	27-Eu penso que realizar exame médico periódico para a tuberculose ajuda na prevenção dessa doença.
	28-I think that one should be examined for tuberculosis if there is a tuberculosis patient among one's family or friends.		28-Eu acho que eu deva ser examinado para tuberculose caso um familiar ou amigo esteja com essa doença
	29-I think that it is not too difficult to get a tuberculosis checkup in the military if one has symptoms of tuberculosis.		29-Penso que não é muito difícil fazer um exame de tuberculose nas unidades de saúde se alguém tiver sintomas da doença.
Treatment	30-If I am diagnosed with tuberculosis, I will take an anti-tuberculosis drug steadily for at least 6 months under a doctor's direction.	Tratamento	30-Se eu for diagnosticado com tuberculose, tomarei os medicamentos regularmente por pelo menos 6 meses sob supervisão de profissionais da saúde.
	31-If a friend discontinues taking an anti-tuberculosis medication, I will persuade the friend to take anti-tuberculosis medication continuously.		31-Se um amigo interromper o uso de medicamentos antituberculose, eu o convencerei a tomar os remédios de forma contínua.
	32-I will encourage tuberculosis patients around me to get treatment.		32-Eu incentivarei os pacientes com tuberculose ao meu redor a receberem tratamento.
	33-I think that tuberculosis can be cured completely if detected and treated early.		33-Eu penso que a tuberculose pode ser curada completamente se detectada e tratada o quanto antes.
Preventive education	34-I am interested in tuberculosis.	Educação preventiva	34-Tenho interesse em tuberculose.
	35-I think that education about tuberculosis is needed.		35-Eu acho que é necessária a educação sobre tuberculose.
Preventive behavior towards tuberculosis		**Comportamento preventivo em relação à tuberculose**	
Infection route	36-I try not to spend for a long time in places where air does not circulate well, such as Internet cafes, karaoke establishments etc.	Transmissão	36-Procuro não ficar muito tempo em locais onde o ar não circula bem, como bares ou estabelecimentos semelhantes etc.
	37-If I expectorate or spit out sputum, I wrap it in tissue paper and throw it out.		37-Se eu tossir com catarro, faço isso em um lenço de papel e o jogo no lixo.
	38-When I sneeze or cough, I cover my mouth.		38-Quando espirro ou tusso, cubro minha boca.
	39-In order to maintain fresh air indoors, I often open windows or find another way to ventilate the space.		39-Para manter o ar fresco em ambientes fechados, geralmente abro as janelas ou encontro outra maneira de ventilar o espaço.
	40-I cover my mouth with a handkerchief or tissue when coughing.		40-Cubro minha boca com um lenço de papel ao tossir.

Continue...▶

▲ Voltar ao sumário

Original version (in English) Knowledge of, Attitude towards, and Preventive Behavior towards Tuberculosis questionnaire			Translated version (in Brazilian Portuguese) Instrumento de avaliação de conhecimento, atitudes e comportamento sobre tuberculose
Preventive examinations	41-If a cough lasts more than 2 or 3 weeks, I go to the army medical corps or an army hospital to get a checkup.	Exames preventivos	41-Se a tosse durar mais de 2 ou 3 semanas, procuro uma unidade de saúde para fazer exames.
	42-I obtain a chest X-ray regularly every year.		42-Eu faço um raio-X de tórax regularmente todos os anos.
Preventive education	43-I frequently read materials designed to raise awareness about tuberculosis.	Educação preventiva	43-Com frequência, leio materiais informativos sobre tuberculose.
	44-I actively participate in education about tuberculosis.		44-Eu participo ativamente da educação sobre tuberculose.
Healthy lifestyle	45-If I suffer from stress, I have ways of dealing with it.	Estilo de vida saudável	45-Se eu sofrer de estresse, tenho maneiras de lidar com isso.
	46-I do not smoke for health reasons.		46-Eu não fumo por motivos de saúde.
	47-I usually eat well-balanced meals to maintain good health.		47-Costumo fazer refeições balanceadas para manter uma boa saúde.
	48-I do not eat excessively because doing so harms the immune system and overall health.		48-Eu não como excessivamente, pois isso prejudica o sistema imunológico e a saúde em geral.
	49-I am sure to wash my hands after going out or exercising.		49-Tenho certeza de que lavo as mãos depois de sair ou praticar atividades físicas.
	50-I usually engage in regular exercise to maintain good health.		50-Eu costumo praticar atividade física regularmente para manter uma boa saúde.

*Reverse questions.

The use of international scales facilitates comparisons of studies across countries, expanding opportunities for successful interventions. However, cross-cultural adaptation of instruments requires a meticulous process involving multiple stages that address both textual and technical aspects.[20] This demands methodological rigor to maintain the reliability and validity of the original instrument.[21]

The Consensus-based Standards for the Selection of Health Measurement Instruments initiative recommends that translated versions of assessment tools undergo review by a committee of experts and pretesting to improve the selection of instruments for measuring outcomes in research and clinical practice, thus contributing to the development of assessment tools that are more appropriate.[22]

Although the Knowledge of, Attitude towards, and Preventive Behavior towards Tuberculosis questionnaire is a comprehensive, 50-item questionnaire, its concise, objective, and easy-to-understand sentences facilitated the process of translating it into the target language. Backward translation ensured equivalence between the translations and the original English-language questionnaire.

In making necessary adaptations to the local culture, the expert committee compared translations without major controversies or disagreements among members, consistently considering scientific evidence on the subject[23] and focusing on effective communication by selecting the terms that are most commonly used by patients and laypeople in general,[24] aiming for an approach aligned with the Brazilian reality. The clear and detailed completion guidelines appear to have been fundamental to data collection. Similar results can be found in the literature, highlighting the importance of pretesting, given that this stage can identify potential difficulties in completing, applying, or understanding the items.[25]

Because the Knowledge of, Attitude towards, and Preventive Behavior towards Tuberculosis questionnaire was originally developed with the use of simple language, our study sought to expand its use. We examined each item in detail and its appropriateness within any scope of practice and determined that no items needed to be excluded. The pretest results indicated that the participants understood the questionnaire well.

Although Cronbach's alpha remains the most commonly used reliability index in research, several other aspects of test capability should be considered, including validity evidence, intercultural fairness, and practicality. The limitations of Cronbach's alpha have been discussed elsewhere,[17] with better alternatives including omega coefficients, which offers advantages for applied research in which items differ in quality or have skewed distributions. Omega coefficients can extend the usefulness of alpha coefficients in estimating the reliability of internal consistency scores

on a multidimensional scale with smaller samples,[17] such as the one evaluated in the present study.

In general, most of the students in our sample did not have adequate knowledge of tuberculosis at the time of questionnaire administration, despite their attitudes and behaviors being considered positive. Our results regarding tuberculosis knowledge are similar to those obtained in Korea, where the instrument was developed (11.64; 58.2%), with low recognition of populations more vulnerable to tuberculosis, as well as low scores on questions related to behavior, especially those concerning examinations and preventive education.[10]

In a scenario in which tuberculosis continues to be a neglected disease, translating and adapting a tuberculosis questionnaire fulfills the objective of providing an instrument that can enable comparisons and identification of gaps in teaching, as well as the implementation of policies to ensure that tuberculosis becomes an integral part of any educational curriculum for health professionals. Given the widespread need to promote public policies that guarantee continuous improvement of care and effectiveness of measures to control and prevent tuberculosis, it is essential to include tuberculosis education in the curricula of future health professionals.[26]

The absence of experts from other regions of the country in the evaluation may have been a limiting factor in the present study, given that Brazil is a large, culturally diverse country. Future studies should focus on the application of the final version of the questionnaire, its psychometric validation, and its use in other health professionals .

The recommendation to use internationally standardized instruments is aimed at improving research quality and enabling more reliable comparisons between countries and regions. Our translation and cross-cultural adaptation of a questionnaire for assessing knowledge, attitudes, and behaviors regarding tuberculosis offers an important resource for researchers in Brazil by providing a version translated and revised by an expert committee, and subjected to pretesting and statistical analysis in accordance with international guidelines. The use of the translated questionnaire can contribute to collecting information on tuberculosis and support changes in health education curricula.

AUTHOR CONTRIBUTIONS

RMBC and SPFF: study conception and design; and drafting of the manuscript. RMBC, SPFF, RCA, and HRCN: analysis and interpretation of data. RMBC, SPFF, RCA, HRCN, and SAML: revision of the manuscript. All authors approved the final version of the manuscript.

CONFLICTS OF INTEREST

None declared.

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J Bras Pneumol. 2025;51(2):e20240314
https://dx.doi.org/10.36416/1806-3756/e20240314

Brazilian guidelines for the pharmacological treatment of pulmonary embolism. Official document of the Brazilian Thoracic Association based on the GRADE methodology

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Submitted: 16 September 2024.
Accepted: 3 February 2025.

ABSTRACT

Venous thromboembolism (VTE) is the third most common acute cardiovascular syndrome after acute myocardial infarction and stroke. In recent years, there has been an increase in the incidence of VTE, related to population aging and common comorbidities in the elderly, including chronic cardiorespiratory disease and cancer. On the other hand, disease-related mortality, particularly for pulmonary embolism (PE), shows a decreasing trend, which can be explained by improvements in diagnostic imaging, advances in available therapies, and greater adherence to patient management protocols. The guidelines presented here provide recommendations for the pharmacological treatment of PE in Brazil, on the basis of scientific evidence and with a focus on common practical issues. Six Patient, Intervention, Comparison, and Outcome questions were developed by a group of experts on the topic. Systematic reviews of randomized clinical trials were conducted for each question, with meta-analyses being performed when possible. The level of evidence and strength of recommendation were defined in accordance with the Grading of Recommendations Assessment, Development, and Evaluation approach. With these guidelines, we expect to provide relevant, up-to-date information on the pharmacological treatment of PE.

Keywords: Pulmonary embolism; Heparin; Heparin, low-molecular-weight; Factor Xa inhibitors; Fibrinolytic agents.

INTRODUCTION

Venous thromboembolism (VTE) can clinically present as deep vein thrombosis (DVT), pulmonary embolism (PE), or both. In general terms, VTE results from conditions involving hypercoagulability, blood stasis, and endothelial injury (Virchow's triad). VTE is the third most prevalent acute cardiovascular syndrome, after acute myocardial infarction and stroke. PE has a greater potential for severity and can lead to death either on its own or in association with other comorbidities. In the literature, the incidence of PE ranges from 38 to 99 cases per 100,000 population/year.[1] In recent years, there has been a trend of increasing incidence of PE; this trend can be attributed to population aging and increased oncological and cardiopulmonary comorbidities in patients > 60 years of age.[2]

Despite the increase in the incidence of PE, the mortality of PE shows a decreasing trend, which is largely explained by improved diagnostic imaging and the emergence of new therapeutic options, such as direct oral anticoagulants (DOACs, including anti-Xa and antithrombin), as well as greater adherence to diagnostic protocols.[2,3]

The last recommendation of the *Sociedade Brasileira de Pneumologia a Tisiologia* (SBPT, Brazilian Thoracic Association) for the treatment of PE was published in 2010.[4] Since then, there have been fundamental changes in therapeutic strategies, an update therefore being required. The objective of these guidelines is to provide updated, practical, and relevant information on the pharmacological treatment of PE and contribute to the advancement of good medical practice in managing PE, which remains a challenge in daily clinical practice. Additionally, it is hoped that these guidelines will assist in discussions with public and private managers regarding treatment options at the hospital and outpatient levels. To this end, the Grading of Recommendations Assessment, Development, and Evaluation (GRADE) approach is the most robust way to address the evidence that is currently available in the literature.[5]

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Financial support: None.

◄ Voltar ao sumário
ISSN 1806-3756

METHODOLOGY

The current guidelines were developed in accordance with the SBPT. First, a coordinating group was formed, including two specialists in the pharmacological treatment of PE and three experts in evidence-based medicine. Specialists from across the country were invited to join the expert panel. An online meeting was held in April of 2019. After reaching an agreement on the methodology to be employed, the experts were trained in the GRADE approach through written materials and training videos.[6] After the training, the expert panel formulated questions regarding the pharmacological treatment of patients diagnosed with PE. The questions followed the Patient, Intervention, Comparison, and Outcome (PICO) format. The coordinating group reviewed and adjusted the questions in accordance with the PICO format. The outcomes of interest for each question were defined a priori as critical, important, or not important (Chart 1).

The team of experts in evidence-based medicine searched for articles and conducted a meta-analysis. The systematic review and meta-analysis was registered with the International Prospective Register of Systematic Reviews (Protocol no. CRD42023481041). The following databases were searched for articles published in English, Portuguese, Spanish, or French and reporting on clinical trials: MEDLINE, EMBASE, and ClinicalTrials.gov. The search terms were defined by the coordinating team, and no date restrictions were applied (supplementary material, Chart S1).

After selecting the articles, the experts in evidence-based medicine (one of whom is also an expert in managing PE) independently evaluated the titles and abstracts. In case of disagreement, discussions were held until a consensus was reached. Subsequently, the full-text articles underwent qualitative analysis, being evaluated for eligibility. Again, if disagreement occurred, further discussions were held until consensus was reached. The selected articles were then quantitatively evaluated. The reasons for inclusion or exclusion were recorded and presented in accordance with the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) guidelines,[7] being available in the supplementary material (Figure S1).

Only results from studies assessing the same intervention were combined in meta-analysis (Chart 2 and Figure S2). For each of the six PICO questions, the quality of the evidence was assessed with GRADE, evidence tables being created with the GRADEpro Guideline Development Tool (McMaster University, Hamilton, ON, Canada).[6]

For any given study, the quality of evidence depends on the design, implementation, and risk of bias, and can be classified as high, moderate, low, or very low.

Chart 1. Questions and outcomes included in the present guidelines.

Questions	Critical outcomes	Important outcomes	Minimally important outcome
1. Should home anticoagulation be used in comparison with hospitalization in patients with low-risk PE?	Recurrence of venous thromboembolism; death	Bleeding within 90 days	–
2. Should anticoagulation with DOACs* be used in comparison with anticoagulation with LMWH in PE patients diagnosed with cancer?	Major bleeding**; recurrence of venous thromboembolism; death	Any bleeding	–
3. Should extended anticoagulation be maintained in comparison with placebo or aspirin in patients who have been diagnosed with unprovoked PE and who have completed at least 3 months of anticoagulation?	Major bleeding**; recurrence of venous thromboembolism; death	Any bleeding	–
4. Should treatment with DOACs* be recommended for at least 3-6 months in comparison with conventional anticoagulation (LMWH or UFH, followed by warfarin) in patients diagnosed with low-risk PE, intermediate-risk PE, intermediate high-risk PE after stabilization, or high-risk PE after reperfusion and stabilization?	Major bleeding**; recurrence of venous thromboembolism; death	Any bleeding or clinically significant bleeding	–
5. Should systemic thrombolysis be recommended in comparison with anticoagulation alone (LMWH or UFH) in patients with intermediate-high-risk PE?	Major bleeding**; recurrence of venous thromboembolism; death	Any bleeding; chronic thromboembolic pulmonary hypertension	–
6. Should systemic thrombolysis be recommended in comparison with anticoagulation alone (LMWH or UFH) in patients with high-risk PE?	Major bleeding**; recurrence of venous thromboembolism; death	Any bleeding	–

PE: pulmonary embolism; DOACs: direct oral anticoagulants; LMWH: low-molecular-weight heparin; and UFH: unfractionated heparin. *Apixaban, dabigatran, edoxaban, and rivaroxaban. **Evident bleeding associated with a ≥ 2 g/dL reduction in hemoglobin leading to transfusion of two or more units of blood, occurring in a critical location or organ, or contributing to death.

The quality may be downgraded by one or two levels when there is evidence of risk of bias, indirect evidence, inconsistency, imprecision, or publication bias. On the other hand, the quality may be upgraded when there is a strong association with the effect without any plausible confounders; when there is evidence of a dose-response relationship; or when all plausible confounders would act to reduce the effect size (Chart 3).[8-10] The methodologists independently assessed the quality of the evidence, and all discrepancies were reviewed until consensus was reached.

In February of 2024, the coordinating committee met with members of the expert panel in São Paulo to review all tables containing evidence summaries (Chart S3). Recommendations for each question were made on the basis of critical outcomes, in accordance with the GRADE approach. The recommendations were classified as strong or conditional, depending on the degree of certainty regarding the strength and quality of evidence, among other factors. In accordance with the GRADE approach, we used the term "recommend" for strong recommendations and "suggest" for conditional recommendations. Chart 4 outlines suggested interpretations for all stakeholders, including patients, health care professionals, and policymakers. We used the GRADE evidence to decision framework to organize the discussion and ensure that each of the following factors was considered in formulating the recommendations: balance between desirable and undesirable effects of the intervention; degree of certainty based on the quality of existing evidence; patient values and preferences; resource use implications; and feasibility of implementation (Chart S3).[9,10] Whenever a consensus was not reached, votes were taken, and the results were recorded.

Question 1. Should home anticoagulation be used in comparison with hospitalization in patients with low-risk PE?

The possibility of home treatment for low-risk patients with PE has gained traction in recent years with the emergence of DOACs. However, the decision to start home treatment must be based on the following: social support (i.e., understanding of the disease and possible complications; correct use of medications and recognition of potential side effects; and quick access to health care services if needed); and patient preference, a shorter hospital stay being a possibility.[11]

Evidence

A total of 6,965 articles were identified. Of those, 4,626 were excluded due to the duplicity. Of the remaining 2,360 articles, 2,247 were excluded after title review. The abstracts of 113 articles were read, and 5 articles were selected for inclusion. After discussions between methodologists and specialists, 2 studies were excluded—one because it was a conference abstract and the other because it was not a controlled study. Thus, the meta-analysis included 3 randomized, controlled, open-label studies evaluating early hospital discharge (discharge within the first 24 h of admission in 2 studies and discharge after 24 h of randomization in 1) followed by home treatment for patients diagnosed with acute PE who were classified as having low-risk acute PE in accordance with European Respiratory Society criteria[12] or the Hestia criteria.[13,14] Two studies initiated treatment with low-molecular-weight heparin (LMWH) and warfarin and assessed noninferiority in comparison with conventional hospital treatment.[12,14] One study initiated treatment with rivaroxaban and compared it with conventional treatment, which was at the discretion of the attending team.[13]

Regarding the critical outcome of recurrent VTE, there was no significant difference between the two strategies (risk difference [RD] = 0.00; 95%

Chart 2. Interpretation of the quality of evidence in accordance with the Grading of Recommendations Assessment, Development, and Evaluation system.[a]

Quality of evidence	Implications	Examples
High (⊕⊕⊕⊕)	Future research is unlikely to change confidence in the estimated effect; we are confident that we can expect a very similar effect in the population for which the recommendation is intended.	Randomized trials without serious limitations. Well-executed observational studies, with a very large effect.
Moderate (⊕⊕⊕O)	Future research is likely to have an important impact on confidence in the estimated effect and may change this estimate.	Randomized trials with serious limitations. Well-executed observational studies, with a large effect.
Low (⊕⊕OO)	Future research is likely to have an important impact on confidence in the estimated effect and will likely change this estimate.	Randomized trials with very serious limitations. Observational studies without special strengths or important limitations.
Very low (⊕OOO)	Any estimate of an effect is very uncertain.	Randomized trials with very serious limitations and inconsistent results. Observational studies with serious limitations. Nonsystematic clinical observations (e.g., case series and case reports).

[a]Adapted from the Brazilian National Ministry of Health.[10]

Chart 3. Factors affecting the quality of evidence.[a]

Quality of evidence	Situations in which the evidence grade may be reduced	Situations in which the evidence grade may be increased
• High • Moderate • Low • Very low	• Risk of bias • Indirect evidence • Inconsistency • Imprecision • Publication bias	• Strong association, no plausible confounders • Evidence of dose response • Plausible confounders reducing the effect

[a]Adapted from Guyatt et al.[8]

CI: −0.01 to 0.01; p = 0.48], with a low level of evidence. Similarly, the critical outcome of death from any cause showed no significant difference (RD = −0.00; 95% CI: −0.01 to 0,01; p = 0.75), with a very low level of evidence (Figure S2.1).

For the important safety outcome of bleeding of any severity, there was no significant difference between the two treatment strategies (RD = 0.01; 95% CI: −0.01 to 0.02; p = 0.32), with low-quality evidence. The critical outcome of major bleeding was not addressed separately by the selected studies (Figure S2.1).

Recommendation

For patients who have been diagnosed with low-risk acute thromboembolism and who have guaranteed access to health care services, we suggest home treatment. This is a conditional recommendation with very low-quality evidence.

Comments

Early discharge for home treatment of low-risk PE patients remains a challenge. Although it is an appealing strategy and is recommended in international guidelines,[11] the concern about recurrence or early deterioration after discharge may pose imminent risks. For the present guidelines, 3 randomized studies were selected. They found no differences in the risk of recurrence or minor bleeding between patients treated at home and hospitalized patients. Among the available therapeutic options, the use of DOACs or LMWH followed by warfarin was assessed. Regarding DOACs, rivaroxaban was compared with conventional hospital treatment in a randomized clinical trial, which resulted in a shorter hospital stay without an increase in adverse events.[13] Although dabigatran, apixaban, and edoxaban have all been approved for use in patients with acute PE on the basis of studies demonstrating their efficacy and safety in comparison with LMWH and/or warfarin,[15-17] there are currently no randomized clinical trials evaluating these DOACs for home treatment.

Therefore, for early discharge with home anticoagulation to be a feasible option, certain conditions must be met. These include a low risk of early death or severe complications; no major comorbidities or worsening of concomitant conditions; guaranteed access to the recommended anticoagulant treatment; and guaranteed readmission if symptoms worsen. If these conditions are met, we suggest home treatment for low-risk acute PE.

Question 2. Should anticoagulation with DOACs be used in comparison with anticoagulation with LMWH in PE patients diagnosed with cancer?

Venous thromboembolic events are common in cancer patients, and treatment is challenging because of an increased risk of recurrent VTE and because of the risk of bleeding.[18] Anticoagulation with LMWH for 3 months or longer has been shown to be safer than anticoagulation for the same duration with vitamin K antagonists (VKAs). However, with the emergence of DOACs, the choice of medications for prolonged anticoagulation has been reconsidered.

Evidence

A total of 1,381 articles were identified. Of those, 263 were excluded due to the duplicity. Of the remaining 1,118 articles, 1,087 were excluded after title review. The abstracts of 31 articles were read, and 11 articles were fully reviewed. Of those, 5 were excluded. Three were excluded for being duplicate studies, one was excluded for being a post-hoc analysis, and one was excluded for not being in Spanish, French, or English. The meta-analysis included 6 randomized controlled trials evaluating anticoagulation with DOACs in cancer patients with active disease in comparison with standard treatment with LMWH. Two studies evaluated apixaban in comparison with dalteparin.[19,20] One study assessed noninferiority regarding the outcome of recurrent VTE,[20] and the other assessed superiority regarding any bleeding episode.[19] Two studies evaluated rivaroxaban in comparison with dalteparin. Both studies had recurrent VTE as the primary outcome, with one using a noninferiority analysis.[21,22] One clinical trial assessed the noninferiority of edoxaban in comparison with dalteparin regarding the composite primary outcome of recurrent VTE or major bleeding.[23] Finally, one study evaluated the noninferiority of DOACs, for patient convenience, in comparison with LMWH, chosen on the basis of attending physician preference.[24]

Regarding the critical outcome of recurrent VTE, there was a significant difference favoring anticoagulation with DOACs in comparison with LMWH (RD = −0.03; 95% CI: −0.05 to −0.01; p < 0.001), with a moderate level of evidence. The critical outcome of death from any cause showed no significant difference (RD = 0.01; 95% CI: −0.02 to

0.03; p = 0.66), with a moderate level of evidence (Figure S2.2).

Regarding safety outcomes, the critical outcome of major bleeding showed no significant difference between the therapeutic strategies (RD = 0.01; 95% CI: −0.00 to 0.02; p = 0.21), with a low level of evidence. However, when the important outcome of nonmajor bleeding was evaluated, there was a significant difference favoring conventional treatment with LMWH (RD = 0.03; 95% CI: 0.01-0.05; p = 0.001), with a moderate level of evidence (Figure S2.2).

Recommendation

For patients diagnosed with acute thromboembolism and cancer, we suggest treatment with DOACs. This is a conditional recommendation with low-quality evidence.

Comments

Cancer patients have a high incidence of venous thromboembolic events,[25] their risk of developing VTE being 4-7 times as high as that of the noncancer population.[26] Moreover, 20% of cancer patients develop VTE over the course of their disease,[27] highlighting a strong relationship between VTE and cancer. Additionally, VTE is the second leading cause of death in cancer patients,[28] and in up to 10% of cases it may be an indicator of an as-yet unidentified oncological condition.[29] However, conventional VTE treatment with coumarins has never proven effective for this population. The rate of recurrence and bleeding in cancer patients with VTE is 2-3 times as high as that in the noncancer population.[18] This is partly due to the difficulty in maintaining cancer patients with VTE within the therapeutic international normalized ratio (INR) range, the results being generally unsatisfactory.[30,31]

From the publication of the CLOT study[31] in 2003 until 2017, LMWHs were the treatment of first choice for cancer-associated VTE.[32] However, cancer patient adherence to long-term injectable anticoagulant treatment has been shown to be unsatisfactory.[33] Starting in 2017, studies on DOACs and VTE in cancer patients began to be published. Edoxaban[34] and rivaroxaban[22] proved to be superior to dalteparin in preventing VTE but were inferior in terms of bleeding, mainly due to gastrointestinal bleeding in patients with uncontrolled anatomical lesions in the stomach and intestines. Apixaban was shown to be as effective and safe as dalteparin for treating VTE in the cancer population, regardless of the primary site of the lesion.[35] Although the duration of DOAC use in cancer-associated VTE requires further evidence, most studies have evaluated this condition for a period of 6 months, and this seems to be a reasonable minimum interval for maintaining anticoagulation in this population, provided that the cancer has resolved or has been controlled.

Question 3. Should extended anticoagulation be maintained in comparison with placebo or aspirin in patients who have been diagnosed with unprovoked PE and who have completed at least 3 months of anticoagulation?

The decision to maintain anticoagulation for an indefinite period beyond the initial 3 months of treatment after the diagnosis of VTE without a known predisposing factor should carefully consider the associated risks. The recurrence of thromboembolic events represents a significant concern, with an annual incidence ranging from 5.4% to 11% per year after cessation of anticoagulation.[16,36] This risk must be weighed against the potential hemorrhagic complications associated with anticoagulant use. The advent of DOACs has mitigated some of the inconveniences related to the numerous drug and food interactions inherent to VKAs, as well as having eliminated the need for periodic INR monitoring. Moreover, prolonged use of anticoagulants may offer benefits beyond the prevention of VTE recurrence, including a potential reduction in the risk of other cardiovascular complications, such as myocardial infarction and ischemic stroke.[37]

Evidence

A total of 937 articles were identified. Of those, 48 were excluded due to the duplicity, leaving 889 articles. Subsequently, 867 studies were excluded after title and abstract review. A total of 22 articles were therefore selected for full-text review, with 13 articles being excluded for not meeting the inclusion criteria. Nine articles were discussed among the methodologists, with an additional 4 being excluded: 1 for not providing clear information on the treatment, 1 for not being a controlled study, and 2 for having examined topics that were not relevant to the question at hand. The meta-analysis included 5 randomized controlled trials evaluating extended anticoagulation after at least 3 months of initial anticoagulant treatment. Two studies evaluated warfarin, with a therapeutic INR target between 2 and 3, in comparison with placebo. One study evaluated VTE recurrence as the primary outcome over 24 months of treatment,[38] and the other study established a combined outcome of VTE recurrence and major bleeding over 18 months of treatment.[39] One study evaluated three groups: apixaban at the usual dose of 5 mg every 12 h, reduced-dose apixaban at 2.5 mg every 12 h, and placebo for 12 months, with VTE recurrence or death from any cause as the primary efficacy outcome and major bleeding as the primary safety outcome.[16] Another study evaluated three groups: rivaroxaban at the usual dose of 20 mg daily, reduced-dose rivaroxaban at 10 mg daily, and aspirin at 100 mg daily for 12 months. The primary efficacy outcome in that study was VTE recurrence or death from an unknown cause where PE could not be ruled out as the cause of the fatal event. The primary safety outcome was major bleeding.[40] Finally, one study evaluated dabigatran at a dose of 150 mg every 12 h vs. placebo for 6 months. The efficacy outcome was VTE recurrence or death from an unknown cause where PE could not be ruled out as the cause of the fatal event. The primary

safety outcome was major bleeding or nonmajor but clinically relevant bleeding.[36]

For the critical outcome of VTE recurrence, there was a significant difference favoring prolonged anticoagulation in comparison with placebo (RD = −0.07; 95% CI: −0.10 to −0.04; p < 0.001), with a high level of evidence. The critical outcome of death from any cause showed a significant difference favoring prolonged treatment (RD = −0.01; 95% CI: −0.01 to −0.00; p = 0.02), with a high level of evidence (Figure S2.3).

Regarding safety outcomes, there were no significant differences between the therapeutic strategies regarding major bleeding, which is considered a critical outcome (RD = 0.00; 95% CI: −0.00 to 0.01; p = 0.14). The level of evidence was high. However, when the important outcome of nonmajor bleeding was evaluated, there was a significant difference between the therapeutic strategies, with a higher number of bleeding events in patients who were anticoagulated for a prolonged period (RD = 0.03; 95% CI: 0.01-0.06; p = 0.01), with a high level of evidence (Figure S2.3).

Recommendation

For patients who have been diagnosed with unprovoked PE and who have completed at least 3 months of anticoagulation, extended anticoagulation (for an indefinite period) is recommended. This is a strong recommendation with high-quality evidence.

Comments

After a 3-month treatment period for VTE, all patients should be evaluated for extended therapy. Patients who have been diagnosed with VTE and who have a major transient risk factor for thromboembolic events, such as surgeries under general anesthesia lasting longer than 30 min, trauma/fractures, and prolonged hospitalizations with mobility restrictions (longer than 3 days), may discontinue anticoagulation after 3 months of treatment, with a low risk of VTE recurrence.[11,41] For patients with low-risk factors for VTE and a low risk of bleeding, the trend in the literature is to maintain extended anticoagulation, even if the risk factor for thrombosis has been removed; however, this guidance is not consensual.[11,41] For patients who have been diagnosed with unprovoked PE and who have completed at least 3 months of anticoagulation, extended anticoagulation is recommended. For patients with an indication for indefinite anticoagulation, if the bleeding risk is not low, the decision to maintain extended anticoagulation should be individualized and take into account removal of the thrombosis risk factor.

Extended anticoagulation for an indefinite period is an extrapolation of the positive results from studies evaluating this approach, given that those studies analyzed outcomes within 12-24 months of treatment.[16,38,39] Reduced doses of DOACs were assessed in extended treatment studies, showing results similar to conventional doses in terms of effectiveness and safety outcomes, making them an alternative to conventional-dose treatment.[16,40] Periodic reassessment of patients regarding the risk of bleeding during anticoagulation should be conducted using scales specifically designed for this purpose.[11]

If extended anticoagulation is recommended, testing for antiphospholipid antibodies should be included in the diagnostic evaluation of young patients (< 50 years of age), patients with thrombosis in an unusual site, and patients with recurrent thrombosis, as well as those with a history of late pregnancy loss, a history of preeclampsia/eclampsia, or hemolysis, elevated liver enzymes, and low platelet count syndrome.[42] The diagnosis of antiphospholipid antibody syndrome (APS) implies the use of VKAs instead of DOACs for the prevention of new thrombotic events. This recommendation is based on a study comparing rivaroxaban with warfarin for the prevention of thrombotic events in patients with triple-positive APS (lupus anticoagulant, anticardiolipin, and anti-β_2-glycoprotein I). The study was prematurely terminated because of an increased risk of thromboembolic events and a higher number of bleeding events in the group treated with rivaroxaban.[42,43]

Question 4. Should treatment with DOACs[1] be recommended for at least 3-6 months in comparison with conventional anticoagulation (LMWH or unfractionated heparin [UFH], followed by warfarin) in patients diagnosed with low-risk PE, intermediate-risk PE, intermediate high-risk PE after stabilization, or high-risk PE after reperfusion and stabilization?

For decades, conventional treatment for most PE patients involved initial administration of UFH or LMWH, followed by VKAs. Although this regimen is effective, it is complex because of drug and food interactions associated with VKAs and the need for regular INR monitoring. The development of DOACs such as factor Xa antagonists (rivaroxaban, apixaban, and edoxaban) and thrombin antagonists (dabigatran) has mitigated many of the limitations of conventional therapy, eliminating the need for periodic dose adjustments based on mandatory laboratory monitoring and for dietary restrictions, as well as reducing drug interactions.[44]

Evidence

A total of 889 articles were identified. Of those, 7 were excluded for being duplicates, leaving 882 articles. Of those, 874 studies were excluded after title and abstract evaluation. Eight articles were selected for full-text review, with 2 articles being excluded for not meeting the inclusion criteria. The meta-analysis included 6 randomized controlled trials evaluating the noninferiority of long-term (3-6 months) treatment with DOACs in comparison with conventional anticoagulation (warfarin with an INR target of 2 to 3). The efficacy outcome was the

1 apixaban, dabigatran, edoxaban, and rivaroxaban

recurrence of VTE, and safety was assessed by the occurrence of major bleeding or clinically relevant nonmajor bleeding. Two studies assessed dabigatran in comparison with warfarin for a treatment period of 6 months.[15,45] Two studies assessed rivaroxaban vs. warfarin, stratifying patients by treatment periods of 3, 6, or 12 months. The first study evaluated patients with an initial VTE diagnosis,[46] and the second included patients with symptomatic acute PE.[47] One study evaluated apixaban vs. warfarin in patients with symptomatic acute VTE for 6 months and followed patients for up to 24 months after randomization.[48] Finally, one study evaluated edoxaban vs. warfarin for a minimum treatment period of 3 months, with a planned duration of up to 12 months.[17]

Regarding the critical outcome of VTE recurrence, there was no significant difference between DOACs and warfarin (RD = −0.00; 95% CI: −0.01 to 0.00; p = 0.22), with moderate-quality evidence. The critical outcome of death from any cause also showed no significant difference (RD = −0.00; 95% CI: −0.00 to 0.00; p = 0.75), with moderate-quality evidence (Figure S2.4).

For the critical outcome of major bleeding, there was a significant difference favoring DOACs (RD = −0.01; 95% CI: −0.01 to −0.00; p < 0.001), with moderate-quality evidence. The important outcome of clinically relevant nonmajor bleeding was also favorable to DOACs in comparison with warfarin (RD = −0.03; 95% CI: −0.05 to −0.01; p = 0.003), with moderate-quality evidence (Figure S2.4).

Recommendation

For patients with a diagnosis of stable PE or after hemodynamic stabilization, we recommend treatment with a DOAC for at least 3-6 months. This is a strong recommendation with moderate-quality evidence.

Comments

On the basis of the results of the studies included in the meta-analysis, which demonstrated noninferior efficacy in comparison with conventional treatment with warfarin and a better safety profile—with fewer major and clinically relevant nonmajor bleeding events—as well as the dosing advantages, even in obese patients[49] and patients with mild renal dysfunction (creatinine clearance > 30 mL/min),[50] DOACs have become the outpatient treatment of first choice for PE.[11,41] In Brazil, there are currently no clinical protocol and therapeutic guidelines issued by the Brazilian National Ministry of Health for the management of PE, and the incorporation of DOACs for the treatment of PE in the public health care system occurs heterogeneously, depending on the health departments of the federal states.

In this context, it is important to highlight conditions in which DOACs are contraindicated, such as in patients diagnosed with APS, for whom warfarin remains the best therapeutic option, and in pregnant or breastfeeding patients, for whom LMWH is the recommended treatment.[11,41] In patients with severe kidney failure (creatinine clearance ≤ 30 mL/min), DOACs should be avoided, the exception being for apixaban, which can be used in such patients. Warfarin is also an alternative for patients with severe kidney failure.[11,41]

Question 5. Should systemic thrombolysis be recommended in comparison with anticoagulation alone (LMWH or UFH) in patients with intermediate–high-risk PE?

Risk stratification of patients with acute PE is crucial for therapeutic planning. Patients without hemodynamic instability (systemic arterial hypotension—systolic blood pressure [SBP] < 90 mmHg or the need for vasopressors to maintain SBP ≥ 90 mmHg despite adequate filling status, and signs of organ dysfunction, including decreased level of consciousness, cold and clammy skin, oliguria/anuria, and elevated serum lactate; and/or persistent hypotension—SBP < 90 mmHg or a reduction of 40 mmHg from the usual SBP values for more than 15 min, not related to the onset of arrhythmias, hypovolemia, and/or sepsis, and/or cardiorespiratory arrest) but who have signs of right ventricular failure on imaging tests, such as echocardiography or chest CT angiography, as well as elevated biomarkers of myocardial injury, such as troponins T and I, and/or right ventricular overload and dilatation, such as B-type natriuretic peptide/N-terminal pro–B-type natriuretic peptide, are considered to be at intermediate-high risk, with an early mortality rate of approximately 9% and a 30-day mortality rate twice as high as that of patients without signs of right ventricular dysfunction.[11,51,52] Given the severity of these patients, fibrinolytic treatment could be an alternative with the potential to reduce the risk of hemodynamic instability and death in comparison with conventional treatment with UFH or LMWH. However, the risk of severe hemorrhage, especially hemorrhagic stroke, counterbalances the proposed benefits and must be carefully considered when choosing the treatment.[11]

Evidence

A total of 1,517 articles were identified. Of those, 22 were excluded because of duplication, leaving 1,495 articles. After evaluation of the titles and abstracts, 1,436 studies were excluded. Fifty-nine articles were selected for full-text review, with 45 articles being excluded for not meeting the inclusion criteria. The remaining 14 articles were jointly evaluated by the methodologists, who excluded 1 article for data analysis without a clear intervention, 1 article for having a different research question, 1 article for being a phase 2 study, and 4 articles for having inclusion criteria that were not relevant to the research question. The meta-analysis included 7 randomized controlled trials comparing peripheral fibrinolysis with conventional anticoagulation for the treatment of patients diagnosed with intermediate–high-risk acute PE.

Three studies compared alteplase combined with UFH or LMWH and anticoagulation with UFH or LMWH alone.[53,54] One of the studies allowed the use of streptokinase as an alternative to alteplase.[55] In two studies, the primary outcomes were death and hemodynamic deterioration,[53,55] whereas, in one, improvement of right ventricular dysfunction was the primary outcome.[54] All studies evaluated the occurrence of major or other types of bleeding as safety outcomes. Four studies used tenecteplase as a fibrinolytic drug in comparison with anticoagulation with UFH or LMWH. In three studies, the primary outcome was death or hemodynamic deterioration within 5-7 days of hospitalization.[56-58] One study analyzed mortality at 30 days and 24 months.[59] The occurrence of bleeding was evaluated by the three studies that analyzed the acute phase.

Regarding the critical outcome of VTE recurrence, there was no significant difference between fibrinolytic treatment and anticoagulation alone (RD = −0.01; 95% CI: −0.02 to 0.00; p = 0.18), with a moderate level of evidence. The critical outcome of death from any cause did not show a significant difference (RD = −0.00; 95% CI: −0.02 to 0.02; p = 0.12), with a moderate level of evidence. The important outcome of chronic thromboembolic pulmonary hypertension was evaluated in one study only and did not show a significant difference between the two treatment strategies, with a value of p = 0.79. The evidence was considered weak (Figure S2.5).

There was no significant difference between fibrinolytic treatment and anticoagulation regarding the critical outcome of major bleeding (RD = 0.02; 95% CI: −0.04 to 0.09; p = 0.49), with a moderate level of evidence. The important outcome of nonmajor bleeding tended to occur more frequently with the use of fibrinolytics, but the difference was not significant (RD = 0.13; 95% CI: −0.00 to 0.26; p = 0.06), with a moderate level of evidence (Figure S2.5).

Recommendation

For patients with intermediate–high-risk PE, we suggest not using systemic pharmacological thrombolysis. This is a conditional recommendation with moderate-quality evidence.

Comments

The management of hemodynamically stable patients with right ventricular dysfunction is challenging in practice because they are relatively common and because approximately 9% of cases have an unfavorable outcome.[52] The use of diagnostic tools such as bedside point-of-care ultrasound contributes to the characterization and prognosis definition, as well as therapy planning.[60] Therefore, the use of a more aggressive management strategy that adds risk (especially of bleeding) in comparison with standard treatment with full anticoagulation does not seem to be the best strategy for this particular group of patients. However, fibrinolysis may be beneficial in selected cases, in the context of right ventricular overload and hemodynamic stability. In addition to the combination of right ventricular dysfunction on imaging tests and biomarker alterations (especially when both are abnormal, such as troponins and natriuretic peptides), other parameters may be considered and may contribute to therapeutic decision-making. These include prognostic scores (e.g., the Bova score and the Thromboembolism Lactate Outcome Study score); age; relative hypotension; signs of hypoperfusion (elevated lactate, creatinine, and liver transaminases); concomitant DVT; more severe findings on echocardiography (free thrombus in the right heart chambers) and/or on CT angiography (reflux into hepatic veins and thrombus in the pulmonary arterial trunk or main branches); the need for increased oxygen therapy; severe comorbidities/limited life expectancy; and bleeding risk.[61]

The decision to use a primary, nonsurgical reperfusion strategy in the context of intermediate-high risk (evident right ventricular dysfunction associated with increased afterload caused by PE) should consider the higher likelihood of severe bleeding, particularly in women > 75 years of age.[58] There are options that can minimize the risk of bleeding, such as using a reduced dose of thrombolytics (via peripheral or catheter-directed administration) and percutaneous pulmonary embolectomy. Some studies suggest that using a reduced dose of thrombolytics (e.g., alteplase at 50 mg over 2 h in comparison with the standard regimen of 100 mg over 2 h via peripheral access) may reduce the incidence of bleeding with similar efficacy.[62,63] A large randomized clinical trial is currently in progress and is expected to shed light on this matter.[64] There are also data on the use of catheter-directed pulmonary embolectomy in the management of PE, although the current recommendation for this modality is for patients with hemodynamic instability who have contraindications to or did not respond to pharmacological thrombolysis.[63] Studies have shown hemodynamic improvement with the use of catheter-directed embolectomy, with a low rate of complications.[63,65] The limitations of this technology include the cost of supplies, the availability of the method in hospitals, the expertise of the performing physician, and the logistics required to optimize the time between patient admission and the procedure. However, the absence of control groups treated with anticoagulation (UFH or LMWH) in these studies weakens them methodologically and does not allow a proper assessment of the true benefit of these therapeutic modalities in comparison with conventional treatment. Research with more robust design and outcomes involving these approaches is ongoing.

Question 6. Should systemic thrombolysis be recommended in comparison with anticoagulation alone (LMWH or UFH) in patients with high-risk PE?

Chart 4. Summary of recommendations for the pharmacological treatment of patients with acute pulmonary embolism.

Questions	Recommendations	Degree of recommendation	Quality of evidence
Should home anticoagulation be used in comparison with hospitalization in patients with low-risk PE?	We suggest home treatment for patients who have been diagnosed with low-risk acute PE and who have guaranteed access to health care services.[a]	Conditional	Very low-quality evidence
Should anticoagulation with DOACs be used in comparison with anticoagulation with LMWH in PE patients diagnosed with cancer?	We suggest treatment with DOACs.	Conditional	Low-quality evidence
Should extended anticoagulation be maintained in comparison with placebo or aspirin in patients who have been diagnosed with unprovoked PE and who have completed at least 3 months of anticoagulation?	We recommend treatment with a DOAC for at least 3-6 months.	Strong	High-quality evidence
Should treatment with DOACs be recommended for at least 3-6 months in comparison with conventional anticoagulation (LMWH or UFH, followed by warfarin) in patients diagnosed with low-risk PE, intermediate-risk PE, intermediate high-risk PE after stabilization, or high-risk PE after reperfusion and stabilization?	We recommend treatment with a DOAC for at least 3-6 months.	Strong	Moderate-quality evidence
Should systemic thrombolysis be recommended in comparison with anticoagulation alone (LMWH or UFH) in patients with intermediate-high-risk PE?	We suggest not using systemic pharmacological thrombolysis.	Conditional	Moderate-quality evidence
Should systemic thrombolysis be recommended in comparison with anticoagulation alone (LMWH or UFH) in patients with high-risk PE?	We suggest systemic pharmacological thrombolysis.	Conditional	Very low-quality evidence

PE: pulmonary embolism; DOACs: direct oral anticoagulants; LMWH: low-molecular-weight heparin; and UFH: unfractionated heparin. [a]This strategy has as basic premises the following: social support (i.e., understanding of the disease and possible complications; correct use of medications and recognition of potential side effects; and quick access to health care services if needed); and patient preference, a shorter hospital stay being a possibility. Note: Classification of risk for in-hospital mortality or 30-day mortality from acute PE[11]: Patients with a Pulmonary Embolism Severity Index (PESI)[68] = I or II, or a simplified PESI (sPESI)[69] = 0. If biomarkers (troponins, B-type natriuretic peptide, or N-terminal pro–B-type natriuretic peptide are negative or normal and there are no signs of right ventricular overload on imaging (CT angiography and/or transthoracic echocardiogram). Patients with a PESI = III-V or an sPESI ≥ 1, as well as signs of right ventricular overload as assessed by elevated biomarkers or imaging. Patients with a PESI = III-V or an sPESI ≥ 1, as well as signs of right ventricular overload as assessed by elevated biomarkers and imaging. Hemodynamically stable patients despite right ventricular overload. Patients with obstructive shock (systemic arterial hypotension—systolic blood pressure [SBP] < 90 mmHg or the need for vasopressors to maintain SBP ≥ 90 mmHg despite adequate volume replacement, and signs of organ dysfunction, including decreased level of consciousness, cold and clammy skin, oliguria/anuria, and/or elevated serum lactate; and/or persistent hypotension—SBP < 90 mmHg or a reduction of 40 mmHg from the usual SBP values for more than 15 min, not related to the onset of arrhythmias, hypovolemia, and/or sepsis, and/or cardiorespiratory arrest).

Patients diagnosed with massive PE can also be classified as being at high risk of death during hospitalization or within 30 days after the acute event. They are characterized by obstructive shock (systemic arterial hypotension—SBP < 90 mmHg or the need for vasopressors to maintain SBP ≥ 90 mmHg despite adequate filling status, and signs of organ dysfunction, including decreased level of consciousness, cold and clammy skin, oliguria/anuria, and elevated serum lactate; and/or persistent hypotension—SBP < 90 mmHg or a reduction of 40 mmHg from the usual SBP values for more than 15 min, not related to the onset of arrhythmias, hypovolemia, and/or sepsis, and/or cardiorespiratory arrest).[11]

Because patients with massive PE are at a high risk of death, they need to be diagnosed quickly in order to initiate reperfusion therapy, with fibrinolysis via peripheral venous access being the most commonly used treatment, in the absence of formal contraindications.[11]

Evidence

A total of 1,517 articles were identified. Of those, 22 were excluded because of duplication, leaving 1,495

articles. After evaluation of the titles and abstracts, 1,488 studies were excluded. Seven articles were selected for full-text review, with 6 articles being excluded for not meeting the inclusion criteria. Only one article remained for evaluation; therefore, a meta-analysis of the data was not conducted.[66]

The study evaluated only eight patients diagnosed with acute PE, all of whom had hemodynamic instability. The study was terminated early by the research ethics committee, who considered the unfavorable outcome in the control group. Four patients in the intervention group received streptokinase via peripheral intravenous access, whereas the four patients in the control group received UFH. All patients in the control group died during hospitalization. Three patients underwent autopsy, which revealed massive PE and right ventricular infarction, with no significant coronary obstructions in any of them. The patients who received streptokinase were followed for 2 years and showed no signs of pulmonary hypertension or recurrence of PE. No bleeding events occurred in the patients studied. Although fibrinolysis was considered superior to anticoagulation with UFH or LMWH on the basis of the characteristics of the study, the quality of the evidence was very low.[66]

Recommendation

For patients diagnosed with high-risk PE, we suggest systemic pharmacological thrombolysis. This is a conditional recommendation with very low-quality evidence.

Comments

In PE, systemic pharmacological thrombolysis has been recognized as a therapeutic option in cases of hemodynamic instability for many years.[67] It has been recommended as one of the reperfusion therapy options for high-risk patients.[11] However, randomized controlled studies supporting this intervention are scarce.

Because of the criteria used in order to select articles for the present guidelines, only one study was selected. The study by Jerjes-Sanchez et al.[66] evaluated eight patients: four in the intervention group (who received systemic streptokinase) and four in the control group (who received UFH). All of the patients in the UFH group died. In the intervention group, there were no deaths, and the patients were followed for 2 years without signs of pulmonary hypertension or recurrence of PE. These results, combined with the imminent risk of death, the difficulty in conducting randomized controlled studies with this patient profile, and the availability of fibrinolytic medications in most hospitals, led us to suggest pharmacological thrombolysis for patients with high-risk PE.

There is, however, a growing number of studies evaluating options for pulmonary reperfusion that carry a lower risk of hemorrhagic complications. These options include catheter-directed thrombolysis, catheter-directed embolectomy, and, in selected cases, surgical embolectomy. These alternatives require infrastructure and a team trained in the procedures, which are costly.[63]

AUTHOR CONTRIBUTIONS

VMA: formulation of the PICO questions; systematic review and meta-analyses; discussion of results and formulation of recommendations; writing the final version of the text. CJCSF, MBG, ATR, and HHBY: formulation of the PICO questions; discussion of results and formulation of recommendations; writing the final version of the text. WSF: discussion of results and formulation of recommendations; writing the final version of the text. WMB: systematic review and meta-analyses; discussion of results and formulation of recommendations. ST: systematic review and meta-analyses; discussion of results and formulation of recommendations; Writing the final version of the text. All authors read and approved the final version of the manuscript.

CONFLICTS OF INTEREST

None declared.

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Exploring perspectives on the benefits of a tuberculosis short-treatment regimen: a cross-sectional study on treatment experiences and perceptions

Fernando Pereira da Silva[1], João Pedro Ramos[2,3], Pedro Barbosa[2,3], Mariana Vieira[2,3], Raquel Duarte[2,3,4]

TO THE EDITOR:

Tuberculosis is a transmissible disease and a leading cause of global mortality.[1] Without proper treatment, the mortality rate can reach up to 50%,[1,2] and is even higher in cases of poor adherence, infection with resistant strains, and immunosuppression.[3] The standard treatment for drug-sensitive tuberculosis includes 2 months of isoniazid (H), rifampin (R), pyrazinamide (Z), and ethambutol (E), followed by 4-10 months of H and R, depending on clinical factors.[3,4] However, adherence is also influenced by structural, personal, and social factors.[5] The 4-month regimen incurs higher costs due to increased expenditure of rifapentine (Rpt) but requires fewer doses than the 6-month regimen. In contrast, the 6-month regimen involves longer follow-ups and more extensive directly observed therapy (DOT), raising costs for health care professionals (HCPs) and society.[6-8] This study aimed to assess which tuberculosis treatment regimen, whether the gold standard or an alternative, was preferred by people with tuberculosis and by HCPs, as well as identifying the factors that most heavily influence their decision making.

In this cross-sectional study, HCPs and people with tuberculosis were asked to complete specific questionnaires between January and October of 2024. The HCP sample was intentionally selected, including pulmonology specialists, residents, and nurses registered with the *Sociedade Portuguesa de Pneumologia* and potentially interacting with tuberculosis patients in Pulmonology Diagnostic Centers (PDCs). That questionnaire was distributed online via the Society and senior professionals. A different questionnaire was administered to people with tuberculosis under treatment at the Vila Nova de Gaia PDC in Portugal, over the telephone or in person, using convenience sampling. Both questionnaires assessed the perceptions of participants regarding the two regimens (Figure 1), requiring them to choose from the perspective of a person with tuberculosis and to justify their reasoning. Participants reflected on treatment impact, challenges, duration, and medication intake burden. The HCP questionnaire additionally addressed financial and medication intake burden, treatment challenges, and the impact of DOT on mental health, social life, expenses, and treatment adherence. A descriptive statistical analysis was conducted using the IBM SPSS Statistics software package, version 29.0.1.0 (IBM Corporation, Armonk, NY, USA), alongside inductive and thematic analysis,[9] to identify themes that could lead us to understand and describe the choice of the most appropriate/preferable treatment regimen. The study was approved by the Research Ethics Committee of the Local Health Care Unit of Vila Nova de Gaia/Espinho (CES 116/2024).

The HCP group comprised 41 participants. They were predominantly female (70.8%) with a mean age of 46.8 ± 14.8 years. Most were specialist physicians (63.4%), primarily pulmonologists (48.8%). Over half of these participants (56.1%) worked at a PDC during a mean period of 10.0 ± 9.4 years. The mean age of the patients with tuberculosis was 57.7 ± 14.7 years, with varying levels of education levels, half of whom having completed the 5th-6th school year. Only two of the patients were employed, and half reported a household income between €2,501 and €3,500 per month (Table 1).

A significant knowledge gap among HCPs regarding the shorter tuberculosis treatment regimen was noted; 56.1% of the HCPs were unaware of the alternative, mentioning their "unaware[ness] of the real effectiveness of the second [short] treatment and the scientific basis," as well as their "lack of familiarity and limited experience" with it. However, 63.4% indicated they would choose to prescribe it, due to a "shorter treatment time." Most HCPs (80.5%) believed people with tuberculosis would prefer a shorter regimen, as "patients want to resolve the situation as quickly as possible," leading to "less psychological distress," as prolonged treatment time was described as "one of the biggest complaints from users."

Most people with tuberculosis preferred the shorter regimen due to the "shorter time of treatment" allowing them to "go back to normal life sooner; being with people and living my life without using a mask and having people stare at me." They also valued "shorter time taking pills, going to consultations, and having to tell people what I have." A person with tuberculosis mentioned, "It's hard to take so many pills; I don't like the amount I'm taking now, but then they taper off. [...] I'm living with my daughter, and she organizes my medication and gives it to me, so it wouldn't be easy for her." Additional considerations included the number of daily pills and potential side effects, as "patients usually get scared with the number of daily pills."

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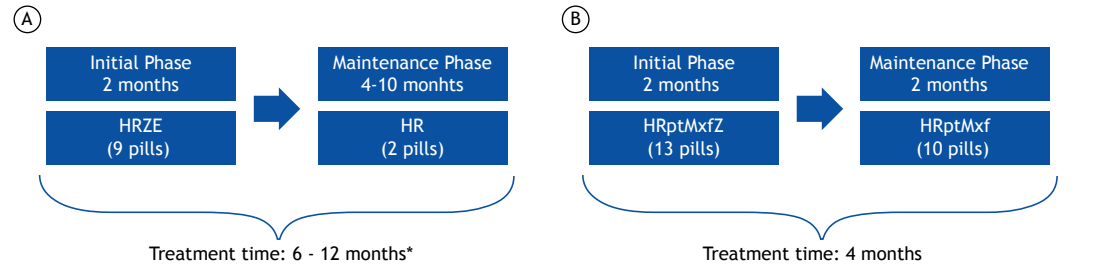

Figure 1. Diagram comparing the classic (A) and the alternative/shorter (B) treatment regimens.

Table 1. Sociodemographic characteristics.

Health Care Professionals (n = 41)		
Characteristic		**Participants**
Sex, n (%)	Male	12 (29.27%)
	Female	29 (70.75%)
Age, years	Mean [min-max]	46.80 [25-73]
Professional class, n (%)	Nurse	10
	Specialist Physician	26
	Medical Resident	5
Currently working at a PDC, n (%)	Yes	23 (56.10%)
	No	18 (43.90%)
Time working at a PDC, years	Mean [min-max]	10.0 [1-33]
Frequency of tuberculosis treatment prescription	1: Never	13 (31.7%)
	2: Rarely	6 (14.6%)
	3: Occasionally	8 (19.5%)
	4: Often	5 (12.2%)
	5: Very often	9 (22.0%)
Patients (n = 6)		
Characteristic		**Participants**
Sex, n (%)	Male	2
	Female	4
Age, years	Mean [min-max]	57,7 [36-81]
Tuberculosis involvement	Lung	4 (66.7%)
	Lymph nodes	1 (16.7%)
	Osteoarticular	1 (16.7%)
Expected treatment duration, months	6	5 (83.3%)
	12	1 (16.7%)
Current treatment phase	Initial	4 (66.7%)
	Maintenance	2 (33.3%)
Level of Education	5th to 6th grade	3 (50.0%)
	7th to 9th grade	1 (16.7%)
	High School	2 (33.3%)
Number of household members	1	2 (33.3%)
	2	1 (16.7%)
	3	2 (33.3%)
	4	1 (16.7%)
Professional situation	Employed	2 (33.3%)
	Unemployed	2 (33.3%)
	Retired	2 (33.3%)
Average household monthly income	Up to 500€	2 (33.3%)
	1501€ - 2500€	1 (16.7%)
	2501€ - 3500€	3 (50.0%)

PCD: Pulmonology Diagnostic Center.

Mental health was predominantly perceived as negative (48.8%) or neutral (29.3%), with "social stigma" and "prolonged isolation" cited as key concerns. However, one participant noted that treatment could "have a positive impact on mental health when the patient starts feeling better."

Regarding financial burden, 39.0% of respondents rated treatment impact as "very negative" or "negative," citing logistical challenges such as "the need for frequent trips to appointments", which makes it more difficult by limited public transportation, and "the mandatory DOT" with "inflexible opening hours of health institutions." as the most common issues. HCPs acknowledged these challenges, emphasizing that "emotional balance and social support are often key to successful treatment adherence," and that "patients with financial issues, such as inability to work or lack of financial resources for basic needs, must be supported." One respondent noted that "the sick leave is paid 100%," while others reported, "remuneration during sick leave is lower than the wage." These responses highlight the complexity of assessing the financial burden of tuberculosis treatment. Proposed solutions included "payment of travel expenses" and creating a "transport network that reduces patients' travel costs."

Tuberculosis treatment adherence was linked to personal, treatment-related, health care system-related, and social factors. Literacy about tuberculosis emerged as a key determinant, with professionals stressing the importance of "understanding the importance of medication, its purpose, duration, and side effects." They emphasized the need to "inform and educate at the time of diagnosis and during treatment" to enhance "motivation for treatment" and adherence. However, many highlighted "the prolonged time [of treatment] and number of pills" and "side effects" as major issues. One person noted that "in the beginning, it felt like I was weak and sick."

Prolonged treatment, a high number of pills, and the "need to be 'watched' daily" affected adherence, calling for "shorter treatments and better-tolerated regimens" with "differentiated and adapted monitoring." People with tuberculosis consistently rated treatment duration as "important" or "very important," although opinions on the number of daily pills varied from "very Important" to "neutral." Social support, particularly from family and the broader social context, was deemed crucial, with "poor social/family support, financial need, precarious work, (...) and chemical dependency" cited as major challenges.

This study examines the perspectives of HCPs on tuberculosis treatment preferences, comparing them with those of people with tuberculosis. A strong preference for shorter treatment regimens emerged, driven by reduced treatment duration, fewer health care visits, and psychological benefits. However, many HCPs were unaware of this option, revealing a knowledge gap. While shorter regimens may improve adherence, the higher pill burden remains a concern. Findings are limited to a single unit in one region and may not be fully generalizable. However, replicable methodologies can guide similar studies. Continued research, education, and tailored support are essential to improving adherence and treatment outcomes.[10] Shorter regimens seem to be a promising step forward, but continued research is needed to evaluate their acceptability and improve health literacy and support, ultimately improving adherence and treatment outcomes.

AUTHOR CONTRIBUTIONS

FPS collected data and performed the statistical analysis. JPR, PB, and MV collected data. RD conceived and designed the study. All authors took part in drafting the manuscript and did the final manuscript review. All authors read and approved the final manuscript.

CONFLICTS OF INTEREST

None declared.

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Granulomatosis with polyangiitis

Roberta Wartchow Machado[1], Felipe Welter Langer[2], Dionatta Halle Flores Lisboa[3]

A 42-year-old male smoker presented with a two-month history of fever, hemoptysis, weight loss, and palpable purpura (Figure 1A). Chest CT revealed bilateral peribronchovascular consolidations with a halo of ground-glass opacity (Figure 1B). Follow-up imaging evidenced splenic infarction and progression of the pulmonary lesions, most developing central cavitation (Figures 1C-1D). Laboratory investigation disclosed anemia (10.3 g/dL), leukocytosis (26,000/mm³ with left shift), thrombocytosis (614,000/mm³), glomerulonephritis, complement consumption, elevated C-reactive protein (196 mg/L), and positive c-ANCA antibody; rheumatoid factor, antinuclear antibodies, and tuberculosis testing were negative. Segmentectomy with histopathological analysis confirmed pulmonary granulomatous vasculitis. These findings were compatible with granulomatosis with polyangiitis (GPA). A pulse of high-dose corticosteroid therapy was initiated, but the patient eventually passed away due to massive hemoptysis.

GPA, formerly known as Wegener's granulomatosis, is a multisystem granulomatous vasculitis that affects small and medium-sized vessels of the upper respiratory tract, lungs, and kidneys.[1] Diagnosis of GPA relies on clinical, laboratory, imaging, and histopathological findings. On imaging, identification of cavitating pulmonary lesions with peribronchovascular distribution and concomitant halo sign, as seen in this case, may help narrowing the differential diagnosis.[2,3] Massive hemoptysis and diffuse alveolar hemorrhage are rare and life-threatening complications of GPA. Treatment usually involves systemic corticosteroids and immunosuppressive agents.

AUTHOR CONTRIBUTIONS

RWM was directly involved in reporting the CT scans depicted in this article. RWM, FWL, and DHFL were equally involved in writing, reviewing, conceptualizing, supervising, drafting, and editing the manuscript. Written consent for publication was obtained from the patient.

CONFLICTS OF INTEREST

None declared.

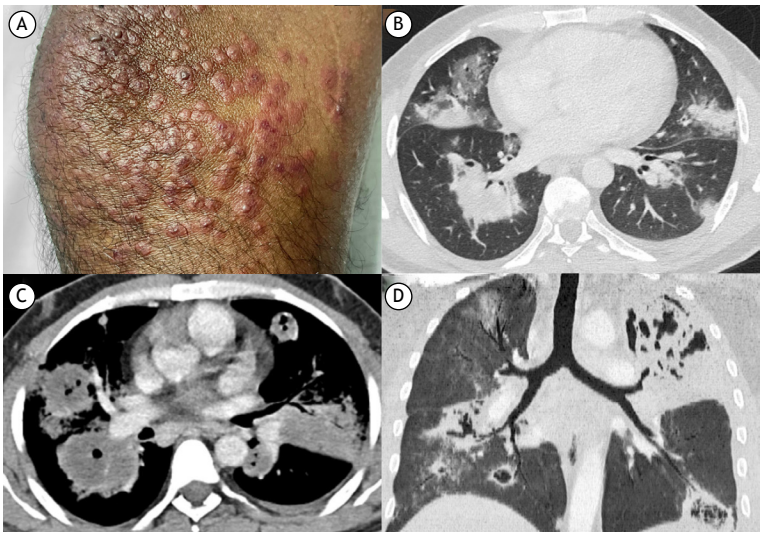

Figure 1. In A, clinical photograph showing palpable purpuric lesions in the lower extremities. In B, non-contrast-enhanced chest CT showing bilateral peribronchovascular consolidations with a surrounding halo of ground-glass opacity. In C, contrast-enhanced chest CT evidenced central cavitation and hypoenhancement within the pulmonary consolidations, suggestive of intralesional necrosis. In D, coronal non-contrast-enhanced chest CT with minimum intensity projection showing progression of the peribronchial lesions, most of which cavitated.

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The Jornal Brasileiro de Pneumologia (J Bras Pneumol, Brazilian Journal of Pulmonology) ISSN-1806-3756, published once every two months, is the official organ of the *Sociedade Brasileira de Pneumologia e Tisiologia* (Brazilian Thoracic Society) for the publication of scientific papers regarding Pulmonology and related areas.

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(Assistente Editorial - Luana Campos)

Online submission of articles:

www.jornaldepneumologia.com.br

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