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HIGHLIGHT

Brazilian Thoracic Association recommendations for the management of lymphangioleiomyomatosis

Joint statement on evidence-based practices in mechanical ventilation: suggestions from two Brazilian medical societies

Diagnostic contribution of GeneXpert Ultra in pediatric pulmonary tuberculosis

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What's new in the 2025 GOLD report

David M G Halpin[1], Dave Singh[2,3]

The GOLD reports serve to enable health care professionals to better manage COPD. The GOLD science committee updates the report every year by incorporating the latest evidence relevant to clinical practice, aiming to be as practical and easy to follow as possible. The 2025 GOLD report contains important changes (Figure 1), notably regarding diagnosis and pharmacological management, as well as a new section on climate change and COPD.[1]

The diagnosis of COPD requires initial clinical assessment of respiratory symptoms and exposure to risk factors. Diagnostic confirmation is obtained using spirometry to demonstrate the presence of airflow obstruction, which is defined as an FEV_1/FVC ratio of < 0.7. The 2025 GOLD report considers the merits of using pre- or post-bronchodilator measurements for this purpose. Large cohort studies have demonstrated that although pre-bronchodilator spirometry and post-bronchodilator spirometry give the same diagnostic results in the majority of individuals, post-bronchodilator values can result in up to 36% fewer diagnoses due to a "flow" response characterised by an increase in FEV_1 that pushes FEV_1/FVC > 0.7.[2] However, administration of a bronchodilator can reduce gas trapping ("volume" response). This improves FVC, thereby reducing the FEV_1/FVC ratio; there are a small number of "volume" responders who move from > 0.7 to < 0.7 after bronchodilator administration.[2] The 2025 GOLD report recommends using pre-bronchodilator spirometry > 0.7 to rule out COPD, unless a volume responder is suspected on the basis of low FEV_1 or a high symptom burden. This recommendation can avoid unnecessary post-bronchodilator spirometry being performed. If pre-bronchodilator spirometry is < 0.7, then post-bronchodilator measurements are needed for diagnostic confirmation. Flow responders who move to > 0.7 after bronchodilator administration have a high prevalence of developing COPD over time and need careful prospective monitoring.[3] There has been considerable debate concerning the use of the fixed ratio (0.7) versus lower limit of normal (LLN) values (which classify the bottom 5% of the healthy population as abnormal) for diagnostic purposes. The 2025 GOLD report includes some discussion on this issue. The LLN depends on the reference equation used, which are mostly based on pre-bronchodilator values that will over-estimate the number of cases.[2,4] On the basis of simplicity for a worldwide diagnostic test and the fact that there is no absolute right or wrong, GOLD continues to recommend the use of the fixed ratio over the LLN.

Clinical trials in COPD patients with a history of exacerbations in the previous year have consistently demonstrated superiority of triple therapy over the combination of an inhaled corticosteroid (ICS) and a long-acting β_2 agonist (LABA) for exacerbation prevention, lung function and quality of life.[5,6] Exacerbations have important detrimental effects on other outcomes, including prolonged impaired quality of life, greater lung function loss and increased mortality. Given the clinical importance of exacerbation prevention, GOLD recommends triple therapy over the ICS-LABA combination if treatment with ICS is indicated. For patients who have been historically treated with the ICS-LABA combination, there is an opportunity to optimise treatment. The 2025 GOLD report includes a new algorithm to help decide the next step, which may include escalation to triple therapy for patients who currently have exacerbations and have blood eosinophil counts > 100 cells/μL (a marker of corticosteroid-sensitive inflammation). For patients who are not currently exacerbating, it is crucial to understand whether there was no prior history of exacerbations, and therefore inappropriate use of ICS, or if previous exacerbations responded to ICS treatment, because this changes the next step.

The 2025 GOLD report includes recommendations on two novel classes of medications to treat COPD: a dual phosphodiesterase 3 (PDE3)/phosphodiesterase 4 (PDE4) inhibitor and the first biologic therapy to be approved for COPD. The inhaled PDE3/PDE4 inhibitor ensifentrine has both anti-inflammatory activity and bronchodilator effects. It significantly improved lung function and dyspnoea but had inconsistent effects on quality of life in parallel phase III studies[7]; however, the studies did not assess the impact of ensifentrine on top of LABA plus a long-acting muscarinic antagonist (LAMA) or LABA+LAMA+ICS, making it difficult to assess the relevance of its effects on exacerbations when positioning it in the treatment algorithm. The 2025 GOLD report recommends that ensifentrine be added to dual bronchodilator therapy if the patient continues to experience dyspnoea.

Dupilumab is a fully human monoclonal antibody that blocks the shared IL4 and IL13 receptor. It reduced exacerbation rate and improved lung function and health status in two large randomised trials.[8,9] The patients in those studies all had chronic bronchitis; a history of two or more moderate exacerbations or one or more severe exacerbations in the last year despite treatment with LABA+LAMA+ICS; and blood eosinophil counts ≥ 300 cells/μL. Reflecting the trial entry criteria, the

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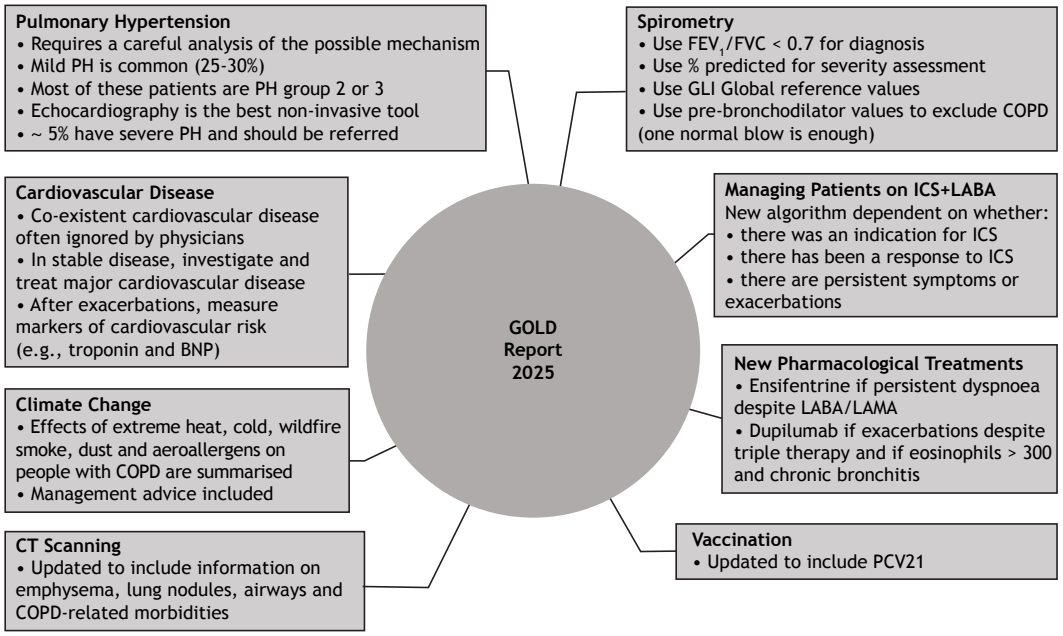

Figure 1. Key updates in the 2025 GOLD report. PH: pulmonary hypertension; GLI: Global Lung Function Initiative; BNP: brain natriuretic peptide; ICS: inhaled corticosteroid(s); LABA: long-acting β2 agonist; LAMA: long-acting muscarinic antagonist; and PCV21: 21-valent pneumococcal conjugate vaccine.

2025 GOLD report recommends that dupilumab be added to triple therapy if patients continue to have exacerbations and have a blood eosinophil count ≥ 300 cells/μL and symptoms of chronic bronchitis.

It is well known that the prevalence of cardiovascular disease is high in COPD patients. Cardiovascular disease often goes unnoticed and untreated in patients with COPD.[10] Clinicians are perhaps less aware that the risk of cardiovascular events, including myocardial infarction and stroke, increases during and after an exacerbation.[10,11] Although the mechanisms remain to be fully elucidated, systemic inflammation and hypoxia are likely to play key roles in causing cardiovascular stress. A post-hoc analysis has recently demonstrated that triple therapy reduces cardiovascular events in comparison with LAMA/LABA, presumably through exacerbation prevention.[12] The 2025 GOLD report includes a new section on cardiovascular risk, with the aim of raising awareness and encouraging proactive investigation and therapeutic intervention. It also includes a more detailed section on pulmonary hypertension and its investigation and management in patients with COPD, as well as updated sections on vaccination and the role of CT scanning in assessing emphysema, lung nodules, airways and COPD-related comorbidities.

The 2025 GOLD report includes a new section on climate change and the impact of the more frequent and extreme weather events it has caused on people with COPD. Extreme heat and cold are both associated with an increased risk of death in people with COPD,[13-15] with the risk being greater with cold.[16,17] High outdoor temperatures are also associated with an increased risk of hospitalisation for COPD,[15,18,19] as well as with increased dyspnoea and use of short-acting β_2 agonists,[20,21] whilst lower outdoor temperatures are associated with an increased risk of exacerbations, increased cough and sputum, increased use of short-acting β_2 agonists and a fall in FEV_1.[20,22-25] Weather also has a significant impact on air quality, and several studies have examined the interactive effects of pollution and temperature in people with COPD. There appears to be a greater effect of pollutants on COPD hospital admissions and emergency visits at low temperatures or during winter.[26-28]

GOLD recommends that patients keep adequately hydrated, keep out of the heat and try to keep living spaces at temperatures of < 32°C and sleeping spaces at temperatures of < 24°C during heatwaves, as well as keeping bedroom temperatures above 18°C during cold weather, as recommended by the WHO. Prior identification and management of cardiovascular comorbidities are also important to reduce adverse outcomes. The 2025 GOLD report also points out that the selection of inhalers and the correct disposal of inhalers by patients can have important implications for global warming and climate changes, and these should be considered when prescribing therapy.

The GOLD reports provide recommendations on the diagnosis and assessment of patients with COPD, as well as comprehensive recommendations on the management of stable disease, exacerbations and comorbidities. The updates and additions in the 2025 report ensure that these reflect the current evidence base and include newly available treatment options.

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Reflections on medical education in Brazil

Clystenes Soares Silva[1], José Roberto Jardim[1]

For most of the period during which Brazil was a colony of Portugal (1500-1815), physicians from Brazil were trained at universities in Europe. In 1808, the first medical school in Brazil was established in Rio de Janeiro by King Dom João VI (aka, King John VI of Portugal). That medical school is now part of the Federal University of Rio de Janeiro. After the Proclamation of the Republic, in 1889, when Brazil first became a democracy, several medical schools were created. In 1912, the Brazilian National Education Council was created and established standards for the implementation of medical education in the country. In 1930, the Brazilian government created the Ministry of Education and Public Health, from which curricular guidelines, supervision, and new courses were established.

An initial, fundamental question arises concerning public health in Brazil: does the country have an adequate number of physicians and medical schools? According to data from the Federal Council of Medicine, Brazil had approximately 575,000 physicians in 2024, equating to a ratio of 2.81 physicians per 1,000 population. This places Brazil ahead of countries such as China, Japan, and the United States. Over the past few decades, the number of physicians in Brazil has significantly increased (339%). During the same period, the population increased by 42%, from 144 million to 205 million. The rise in the number of physicians, which has outpaced population growth by a factor of eight, can be attributed to the nearly 400 medical schools in Brazil, second only to India, a country with a population that is six times larger. However, the high number of physicians does not translate to equitable distribution of the same. The number of physicians per 1,000 population in Brazil is only 1.73 in the northern region and 2.22 in the northeastern region, whereas it is 3.76 in the southeastern region. By 2028, Brazil is projected to have 3.63 physicians per 1,000 population, surpassing the density of 38 countries in the Organization for Economic Cooperation and Development. One noteworthy development is the anticipated increase in the annual number of medical graduates in the country, which could exceed 40,000 in the near future, driven by the growing number of medical schools. The persistent regional disparity in physician density has prompted discussions about its causes, which include low financial compensation, geographic remoteness, limited access to diagnostic tools, lack of opportunities for the children of physicians, and insufficient technical support.

It is crucial to go beyond numerical analyses when assessing the medical workforce in Brazil, particularly given the high expectations for the performance of physicians and health care teams in the public system. This leads to another vital question: are Brazilian medical schools adequately preparing physicians to meet the needs of the public and private health care systems?

Medical education in Brazil is a six-year course. However, the rapid pace of scientific advancement has outstripped the traditional curricula. For instance, knowledge in nanotechnology doubles every 2-3 years and that in computer science doubles every 2 years. In medicine, the "half-life" of knowledge—defined as the time required for half of the information in a field to be replaced by new findings—is estimated at only 7-10 years because of advances in technology and biomedical research. These rapid changes highlight the need for medical education to be continually evolving.

The traditional lecture-based teaching model has gradually given way to problem-based learning, a student-centered pedagogical approach that fosters critical thinking, teamwork, and communication skills through problem-solving. However, some critics argue that problem-based learning may limit hands-on clinical experience, such as physical examinations and patient interactions. However, for both approaches, it has to be assumed that medical schools have adequate faculty, infrastructure, and opportunities for students to engage with patients in outpatient and hospital settings, alongside classroom learning of fundamental theoretical principles. However, the proliferation of new medical schools, particularly in smaller cities, raises concerns about their ability to recruit experienced faculty and provide high-quality education. In addition, disparities exist in teaching methodologies. Research-intensive institutions often focus on rare or complex cases seen at tertiary care centers, whereas medical schools in resource-limited settings and smaller cities may not expose students to sufficient complexity.

Currently, there is no standardized national licensing exam for medical graduates in Brazil, but the *Revalida* ("Revalidate") exam, designed for foreign-trained physicians seeking to obtain a license to practice in Brazil, showed clearly concerning results in 2023: among 43 Latin-American universities that tested candidates, only 2 achieved a first-phase approval rate above 50%, whereas 18 had first-phase approval rates below 10%.

Medical education in Brazil faces a number of challenges, including regional inequality; the rapid expansion of private courses; insufficient infrastructure for practical skills acquisition; and insufficient access to internship and residency programs. The reality of medical education in Brazil calls for the engagement of society, medical associations, and government bodies in the search for

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the best alternatives to minimize the problem, which is quite complex. Harmonizing factors such as the excessive number of medical schools, the quality of teaching, the competence of instructors, and the judicious use of new technologies, and thus training and qualifying physicians to practice responsibly in patient care, represent a challenge that cannot be dispensed with, otherwise the supreme duty of the physician will not be fulfilled, which is to provide proper care for the sick, thereby preserving sovereign respect for human dignity. There is no question about the importance of residency or an accredited internship for the necessary training of physicians. Unfortunately, even at large universities, there has been a significant decrease in the number of students who, upon graduating, complete their training to practice medicine.

We cannot miss the opportunity to offer a medical course in which future professionals are prepared to stay up to date with scientific and technological advances, are familiar with new equipment used in diagnosis and surgical techniques, and are aware of advances in personalized therapy with medications that reach specific disease targets, such as biologics, and genomic techniques. Certainly, artificial intelligence is not a threat to physicians. On the contrary, artificial intelligence is an instrument capable of enhancing learning, allowing realistic simulation of clinical cases so that students can develop their technical skills and decision-making in a safe, controlled environment. It is also important to impart information about the management of financial resources, patient safety, organizational strategies, health policy planning, a broader vision of the problems, and the use of an efficient, accessible method of allocating available resources.

According to the Brazilian Institute of Geography and Statistics Synthesis of Social Indicators, 71.4% of physicians in Brazil have some connection with the Unified Health Care System, a large number of them in primary care. That raises two questions: Are six years of medical school enough to prepare students to work as physicians in a primary care setting?; and Is there an urgent need for medical residency to complement medical training? There may be several answers to and several pathways to answer those two questions. Starting with the second question, yes, medical residency is practically an obligatory complement for recent graduates, although there are not enough medical residency positions for recent graduates and this shortage of positions is likely to worsen as more physicians graduate in a short length of time. This brings us back to the first question, which is about the training of physicians and their ability to provide care in primary care or even in private practice. Knowledge in medical training should be such as to make physicians comfortable and confident in treating the most prevalent diseases in all specialties. In the short term, a small change in the medical education curriculum would achieve this goal. Students would be specifically exposed to the most prevalent diseases in each specialty, learning to recognize and treat them. In our specialty, pulmonology, graduating physicians should be very confident in recognizing and treating respiratory infections, asthma, COPD, smoking, pleural effusion, and lung cancer, being able to distinguish differential diagnoses for the most common respiratory symptoms. Other, difficult diagnoses, such as interstitial disease and pulmonary hypertension, would be referred to specialized centers. Increasing the number of positions in medical residency programs so that all new graduates can attend them will be possible only in the medium and long term.

Undoubtedly, there is a need to constantly update curricula and teaching methods to avoid a gap between dynamic knowledge and medical learning. However, and above all, interaction with human beings in order to transmit affection, welcome, and understanding, as well as to practice listening skills, is essential and can improve physician-patient relationships. Informing students on the subject of health management is quite relevant and absolutely necessary to prepare future physicians. With the aim of reaching those targets, medical education curricula should include competencies, skills, and knowledge that go beyond traditional clinical practice and are necessary to promote the sustainability of health care systems.

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Evidence, implementation, and challenges in mechanical ventilation

Rodrigo Cavallazzi[1]

A lot of what we do in medicine is either not informed by data or not supported by conclusive research. In 49% of all Cochrane systematic reviews, the conclusion is that the data do not support either benefit or harm. Further studies are recommended in the majority of the reviews.[1] In a more recent analysis of Cochrane reviews, it was found that for only 1 in 10 health care interventions is there a published high-quality primary outcome. Overall, only 5.6% of all health care interventions are deemed to be effective on the basis of the available data.[2] Of course, one should not be dogmatic, and not every aspect of the care we provide requires a multicenter clinical trial. Overall, however, there is a knowledge gap for much of what we do in medicine. High-quality data generated by multicenter clinical trials are of paramount importance to inform clinicians.

An intriguing phenomenon is that the limited number of health care interventions that are deemed effective are often not implemented in clinical practice. In a study conducted in 118 ICUs in Brazil, it was found that 42% of the mechanically ventilated patients did not receive a tidal volume ≤ 8 ml/kg of predicted body weight.[3] Prone positioning was implemented in only 16.3% of patients with severe ARDS in an international study that included 459 ICUs in 50 countries.[4] Another concept that is closely associated with implementation of effective health care interventions is that of variation in health care.[5] Some degree of variation may not necessarily be harmful and could drive innovation. The problem is substantial variation, a lack of standardization, and the consequent failure to implement effective interventions consistently.

Important steps to improve the implementation of effective interventions and reduce variation in health care include increasing the knowledge base of clinicians and adopting protocols. To that end, medical societies produce documents that summarize the medical literature and provide evidence-based recommendations such as guidelines and consensus statements. In this issue of the JBP, Ferreira et al.[6] publish a joint statement on evidence-based practices in mechanical ventilation. The project is sponsored by two Brazilian medical societies: the *Sociedade Brasileira de Pneumologia e Tisiologia* and the *Associação de Medicina Intensiva Brasileira*. The document was produced by 75 authors with expertise in the field. It includes 38 topics. For each topic, there is a comment, which is a brief explanation of the theme to be addressed. This may be followed by one or more suggestions in the presence of at least one randomized trial with low risk of bias or existing statements endorsed by well-established health organizations, or one or more considerations in the absence of a high level of evidence. In this issue, JBP readers will find an article containing a detailed explanation of the methodology used in order to generate the document, as well as a useful and practical table highlighting the suggestions and/or considerations for each topic. The full document, which is freely available on the websites of the two societies, can be accessed through a link in the published article.

The end result of the work by Ferreira et al.[6] is a comprehensive, evidence-based guide to mechanical ventilation. There are core or essential topics, as well as topics that are quite unique and not easily found elsewhere, such as mechanical ventilation in pregnancy, dental care in mechanically ventilated patients, and respiratory support for patients under palliative care. Finally, there are chapters that address themes that could be considered trending because they reflect recent research or renewed interest. These include mechanical ventilation in patients with COVID-19, awake prone positioning, and patient self-inflicted lung injury. The results of studies by Brazilian scientists inform many chapters, including the use of protective ventilation to improve survival in ARDS,[7] the benefit of low tidal volume that extends to patients without ARDS,[8] the lack of benefit and potential harm with lung recruitment maneuvers in moderate to severe ARDS,[9] the association of driving pressure and survival in ARDS,[10] the relative effect of ventilator variables on mortality in ARDS,[11] the effect of spontaneous breathing on the pleural pressure in different regions of the lung during mechanical ventilation,[12] and the effect of assisted breaths on lung histology in patients ventilated with pressure-limited modes.[13]

The authors recognize that some of the suggestions and considerations might be difficult to adopt widely in Brazilian ICUs because of the lack of resources. For example, take two technologies that have been game changers in the ICU. One is video laryngoscopy, which has recently been shown to be superior to direct laryngoscopy for critically ill adults undergoing endotracheal intubation.[14] In the document, video laryngoscopy is part of the difficult airway and failed airway algorithms. Another is high-flow nasal cannula, for which there is now a large body of evidence showing it is either noninferior[15] or superior[16] to other forms of oxygen delivery in acute respiratory failure. These technologies may be found in select major academic centers or large private hospitals but are unlikely to be currently found elsewhere in Brazil. A recent publication by the *Associação de Medicina Intensiva Brasileira* shows that there is an enormous regional disparity in ICU resources in Brazil. Although there are 7.35 intensivists per 100,000 population in southeastern Brazil, there are only 2.01 per 100,000 population in northern Brazil and

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3.02 per 100,000 population in northeastern Brazil. Although there are 42.58 ICU beds per 100,000 population in southeastern Brazil, there are only 27.52 per 100,000 population in northern Brazil and 29.28 per 100,000 population in northeastern Brazil.[17] Early in the COVID-19 pandemic, invasive ventilatory support outside of the ICU was provided to 13% of invasively ventilated patients with COVID-19 in southeastern Brazil; this contrasts with 17% in northern Brazil and 16% in northeastern Brazil. The ICU mortality for patients with COVID-19 was 49% in southeastern Brazil; this contrasts with a staggering 79% in northern Brazil and 66% in northeastern Brazil.[18] Resource disparities also exist when capitals are compared with the countryside or when the public health system is compared with the private sector.[17] How can these inequalities be factored in when an attempt is made to produce a unifying evidence-based document on mechanical ventilation? I agree with the approach of the authors, who favored the inclusion of evidence-based interventions even if they require extensive expertise or advanced technologies. As the authors point out, it is the hope that the suggestions and considerations in the document will inform health policy and ultimately improve access to ICUs that are adequately structured, equipped, and staffed.

The document is of interest to a broad readership, including clinicians, nurses, and respiratory therapists working in the ICU. Table 2, which summarizes the suggestions and considerations, can be easily adapted into a checklist for use at bedside. I suggest that Table 2 and the full document both be added to the curriculum of the Brazilian medical residencies. Ideally, the document should be periodically updated at short intervals—and this might be a challenge. The authors and the medical societies deserve congratulations for such an important work.

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Pulmonary talcosis due to aspiration

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

A 41-year-old man with dry cough and progressive dyspnea on moderate/high exertion was admitted to our service. He worked for 8 years in a cosmetics industry. A chest CT scan showed bilateral conglomerate masses (Figure 1). Tomographic findings associated with the occupational history allowed the diagnosis of pulmonary talcosis.

Conglomerate masses can occur in four basic pulmonary conditions: silicosis, coal workers' pneumoconiosis, sarcoidosis, and talcosis. Although the identification of conglomerate masses on chest CT restricts the diagnostic possibilities to these four diseases, clinical and occupational history, both current and past, is essential for final diagnosis.

Talcosis is an uncommon pneumoconiosis, related to the aspiration or injection of talc (magnesium silicate). Patients may be asymptomatic or present with a severe disease course. Symptomatic patients usually present with nonspecific complaints, including progressive dyspnea on exertion and cough.

Late complications include chronic respiratory failure, emphysema, pulmonary arterial hypertension, and *cor pulmonale*. Two distinct forms of lung disease caused by talc have been defined. One is associated with aspiration of the product, and one results from intravenous administration of talc, seen in drug users. Talc is a mineral widely used in various industries. Inhalation of a large amount of talc can occur during its extraction from mines, separation, milling, packaging, loading, and transportation. There have also been reports of talcosis in workers exposed to talcum powder in secondary industries such as rubber, paper, textiles, leather, ceramics, pharmaceuticals, cosmetics, insecticides, and herbicide manufacturers, as well as in soapstone workers. In addition to the possible occupational history, the possibility of the patient being a drug addict should be carefully evaluated, especially those who intravenously inject oral substances.

On CT, findings of small centrilobular nodules associated with heterogeneous conglomerate masses containing amorphous areas of high attenuation within them, determined by talc deposition, with or without panlobular emphysema in the lower lobes, are highly suggestive of pulmonary talcosis. On CT, the main difference between inhaled and intravenous forms is the possibility of emphysema developing in the latter. The histopathological feature of talc pneumoconiosis is the presence of birefringent, needle-shaped talc particles seen within giant cells and in areas of pulmonary fibrosis using polarized light.

Our patient also underwent BAL, which showed birefringent particles, confirming the diagnosis of pulmonary talcosis.

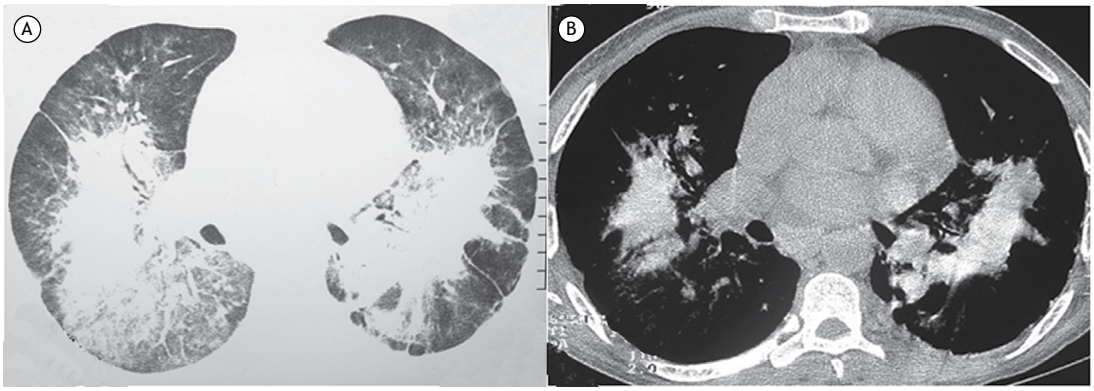

Figure 1. CT scans of the lower lobes with lung window setting (in A) showing bilateral conglomerate masses, ground-glass opacities, areas of emphysema, and dense streaks in the periphery. In B (mediastinal window setting), areas of increased attenuation within the conglomerate masses are revealed, compatible with talc deposition.

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Cross-sectional studies: understanding applications, methodological issues, and valuable insights

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PRACTICAL SCENARIO

Investigators from Latin America conducted a cross-sectional study to estimate the prevalence of COPD in adults ≥ 40 years of age in five major Latin American cities.[1] Key variables, including smoking history, pre and post-bronchodilator spirometry, were measured at a single point in time in all participants. The authors of the PLATINO study reported the prevalence of COPD in São Paulo (Brazil), Santiago (Chile), Mexico City (Mexico), Montevideo (Uruguay), and Caracas (Venezuela), with prevalences ranging from 8% to 20%.

WHAT IS A CROSS-SECTIONAL STUDY?

A cross-sectional study is a type of observational study widely employed across diverse disciplines, and its use is particularly relevant to public health, epidemiology, and the social sciences. It provides a snapshot of a population on a single occasion and enables the analysis of associations between variables without the influence of temporal factors.[2] This design is particularly well-suited to estimate the prevalence of diseases and health outcomes, describe population characteristics, and evaluate associations in a defined population. Since the exposure and outcome are measured concurrently and with no follow-up period, investigators analyze the distribution of outcome variables across the exposures based on biological plausibility and prior evidence.[3]

The strengths of cross-sectional studies lie in their cost-effectiveness and efficiency, as they are relatively fast to complete and inexpensive. They are also the appropriate design to estimate disease prevalence. Additionally, minimal ethical concerns arise since participants are not deliberately exposed to interventions.[2] However, cross-sectional studies have notable limitations. Investigators cannot use them to assess disease incidence, and they are unfeasible for studying rare conditions. Importantly, cross-sectional studies do not allow investigators to evaluate causality, because it is not possible to establish whether a suspected exposure variable preceded the suspected outcome. We summarized the advantages and disadvantages of cross-sectional studies in Chart 1.

RESEARCH QUESTIONS SUITABLE FOR CROSS-SECTIONAL STUDIES

Selecting the appropriate study design for a specific research question is a critical and often challenging step in developing the research plan. Cross-sectional studies help estimate the prevalence of a condition or outcome within the study population. This design is well-suited for descriptive and exploratory analyses. Large-scale epidemiological studies have leveraged this approach to provide valuable insights into the distribution of risk factors and the impact of social determinants of health on the development of prevalent diseases, contributing to the formulation of public health policies worldwide. Diagnostic test accuracy studies are particularly appropriate for a cross-sectional design.

Although cross-sectional studies are not suitable for research questions that evaluate causality, they can be employed to investigate associations among variables. In this context, the decision to label variables as exposures or outcomes is guided by the investigator's cause-and-effect hypothesis rather than determined by the study design itself.[3]

INTERPRETATION OF FREQUENCY AND ASSOCIATION MEASURES IN CROSS-SECTIONAL STUDIES

In contrast to longitudinal studies, cross-sectional studies are designed to capture prevalence, representing the proportion of individuals with a disease or condition at a specific point in time among a population of interest. Investigators should report the number of events in participants with and without the exposure and provide prevalence precision with a 95% confidence interval (95% CI).[4] The prevalence of an outcome can be compared between exposed and unexposed, providing measures of association such as the odds ratio (OR) and the prevalence ratio (PR). In the practical scenario described, the authors reported that the prevalence of COPD ranged from 7.8% (95% CI: 5.9-9.7) in Mexico City to 19.7% (95% CI: 17.2-22.2) in Montevideo.

Drawing inferences regarding causality, prognosis, or natural history of disease from cross-sectional data requires caution. A variable associated with the outcome of interest may be a causal factor, but it could also simply reflect an association with the disease's duration.[3] Exposures may be influenced by confounding factors that also impact the outcome. Therefore, it is crucial to identify potential confounders during the study design phase and apply appropriate statistical methods to minimize distortion in the associations between the variables of interest.

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Chart 1. Cross-sectional studies: advantages and disadvantages

Advantages	Disadvantages
Less time-consuming; cost-effective.	Unpractical for studying rare diseases
Efficiency	Unable to assess incidence
Facilitates hypothesis generation	Pitfalls inferring causality, prognosis, or natural history of disease
Multiple outcomes and exposures can be studied simultaneously	Selection bias risk
Minor ethical concerns	Cannot establish temporal relationships between exposure and outcome
Suitable for large sample sizes	Potential confounding factors may bias associations

KEY MESSAGES

1. Cross-sectional studies provide valuable insights into prevalence and associations within populations.
2. Although these studies provide a population snapshot at a specific point, their design limits inferences regarding causality.
3. Quality control during the conception and conduct of cross-sectional studies and awareness of its limitations are crucial to maximizing their utility in advancing evidence-based practice.

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The laboratory of lung function in the follow-up of lung transplant recipients

José Alberto Neder[1], Denis E O'Donnell[1], Danilo C Berton[2]

BACKGROUND

Lung transplantation significantly affects various domains of respiratory physiology. Some changes result from the procedure itself and any direct lung injury related to it. Post-transplantation chronic lung allograft dysfunction (CLAD) remains a major cause of morbidity and mortality.[1] Therefore, lung transplant recipients should undergo regular pulmonary function tests (PFTs) as part of ongoing monitoring.[1,2]

OVERVIEW

A 60-year-old woman underwent right lung transplantation because of severe emphysema. Despite mild acute lung rejection in the first post-transplant year, she remained largely asymptomatic with relatively preserved lung function over several years. However, she reported progressive exertional dyspnea after a severe lower respiratory tract infection six years later. Despite treatment optimization, there had been a persistent (> 3 months) decline in FEV_1 (≥ 20%) relative to baseline (Figure 1A). The presence of obstruction (low FEV_1/FVC) without restriction (preserved TLC) or new opacities on chest CT suggested the obstructive phenotype of CLAD (Figure 1B).[1]

Changes in PFTs after lung transplantation are influenced by the underlying lung disease of the recipient and whether the transplant is single or bilateral.[3,4] Clinical interpretation of PFTs in recipients of single transplants is more complex because changes may reflect the progression of the underlying disease in the native lung. Most centers recommend (at least) spirometry once a month for the first post-transplant year and every 3-4 months subsequently. FVC and FEV_1 usually improve over the first three months following surgery, and there is a slight further improvement up to 24 months after bilateral transplantation.[3,4] The average of two maximal post-transplant FEV_1 values obtained at least three weeks apart should be recorded as a baseline for monitoring allograft function.[1] Supranormal FEV_1/FVC might be seen, secondary to a restrictive thoracic cage due to the operative procedure and/or transplantation of large lungs, causing a mismatch between higher airflow capacity and thoracic cage volume. A persistent (> 2 days) decline of 10% in spirometric values has been reported to indicate either rejection or infection.[5]

CLAD is an umbrella term describing a significant decline in lung function after lung transplantation in the absence of other identifiable causes. The most common manifestation of CLAD is bronchiolitis obliterans syndrome. However, up to 30% of patients with CLAD develop a restrictive phenotype. A diagnostic workup is provided in Figure 1B. More sensitive metrics of smaller airway dysfunction (such as low mid-expiratory flows and impulse oscillometry measurements) and/or air trapping (high functional residual capacity and RV) are not widely considered given the great variability and the lack of data from large studies examining this issue. However, persistent changes in these parameters and those reflecting impaired gas transfer (hemoglobin-corrected DL_{CO} and carbon monoxide transfer coefficient) might be relevant in individual subjects.

CLINICAL MESSAGE

PFTs are critical for monitoring allograft (dys)function; for early detection of rejection and infection; and for monitoring response to treatment. Careful clinical and imaging correlation is paramount. Close attention should be given to factors that can negatively impact lung function, such as weight gain, aging, comorbidities, and concurrent local or systemic pathological processes (Figure 1, footnotes).

AUTHOR CONTRIBUTIONS

All authors contributed equally to this manuscript.

CONFLICTS OF INTEREST

None declared.

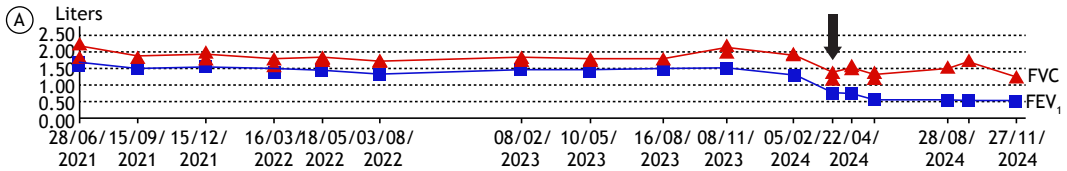

Figure 1. In A, serial spirometric measurements in a woman who underwent right lung transplantation because of severe COPD. The onset of chronic lung allograft dysfunction (CLAD) is indicated by a persistent drop (> 20%) in FVC and FEV_1 (arrow) in the absence of new lung opacities. Given a greater reduction in the latter, FEV_1/FVC turned abnormally low, signaling the presence of bronchiolitis obliterans syndrome (BOS). Continued...

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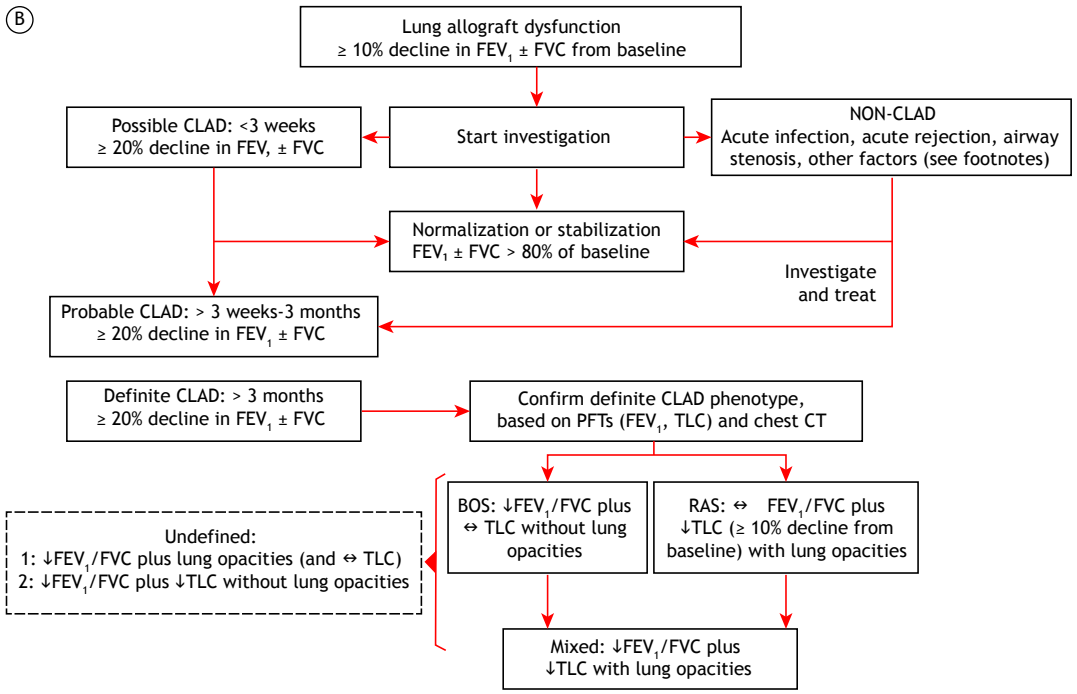

Figure 1. In B, a simplified approach to the diagnosis of CLAD in patients with lung allograft dysfunction.[1] As outlined below, there are several modifiers that should be considered in the longitudinal interpretation of pulmonary function tests (PFTs) in this patient population.[1] ↓: reduced; ↔: preserved; and RAS: restrictive allograft syndrome.
A. Factors where recalculation/resetting of the FEV_1 reference value may be valid (if FEV_1 remains stable for at least 6 months):
1. decreasing lung function as a result of the normal aging process
2. surgical factors, including transplant lung resection, chest wall surgery, and phrenic nerve damage
3. mechanical factors, including persistent pleural effusion, persistent lung edema caused by significant kidney/heart/liver failure, myopathy, neuropathy, weight gain, and native lung hyperinflation after single-lung transplantation
4. localized infection with chronic scarring—abscess, empyema, and/or mycetoma
B. Factors that cannot be differentiated easily from CLAD and do not ever allow recalculation/resetting of the FEV_1 reference value:
1. any from (A) when there is not at least 6 months of stability
2. infiltration with tumor
3. infiltration of the allograft with proven disease recurrence from the underlying transplant indication (e.g., sarcoidosis and lymphangioleiomyomatosis)
4. drug or other induced pulmonary toxicity (e.g., sirolimus, methotrexate, amiodarone, and radiation therapy)
5. pulmonary arterial strictures or emboli
6. acute/subacute generalized infection
7. acute/subacute cellular or antibody-mediated rejection
8. acute/subacute effects of aspiration
C. Failing to reach normal predicted lung function (i.e., low FEV_1 reference value such that FEV_1 is ≤ 80% of the recipient predicted value). This may occur when older donor lungs are implanted or when an intraoperative allograft reduction surgery/lobectomy is performed.

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Diagnosis and management of tuberculosis in children

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INTRODUCTION AND EPIDEMIOLOGY

Tuberculosis is a communicable disease caused by *Mycobacterium tuberculosis*.[1] Although preventive measures and effective treatment are available, tuberculosis remains a major cause of morbidity and mortality worldwide, particularly in resource-limited settings, exacerbating social inequality.[1] Transmission occurs through the respiratory tract, with the inhalation of airborne particles produced by coughing, speaking, or sneezing from individuals with active pulmonary or laryngeal tuberculosis.[2]

Children and young adolescents account for approximately 11% of all tuberculosis cases globally, with an estimated 1.1 million children developing the disease each year, nearly half of whom are < 5 years of age. Tuberculosis in children presents unique challenges; although children are less contagious than adults, they have a higher risk of primary progression to active disease, especially infants and younger children.[3,4] Extrapulmonary involvement and forms that are more severe, such as miliary tuberculosis and tuberculosis meningitis, are more common in pediatric tuberculosis than in adult tuberculosis.[1]

CONTACT INVESTIGATION

Contact investigation is an evidence-based method that plays a significant role in preventing tuberculosis infection by interrupting the chain of transmission.[2,3] The risk of developing tuberculosis is substantially higher in children who are in contact with adults and adolescents with tuberculosis. This is confirmed by the fact that the prevalence of latent tuberculosis infection (LTBI) is high among contacts.[2] Investigation of contacts of patients with tuberculosis has been shown to increase case detection, and tuberculosis preventive treatment (TPT) can reduce the prevalence of *M. tuberculosis* transmission in the community. Assessment of people who have been exposed to tuberculosis can contribute to early diagnosis and facilitate treatment initiation, even in patients with LTBI.[2]

The first step in contact investigation is communicating with tuberculosis patients to determine who their contacts are and inform them of the risk of developing tuberculosis.[3] In children, combined tuberculosis screening is required, typically including symptom screening, chest X-rays, and tuberculin skin tests (TSTs) or interferon gamma release assays (IGRAs), according to the WHO (Figure 1).

In a recently published systematic review and meta-analysis,[2] tuberculosis prevalence among contacts was reported to be higher in low-income and high-incidence settings, a finding that shows that tuberculosis can act as a biological representation of social inequality. Because of that, contact investigation is essential not only in case detection but also in decreasing community prevalence of tuberculosis and tuberculosis mortality, especially in more vulnerable settings.[3]

DIAGNOSIS AND TREATMENT OF LTBI IN CHILDREN

People who are infected with *M. tuberculosis* but do not have active disease are classified as having LTBI. They require TPT, which reduces the risk of progression to active tuberculosis.[1] The diagnosis of LTBI in children can be made by a variety of methods, including the TST and IGRA. These methods are particularly important in the case of children ≤ 5 years of age with a history of contact with pulmonary tuberculosis.[4] In Brazil, a positive (or indeterminate) IGRA result or a TST ≥ 5 mm is an indication for TPT, regardless of the time elapsed since BCG vaccination, after active tuberculosis is ruled out.[5] According to the WHO, children < 5 years of age should be prioritized (Figure 1). Active tuberculosis should be excluded by clinical and radiological examination.

Rifampin and isoniazid constitute the preferred TPT regimen, with daily doses of medication for three months. The recommendation is that patients receive 90 doses, ideally for three months, the number of doses being more important than the duration of the treatment. The focus should be to ensure that patients complete the full prescribed dose of medications within the specified time frame. Another option is the isoniazid-only regimen, with daily doses for six to nine months. There is evidence that 270 doses are more effective than 180 doses for patient protection.[5]

ACTIVE TUBERCULOSIS IN CHILDREN

The diagnosis of active tuberculosis in children (< 10 years of age) is challenging because of nonspecific symptoms that are also present in common childhood

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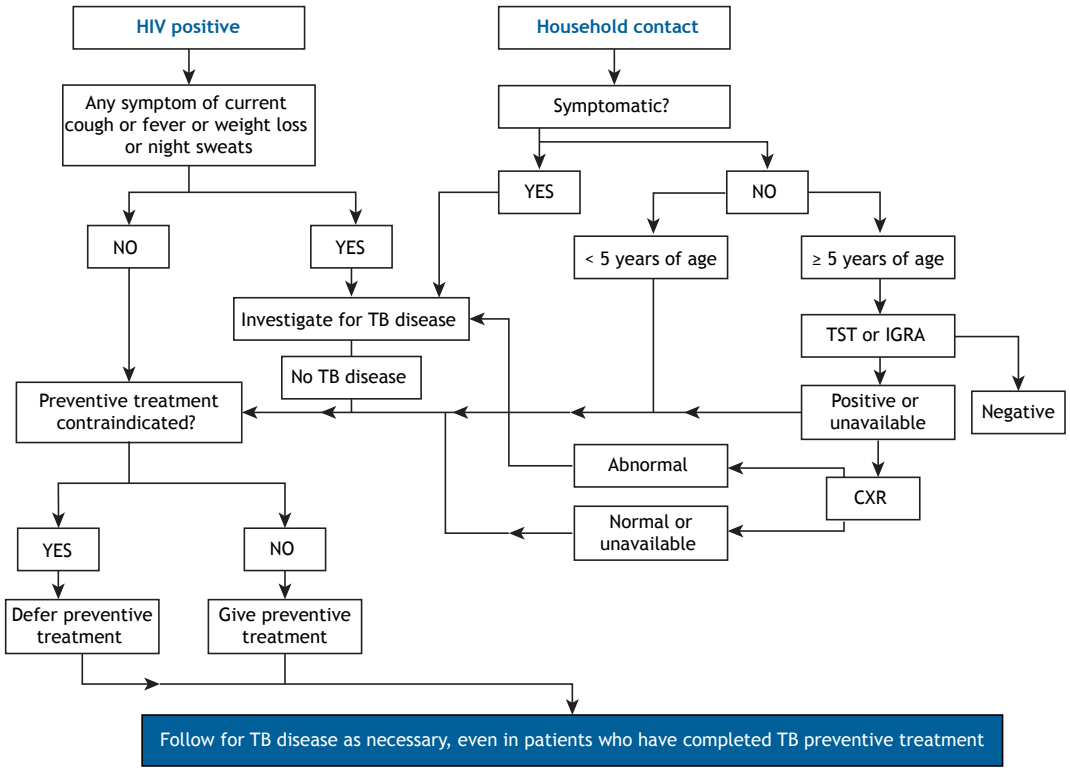

Figure 1. WHO algorithm for tuberculosis (TB) infection testing and TB preventive treatment in children and adolescents.[4] TST: tuberculin skin test; IGRA: interferon gamma release assay; and CXR: chest X-ray.

infections.[1,4] These symptoms include decreased appetite, weight loss, and chronic cough. Although active tuberculosis most commonly presents as a pulmonary disease, persistent cough (for more than three weeks) may be the only respiratory symptom, associated with progressive worsening.[5] Although fever is not always present, it is typically above 38°C and occurs in the late afternoon. Other general signs and symptoms include anorexia, asthenia, night sweats, hepatosplenomegaly, and lymphadenopathy.[1]

Another difference between active tuberculosis in adults and active tuberculosis in children is that pulmonary tuberculosis in children is often AFB-negative, meaning that microbiological examination results are negative because of the low number of bacilli in the lesions.[5] Therefore, the diagnosis of active tuberculosis in children is based on a combination of clinical and epidemiological criteria, associated with a nonspecific immunological test for tuberculosis infection and chest X-rays.[5] There is no gold standard for the diagnosis of active tuberculosis in children, nor is there a universal diagnostic algorithm.[4]

The basic treatment regimen for children with active tuberculosis initially includes an intensive phase with daily doses of rifampin, isoniazid, and pyrazinamide for two months, depending on the body weight of the patient. The maintenance phase, which encompasses the next four months, includes a daily dose of rifampin and isoniazid only, also depending on the body weight of the patient.[5] In Brazil, children and adolescents in the 3-month to 16-year age bracket with nonsevere tuberculosis, a four-month treatment course is recommended as an alternative regimen. This recommendation is based on a trial showing that a four-month treatment regimen (two months of isoniazid, rifampin, and pyrazinamide with or without ethambutol, followed by two months of isoniazid and rifampin) was noninferior to the standard six-month regimen.[6]

In conclusion, treatment outcomes for children completing tuberculosis treatment are generally excellent. Most deaths attributable to tuberculosis in children occur in those who do not receive treatment. The key to stopping the spread of tuberculosis, including children and adolescents, is to start effective tuberculosis treatment as soon as possible in people who are infected and to prevent tuberculosis disease in people at high risk of developing tuberculosis.[6]

FINANCIAL SUPPORT

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AUTHOR CONTRIBUTIONS

MFGMF, GBS, and JGK: research and manuscript writing. MFS, CCS, and LAP: manuscript writing and editing. All authors approved the final version of the manuscript.

CONFLICTS OF INTEREST

None declared.

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Evaluation of the IMPROVE-DD score in COVID-19 patients submitted to venous thromboembolism investigation at a hospital in Brazil

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Study carried out at the Universidade Federal da Bahia (UFBA), Salvador (BA), Brasil.

ABSTRACT

Objectives: To evaluate the incidence of venous thromboembolism (VTE) in hospitalized patients with COVID-19 who underwent diagnostic tests for suspected VTE, and to correlate the IMPROVE-DD score with the incidence of VTE in this cohort. **Methods:** This retrospective study included consecutive patients with COVID-19 and suspected VTE, admitted between March 2020 and September 2021 at a private hospital in Salvador (BA), Brazil, who underwent lower or upper limb venous Doppler ultrasound or chest angiotomography. Descriptive analyses and comparisons using the chi-square test were performed to identify factors potentially associated with the risk of VTE. **Results:** A total of 517 patients were included, with an in-hospital VTE incidence of 18.6% (96 events). Risk factors significantly associated with VTE included obesity, ICU admission, central venous catheter use, longer hospital stays, greater lung tomographic involvement/severity, the need for mechanical ventilation, D-dimer levels at least twice the upper limit of normal (2xULN), and the IMPROVE-DD score. The mean IMPROVE-DD score among patients with VTE was 4.7 (±3) versus 3.3 (±2.4) in those without VTE ($p < 0.0001$). D-dimer 2xULN was sensitive in identifying 94% of the 96 patients with VTE ($p < 0.0001$). The in-hospital mortality rate was 14.1%, with higher rates observed in patients with VTE (24%) compared to those without VTE (11.9%) ($p = 0.003$). **Conclusions:** The incidence of VTE in hospitalized COVID-19 patients was high and correlated with increased mortality. The IMPROVE-DD score effectively identified patients at risk for in-hospital VTE, suggesting it could help to identify a high-risk subgroup that may benefit from extended thromboprophylaxis.

Keywords: Venous thromboembolism, COVID-19, IMPROVE-DD.

INTRODUCTION

Severe Acute Respiratory Syndrome Coronavirus 2 (SARS-CoV-2) causes Coronavirus Disease 2019 (COVID-19), which may require hospitalization and is associated with an increased risk of venous thromboembolism (VTE). In severe cases, the disease can affect the lower respiratory tract, leading to severe acute respiratory syndrome, acute cardiac injury, increased susceptibility to secondary infections, and coagulation disorders.[1-3]

COVID-19 can cause endothelial injury during the process of virus penetration and release, as well as through the release of cytokines, primarily interleukin-6 (IL-6), which exacerbates the process of thromboinflammation.[4,5] Severely ill patients may experience reduced mobility, which promotes venous stasis—a key factor in thrombosis. Additionally, increased blood hyperviscosity, evidenced by elevated levels of fibrinogen and factor VIII, has been observed.[5] Consequently, Virchow's triad is fulfilled, and the association between COVID-19, microthrombosis, and VTE has been documented in several studies, even in patients receiving thromboprophylaxis.[6]

Given the high risk of developing VTE in hospitalized patients with COVID-19, it has become crucial to determine whether a scoring system could identify patients who would benefit from both therapeutic anticoagulation during hospitalization,[7] and extended post-discharge thromboprophylaxis.[8-10] The International Medical Prevention Registry on Venous Thromboembolism Risk Assessment Model + D-dimer twice the upper limit of normal (2xULN) (IMPROVE-DD VTE RAM) score[11,12] is an adaptation of the widely validated International Medical Prevention Registry on Venous Thromboembolism Risk Assessment Model (IMPROVE VTE RAM) score.[13] The incorporation of D-dimer levels into the IMPROVE score, thereby creating the IMPROVE-DD score, was designed to enhance its accuracy in predicting VTE risk.[11]

A study conducted between March and May 2020, involving 4,906 patients from the Northwell Health System health plan, guided the implementation of the

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IMPROVE-DD score throughout its healthcare network, and indicated the use of rivaroxaban (10 mg orally) or low-molecular-weight heparin (LMWH) enoxaparin (40 mg subcutaneously daily, if creatinine clearance ≥ 15 mL/min) for 30 days in COVID-19 patients with IMPROVE-DD scores ≥ 4. The researchers concluded that the use of the scoring system reduced the risk of major thromboembolic events and death by 46%.[10]

Studies on the utility of the IMPROVE-DD score in COVID-19 patients, however, are limited and mostly confined to the United States. This study investigates the incidence of VTE in hospitalized COVID-19 patients with suspected VTE who underwent diagnostic tests at a hospital in Salvador, Brazil, between March 2020 and September 2021. Using these data, the IMPROVE-DD score was evaluated in this population to identify patients at a higher risk of VTE.

METHODS

Study design: This retrospective, non-interventional observational study was conducted among hospitalized patients diagnosed with COVID-19 at a private hospital in Salvador, Brazil. The study utilized data from the Clinical Registry (CR) of COVID-19 patients who underwent diagnostic tests for VTE. Suspicion of VTE was based on clinical variables and laboratory findings, such as significant increases in D-dimer levels.

From March 2020 to September 2021, all hospitalized patients at the institution with confirmed COVID-19 via RT-PCR or antigen testing, who underwent lower or upper extremity venous Doppler ultrasound (US) and/or chest computed tomography angiography (CTA), were included. Patients were excluded if COVID-19 was not confirmed or if they had not undergone at least one of the specified diagnostic tests required for cohort selection.

Demographic and biometric data, along with admission diagnoses, were collected. They included systemic arterial hypertension (SAH), diabetes mellitus (DM), coronary artery disease (CAD), history of previous VTE, smoking history, cancer, thrombophilia, obesity - BMI ≥ 30 kg/m^2 and overweight - BMI ≥ 25 kg/m^2, lower limb immobilization, patient care units (general ward, intensive care unit [ICU], and step-down unit), D-dimer levels (normal range: ≤ 500 ng/mL, measured using enzyme-linked immunosorbent assay [ELISA]), chest CT and CTA findings, lower or upper extremity venous Doppler ultrasound results, and mechanical ventilation data.

Descriptive data analyses of the study sample were presented as percentages, means (± standard deviations [SD]), and medians (interquartile ranges [IQR]), as appropriate. The percentages of patients with positive, negative, and inconclusive VTE test results and their characteristics were compared, focusing mainly on the IMPROVE-DD score, which comprises eight criteria: 1 - history of previous VTE (+3 points); 2 - known thrombophilia (+2 points); 3 - lower limb paralysis during hospitalization (+2 points); 4 - active cancer (+2 points); 5 - immobilization for seven days or more (+1 point); 6 - ICU admission (+1 point); 7 - age ≥ 60 years (+1 point); 8 - D-dimer levels at least twice the upper limit of normal (+2 points). Patients scoring 0–1 were considered low risk; 2–3, moderate risk; and ≥4, high risk, with potential benefit from extended VTE prophylaxis.[8,11,12,14]

Pearson's chi-square test or Fisher's exact test, as appropriate for categorical variables, and Student's t-test or Wilcoxon's test for continuous variables, were performed using IBM Statistical Package for the Social Sciences (SPSS 21) software. A Receiver Operating Characteristic (ROC) curve was plotted for IMPROVE-DD scores ≥4, and the Area Under the Curve (AUC), sensitivity, specificity, positive predictive value (PPV), and negative predictive value (NPV) were calculated.

The study protocol was approved by the Research Ethics Committee of the D'Or Research Institute (Process No. 4,383,979).

RESULTS

A total of 535 patients were evaluated; 18 were excluded due to either lack of confirmed COVID-19 or failure to undergo VTE imaging tests during hospitalization. Among the 517 patients included, 232 (44.87%) were female and 285 (55.13%) were male, with a mean age of 60 years (±17). Of the included patients, 201 (38.88%) were aged < 55 years, 152 (29.4%) were aged 55 to 69 years, and 164 (31.72%) were aged ≥ 70 years.

Among the total of 686 diagnostic tests performed for VTE, 286 were lower limb US, 23 were upper limb US, and 377 were chest CT angiography (CTA) scans. During hospitalization, 96 VTE events (18.6%) were diagnosed. Approximately 76.2% of patients received pharmacological prophylaxis for VTE, and among those hospitalized for more than 48 hours, 95.3% received pharmacological prophylaxis.

The clinical characteristics and comorbidities of patients with COVID-19 and suspected VTE are presented in Table 1. The most frequent risk factors for VTE were overweight and obesity, advanced age, ICU admission, presence of central venous catheters (CVC), mechanical ventilation, recent surgery, and more severe tomographic findings related to COVID-19. Common cardiovascular comorbidities included SAH and DM. D-dimer levels upon admission were higher in patients with VTE, with a mean of 12,021 (± 15,473), compared to those without VTE, whose mean was 3,121 (± 5,132) ($p < 0.0001$).

Lung involvement due to COVID-19 on chest CT was classified as absent (0%), mild (1–25%), moderate (26–50%), and severe (>50%). Moderate alterations were observed in 35.4% of patients, while severe changes were found in 30.6%. A total of 253 patients (48.94%) required ICU or step-down unit care, and 23.6% required MV. The mean length of hospital stay was 13 days (±18), which was longer

Table 1. Clinical characteristics and comorbidities of hospitalized patients with COVID-19 submitted to VTE investigation.

Variable All	All (%) 517 (100)	With VTE (%) 96 (18.57)	Without VTE (%) 421 (81.43)	p-value
Women	232 (44.9)	38 (39.6)	194 (46.1)	0.26
Men	285 (55.13)	58 (60.4)	227 (53.9)	
≥ 55 years old	316 (61.1)	64 (66.78)	252 (59.9)	0.47
≥ 70 years old	164 (31.7)	29 (30.2)	135 (32.1)	0.81
Mechanical ventilation	122 (23.6)	45 (46.9)	77 (18.3)	<0.0001
ICU-level care	253 (48.9)	73 (76.0)	180 (42.8)	<0.0001
Chronic lung disease	24 (4.60)	2 (2.1)	22 (5.2)	0.28
Rheumatologic diseases	15 (2.9)	1 (1.0)	14 (3.3)	0.33
Asthma	34 (6.6)	2 (2.1)	32 (7.6)	0.65
Recent surgery	76 (14.7)	19 (19.8)	57 (13.5)	0.15
Chronic renal insufficiency	23 (4.4)	5 (5.2)	18 (4.3)	0.78
Central venous catheter	137 (26.5)	45 (45.9)	92 (21.9)	<0.0001
Pharmacological VTE prophylaxis	395 (76.4)	91 (94.8)	304 (72.2)	<0.0001
Death during hospitalization	73 (14.1)	23 (24)	50 (11.9)	0.003
Hospital stay, mean (SD)	**13.2 (17.7)**	**24.4 (26.5)**	**10.6 (13.8)**	**<0.0001**
≥ 48 hours	401 (77.6)	92 (95.8)	309 (73.4)	<0.0001
≥ 7 days	288 (55.7)	67 (69.8)	221 (52.5)	0.002
Chest CT abnormalities				**0.015**
Absent	92 (17.8)	13 (13.5)	79 (18.8)	
Mild	84 (16.2)	10 (10.4)	74 (17.6)	
Moderate	183 (35.4)	31 (32.3)	152 (36.1)	
Severe	158 (30.6)	42 (43.8)	116 (27.6)	
Other risk factors for VTE				
Previous VTE events	21 (4.1)	7 (7.3)	14 (3.3)	0.87
Diabetes mellitus (DM)	109 (21.1)	21 (21.9)	88 (20.9)	0.89
Systemic arterial hypertension (SAH)	246 (47.6)	47 (49)	199 (47.3)	0.82
Coronary artery disease (CAD)	43 (8.3)	7 (7.2)	36 (8.6)	0.84
Known thrombophilia	5 (1.0)	2 (2.1)	3 (0.7)	0.23
Paralysis of lower extremity	2 (0.4)	0 (0)	2 (0.5)	1.0
Cancer	21 (4.1)	5 (5.2)	16 (3.8)	0.57
D-dimer level, mean (SD)	4,773 (8,804)	12,021 (15,473)	3,121 (5,132)	<0.0001
BMI ≥ 25	419 (81)	74 (77.1)	345 (81.9)	0.312
BMI ≥ 30	140 (27.1)	35 (36.5)	105 (24.9)	0.03
Smoker	7 (1.4)	1 (1.0)	6 (1.4)	1
Former smoker	58 (11.2)	12 (12.5)	46 (10.9)	0.72

ICU, intensive care unit; CT, computed tomography; VTE, venous thromboembolism; BMI, body mass index; SD, standard deviation.

in patients with VTE (24.4 days) compared to those without VTE (10.6 days) (p < 0.0001).

Approximately three-quarters (73; 76.04%) of the VTE events were detected among ICU and step-down unit patients, while 23 (23.96%) were detected in general wards. The incidence of VTE was 28.9% among ICU patients and 8.7% in general wards. Among the VTE events, 49 were pulmonary embolism (PE), 49 were deep vein thrombosis (DVT), four were catheter-associated DVT, and eight were superficial vein thrombosis (SVT). Some patients experienced more than one VTE event. The mortality rate was 14.1%, which was higher among VTE patients compared to those without VTE (24% vs. 11.9%) (p = 0.003).

The IMPROVE-DD score is shown in Table 2. Overall, 50.9% of the patients had an IMPROVE-DD score ≥ 4. The mean score for all patients was 3.5 (± 2.6), significantly higher among patients with VTE (4.7 ± 3) compared to those without VTE (3.3 ± 2.4) (p < 0.0001). The most frequent variables contributing to the IMPROVE-DD score, which were also significantly more common in patients with VTE, included immobilization for ≥ 7 days, ICU/step-down unit admission, and D-dimer levels ≥ twice the upper limit of normal (2xULN). Although age ≥ 60 years was a frequent variable, it did not differ significantly between patients with and without VTE.

Regarding the prediction of VTE risk based on the IMPROVE-DD score, 94.8% (91) of the patients with VTE had a moderate-to-high-risk score; 75% (72) had a high risk, with a score ≥ 4; and only 5.2% (4 men and 1 woman) of patients with VTE had a low-risk score (< 2). Of these, three scored "0" and two scored

Table 2. IMPROVE-DD score among hospitalized patients with COVID-19 submitted to VTE investigation.

Risk factors	Points	All N = 517 (%)	With VTE N = 96 (%)	Without VTE N = 421 (%)	p-value
Previous VTE events, n (%)	3	21 (4.1)	7 (7.3)	14 (3.3)	0.09
Thrombophilia, n (%)	2	5 (1.0)	2 (2.1)	3 (0.7)	0.23
Paralysis of lower extremity during hospitalization, n (%)	2	2 (0.4)	0 (0)	2 (0.5)	1.0
Cancer, n (%)	2	21 (4.1)	5 (5.2)	16 (3.8)	0.57
Immobilization for at least 7 days, n (%)	1	288 (55.7)	67 (69.8)	221 (52.5)	0.002
ICU stay, n (%)	1	253 (48.9)	73 (76)	180 (42.8)	<0.0001
Age ≥ 60 years old, n (%)	1	253 (48.9)	50 (52.1)	203 (48.2)	0.5
Max D-dimer ≥ 2x ULN, n (%)	2	386 (74.7)	90 (93.8)	296 (70.3)	<0.0001
Sum of points	(0 to 14)				
Mean (±)		3.5 (2.6)	4.7 (3)	3.3 (2.4)	<0.0001
Median (IQR)		4	4 (2)	3 (2)	
Score 0-1, n (%)		97 (18.8)	5 (5.2)	92 (21.9)	<0.0001
Score 2-3, n (%)		157 (30.4)	19 (19.8)	138 (32.8)	
Score ≥ 4, n (%)		263 (50.9)	72 (75)	191 (45.4)	

VTE, venous thromboembolism; ICU, intensive care unit; ULN, upper limit of normal; IQR, interquartile range; SD, standard deviation.

"1" due to age ≥ 60 years and ICU/step-down unit admission. Significantly more patients with VTE than without VTE had an IMPROVE-DD score ≥ 4 (75% vs. 45.4%) (p < 0.0001).

The ROC AUC was 0.66 (Figure 1). In this sample of hospitalized patients with COVID-19 and suspected VTE, the sensitivity of IMPROVE-DD scores ≥ 4 for predicting in-hospital VTE was 75%, the specificity was 54.6%, the PPV was 27.4%, and the NPV was 90.5%.

DISCUSSION

Among the COVID-19 patients evaluated for VTE in our study, 18.5% were found to have some form of VTE. A meta-analysis of 33 published trials conducted between January and June, 2020, involving 4,009 patients, reported an incidence of VTE in 9%, DVT in 3%, and PE in 8%. In ICU patients, these values increased to 21%, 8%, and 17%, respectively.[15] In the present study, the incidence of VTE was three times higher in the ICU compared to general wards (28.9% vs. 8.7%), despite 94.8% of the patients who developed VTE receiving pharmacological VTE prophylaxis prior to diagnosis. A meta-analysis identified that the pooled incidence of VTE in studies where COVID-19 patients did not receive thromboprophylaxis was 21%, compared to 18.2% in studies where patients received standard-dose thromboprophylaxis, evidencing a minimal difference between the two groups.[6] These findings are consistent with other systematic reviews and meta-analyses, highlighting the ongoing debate over the appropriate dose for effective prophylactic anticoagulation in these patients.[16,17]

Among the VTE events, PEs were more common than DVTs when compared to other clinically ill patient populations; however, most PEs in patients with COVID-19 were smaller in magnitude (segmental or subsegmental). On the other hand, patients with COVID-19 and VTE had significantly higher severity and hospital mortality rates (24% vs. 11.9%). This finding aligns with observations from other cohort studies.[18,19]

Significant risk factors for VTE included obesity, ICU/step-down unit admission, CVC use, prolonged hospital stays, more tomographic lung alterations/severity, the need for mechanical ventilation, and D-dimer levels at least 2xULN. As expected, patients with VTE had significantly higher D-dimer levels than those without VTE (mean: 12,021 vs. 3,121; p < 0.0001). Both the use of CVCs and elevated D-dimer levels are well-established risk factors for VTE and are incorporated into several risk assessment scores.[14,20–22]

Patients with VTE experienced worse clinical outcomes, including longer average lengths of stay in the ICU/step-down unit (24.4 vs. 10.6 days) and prolonged hospitalization. These outcomes are associated with case severity and have a direct relationship with thromboembolic events, primarily due to the promotion of venous stasis.[23,24] Among the 73 deaths, 68 (93.2%) occurred in patients hospitalized for more than 7 days, and 71 (97.3%) were among those admitted to the ICU.

The need for mechanical ventilation, a clear indicator of severity, was identified as a risk factor for VTE: 46.9% of patients who received MV developed VTE, compared to 18.3% of those who did not. The mortality rate was significantly higher among COVID-19 patients requiring MV. This association has been consistently documented in the literature throughout the waves of the pandemic.[25-27]

Obesity is another factor associated with worse outcomes in COVID-19 and is also a known risk factor for VTE.[23,28,29] The relationship between obesity, VTE, and COVID-19 is multifactorial and is believed to stem from chronic inflammation caused

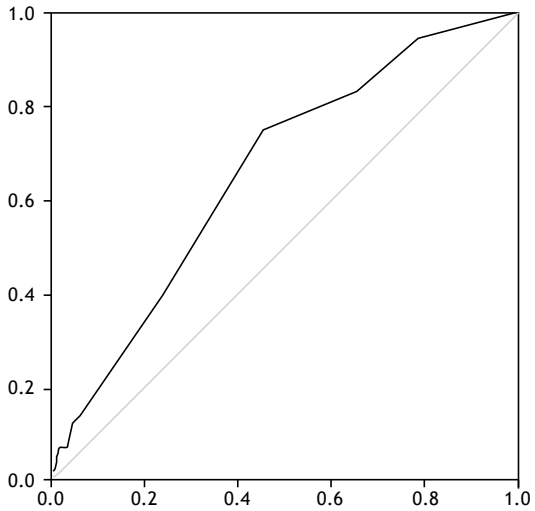

Figure 1. Receiver operating characteristic (ROC) curve for the IMPROVE-DD score and VTE. Notes (from top to bottom): first line, ROC curve; second line, null line.

by obesity, which is exacerbated by COVID-19, as well as reduced mobility and endothelial injury resulting from the pro-inflammatory state.[23,30,31] In the present study, 25% of patients had a BMI ≥ 30 kg/m^2, and obesity was significantly more common among patients with VTE compared to those without VTE (36.5% vs. 24.9%, respectively).

Parenchymal changes observed on chest computed tomography, indicating more severe lung involvement due to COVID-19, were also predictors of poor outcomes, with a mortality rate of approximately one-quarter for patients with moderate findings and over half for those with severe findings. The use of imaging exams to predict severity and poor outcomes has been suggested in other studies and was supported by the findings of this sample.[32–34]

Other known risk factors for VTE and COVID-19 include active cancer, advanced age, lower limb paralysis, male sex, a previous history of VTE, known thrombophilia, smoking, diabetes, and cardiovascular diseases (*e.g.*, SAH and CAD).[19,23,31,33–36] However, in the studied sample, these factors were not significant in predicting VTE or poor outcomes.

A noteworthy finding of the present study was the ability to demonstrate, in a Brazilian cohort, that the IMPROVE-DD score can effectively identify the risk of in-hospital VTE in COVID-19 patients. The IMPROVE-DD score, proposed in 2017,[14] has been evaluated in recent studies, including efforts to validate its use among COVID-19 patients.[8,10–12] In a validation study involving 9,407 patients with COVID-19 between March and April 2020, researchers reported a sensitivity of 0.971, specificity of 0.218, PPV of 0.036, and NPV of 0.996. The AUC generated by the ROC curve was 0.703, and the IMPROVE-DD score showed a 6.8% better discrimination compared to the original IMPROVE score in COVID-19 patients, which was statistically significant.[8] Similar findings have been reported by other authors.[9]

In the present study, IMPROVE-DD scores ≥ 4 were significantly associated with VTE, primarily driven by ICU/step-down unit admission, immobilization for ≥ 7 days, and D-dimer levels ≥ 2xULN. Notably, as a patient with a D-dimer level ≥ 2xULN scores "2" on the IMPROVE-DD scale, this single finding alone would be sufficient for the risk to be considered moderate. The MICHELLE study demonstrated improved combined clinical outcomes for VTE and mortality without an increase in major bleeding events by using extended post-hospital discharge prophylaxis with 10 mg/day rivaroxaban for 35 days, following in-hospital prophylaxis with 40 mg/day subcutaneous enoxaparin, in hospitalized COVID-19 patients with an IMPROVE-DD score ≥ 4, or a score of 2–3 with D-dimer levels > 500 ng/mL, provided they had a low risk of bleeding.[37] Based on the IMPROVE-DD score cutoff of ≥ 4 to indicate the need for extended pharmacological VTE prophylaxis post-discharge, our findings suggest that 263 patients, or 50.9% of the total cohort, would be candidates for such prophylaxis, assuming no bleeding risk factors are present.

IMPROVE-DD criteria that were not significantly associated with VTE in our study included active cancer, lower limb paralysis, known thrombophilia, age ≥ 60 years, and a previous history of VTE. These risk factors were less common in our cohort, and the sample size was relatively small. However, age ≥ 60 years correlated with greater COVID-19 severity and higher mortality rates compared to the younger group (22% vs. 7%). The impact of aging, as highlighted in other studies,[8–10,19,25,27,33] remains one of the most critical predictors of poor outcomes in severe COVID-19 patients. Although age did not show a significant association with in-hospital VTE in our cohort, it is an integral component of the IMPROVE-DD score.

An IMPROVE-DD score ≥ 4 does not serve as a diagnostic tool for in-hospital VTE due to its low sensitivity and specificity. However, it may be useful for ruling out in-hospital VTE in COVID-19 patients because of its relatively high negative predictive value (91%). In our study, 97 patients were categorized as "low VTE-risk" based on the IMPROVE-DD score. Nevertheless, five of these patients (5%) experienced thromboembolic events during hospitalization. Conversely, 81% of the patients (420/517) were classified as moderate-to-high VTE-risk and could be considered candidates for post-discharge VTE prophylaxis. This approach, however, could potentially result in the overuse of pharmacological prophylaxis. Prophylactic anticoagulation has potential drawbacks, including an increased risk of bleeding, high medication costs, drug interactions, and possible treatment non-adherence.[38,39] Therefore, it is essential to carefully weigh the risks and benefits of post-discharge VTE prophylaxis.[40] The original validation study of the IMPROVE-DD score reported a receiver operating characteristic (ROC) area under the curve

(AUC) of 0.703.[8] In the present study, the AUC ROC was 0.66, which is lower for in-hospital estimation. However, since the patients were not followed up after discharge, the ROC curve for the standard three-month follow-up period could not be calculated, representing a limitation of this study.

Finally, although many hospitalized COVID-19 patients have multiple risk factors for VTE and a high incidence of events despite receiving prophylactic anticoagulation with low-molecular-weight heparins during hospitalization, not all patients will benefit from extended post-discharge VTE prophylaxis. The use of IMPROVE-DD scores ≥ 4 in this population can aid in identifying higher VTE-risk patients; however, their risk of bleeding must be carefully assessed before they can be considered candidates for extended post-discharge VTE prophylaxis.

AUTHOR CONTRIBUTIONS

The first author contributed to data collection and took primary responsibility for writing the manuscript. The other authors assisted with data collection and manuscript preparation. The last author contributed to data collection, writing, and provided overall research guidance.

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Machine learning algorithms applied to the diagnosis of COVID-19 based on epidemiological, clinical, and laboratory data

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ABSTRACT

Objective: To predict COVID-19 in hospitalized patients with SARS in a city in southern Brazil by using machine learning algorithms. **Methods:** The study sample consisted of patients ≥ 18 years of age admitted to the emergency department with SARS and hospitalized in the *Hospital Escola - Universidade Federal de Pelotas* between March and December of 2020. Epidemiological, clinical, and laboratory data were processed by machine learning algorithms in order to identify patterns. Mean AUC values were calculated for each combination of model and oversampling/undersampling techniques during cross-validation. **Results:** Of a total of 100 hospitalized patients with SARS, 78 had information for RT-PCR testing for SARS-CoV-2 infection and were therefore included in the analysis. Most (58%) of the patients were female, and the mean age was 61.4 ± 15.8 years. Regarding the machine learning models, the random forest model had a slightly higher median performance when compared with the other models tested and was therefore adopted. The most important features to diagnose COVID-19 were leukocyte count, $PaCO_2$, troponin levels, duration of symptoms in days, platelet count, multimorbidity, presence of band forms, urea levels, age, and D-dimer levels, with an AUC of 87%. **Conclusions:** Artificial intelligence techniques represent an efficient strategy to identify patients with high clinical suspicion, particularly in situations in which health care systems face intense strain, such as in the COVID-19 pandemic.

Keywords: COVID-19/diagnosis; Artificial intelligence; Machine learning.

INTRODUCTION

COVID-19 has been the most important health problem in the world since 2020. Following its emergence in December of 2019, in Wuhan, China, the disease spread quickly across the world and, in February of 2020, the WHO declared it a pandemic because of its global impact.[1]

There are currently around 750 million confirmed cases of COVID-19 and 7 million COVID-19–related deaths worldwide. In Brazil, the number of COVID-19 cases and deaths were extremely high during the pandemic, and the disease had a harmful impact on the public health system.[2]

Viral infections such as SARS-CoV-2 infection are dangerous because they spread very quickly; therefore, early detection and diagnosis have a positive impact on health strategies.[3] Early in the COVID-19 pandemic, there were few diagnostic tests available in many countries, including Brazil; therefore, there was a need to select clinical and laboratory variables that could predict COVID-19 in order to proceed to nasal swab collection for RT-PCR to detect SARS-CoV-2 infection.[4] Although COVID-19 mortality has declined, the existence of other circulating viruses makes it necessary to establish the correct diagnosis and reduce the risk of transmission.

Artificial intelligence (AI) has been deployed at various levels of the health care system, including diagnosis,[5-7] public health, clinical decision making, and therapeutics. Particularly, AI algorithms have been shown to be effective in improving the diagnosis and prognosis of COVID-19 through the creation of models including clinical and epidemiological characteristics, as well as biochemical data.[8-10] The present study evaluated clinical and laboratory data to predict COVID-19 in hospitalized patients with SARS in a city in southern Brazil by using machine learning algorithms.

METHODS

The present study was conducted in the city of Pelotas, Brazil, which is the fourth most populated city in the state of Rio Grande do Sul, with a population of 325,685 inhabitants.[11] The city of Pelotas is the largest of the 22 municipalities in the Third Regional Health District. Therefore, patients from some of the other municipalities are referred to health care facilities in Pelotas, and this was especially true during the COVID-19 pandemic.

During the data collection period, the emergency department became the point of entry into the public health care system for patients from the city of Pelotas (and other municipalities) presenting with SARS. After

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undergoing an initial evaluation and RT-PCR for COVID-19, patients meeting the criteria for hospital admission were transferred to a public hospital able to receive them. In this context, the *Hospital Escola-Universidade Federal de Pelotas* became the most important center for receiving and treating patients with SARS during the COVID-19 pandemic.

The study sample consisted of patients ≥ 18 years of age admitted to the emergency department with SARS and hospitalized in the *Hospital Escola - Universidade Federal de Pelotas* between March and December of 2020. Because the data were collected retrospectively, the requirement for written informed consent was waived. The study project was approved by the Brazilian National Research Ethics Committee (Protocol no. 37337720.2.0000.5317).

We collected data on patient characteristics, including demographics (sex and age); comorbidities (e.g., obesity, diabetes, hypertension, cancer, and chronic respiratory disease); symptoms (e.g., cough, shortness of breath, chest pain, sore throat, and headache); vital signs (HR, RR, systolic blood pressure, diastolic blood pressure, and axillary temperature); and laboratory test results (e.g., hemoglobin level, leukocyte count, platelet count, and creatinine level). Table 1 shows the clinical and epidemiological characteristics of the patients suspected of having COVID-19. The missing values in the dataset were imputed by using the mean value of the features. The 100 rows were randomly divided into 70% for training and 30% for test. The continuous variables were normalized on the basis of the mean and standard deviation of the training sample. For the discrete variable, all values were in the interval between 0 and 1; therefore, no normalization was applied.

Several machine learning algorithms were examined in the present study, including support vector machines, gradient boosting, multilayer perceptron (MLP), adaptive boosting, and decision trees. All these algorithms are known as supervised learning algorithms. In supervised learning, the model observes input-output pairs and the learning algorithm finds the optimal configuration of parameters resulting in a function that maps from input to output while minimizing a certain loss function.[12,13]

The choice to use several algorithms allows one to cover different methods, from more classic and simple statistical methods such as decision trees to ensemble learning, convex optimization, and gradient-based methods such as MLPs. Each approach has advantages and peculiarities that could or could not be suitable for the problem tackled in the present study. Therefore, a cross-validation step allowed us to verify which methods optimized a certain metric.

In addition to the classification methods, because the collected dataset was imbalanced, techniques for oversampling were used in order to improve the overall performance of the system. Class imbalance poses serious problems for machine learning techniques. Some of the most conventional approaches to these problems are undersampling and oversampling. Oversampling consists in creating artificial data on the basis of the statistical behavior of the elements of the minority class, whereas undersampling consists in sampling the majority class in such a way that the dataset becomes balanced.[14]

Synthetic Minority Oversampling Technique (SMOTE) is one of the most notable oversampling methods available.[15] SMOTE works by taking each sample in the minority class and creating synthetic samples in the lines that connect the sample with each *k*-nearest neighbors. Other oversampling methods include a variation of SMOTE, known as Borderline-SMOTE, and an adaptive synthetic sampling approach for imbalanced learning,[15-17] both of which were tested in the present study.

Each combination of model and sampling technique was optimized by using a grid search approach. In grid search, a list of possible values for each hyperparameter is created, and all combinations of between-values are examined. The cross-validation method used was k-fold, with k = 5. The programming language used was Python 3.6, and the following libraries were used: NumPy 1.19.5; imbalanced-learn 0.4.3; pandas 0.22.0; scikit-learn 0.21.0; SciPy 1.4.1; and statsmodels 0.9.0.

After finding the best model, we were able to analyze other metrics, such as sensitivity, specificity, precision, and confusion matrix. We analyzed the relevance of the variables present in the data for the classification of the models. This allowed us to determine the importance of the variables used and the level of agreement between the model and previously established knowledge.

RESULTS

A total of 78 patients had information for RT-PCR testing for SARS-CoV-2 infection and were therefore included in the analysis. The study sample did not differ from the original sample (n = 100) with regard to the baseline characteristics (Table 1). The median value and interquartile range for each variable are shown in Table 1. Of the sample as a whole (N = 78), 42% were male, and the mean age was 61.4 ± 15.8 years. Nearly 60% of the study participants had two or more comorbidities, with hypertension and diabetes being the most prevalent (in 58.5% and 44.3%, respectively). One quarter of the study participants were current smokers. The median time elapsed since the onset of symptoms was 9 days (IQR: 3-14 days), the most common symptoms being shortness of breath (in 66%), cough (in 59%), fever (in 44%), and muscle or joint pain (in 43%).

For a comprehensive analysis, each combination of classification model and oversampling/undersampling method was trained and cross-validated 30 times. This approach allowed the construction of a performance distribution for each pair. Given the imbalanced nature

Table 1. Epidemiological and clinical characteristics of patients suspected of having COVID 19.[a]

Variable	Original sample (n = 100)	Study sample (N = 78)
Sex, male	42 (42)	31 (39.7)
Age, years	61.4 ± 15.8	61.3 ± 15.4
Multimorbidity[b]	55 (58.5)	43 (57.3)
Hypertension	53 (54.6)	41 (53.2)
Diabetes	43 (44.3)	33 (42.9)
Obesity	13 (13.5)	11 (14.3)
Cancer	14 (14.6)	11 (14.3)
Chronic respiratory disease	18 (18.7)	15 (19.5)
Smoking	24 (25.5)	18 (24.0)
Days to onset of symptoms	9 [3-14]	9 [3-14]
Symptoms		
Cough	59 (59.0)	48 (61.5)
Shortness of breath	66 (66.0)	49 (62.8)
Chest pain	15 (15)	11 (14.1)
Sore throat	6 (6)	6 (7.7)
Runny nose or sneezing	10 (10)	9 (11.5)
Loss of smell or taste	6 (6)	5 (6.4)
Headache	11 (11.0)	10 (12.8)
Muscle or joint pain	43 (43)	34 (43.6)
Digestive symptoms	13 (13.0)	11 (14.1)
Fever	44 (44.0)	36 (46.1)
Vital signs		
HR, bpm	101 ± 19	100 ± 21
RR, cycles/min	24 ± 14	25 ± 16
Systolic blood pressure, mmHg	132 ± 25	130 ± 26
Diastolic blood pressure, mmHg	80 ± 15	80 ± 15
Axillary temperature, °C	36.7 ± 0.9	36.7 ± 0.9
Laboratory findings		
Hemoglobin, g/dL	12.5 ± 1.9	12.4 ± 2.0
Leucocytes, $\times 10^3$ cells/mm^3	9.3 [6.8-13.7]	8.6 [6.5-13.7]
Band forms, %	4 [2-6]	4 [2-6]
Lymphocytes, %	13 [6-18]	13 [6-20]
Platelets, cells/μL	235,494 ± 100,953	240,787 ± 96,327
Creatinine, mg/dL	0.9 [0.7-1.2]	0.8 [0.7-1.1]
Troponin	10.8 [4.1-33.2]	9.7 [3.4-30.5]
D-dimer, mg/L	1.0 [0.7-1.6]	1.0 [0.7-1.5]
C-reactive protein, mg/L	98.2 [48.9-159.6]	80.7 [42.8-145.9]
ESR, mm	89 [52-126]	89 [51.5-122.5]
LDH, U/L	336 [280-441]	326 [269-441]

[a]Data presented as n (%), mean ± SD, or median [IQR]. [b]Two or more of the following comorbidities: hypertension, diabetes, obesity, respiratory disease, smoking, cancer, HIV infection, and rheumatic disease.

of the dataset, the performance was evaluated by means of the AUC metric. Models such as MLP, the random forest method, and gradient boosting achieved similar performance levels. Of those, the random forest model without any oversampling method showed the highest median performance, although it was only slightly higher than the median performance of the other models. Given that this combination not only yielded the best performance but also entailed lower computational costs than did the other two methods, it was selected for further analysis.

The step of feature selection is also significantly important in the implementation of machine learning models. Additionally, when considering the practical aspects of implementing a process that will be directly dependent on data collection, it is useful to find the best trade-off between performance and number of features. First, to select which features can be useful for classification, one must have a measure of their importance in the overall performance of the algorithm. Different approaches can be used in order to extract feature importance in machine learning models, including permutation importance, SHAP, and mean decrease in impurity (MDI), the last being particularly suitable for models such as the random forest. MDI, also known as the Gini importance,

explores the structure of the random forest to evaluate feature importance. Given that a random forest is an ensemble learning algorithm based on decision trees, MDI counts the times a feature is used to split a node in a tree, weighted by the number of samples it splits. This allows us to identify how relevant a certain feature is for generating a prediction. By evaluating the MDI for the trained model, we identified the ten most important features (Figure 1).

The process of analyzing feature relevance helps reduce computational cost, and, by reducing the number of features, it is possible to decrease the probability of introducing undesired bias due to the size of the training dataset. However, it is still important to evaluate the performance of the model with different numbers of features. As can be seen in Figure 2A, ROC curves were plotted for three different scenarios: all features; the five most relevant features; and the ten most relevant features. The best performance in terms of AUC was achieved by the model containing the ten most relevant features. As can be seen in Figure 2B, a confusion matrix of the model containing the ten most relevant features shows the relationship between the output of the model and the RT-PCR results, highlighting each type of correct and incorrect prediction.

Table 2 presents key metrics that highlight the performance of the model across different feature

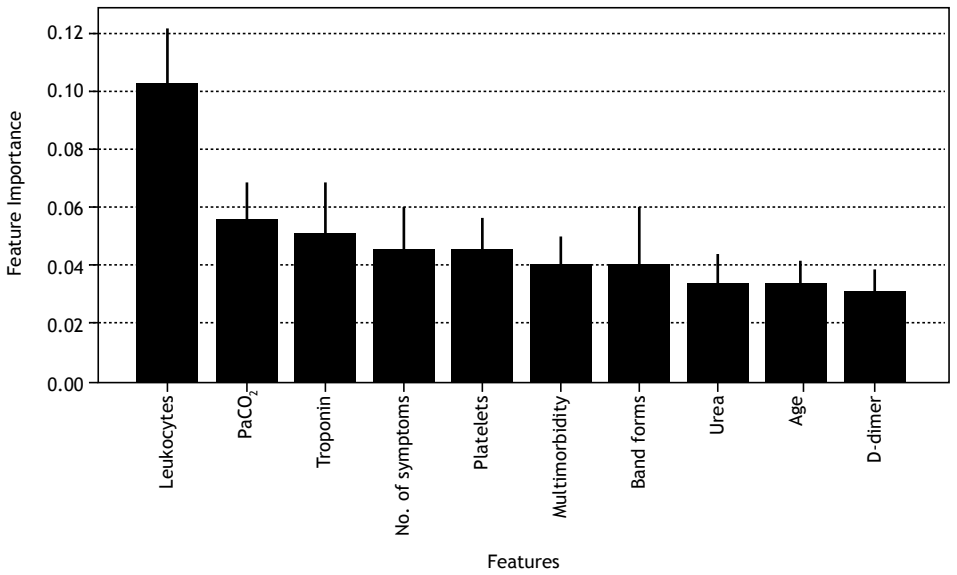

Figure 1. The ten most important features to diagnose COVID-19 with the use of a random forest algorithm.

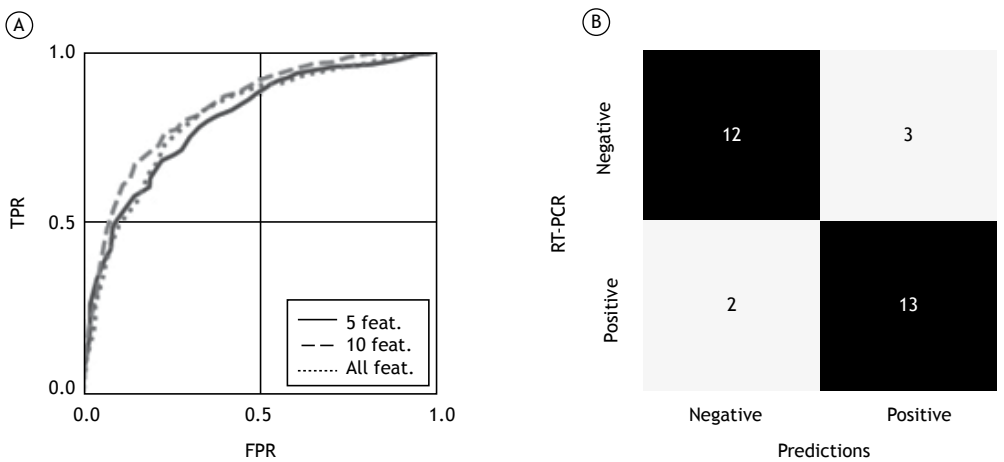

Figure 2. Random forest metrics. In A, ROC curves for different numbers of variables (all variables, five variables, and ten variables). In B, confusion matrix for the best model (i.e., the model including ten features). The ROC curve was plotted by averaging the ROC curves for 20 different trials, with random splits between training and test datasets. TPR: true-positive rate; and FPR: false-positive rate.

Table 2. Key metrics of the random forest classifier used in the present study, by number of features included.[a]

Number of variables	Sensitivity	Precision	F1 score	AUC
All	0.714 [0.642-0.827]	0.742 [0.618-0.818]	0.717 [0.689-0.752]	0.824 [0.796-0.856]
5	0.721 [0.673-0.825]	0.659 [0.612-0.717]	0.695 [0.661-0.743]	0.795 [0.706-0.820]
10	0.757 [0.659-0.822]	0.746 [0.667-0.862]	0.75 [0.694-0.776]	0.867 [0.832-0.894]

[a]Data expressed as median [IQR].

sets. Notably, when the ten most relevant features were used, the performance of the model improved not only in terms of AUC (as can be seen in Figure 2A) but also in terms of sensitivity. It is important to emphasize that the output of the model can be interpreted similarly to a probability, which allows the definition of a threshold (a value between 0 and 1) to determine whether a numerical output results in a positive or negative result. This provides flexibility to balance between sensitivity and precision, thus reducing the occurrence of false positives and false negatives. For the results presented herein, a threshold of 0.5 was considered.

DISCUSSION

Since the WHO declared COVID-19 a pandemic on March 12, 2020, health care systems worldwide faced intense strain. This raised the need for exploring new and emerging technologies to meet the increasing health demand. One important challenge was the scarcity of medical supplies and diagnostic tools, especially in the first year of the pandemic. The limited availability of resources, including COVID-19 diagnostic tests, highlighted the need for developing tools to identify patients with high clinical suspicion of COVID-19. In this context, AI techniques represent an efficient strategy for detection, severity assessment, and therapeutic approach.

In the last three years, many studies have investigated the role of imaging tests such as X-rays, CT scans, and ultrasound examination in the early diagnosis of COVID-19 through AI techniques.[18] On the other hand, the integration of clinical data into AI algorithms has been less studied and could represent an effective strategy to face the challenges of COVID-19, particularly in scenarios in which imaging tests are not readily available. Previous studies evaluating the use of AI in COVID-19 diagnosis showed accuracy values of approximately 85%.[19] Ahamad et al. reported that the most relevant predictive symptoms were fever (41.1%), cough (30.3%), lung infection (13.1%), and runny nose (8.43%).[20] Similarly, we found an accuracy of 84% when we included ten variables in the model. However, the most relevant predictors in our study were leukocyte count, $PaCO_2$, troponin levels, duration of symptoms in days, platelet count, multimorbidity, presence of band forms, urea levels, age, and D-dimer levels. In this context, Silveira found an association between blood count and COVID-19 diagnosis through a gradient boosting model, with an accuracy of 80.0%, a sensitivity of 75.6%, and a specificity of 82.0%.[21] The variables that had the greatest influence on the predictive decision were basophil count, eosinophil count, and leukocyte count.[21] It is important to highlight that our objective was to predict the probability of a COVID-19 diagnosis in patients hospitalized with SARS.

One of the main limitations of the present study is the relatively small number of samples, especially in comparison with most machine learning applications.[18-20] However, despite this limitation, the achieved performance demonstrates the value of the method as a useful tool for the health care system. To enhance the performance of the model, it is crucial to expand data collection to different municipalities. This would not only increase the size of the dataset but also improve the generalization capability of the model. Additionally, continuous retraining of the model would enable it to adapt to the evolving effects of the virus on the population. Such efforts would not only increase the impact of the model but also provide a deeper understanding of the long-term effects and behavior of the COVID-19 pandemic.

Although AI-based tools do not replace medical evaluation, their contribution is unequivocal in improving the management of several issues and health problems. Particularly in pandemic situations, AI-based tools can help to make rapid decisions related to the diagnosis and prevention of disease spreading. Thus, given that in the future the health care system might be faced with other pandemics, there is a need for continued improvement of AI technologies. Future studies should focus on strengthening current technologies to detect, monitor, and diagnose emerging and potentially life-threatening medical conditions.

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AUTHOR CONTRIBUTIONS

SECM, MBOF, OSK and MABC participated in the design of the study; in the analysis and interpretation of data; and in the writing and critical review of the article. RBN and FSM participated in the conception and design of the study; and in the acquisition, analysis, and interpretation of data. All authors approved the final version to be published.

CONFLICTS OF INTEREST

None declared.

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ORIGINAL ARTICLE

Timed "up and go" to identify physically inactive individuals with interstitial lung disease

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ABSTRACT

Objective: To investigate the relationship between the timed "up and go" (TUG) test and physical activity in daily life (PADL) in patients with interstitial lung disease (ILD) and propose a cutoff point to identify physically inactive individuals. **Methods:** Participants performed the TUG test at a usual pace (TUG_{usual}) and at a fast pace (TUG_{fast}). Exercise capacity was assessed by the six-minute walk test, lung function was assessed by whole-body plethysmography, quadriceps strength was assessed by maximal voluntary isometric contraction, and PADL was assessed by an activity monitor worn for six consecutive days. PADL variables included number of steps/day, time spent/day in activities of different intensities, and time spent/day in different postures. A ROC curve was plotted to identify physically inactive individuals on the basis of daily steps (5,000 steps/day) and moderate to vigorous physical activity (MVPA; 30 min/day). **Results:** Fifty-three ILD patients (26 women, with a mean age of 60 ± 11 years) were included in the study. TUG_{usual} and TUG_{fast} correlated moderately with the number of steps/day and time spent/day in light physical activity and MVPA ($-0.60 < r < -0.41$; $p < 0.05$ for all). ROC curves for TUG_{usual} showed that the cutoffs of ≥ 9.25 s and ≥ 7.9 s can identify physically inactive individuals on the basis of 5,000 steps/day (AUC: 0.73; sensitivity, 76%; specificity, 70%) and 30 min/day of MVPA (AUC: 0.85; sensitivity, 90%; specificity, 75%). Participants who performed worse on TUG_{usual} (i.e., ≥ 9.25 s) showed lower peripheral muscle strength, exercise capacity, and PADL. **Conclusions:** Performance on TUG_{usual} and TUG_{fast} correlates moderately with PADL in patients with ILD. A TUG_{usual} performance ≥ 9.25 s appears to be able to identify physically inactive individuals in this population.

Keywords: Physical functional performance; Lung diseases, interstitial; Activities of daily living.

INTRODUCTION

Patients with interstitial lung disease (ILD) can experience progressive loss of lung function and physical performance, as well as worsening of symptoms and deterioration in health-related quality of life.[1] It is increasingly recognized that extrapulmonary manifestations are associated with worse prognosis in patients with ILD.[2] Extrapulmonary manifestations include low levels of physical activity in daily life (PADL), which are known to be present in patients with respiratory conditions.[3] Inactivity plays a critical role in the vicious cycle of chronic respiratory diseases and is associated with worse prognosis in patients with idiopathic pulmonary fibrosis.[4]

Reduced exercise capacity and muscle strength are common in patients with ILD[5] and contribute to reducing their ability to perform daily functional tasks.[6] Therefore, in addition to PADL, functional performance is increasingly assessed in patients with chronic respiratory diseases,[7] mainly by functional tests such as the timed "up and go" (TUG) test. The TUG test is reliable in patients with ILD, assessing exercise capacity and muscle strength[8] through a series of tasks necessary for independent living, such as walking, sitting/standing, and changing directions[9] at a usual pace (TUG_{usual}) or as fast as possible (TUG_{fast}). In patients with chronic respiratory diseases other than ILD, the TUG test is used in order to assess functional mobility, walking ability, and dynamic balance,[10] as well as clinical outcomes such as the risk of falling.[11] Additionally, performance on the TUG test reflects disease severity and is responsive to pulmonary rehabilitation in patients with COPD.[12,13]

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Functional performance tests are generally simple and practical. Because accelerometers are not readily available in clinical practice, instruments that can accurately assess PADL in the clinical setting are important.[14,15] Functional performance and PADL have been reported in association with respiratory conditions.[16-18] However, there are currently no studies exploring the relationship between the TUG test and PADL in ILD patients. Therefore, a cutoff point to identify inactivity in ILD patients could guide clinicians in their decision to investigate PADL or intervene when necessary.

Given that the TUG test requires the ability to walk and perform movements that are commonly performed during activities of daily living, and given that patients with ILD show significantly lower levels of PADL than do those with other respiratory diseases,[19,20] we hypothesized that the TUG test might be associated with PADL and sedentary behavior in patients with ILD. Furthermore, we hypothesized that the performance of ILD patients on the TUG test could be used in order to identify physically inactive individuals. Therefore, the objective of the present study was to investigate the relationship between the TUG test and PADL in patients with ILD and propose a cutoff point to identify physically inactive individuals.

METHODS

This cross-sectional study was part of a larger trial conducted in the outpatient clinic of the University Hospital of the State University at Londrina, located in the city of Londrina, Brazil. The study was approved by the local institutional review board (CAAE no. 69598317.5.0000.5231), and all participants gave written informed consent.

The convenience sample included patients who had been diagnosed with ILD in accordance with international guidelines[21] and who had been clinically stable (i.e., with no respiratory exacerbations) for at least one month before recruitment. The inclusion criteria were being in the 40- to 75-year age bracket and being clinically able to undergo testing. Patients who at the time of testing presented with comorbidities that could affect their functional performance—comorbidities such as cognitive deficit and pain—were excluded, as were those who presented with respiratory diseases (as assessed by pulmonary function tests) and those who withdrew consent.

All participants answered a sociodemographic questionnaire. Participants then underwent the TUG test twice at a usual pace (TUG_{usual}) and twice at a fast pace (TUG_{fast}).[22] During the tests, individuals were requested to stand up from a chair; walk a distance of 3 m at a usual pace (TUG_{usual}) or as fast as possible (TUG_{fast}); and then turn and walk back to the chair at the same pace to sit down again.[23] TUG_{usual} reflects the majority of tasks performed in daily life and is the more commonly used test,[12] whereas TUG_{fast} reflects the greatest speed at which an individual can perform activities of daily living, being more closely associated with the risk of falls.[24]

Participants were allowed to use walking aids and oxygen.[25] For those who required oxygen therapy, a trained physical therapist was recruited to carry the oxygen delivery device.[25,26] The time in seconds to complete the test was recorded and used as the primary outcome measure. A stopwatch was used in order to time the tests. The stopwatch was started when participants got up from the chair and stopped when they sat down again after the three-meter walk.[8] Faster walking speeds indicated better mobility. The faster of two attempts was used for analysis of the TUG_{usual} and TUG_{fast} tests, in accordance with previous validation studies reporting a significant learning effect between tests.[8,25,26] Participants were allowed to rest between tests until their heart rate and SpO_2 returned to baseline values or until they confirmed that they were ready to proceed.[25] Reference equations for the Brazilian population were used in order to analyze performance on the TUG_{usual} and TUG_{fast} tests, expressed as a percentage of the predicted value.[27]

The levels of PADL were assessed with an activity monitor (wGT3X-BT®; ActiGraph LLC, Pensacola, FL, USA), which participants wore on their waist 24 h a day for six consecutive days. The aforementioned activity monitor has been validated for use in patients with respiratory diseases, being a reliable method to assess PADL.[28] The assessment was considered valid if participants wore the monitor for at least 8 h/day for four weekdays.[29] Participants were instructed to remove the monitor during water activities. The device measures wearing time and records daily steps, time spent in different postures (i.e., lying, sitting, and standing), and time spent in physical activity of different intensities during waking hours, as follows: sedentary behavior, < 1.5 metabolic equivalents of task (METs); light physical activity (LPA), between 1.5 and 3 METs; and moderate to vigorous physical activity (MVPA), > 3 METs.[29] Data on PADL were analyzed with ActiLife® software (ActiGraph LLC). Inactivity was defined as < 30 min/day of MVPA[30] and < 5,000 steps/day.[31,32]

Exercise capacity was evaluated by the six-minute walk test (6MWT), which was performed in accordance with international guidelines,[33] with a 30-min rest between tests. The longest six-minute walk distance (6MWD) was used for analysis, being compared with normative values. One week later, participants returned to the laboratory to return the activity monitor and undergo lung function and peripheral muscle strength assessment. Lung function was assessed by post-bronchodilator spirometry, whole-body plethysmography, and DL_{CO} measurement, all of which were performed with a Vmax plethysmograph (CareFusion, San Diego, CA, USA) and in accordance with international guidelines.[34-37] The obtained values were compared with normative data for the Brazilian population.[38] Quadriceps strength was assessed by maximal voluntary isometric contraction of the

dominant limb, with the use of a strain gauge (EMG System do Brasil, São José dos Campos, Brazil) attached to a multigym. Participants were instructed to perform a maximal voluntary isometric contraction for 6 s, with 90° hip and knee flexion. At least four and at most 15 attempts were made, and the highest value was used for analysis. Finally, handgrip strength of the dominant hand was evaluated with a handheld dynamometer (SH1001; Saehan Corporation, Changwon, South Korea). Three attempts were made with the arm unsupported and the elbow flexed at 90°,[39] and the highest value was used for analysis.

Statistical analysis

Statistical analysis was performed with the Statistical Analysis System, version 9.4 (SAS Institute Inc., Cary, NC, USA), and GraphPad Prism, version 6.0 (GraphPad Software, Inc., San Diego, CA, USA). Depending on the data distribution, variables are expressed as frequency (percentage), mean (standard deviation), or median [interquartile range]. Data normality was assessed by the Shapiro-Wilk test. Correlations among the TUG tests (TUG_{usual} and TUG_{fast}), number of daily steps, time spent in different postures (sitting, standing, and lying), and time spent in activities of different intensities (sedentary behavior, LPA, and MVPA) were made by using Spearman's correlation coefficient. To establish cutoffs to identify physically inactive individuals, a ROC curve analysis was performed. The AUC, as well as the sensitivity and specificity of the proposed cutoffs, were calculated. Relevant characteristics for ILD patients were compared on the basis of the proposed cutoff points by using the unpaired t-test or the Mann-Whitney test, depending on the data distribution. Values of $p < 0.05$ were considered significant.

RESULTS

A total of 55 patients with ILD were assessed. Of those, 53 were included in the present study (Figure 1). Of the 53 ILD patients included in the study, 49% had connective tissue disease-associated ILD and 41% had idiopathic pulmonary fibrosis. The characteristics of the study participants and their performance on TUG_{usual} and TUG_{fast} are described in Table 1. Significant correlations were found among TUG_{usual} and TUG_{fast} (in s and % of predicted), number of steps/day, LPA, MVPA, and time spent standing ($-0.59 < r < -0.31$; $p < 0.05$ for all). A complete description of correlations is provided in Table 2.

Twenty-nine ILD patients (55% of the sample) performed < 5,000 steps/day, and 49 (92%) performed < 30 min/day of MVPA. Analysis of the ROC curves showed that cutoffs of ≥ 9.25 s and ≥ 7.9 s on the TUG_{usual} test can identify physically inactive individuals on the basis of 5,000 steps/day (AUC: 0.73; sensitivity, 76%; specificity, 70%) and 30 min/day of MVPA (AUC: 0.85; sensitivity, 90%; specificity, 75%; Figure 2). Analysis of the ROC curves for TUG_{fast} in seconds and for TUG_{usual} and TUG_{fast} in % of predicted showed that they were less effective in distinguishing between physically active and physically inactive individuals (AUC: 0.60-0.79; sensitivity, 61-74%; specificity, 55-87%). Table 3 shows a complete description of sensitivity, specificity, and AUC values for TUG_{usual} and TUG_{fast} in seconds and % of predicted.

Thirty ILD patients (57% of the sample) showed a performance of ≥ 9.25 s on the TUG_{usual} test (the cutoff for < 5,000 steps/day), whereas 48 (91%) showed a performance of ≥ 7.9 s (the cutoff for < 30 min/day of MVPA). Table 4 shows the demographics of the sample, as well as data on exercise capacity, muscle strength, lung function, and PADL for the cutoff of ≥ 9.25 s. The ILD patients who performed worse on the TUG_{usual} test (i.e., ≥ 9.25 s) showed a lower number of steps/day ($p < 0.001$), less time spent in LPA ($p < 0.001$), less time spent in MVPA ($p = 0.0008$), and less time spent in a standing position ($p = 0.0005$), as well as more time spent in a lying position ($p = 0.003$), than did those who performed better. They also performed worse on the 6MWT and on the peripheral muscle strength assessment, with no significant differences in demographics and lung function.

DISCUSSION

In the present study, the TUG test was moderately correlated with PADL variables (i.e., number of steps/day, LPA, MVPA, and time spent standing) in patients with ILD. Although TUG_{usual} in seconds identified inactivity in ILD patients, TUG_{fast} did not. Additionally, our results show that a cutoff of ≥ 9.25 s can distinguish physically inactive individuals (i.e., those who walk < 5,000 steps/day) from individuals who are more active. Furthermore, we found that individuals who performed worse on the TUG_{usual} test (i.e., ≥ 9.25 s) were less active, more deconditioned, and weaker than those who performed better.

To date, only two studies[8,22] investigated the performance of ILD patients on TUG_{usual}. The mean duration of the test was 9.6 s in one of the studies and 9.8 s in the other, a finding that is consistent with those of the present study. The two aforementioned studies also investigated the correlations between performance on the TUG test and clinical outcomes.[8,22]. One of the studies[22] found that TUG_{usual} correlated weakly with quadriceps femoris strength ($r = -0.28$; $p = 0.164$) and the 6MWD ($r = 0.37$; $p = 0.062$), whereas the other found that TUG_{usual} correlated moderately with quadriceps strength ($r = -0.48$; $p < 0.05$) and the 6MWD ($r = -0.69$; $p < 0.05$).[8] The results of the present study expand the current knowledge regarding clinical associations of the TUG test, showing its association with PADL variables. In fact, the present study appears to be the first to show that a poor performance on the TUG test is associated with worse patterns of PADL in ILD patients. Given that PADL plays an important role in

the morbidity and mortality of ILD,[4] identification of a poor performance on the TUG test could guide clinicians in their decision to seek a more specific assessment of PADL in this population.

The predictive power of the TUG test for different clinical outcomes has been demonstrated in patients with COPD.[25] The aforementioned study[25] showed that patient performance on the TUG test (i.e., > 11.2 s) has acceptable specificity and sensitivity to predict lower exercise capacity (i.e., a 6MWD of < 350 m). Despite the differences between the cutoffs for COPD and those for ILD proposed in the present study, there is currently no cutoff point to identify (in)activity in patients with ILD. Although functional performance tests such as the Glittre Activities of Daily Living test have been shown to correlate moderately with total energy expenditure,[18] no other PADL variable has been shown to correlate with such tests. To the best of our knowledge, the present study is the first to propose cutoffs to identify ILD patients as inactive on the basis of their performance on a simple functional test.

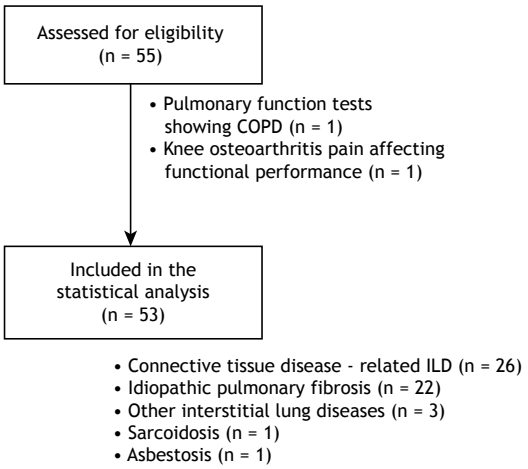

Figure 1. Study flowchart. ILD: Interstitial lung disease.

Table 1. Characteristics of the study sample.[a]

Variable	Patients with ILD (n = 53)
Sex, female	26 (49)
Age, years	60 ± 11
BMI (kg/m^2)	27 [25-30]
Lung function	
FVC, % of predicted	68 ± 17
FEV_1, % of predicted	69 ± 18
FEV_1/FVC ratio	84 [78-87]
DL_{CO}, % of predicted	45 ± 18
Physical activity in daily life	
Sedentary behavior, min/day	742 ± 178
LPA, min/day	298 ± 92
MVPA, min/day	8.8 [2.8-14.0]
Steps, n/day	4,874 ± 1,858
Time spent standing, min/day	290 ± 82
Time spent lying, min/day	295 [228-337]
Time spent sitting, min/day	441 ± 100
Functional performance	
TUG_{usual}, s % of predicted	9.7 ± 1.4 102 [95-114]
TUG_{fast}, s % of predicted	7.7 ± 1.1 104 [95-119]
Exercise capacity	
6MWD, m	449 ± 101
6MWD, % of predicted	81 ± 20
Peripheral muscle strength	
Quadriceps strength, N	271 [227-309]

ILD: interstitial lung disease; LPA: physical activity; MVPA: moderate to vigorous physical activity; TUG_{usual}: timed "up and go" at a usual pace; TUG_{fast}: timed "up and go" at a fast pace; and 6MWD: six-minute walk distance. [a]Data presented as n (%), mean ± SD, or median [IQR].

The TUG_{usual} cutoffs of ≥ 9.25 s (for 5,000 steps/day) and ≥ 7.9 s (for 30 min/day of MVPA) can effectively stratify ILD patients into active and inactive individuals, whereas TUG_{fast} is less effective in identifying inactivity in ILD patients. Similar to accelerometry, TUG_{usual} assesses the speed at which patients with ILD perform daily tasks. This similarity might explain the lack of significance for TUG_{fast} in the present study. When accelerometers are unavailable in clinical practice, TUG_{usual} can be used in order to identify inactive ILD patients and should be preferred over TUG_{fast}. In a study of patients with various respiratory diseases, velocities below 1.07 m/s on the four-meter gait speed test were found to be able to identify inactive individuals.[16] However, patients with ILD show worse prognosis than do those with other respiratory diseases,[1] and the aforementioned cutoff point might therefore not be suitable for ILD patients. According to the authors, one of the limitations of the aforementioned study[16] was that only individuals who did not need oxygen therapy were included. This is perhaps more important for patients with ILD than for those with other diseases, given that oxygen desaturation during exertion is very common. The present study therefore expands on the knowledge of the impact of poor performance on functional tests in patients with ILD.[16,18]

In the present study, a worse performance on TUG_{usual} did not seem to discriminate between different severities of ILD (i.e., lung function). There was no difference between individuals with better or worse performance on the TUG test regarding lung function. This is in disagreement with previous studies reporting that a worse performance on functional tests is associated with worse clinical status in patients with chronic respiratory diseases.[13,16] However, the results of the present study show that performance on the TUG test can identify lower exercise capacity and peripheral muscle strength. Although the proposed cutoffs appear to be able to identify inactive individuals, these findings cannot be extrapolated to a better/worse overall health status. Further studies are needed to confirm whether a worse performance on TUG_{usual} is also associated with other important outcomes in patients with ILD, such as health-related quality of life.

Table 2. Correlation of the timed "up and go" test performed at a usual pace and at a fast pace with physical activity in daily life variables.

Variable	TUG_{usual}		TUG_{fast}	
	seconds	% of predicted	seconds	% of predicted
Sedentary behavior, min/day	0.02	0.01	0.12	0.16
LPA, min/day	−0.46*	−0.40*	−0.42*	−0.30*
MVPA, min/day	−0.59*	−0.55*	−0.47*	−0.35*
Steps, n/day	−0.58*	−0.45*	−0.51*	−0.31*
Time spent standing, min/day	−0.36*	−0.22	−0.25	−0.08
Time spent lying, min/day	0.12	0.06	0.05	0.04
Time spent sitting, min/day	−0.09	−0.13	−0.18	−0.29

TUG_{usual}: timed "up and go" at a usual pace; TUG_{fast}: timed "up and go" at a fast pace; LPA: light physical activity; and MVPA: moderate to vigorous physical activity. *p < 0.05.

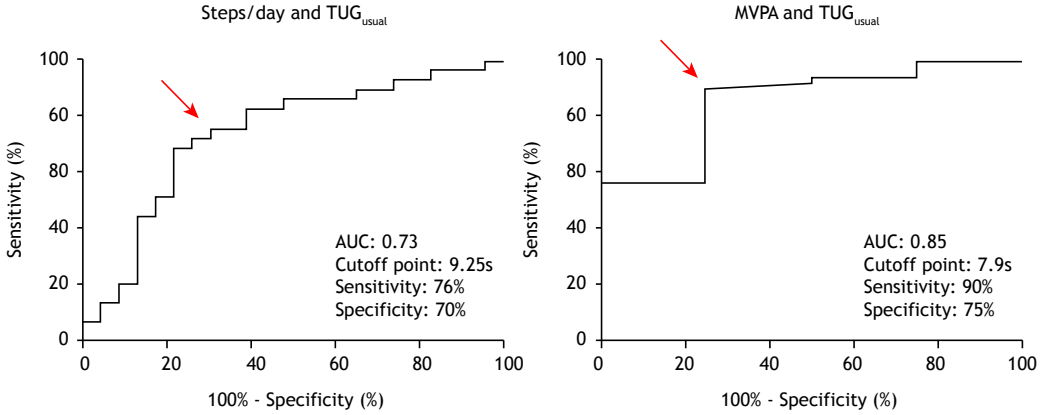

Figure 2. Area under the curve for the timed "up and go" test performed at a usual pace (TUG_{usual}): cutoff points for the number of steps/day and time/day spent in moderate to vigorous physical activity (MVPA).

Table 3. Cutoff points, area under the curve, sensitivity, and specificity for the timed "up and go" test performed at a usual pace and at a fast pace to identify physically inactive individuals with interstitial lung disease.

Variable	TUG_{usual}		TUG_{fast}	
	seconds	% of predicted	seconds	% of predicted
< 5,000 steps/day				
Cutoff point	9.25	101%	7.6	104%
AUC	0.73	0.65	0.69	0.60
95% CI	059-0.87	0.50-0.80	0.54-0.85	0.44-0.76
Sensitivity	76%	62%	66%	61%
Specificity	70%	64%	74%	55%
p	0.003	0.05	0.01	0.20
< 30 min/day of MVPA				
Cutoff point	7.9	90%	8.2	90%
AUC	0.85	0.79	0.69	0.79
95% CI	0.67-1.0	0.63-0.95	0.29-1.0	0.63-0.95
Sensitivity	90%	67%	74%	66%
Specificity	75%	87%	75%	87%
p	0.02	0.09	0.21	0.09

TUG_{usual}: timed "up and go" at a usual pace; TUG_{fast}: timed "up and go" at a fast pace; and MVPA: moderate to vigorous physical activity. *p < 0.05.

The results of the present study should be interpreted with potential limitations in mind. First, the sample size was relatively small. Although this limits the external validity of our findings, our sample size is similar to those in previous studies examining PADL and functional performance tests in patients with ILD.[16,18] In addition, it should be borne in mind that ILD is less prevalent than other respiratory diseases such as COPD and asthma, making recruitment more difficult. Given that the sample size also has an impact on ROC curves, larger samples might be useful to strengthen our findings regarding the discriminative capacity of TUG_{usual} to identify physically inactive individuals. Although TUG_{usual} can estimate inactivity

Table 4. Characteristics of the interstitial lung disease patients who performed worse (≥ 9.25 s) or better (< 9.25 s) on the timed "up and go" test performed at a usual pace, as assessed by ROC curves.[a]

Variable	Worse (slower) performance (n = 30)	Better (faster) performance (n = 23)	p
Sex, female	18 (60)	8 (35)	0.06
Age, years	64 [57-70]	56 [47-67]	0.14
BMI, kg/m^2	27 [25-30]	27 [23-30]	0.58
Lung function			
FVC, % of predicted	66 ± 21	69 ± 12	0.58
FEV_1, % of predicted	69 ± 21	69 ± 14	0.93
FEV_1/FVC ratio	84 ± 6	89 ± 9	0.05
DL_{CO}, % of predicted	42 ± 19	48 ± 18	0.29
Physical activity in daily life			
Sedentary behavior, min/day	756 ± 195	720 ± 159	0.42
LPA, min/day	254 ± 88	360 ± 78	< 0.001
MVPA, min/day	4.1 [1.1-9.2]	10.4 [8.8-21.7]	0.0008
Steps, n/day	4,041 ± 1,787	6,001 ±1,414	< 0.001
Time spent standing, min/day	255 ± 69	333 ± 78	0.0005
Time spent lying time, min/day	334 ± 137	266 ± 59	0.003
Time spent sitting time, min/day	428 ± 109	456 ± 87	0.33
Exercise capacity			
6MWD, m	389 ± 68	532 ± 79	< 0.001
6MWD, % of predicted	75 ± 14	90 ± 23	< 0.001
Peripheral muscle strength			
Quadriceps strength, N	271 [227-309]	417 [284-477]	0.001
Handgrip strength, kgf	21 [18-25]	28 [22-35]	0.005

LPA: physical activity; MVPA: moderate to vigorous physical activity; and 6MWD: six-minute walk distance. [a]Data presented as n (%), mean ± SD, or median [IQR].

on the basis of the number of steps/day and the time/day spent in MVPA, it should not be the method of choice when other, more accurate methods are available to assess PADL.

Second, TUG_{usual}, TUG_{fast}, and the 6MWT were performed within the same period, and the effort required to complete the TUG test may have influenced patient performance on the 6MWT. However, the order of execution was standardized, the protocol adhered to the recommended rest intervals, and baseline values of heart rate, SpO_2, dyspnea, and sensation of fatigue were controlled before the two 6MWTs were performed.

Third, the individuals included in the present study do not cover the entire spectrum of severities and subgroups of ILD. Most of the study participants had connective tissue disease-associated ILD or idiopathic pulmonary fibrosis (49% and 41%, respectively). Although the disease can influence progression, pulmonary manifestations, and extrapulmonary manifestations, the results for these two subgroups were similar in the present study. In addition, only one patient required oxygen therapy during the TUG tests, and only 8% of the study sample met the criterion of performing at least 30 min/day of MVPA. This may have influenced the findings regarding MVPA in the present study. Therefore, the cutoff points for TUG_{usual} might not accurately reflect PADL levels in ILD patients with different characteristics, in those with different disease severities, and in those receiving oxygen therapy. Future prospective studies might be able to address whether the cutoffs proposed in the present study are related to worsening lung function and are valid to assess negative clinical outcomes such as hospitalization and mortality.

In conclusion, performance on TUG_{usual} and TUG_{fast} correlates moderately with PADL in patients with ILD. A TUG_{usual} performance ≥ 9.25 s appears to be able to identify physically inactive individuals in this population.

AUTHOR CONTRIBUTIONS

CLZ: conceptualization, methodology, investigation, formal analysis, and writing—original draft. LDB: methodology, investigation, formal analysis, and visualization. GGK: methodology, investigation, visualization, and revision of the manuscript. HS: investigation, visualization, formal analysis, and revision of the manuscript. HAP and EGJ: investigation and visualization. FP: methodology, visualization, and writing—review and editing. CAC: conceptualization, project administration, methodology, supervision, and writing—review and editing. All authors approved the final version of the manuscript.

CONFLICTS OF INTEREST

None declared.

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ORIGINAL ARTICLE

Relationships that perceived barriers to physical activity have with functional capacity and quality of life in patients with pulmonary hypertension

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ABSTRACT

Objective: Barriers to physical activity can affect the functional capacity and quality of life of patients with pulmonary hypertension (PH). This study aimed to identify the main barriers to physical activity in patients with PH and to examine whether those barriers are related to functional capacity, echocardiographic variables, or quality of life. **Methods:** This was a cross-sectional observational study involving 70 patients. Participants scored seven potential barriers to their activities, with a score ≥ 5 indicating a significant barrier. Participants completed the Medical Outcomes Study 36-item Short-Form Health Survey (SF-36) and Manchester Respiratory Activity of Daily Living questionnaire, as well as the six-minute walk test. Correlation analysis, univariate analysis and multiple logistic regression were performed. **Results:** As a perceived barrier to physical activity, 'lack of will' or 'lack of energy' was cited by 67% of the patients. The 'lack of will' barrier was found to correlate with all SF-36 domains except bodily pain. We also identified a correlation between the SF-36 vitality domain and the barriers 'lack of energy', 'lack of will' and 'lack of structure'. The logistic regression analysis indicated that the vitality domain correlated significantly with the barriers 'social influence', 'lack of energy', 'lack of will', and 'lack of structure'. For each unit decrease in the vitality score, there was a 10% increase in the probability of citing the barrier 'lack of will'. No significant correlations were identified between any of the perceived barriers and echocardiographic parameters. **Conclusions:** The perceived barrier most commonly reported was 'lack of will/energy', which correlated with almost all SF-36 domains, especially vitality. The 'lack of will' barrier also correlated with functional capacity.

Keywords: Pulmonary arterial hypertension; Exercise; Motivation; Quality of life; Surveys and questionnaires; Walk test.

INTRODUCTION

Patients with pulmonary hypertension (PH) engage in less physical activity than do individuals with similar demographics.[1] A variety of tools have been employed to assess reduced physical activity, including accelerometers to count daily steps[2,3]; measures of daily energy expenditure and time spent in moderate-intensity activities[3]; and determination of the prevalence of sedentary behaviour.[4] Studies have found that reduced physical activity correlates with self-reported feelings of fatigue[1] and reduced functional capacity, as measured with the six-minute walk test (6MWT) or one-minute sit-to-stand test.[2]

Reductions in physical activity are primarily attributed to haemodynamic and functional limitations. Psychological factors, such as depression, anxiety and fear of exercise, can contribute significantly to an increase in sedentary behaviour.[5] However, in clinical practice, health professionals often overlook these aspects for a variety of reasons, including time constraints during consultations, pressure on care processes, unfamiliarity with therapeutic options, uncertainty about the safety of exercise, and a lack of referral services for physical activity.

Cascino et al.[6] conducted a study on the factors that contribute to low levels of physical activity in patients with PH, despite recommendations.[7] The study found that health care professionals and patients both lack information on the subject, and questions about the safety and effectiveness of exercise may contribute to the non-referral of patients with PH to exercise programmes. In addition, individuals with PH often face barriers such as low energy levels, lack of motivation and lack of self-discipline, which are associated with low levels of physical activity.[8]

Given the scenario described above, the aim of this study was to identify the main barriers to physical activity in patients with PH and to investigate whether these

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barriers correlate with demographics or the functional class of dyspnoea. It is also worth investigating whether the barriers identified correlate with physical activity levels, functional capacity, echocardiographic variables, or quality of life.

METHODS

Settings

This was a single-centre, cross-sectional observational study conducted between March of 2016 and August of 2021. The sample included in the study was a convenience sample of patients recruited from the PH database of the Pulmonary Vascular Disease Clinic of the Department of Pulmonology of the Hospital de Clínicas, operated by the University of Campinas, in the city of Campinas, Brazil. During the study period, all patients diagnosed with pulmonary arterial hypertension (PAH) or chronic thromboembolic pulmonary hypertension (CTEPH) were screened for eligibility, after which inclusion and exclusion criteria were applied. The study was approved by the Research Ethics Committee of the University of Campinas School of Medical Sciences (Reference nos. 76543617.9.0000.5404 and 28808719.1.0000.5404). All participating patients gave written informed consent.

Participants

Patients were considered eligible if they were between 18 and 70 years of age, had been diagnosed with PH, classified as World Health Organization group 1 (PAH) or group 4 (CTEPH),[9] and were stable at New York Heart Association functional class I-III without adjustment to vasodilator therapy for > 60 days. Patients with a diagnosis of depression were excluded, as were those with any cognitive impairment that might make them unable to complete the questionnaires and those with mobility impairments or any muscular or neurological condition that affected their ability to walk or to engage in physical activity.

Procedures and variables analysed

Patient records were reviewed to collect clinical data, including those related to demographics, comorbidities and medications. Additionally, echocardiographic data was examined, encompassing measurements of tricuspid regurgitation velocity, systolic pulmonary arterial pressure, tricuspid annular plane systolic excursion, right atrial pressure, right ventricular (RV) strain and S wave velocity.

The six-minute walk test (6MWT) and all three of the questionnaires used were completed on the same day. The instruments employed were the Perceived Barriers to Physical Activity Questionnaire (PBPAQ), the Medical Outcomes Study 36-item Short-Form Health Survey (SF-36), and the Manchester Respiratory Activities of Daily Living questionnaire (MRADL).[10-12]

The PBPAQ, created in Brazilian Portuguese,[10] assesses seven domains considered to be potential barriers to physical activity: 'lack of time'; 'social influence'; 'lack of energy'; 'lack of will'; 'fear of injury'; 'lack of ability'; and 'lack of structure'. Each domain consists of three questions, each of which is scored on a scale from zero to three, resulting in a domain score range of zero to nine, with a score of five or above indicating a significant barrier. The linear correlation was calculated on the basis of the total scores obtained for each domain.

The SF-36 is a validated, generic 36-item questionnaire that assesses eight domains: physical functioning; role-physical; bodily pain; general health; vitality; social functioning; role-emotional; and mental health. Scores range from 0 to 100, with lower scores indicating poorer health. The SF-36 has been translated to Portuguese and validated for use in Brazil.[11]

The MRADL is a 21-item scale that measures physical disability and impairment of activities of daily living (ADL) in respiratory disease in four domains: mobility (seven items); kitchen activities (four items); housework (six items); and leisure activities (four items). A perfect total score indicates the absence of any physical disability. The MRADL has also been translated to Portuguese and has been cross-culturally adapted for use in Brazil.[12]

The 6MWT was performed under the supervision of the same technician according to American Thoracic Society guidelines.[13] The six-minute walk distance (6MWD) was assessed in metres and as a percentage of the predicted value according to a reference equation validated for the Brazilian population.[14]

STATISTICAL ANALYSIS

To describe the characteristics of the sample, frequency tables were constructed for the categorical variables, showing the absolute and relative frequencies. In addition, descriptive statistics were calculated for the numerical variables, including mean, standard deviation, minimum/maximum values, interquartile range and median. Initial comparisons among groups, stratified by score (≥ 5) for each barrier, to identify potential differences in age, sex, BMI, 6MWD, SF-36 scores and MRADL scores, were performed with the Mann-Whitney test. The chi-square test and Fisher's exact test were used to test for associations between categorical variables.

Spearman's correlation coefficient was employed to assess the associations between numerical variables. Univariate and multiple logistic regression analyses were used in order to identify the variables associated with the outcome of interest (a PBPAQ score ≥ 5), including sex, age, functional class, BMI and SF-36 by domain. A stepwise procedure was used in order to select variables. In this process, all possible combinations between variables were examined, with the optimal combination being identified on the basis of the p-value. Bivariate correlations between echocardiographic variables and barriers to physical

activity and quality of life were examined by using Pearson's correlation coefficient for normally distributed data and Spearman's correlation coefficient for non-normally distributed data.

The significance level for all statistical tests was set at 5%. Analyses were performed using the Statistical Analysis System, version 9.4 for Windows (SAS Institute Inc., Cary, NC, USA), the Jamovi project (2022) software, version 2.3, (https://www.jamovi.org) and the statistical package R, version 4.1 (R Development Core Team, 2021).

RESULTS

Of a total of 169 patients recruited, 124 were eligible for inclusion. After the study criteria had been applied, only 70 patients (50 with PAH and 20 with CTEPH) were included and underwent all procedures. Figure 1 shows the recruitment and enrolment process. The mean age of the patients was 44 years, and the majority were women. The baseline demographic, clinical, echocardiographic, and 6MWT data are detailed in Table 1.

Using the PBPAQ, we were able to identify the factors most commonly reported by patients as barriers to exercise. 'Lack of will' and 'lack of energy' were the most common barriers cited by the patients in both groups (Figure 2). Taking into account their semantic similarity and removing overlap (patients who mentioned both reasons at the same time), we found that 67% of all patients mentioned 'lack of will', 'lack of energy' or both as a barrier to physical activity.

'Fear of injury' was cited by 32.8% of the patients, 'lack of structure' was cited by 19.4% and 'social influence', which includes a lack of partners or their encouragement to exercise and embarrassment about exercising, was cited by 20.9%.

Table 2 shows the results of the questionnaires used. In relation to the SF-36 quality of life questionnaire, the domains physical functioning, role-physical and general health were the most affected domains, whereas the role-emotional and mental health domains were moderately affected. Notably, the MRADL questionnaire indicated no significant impairment in the majority of the patients.

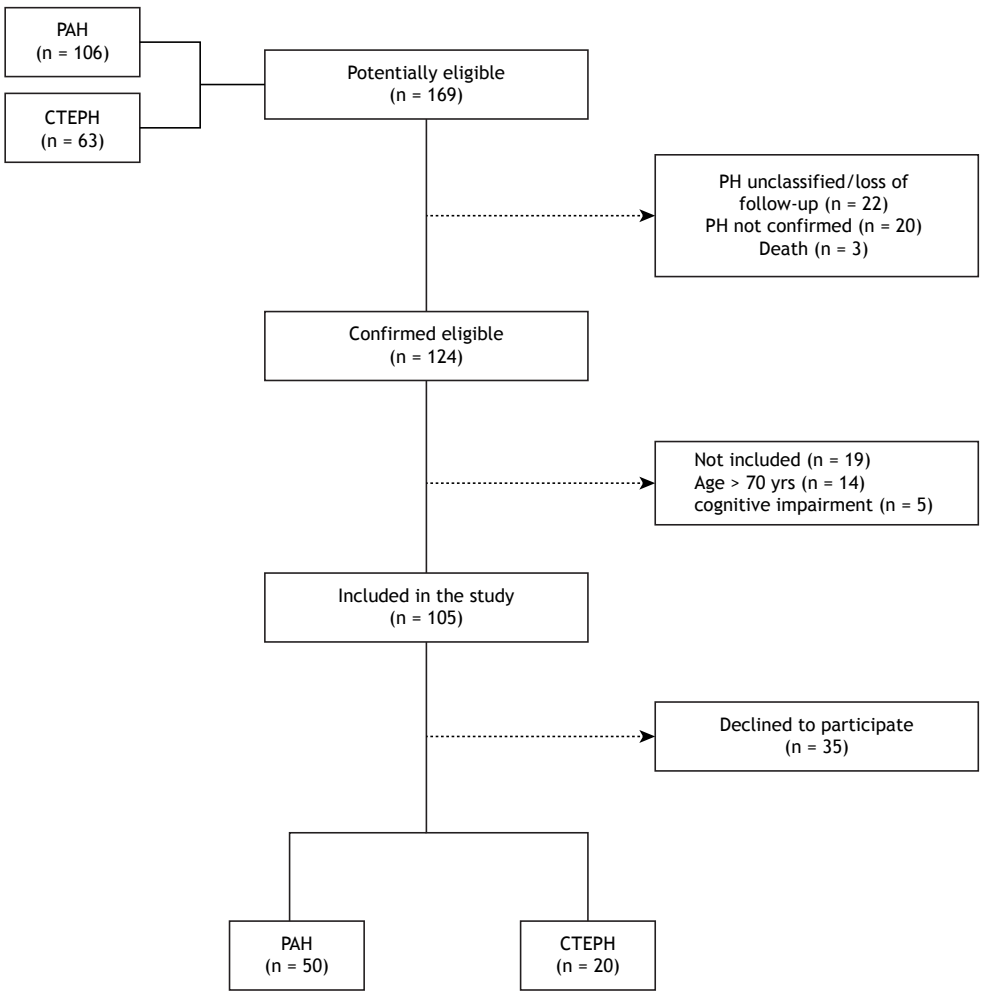

Figure 1. Recruitment flow chart. PAH: pulmonary arterial hypertension; CTEPH: chronic thromboembolic pulmonary hypertension; and PH: pulmonary hypertension.

Table 1. Baseline characteristics of patients with pulmonary hypertension.

Characteristic		(N = 70)
Age (years), mean ± SD		44.0 ± 13.1
Female, n (%)		54 (77.1)
BMI (kg/m^2), mean ± SD		27.3 ± 6.1
PH classification, n (%)	Idiopathic PAH	30 (42.9)
	PAH associated with connective tissue diseases	11 (15.7)
	PAH associated with congenital heart diseases	9 (12.9)
	CTEPH	20 (28.6)
Functional class (NYHA), n (%)	I	24 (34.3)
	II	31 (44.3)
	III	14 (20.0)
	IV	1 (1.4)
	I + II	55 (78.6)
	III + IV	15 (21.4)
Comorbidities*		46 (65.7)
Echocardiography variables	TRV (m/s)	3.9 ± 0.7
	SPAP (mmHg)	73.4 ± 24.9
	TAPSE (mm)	18.2 ± 3.9
	RAP (mmHg)	9.6 ± 3.6
	RV strain	15.9 ± 4.0
	S wave velocity	10.2± 2.3
Treatment	Monotherapy (sildenafil or ambrisentan or bosentan)	21 (30.0)
	Combination therapy (sildenafil plus ambrisentan or bosentan)	41 (58.6)
	No specific therapy	6 (8.6)
	Use of anticoagulation	42 (60.0)
6MWT†	6MWD (m)	
	Mean ± SD	439.00 ± 98.61
	Median (IQR)	447.50 (134.50)
	6MWD (% of predicted‡), mean ± SD	73.96 ± 17.60
	6MWD > 440 m, n (%)	34 (55.7)
	SpO_2 (basal, %), mean ± SD	94.00 ± 3.83
	SpO_2 (6th min, %), mean ± SD	82.13 ± 17.73
	ΔSpO_2 (%), mean ± SD	9.38 ± 7.54

PAH: pulmonary arterial hypertension; CTEPH: chronic thromboembolic pulmonary hypertension; NYHA: New York Heart Association; TRV: tricuspid regurgitation velocity; SPAP: systolic pulmonary arterial pressure; TAPSE: tricuspid annular plane systolic excursion; RAP: right atrial pressure; RV: right ventricle; 6MWT: six-minute walk test; and 6MWD: six-minute walk distance. *In both groups—anxiety, arrhythmia, asthma, ascending aortic aneurysm, chronic kidney disease, depression, diabetes mellitus, dyslipidemia, gout, hypothyroidism, obesity, systemic arterial hypertension, rheumatoid arthritis, polyarthritis, portal hypertension, fibrosing interstitial pneumonia, schistosomiasis, thrombocytopenic purpura, and thrombophilia; in the CTEPH group only—mutation in the prothrombin gene, anti-phospholipid syndrome, heterozygous factor V Leiden mutation, and anti-thrombin deficiency. †6MWT: data available for only 68 patients. ‡Reference equations for 6MWD taken from Iwama et al.[14]

Table 3 summarises the results of the comparisons between the groups, stratified by barriers with a score ≥ 5, by domain. It is of note that women were more likely to cite 'lack of energy' as a barrier to exercising. In addition, older patients cited 'social influence' as a significant barrier. It is also noteworthy that patients who more frequently reported 'lack of will' as a barrier had more dyspnoea (functional class III or IV) and walked shorter distances on the 6MWT.

The main results of the multivariate regression are presented in Table 4. In summary, the SF-36 vitality domain retained its significance and increased the likelihood of the significant barrier cited being 'social influence' (OR = 1.040; 95% CI: 1.006-1.073), 'lack of energy' (OR = 1.036; 95% CI: 1.006-1.067), 'lack of will' (OR = 1.101; 95% CI: 1.049-1.156) or 'lack of structure' (OR = 1.055; 95% CI: 1.016-1.095). The logistic regression analysis confirmed the association between the 'lack of will' barrier and the vitality domain of the SF-36, indicating that for each unit decrease in the vitality score, the likelihood of the patient citing 'lack of will' as a significant barrier increased by 10.1%. Together, the age and vitality domains of the SF-36 were found to increase the likelihood that the 'social influence' barrier would have a significant effect (score ≥ 5): for age, each advancing year increases that likelihood by 6.2%.The full analysis can be found in the supplementary material.

The Spearman's correlation coefficient analysis between the SF-36 and PBPAQ scores revealed that the

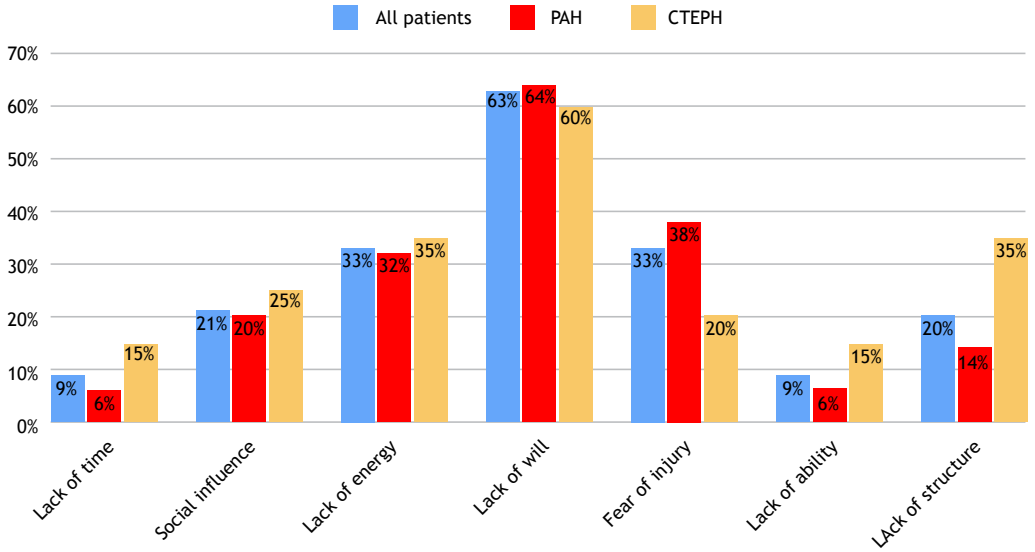

Figure 2. Perceived barriers to physical activity in patients with pulmonary arterial hypertension (PAH) and in patients with chronic thromboembolic pulmonary hypertension (CTEPH).

Table 2. Questionnaire results in patients with pulmonary hypertension (N = 70).

Questionnaire	Subcategory	Median	IQR	Range
SF-36 (score 0-100)*	Physical functioning	45.00	33.75	0-95
	Role-physical	62.50	100.00	0-100
	Bodily pain	62.00	58.75	10-100
	General health	38.50	25.38	0-77
	Vitality	60.00	25.00	10-100
	Social functioning	87.50	50.00	12.5-100
	Role-emotional	83.35	100.00	0-100
	Mental health	58.00	35.00	0-100
PBPAQ (score 0-9)	Lack of time	0.00	2.00	0-9
	Social influence	3.00	3.75	0-8
	Lack of energy	2.00	5.75	0-9
	Lack of will	6.00	3.00	0-9
	Fear of injury	2.00	6.00	0-9
	Lack of ability	0.00	3.00	0-7
	Lack of structure	3.00	1.00	0-9
MRADL (score 0-21)†		18.00	5.00	7-21

SF-36: Medical Outcomes Study 36-item Short-Form Health Survey; PBPAQ: Perceived Barriers to Physical Activity Questionnaire; and MRADL: Manchester Respiratory Activities of Daily Living. *A lower score indicates worse health status. †Maximum score = no physical disability.

SF-36 vitality domain showed moderate correlations with the barriers 'lack of energy' ($\rho = -0.395$; $p = 0.001$), 'lack of will' ($\rho = -0.569$; $p < 0.0001$) and 'lack of structure' ($\rho = -0.459$; $p < 0.0001$), whereas it showed a weak correlation with the 'social influence' barrier ($\rho = -0.291$; $p = 0.015$). The barrier 'lack of will' showed moderate correlations with all SF-36 domains except bodily pain. The full results of these analyses are presented in the online supplementary material.

None of the echocardiogram variables were found to correlate significantly with any of the perceived barriers. Pearson's correlation test revealed that the SF-36 physical functioning domain showed a moderate positive correlation with S wave velocity ($R = 0.589$; $p < 0.001$) and with RV strain ($R = 0.593$). In addition, a moderate positive correlation was observed between the role-physical domain of the SF-36 and RV strain ($\rho = 0.603$; $p < 0.05$), whereas a strong positive correlation was observed between the MRADL score and RV strain ($\rho = 0.822$; $p < 0.001$).

DISCUSSION

Our results show that 67% of the PAH patients identified lack of energy and unwillingness as relevant barriers to exercise. Correlations were found between certain barriers and specific SF-36 domains, vitality in particular. The vitality subscale of the SF-36 measures subjective well-being and consists of four items assessing vitality, energy level and fatigue.

Table 3. Comparison among groups, stratified by barriers to physical activity with a score ≥ 5, by domain.

Barrier	Variable	Barrier score		p-value
		< 5	≥ 5	
Lack of time (n = 6)	Age (years), mean ± SD	44.41 ± 13.48	39.33 ± 5.99	0.350*
	Female, n (%)	48 (75.0)	6 (100.0)	0.325‡
	FC I + II, n (%)	49 (76.6)	6 (100.0)	0.329‡
	FC III + IV, n (%)	15 (23.4)	0 (0.0)	
	6MWD (m), mean ± SD	430.77 ± 96.42	464.50 ± 115.75	0.209*
Social influence (n = 15)	Age (years), mean ± SD	42.35 ± 12.90	49.93 ± 12.27	0.023*
	Female, n (%)	43 (78.2)	11 (73.3)	0.734‡
	FC I + II, n (%)	45 (81.8)	10 (66.7)	0.286‡
	FC III + IV, n (%)	10 (18.2)	5 (33.3)	
	6MWD (m), mean ± SD	442.08 ± 94.22	404.33 ± 107.59	0.321*
Lack of energy (n = 23)	Age (years), mean ± SD	45.17 ± 14.01	41.52 ± 10.73	0.378*
	Female, n (%)	33 (70.2)	21 (91.3)	0.048†
	FC I + II, n (%)	39 (83.0)	16 (69.6)	
	FC III + IV, n (%)	8 (17.0)	7 (30.4)	0.226‡
	6MWD (m), mean ± SD	441.76 ± 96.20	417.00 ± 101.14	0.478*
Lack of will (n = 44)	Age (years), mean ± SD	46.62 ± 15.73	42.41 ± 11.09	0.293*
	Female, n (%)	19 (73.1)	35 (79.5)	0.534†
	FC I + II, n (%)	25 (96.2)	30 (68.2)	0.006†
	FC III + IV, n (%)	1 (3.8)	14 (31.8)	
	6MWD (m), mean ± SD	478.46 ± 99.75	406.07 ± 86.60	0.001*
Fear of injury (n = 23)	Age (years), mean ± SD	44.13 ± 13.05	43.65 ± 13.36	0.905*
	Female, n (%)	36 (76.6)	18 (78.3)	0.876†
	FC I + II, n (%)	40 (85.1)	15 (65.2)	0.070‡
	FC III + IV, n (%)	7 (14.9)	8 (34.8)	
	6MWD (m), mean ± SD	434.83 ± 91.12	431.33 ± 113.63	0.958*
Lack of ability (n = 6)	Age (years), mean ± SD	43.58 ± 13.41	48.17 ± 8.13	0.324*
	Female, n (%)	49 (76.6)	5 (83.3)	1.000‡
	FC I + II, n (%)	53 (82.8)	2 (33.3)	0.017‡
	FC III + IV, n (%)	11 (17.2)	4 (66.7)	
	6MWD (m), mean ± SD	438.61 ± 97.86	383.50 ± 89.00	0.173*
Lack of structure (n = 14)	Age (years), mean ± SD	42.88 ± 13.43	48.36 ± 10.80	0.140*
	Female, n (%)	43 (76.8)	11 (78.6	1.000‡
	FC I + II, n (%)	45 (80.4)	10 (71.4)	0.480‡
	FC III + IV, n (%)	11 (19.6)	4 (28.6)	
	6MWD (m), mean ± SD	439.04 ± 96.58	411.38 ± 103.53	0.458*

FC: (New York Heart Association) functional class; and 6MWD: six-minute walk distance. *Mann-Whitney test. †Chi-square test. ‡Fisher's exact test. §Logistic regression modelling of the probability of a barrier score ≥ 5.

In clinical practice, patients with PAH often report a 'lack of energy' or 'lack of motivation' to carry out their ADL. Although these sensations are subjective, their association with quality of life and functional performance demonstrates their clinical relevance. We find it interesting that patients who identified a 'lack of will as a significant barrier to physical activity have been found to walk shorter distances on the 6MWT, in metres and in percentage of the predicted value.[14]

Fatigue, dyspnoea and chest discomfort on exertion are common symptoms in patients with PAH, with fatigue being reported by 90% of patients.[15] Fatigue is defined as an intense, persistent feeling of exhaustion that can last for long periods of time. It can significantly reduce the ability to perform ADL, work effectively or engage in other physical activities. It is a multidimensional phenomenon with physical, emotional and cognitive components.[1,16] Fatigued patients experience a lack of energy to engage in physical activity. Cognitively, they report a lack of motivation to engage in their ADL. One study using a multidimensional fatigue inventory to assess fatigue in patients with PH found a high prevalence of intense or very intense fatigue in all dimensions of the inventory: general (60%); physical (55.8%); reduced activity (41.7%); reduced motivation (32.5%); and mental fatigue (27.5%).[17] Fatigue is associated with a reduction in physical activity and may even lead to a reduction in the overall level of activity. Research suggests that patients with PAH who have lower energy levels also tend to have lower levels of daily physical activity.[1,2,18]

'Lack of will' was the barrier reported by the majority (64%) of the patients in our study sample. That might be related to the 'lack of interest' described by Cascino

Table 4. Logistic regression modelling of the probability that a patient with pulmonary hypertension will give a barrier to physical activity a score ≥ 5.

Barriers with a score ≥ 5	Multivariate logistic regression
Lack of time (n = 6)	Low frequency, test not performed
Social influence (n = 15)	Age and the SF-36 vitality domain together increase the likelihood that a patient would cite social influence as a significant barrier: each advancing year of age increased the likelihood by 6.2%; and each unit decrease in the vitality score increased the likelihood by 4.0%.
	Age: OR = 1.062; 95% CI: 1.008-1.120*** Vitality: OR = 1.040; 95% CI: 1.006-1.073***
Lack of energy (n = 23)	Vitality was the only SF-36 domain that remained associated with the lack of energy barrier. A decrease of one unit in the score resulted in a 3.6% increase in the likelihood that a patient would cite this as a significant barrier.
	Vitality: OR = 1.036; 95% CI: 1.006-1.067***
Lack of will (n = 44)	Vitality was the only SF-36 domain that remained associated with the lack of will barrier. Each unit decrease in the score resulted in a 10.1% increase in the likelihood that a patient would cite this as a significant barrier.
	Vitality: OR = 1.101; 95% CI: 1.049-1.156*
Fear of injury (n = 23)	Social functioning was the only SF-36 domain that remained associated with the fear of injury barrier. Each unit less in the score increased the chance by 3.8%.
	Social functioning: OR = 1.038; 95% CI: 1.015-1.061*
Lack of ability (n = 6)	Low frequency, test not performed
Lack of structure (n = 14)	Vitality was the only SF-36 domain that remained associated with the lack of structure barrier. Each unit decrease in the vitality score resulted in a 5.5% increase in the likelihood that a patient would cite this as a significant barrier.
	Vitality: OR = 1.055; 95% CI: 1.016-1.095**

SF-36: Medical Outcomes Study 36-item Short-Form Health Survey. *p < 0.001; **p < 0.01; ***p < 0.05.

et al.[6] Those authors investigated perceived barriers to exercise in patients with PAH or CTEPH and used an accelerometer to assess the number of steps taken per day. They found barriers similar to those identified in our study, including 'lack of self-discipline', 'lack of energy' and 'lack of interest'. In addition, they found that the barriers 'lack of interest', 'lack of pleasure' and 'lack of ability' were associated with a decrease in daily step counts, a finding also observed by Lima.[19]

In addition to the associations that 'lack of energy' and 'lack of will' showed with the level of physical activity, we found an association between 'lack of will' and the 6MWD. Among patients with PAH, Lima[19] found an association between the 6MWD and 'lack of energy and structure', as well as between the Borg dyspnoea index in the sixth minute and 'lack of will'. The author also found that several barriers ('social influence', 'lack of energy', 'lack of will' and 'lack of ability') were associated with the number of repetitions in the one-minute sit-to-stand test.

In the present study, we found an association between certain barriers and aspects of quality of life, specifically in the SF-36 domains vitality, social functioning, role-emotional and mental health. In patients with PAH or CTEPH, quality of life is impaired because of several aspects of these complex diseases[2,19]: their chronicity; the limitations they impose; their impact on the social, professional and socio-economic aspects of the life of the affected patients; the uncertainty of the prognosis; the difficulties in accessing medications and specialised centres; and even the typical delay in receiving a diagnosis of PH.

'Lack of energy' and 'lack of will' were found to correlate with several SF-36 domains, including those in the mental component (vitality and role-emotional) and those in the physical component (general health, physical functioning and role-physical). The association that the vitality domain showed with both of those barriers was confirmed by multivariate logistic regression. These findings highlight the need for a more qualitative approach to symptoms in the daily care of patients with PAH. Matura et al.[18] found that the symptoms commonly reported by patients with PAH (dyspnoea on exertion, fatigue and sleep disturbance) were those that most affected their quality of life.

The haemodynamic profile, as assessed by echocardiography, was found to be correlated with the SF-36 (quality of life) domains and with the MRADL score but not with the PBPAQ score. The last was an expected finding. Hemodynamic impairment, assessed here by echocardiography, in measurements already validated with S' wave and RV strain, affects functional and exercise capacity and thus the level of daily activity. However, it does not necessarily mediate the factors that individuals perceive as barriers to physical activity.

In addition to the current trend toward a more sedentary lifestyle, people who experience fatigue and dyspnoea on exertion are more likely to adopt a less active behaviour, which in turn affects their ability to perform physical activity. It is important to identify potential barriers to exercise and mood disorders. A multidisciplinary approach involving

physiotherapists and mental health professionals may help reduce reluctance and increase motivation to exercise. This approach may facilitate the development of strategies that are more comprehensive for the therapeutic management of patients with PH. In addition to haemodynamic impairment, individuals with dyspnoea may have other reasons for not engaging in physical activity, such as fear of adverse events, insecurity about exercising, uncertainty about the need for exercise or its effectiveness, fatigue and lack of energy. Although these subjective aspects are often overlooked in patients with PAH, it is important to consider them.

Our study has some limitations. First, it was a single-centre study with a small sample size and no control arm. However, the fact that the questionnaires employed have been validated in several populations and that their scores are established indicate that our data are valid. In addition, this was a cross-sectional study and causality therefore cannot be established. However, it provides a basis for future research, given that most previous studies on barriers to physical activity in other areas have also been cross-sectional.

The perception of reduced vitality is common among patients with PH and is a crucial aspect of their well-being and quality of life. Our finding that the SF-36 vitality domain correlated with perceived barriers ('lack of will' and 'lack of energy'), physical activity and functional capacity illustrates the interrelationships among the different aspects assessed here.

Because of the chronic, debilitating nature of PH, its therapeutic management must go beyond medical and surgical treatment. Intrinsic barriers such as 'lack of energy', 'lack of willpower' and 'social influence' are often cited by individuals with PH as reasons for reducing physical activity. Research has shown that these barriers are associated with lower levels of physical activity. A multidisciplinary approach involving physiotherapists and mental health professionals may help reduce reluctance and increase motivation to exercise. Future research aimed at optimising physical activity should include multidimensional interventions that take into account the potential impact of intrinsic barriers. Further studies are needed in order to establish causality between self-reported barriers and the level of physical activity.

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AUTHOR CONTRIBUTIONS

MCP had full access to all of the study data and takes responsibility for the integrity of the data, as well as for the accuracy of the data analysis. LNGL, VV, PRAM, TAK, MMM and MCP contributed to the study design, data analysis and interpretation; the writing of the manuscript; and the critical review of the manuscript. All of the authors approved the final version of the manuscript.

CONFLICTS OF INTEREST

None declared.

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Diagnostic contribution of GeneXpert Ultra in pediatric pulmonary tuberculosis

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ABSTRACT

Objectives: To evaluate the contribution of Ultra to the diagnosis of pediatric pulmonary tuberculosis (PTB). **Methods:** We analyzed prospective data from children and adolescents with presumed PTB whose specimens were tested with Ultra between January 2020 and December 2022. Diagnosis was based on clinical-radiological criteria, clinical response after a two-month treatment period, and microbiological analysis. Ultra was considered positive with a result of 'Detected' and 'Traces' in children under 10 years and in HIV-infected individuals. Fisher's exact test was used for group comparisons, and McNemar's test was used to compare Ultra results with the diagnostic presumption. The study was approved by the Ethics Committee (CAAE No. 02173518.2.0000.5264). **Results:** A total of 41 patients were included, of whom 63% (26/41) were diagnosed with PTB. Among these, 9/26 (34%) had positive results only through Ultra, with negative AFB and culture. The sensitivity and specificity of Ultra were 50% (13/26) and 100% (15/15), respectively. The PPV was 100% (13/13), and the NPV was 54% (15/28). Of these 28 (68%) patients with negative Ultra results, 13 (46%) were diagnosed with PTB, mostly by MoH-SS. Considering culture as the reference, the PPV and NPV were 67% and 100%, respectively. **Conclusions:** Ultra significantly contributed to the diagnosis of pediatric PTB, proving to be a promising tool for paucibacillary forms of the disease. However, it should not be used alone. Integrating laboratory tests with clinical evaluation is essential to improving diagnostic accuracy and the management of pediatric TB.

Keywords: Pulmonary tuberculosis; children; adolescents; GeneXpert Ultra.

INTRODUCTION

Tuberculosis is a preventable and treatable communicable disease. However, it remains the world's second leading cause of death from a single infectious agent.[1] Children and adolescents up to 15 years old account for 11% of all tuberculosis cases, with approximately 1.1 million children diagnosed annually, half of whom are under the age of 5.[2]

National tuberculosis control programs have reported fewer than 50% of pediatric tuberculosis cases, highlighting a significant gap in case detection.[2] This disparity largely arises because many cases involve primary tuberculosis, which is either abacillary or paucibacillary, resulting in approximately 80% of diagnoses being made without bacteriological confirmation. The challenge is further compounded by young patients' inability to spontaneously provide sputum samples for smear microscopy.[3] In Brazil, diagnosis has relied on the scoring system (SS) recommended by the Brazilian Ministry of Health (MoH) since 2002.[1] However, whenever feasible, children with symptoms of pulmonary tuberculosis (PTB) should undergo initial rapid molecular testing and rifampicin resistance testing.[2]

To enhance laboratory diagnostics for tuberculosis, the World Health Organization (WHO) recommended in 2017 that the GeneXpert MTB/RIF (Xpert) rapid molecular assay be replaced with GeneXpert Ultra (Ultra) (Cepheid, CA, USA). This updated assay was adopted in Brazil in October 2019.[4] The Ultra test has a lower detection limit for *Mycobacterium tuberculosis* (*M. tb*) than Xpert (15.5 vs. 116 CFU). It utilizes real-time polymerase chain reaction (PCR), incorporates two additional *M. tb* targets, and features changes in the fusion curve to improve rifampicin resistance detection. Results categorize the bacillary load as 'Detected', 'Not detected', or 'Traces detected'. In people living with HIV (PLHIV), children under ten, and cases of extrapulmonary tuberculosis, trace results are considered positive.[2,5]

A systematic review and meta-analysis on pediatric tuberculosis found that the Xpert assay had a sensitivity and specificity of 64.6% and 99.0%, respectively, while the Ultra assay exhibited 72.8% sensitivity and 97.5% specificity.[6] This review included various diagnostic standards, such as culture and a composite reference standard that combined microbiological confirmation with clinical findings, standardized according to Graham et al. (2015).[7] Nevertheless, most studies using Ultra

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focus on adults, with few exploring its diagnostic accuracy in public health settings and resource-limited environments.[8] Therefore, the aim of the present study was to evaluate the effectiveness of the Ultra assay in diagnosing pediatric PTB in a reference hospital in Rio de Janeiro (RJ), Brazil.

METHODS

This observational, cross-sectional, descriptive study analyzed prospective data from children (ages 0–9) and adolescents (ages 10–19) with presumed PTB who were tested using the Ultra assay.[9,10] Conducted between January 2020 and December 2022, the study took place at the Martagão Gesteira Pediatric Institute (IPPMG), a leading pediatric tuberculosis center in Rio de Janeiro (RJ), Brazil.

Eligible participants were those identified by attending physicians as having presumed intrathoracic tuberculosis (here referred to as PTB). Clinical and epidemiological data were collected through interviews with parents or legal guardians and from medical records. The analyzed parameters included age, sex, nutritional status (measured as weight percentile for age based on the Centers for Disease Control and Prevention [CDC] growth charts),[11] MoH SS (> 40 points = very likely, 30–35 points = possible, < 25 points = unlikely),[12] acid-fast bacilli (AFB) detection in Ziehl-Neelsen smears, *M. tb* culture, and human immunodeficiency virus (HIV) antibody testing.[12]

Informed consent was obtained from parents or guardians, while adolescent patients provided informed assent. Samples were then collected and sent to the Mycobacteriology Laboratory at the Clementino Fraga Filho University Hospital – Professor Newton Bethlem Institute of Thoracic Diseases (HUCFF-IDT) of the Federal University of Rio de Janeiro (UFRJ). The samples were processed for the Ultra assay, AFB testing, culture in a Mycobacteria Growth Indicator Tube (MGIT), and antibiotic sensitivity testing (AST) if the MGIT culture was positive.

All specimens were categorized as respiratory (bronchoalveolar lavage, gastric lavage, sputum, induced sputum, or string test [ST])[13] or pleural (pleural fluid or biopsy) samples.

The final PTB diagnosis was established based on clinical-radiological criteria, clinical response two months after the start of treatment, and microbiological analysis.[1,7,14] Children and PLHIV with trace results were considered positive.[4] The samples were grouped into three categories: confirmed tuberculosis (Group 1), which was characterized by an MoH SS score > 30, a positive clinical response after two months of treatment, and microbiological confirmation; unconfirmed tuberculosis (Group 2), characterized by an MoH SS score > 30, a positive clinical response after two months of treatment, but no microbiological confirmation; and non-tuberculosis (Group 3), with an MoH SS score < 25, clinical improvement without PTB treatment, and no microbiological confirmation. These groupings were adapted from the classification proposed by Graham et al. (2015).[7]

The sensitivity, specificity, positive predictive value (PPV), and negative predictive value (NPV) of the Ultra assay were calculated by group, considering Groups 1 and 2 as PTB and Group 3 as non-PTB.

The data were coded and entered into a database using Excel 12.0 software (Office 2007) and analyzed using SPSS software, version 20.0, for Windows. Categorical data were assessed using descriptive statistics and expressed as frequencies and proportions. Fisher's exact test was used for group comparisons. A p-value of less than 0.05 was considered statistically significant. McNemar's statistical test was used to compare results from the Ultra assay with presumptive diagnoses.

This study received approval from the Research Ethics Committee (REC) of the UFRJ IPPMG, under Certificate of Submission for Ethical Appraisal (CAAE) No. 02173518.2.0000.5264.

RESULTS

The study sample consisted of 41 patients with presumed PTB, with no exclusions. Of these, 26 (63.4%) were diagnosed with PTB (Groups 1 and 2), while 15 (36.6%) received other diagnoses (Group 3). The characteristics of the study population are presented in Table 1.

The distribution of patients based on the Ultra test results is shown in Figure 1.

In Groups 1 and 2, children under 10 years and PLHIV with trace results had an Ultra assay sensitivity and specificity of 50% (13/26) and 100% (15/15), respectively. The Ultra assay demonstrated a PPV of 100% (13/13) and a NPV of 54.0 (15/28), based on a population prevalence of 64.0%. These data are shown in Table 2.

Quantitatively, 7/7 (100%) patients with a 'Detected' result and 11/12 (92%) with 'Trace' results were diagnosed with PTB using the Ultra assay. An adolescent with significant hematologic cancer showed trace results but was not diagnosed with PTB. This patient experienced improved respiratory symptoms within the first two weeks of treatment with common antibiotics and was, therefore, considered a false positive.

Among the 41 participants, 28 (68%) received negative results in the Ultra assay. Of these, 13 (46%) were diagnosed with PTB—12 (92%) in Group 2 and 1 (8%) in Group 1. Patients in Group 2 were diagnosed using the MoH SS. Of the 13 patients with PTB and negative Ultra assay results, 9 (82%) were categorized as very likely or possible tuberculosis, 2 (18%) as unlikely, and 2 (15%) lacked complete data for scoring.

Considering the culture as the reference standard, the PPV and NPV were 67.0% and 100%, respectively. The Ultra assay was positive in 31.0% of cases, with

Table 1. Characteristics of the study population (n=41) according to final diagnosis.

	Total		Final diagnosis			
			TB (Groups 1 and 2)		Non-TB (Group 3)	
	(n = 41; 100%)		(n = 26; 63%)		(n = 15; 37%)	
	n	%	n	%	n	%
Sex						
Male	21	100.0	11	52.0	10	48.0
Female	20	100.0	15	75.0	5	25.0
Age						
Child	21	100.0	10	48.0	11	52.0
Adolescent	20	100.0	16	80.0	4	20.0
HIV						
Positive	3	100.0	2	67.0	1	33.0
Negative*	38	100.0	24	63.0	14	37.0
Weight-for-age						
< P3	12	100.0	8	67.0	4	33.0
> P3	29	100.0	18	62.0	11	38.0
TST						
Positive	13	100.0	11	85.0	2	15.0
Negative	16	100.0	10	63.0	6	38.0
WI	12	100.0	5	42.0	7	58.0

*Including the 4 cases with no HIV record. Legend: TB, Tuberculosis; HIV, Human Immunodeficiency Virus; P3, 3rd percentile for weight-for-age; WI, Without information; TST, Tuberculin skin test.

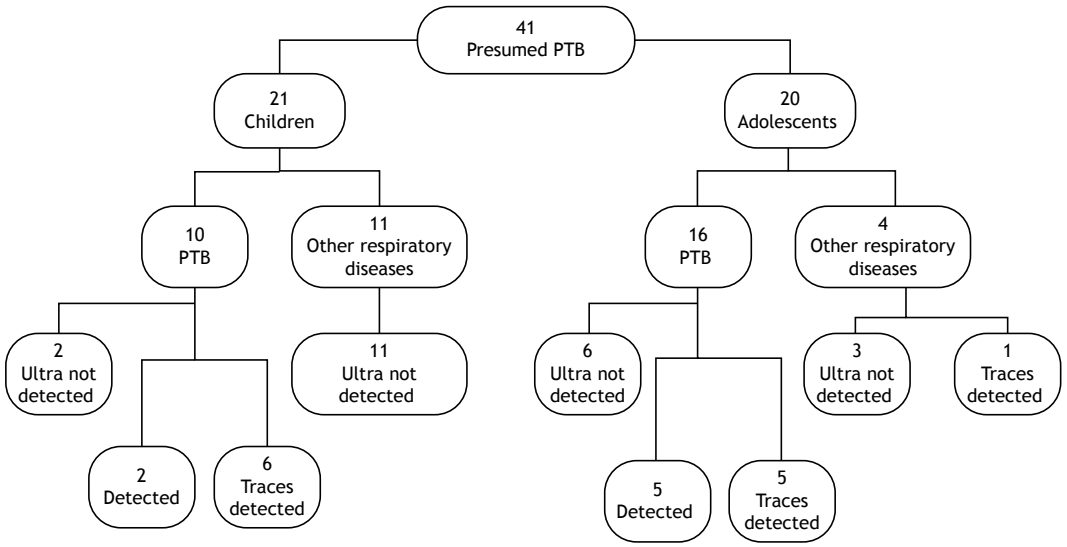

Figure 1. Flowchart illustrating the Ultra test results according to final diagnosis in 41 patients with presumed pulmonary tuberculosis. Legend: PTB, pulmonary tuberculosis.

a specificity of 77.0% and a sensitivity of 80%, as shown in Table 3.

In the 41 cases, 34 (83%) were respiratory and 7 (17%) were pleural, as shown in Figure 2. The Ultra assay yielded positive results in 35.0% of the respiratory samples and 14.0% of the pleural samples.

The accuracy of the Ultra assay was further assessed by comparing its results with those of concurrent positive diagnostic tests. Among the 26 (63%) patients diagnosed with PTB (Groups 1 and 2), 9 (34%) tested positive only with the Ultra assay, despite negative results from AFB and culture tests.

DISCUSSION

This study evaluated the effectiveness of the Ultra assay in diagnosing PTB using respiratory samples from children and adolescents at a reference center in Rio de Janeiro (RJ), Brazil. Overall, 64.0% of the patients were diagnosed with PTB. The Ultra assay proved pivotal in diagnosing over one-third of the participants, even

Table 2. Children and adolescents with presumed pulmonary tuberculosis (n=41) according to the final Ultra test results and final diagnosis.

Final Ultra test result	Total		Final diagnosis				Predictive values		p-value
			TB (Groups 1 e 2)		Non-TB (Group 3)		(for prevalence = 64%)		
	n	%	n	%	n	%	Positive	Negative	
Positive*	13	32.0	13	50.0	0	0.0	100.0%	54.0%	< 0.001
Negative	28	68.0	13	50.0	15	100.0			
Total	41	100.0	26	63.0	15	37.0			

Legend: Ultra, Molecular rapid test; TB, Tuberculosis; PTB, Pulmonary tuberculosis; Positive*, Ultra detected and traces in children under 10 years and/or PLHIV.

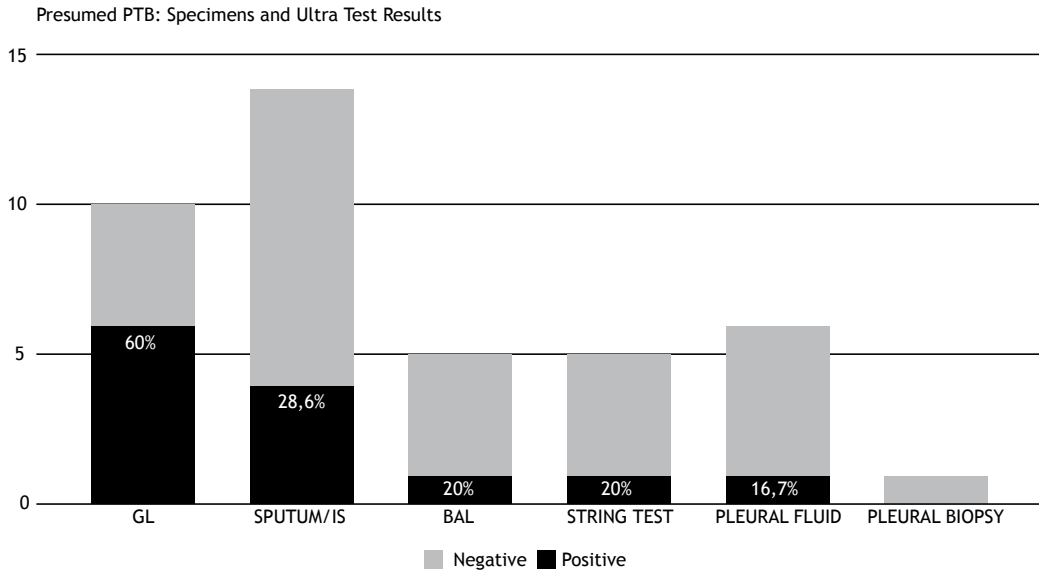

Figure 2. Positivity of the molecular rapid test for tuberculosis by respiratory specimen in 41 patients with PTB. Legend: IS, induced sputum; GL, gastric lavage; BAL, bronchoalveolar lavage; PTB, pulmonary tuberculosis. The percentages indicate the positivity of the Ultra test within each specimen.

Table 3. PPV and NPV of children and adolescents with presumed tuberculosis based on final diagnosis, using culture as the reference.

Ultra	Total		Culture			
			Positive (n = 5)		Negative (n = 34)	
	n = 39*					
	n	%	n	%	n	%
Detected	6	100.0	4	68.0	2	33.0
Not detected	21	100.0	0	0.0	21	100.0
Traces detected	12	100.0	1	8.0	11	92.0

*Excluding the 2 cases with contaminated cultures. Legend: Ultra, Molecular rapid test for TB; TB, Tuberculosis; PTB, Pulmonary tuberculosis.

when both sputum smear microscopy and culture tests were negative. Notably, PTB was identified in half of the cases with negative Ultra assay results, highlighting that a negative mycobacterial test result does not rule out the diagnosis, thus underscoring the necessity of the MoH SS.

The absence of a definitive gold standard test remains a challenge, particularly in pediatric populations, where obtaining high-quality samples is inherently difficult. While a culture-based reference standard is commonly adopted in adults, it is less effective for diagnosing pediatric tuberculosis, as culture techniques may fail to detect up to 40% of PTB cases in this age group.[15] Given the limitations of culture as a diagnostic tool and the variability in bacteriological confirmation, Graham et al. (2015) proposed classifying tuberculosis in children as 'confirmed tuberculosis', 'probable tuberculosis', and 'unlikely tuberculosis.'[7] In this study, the Ultra assay demonstrated a sensitivity of 50% and a specificity of 100% relative to the final PTB diagnosis, aligning with the findings of a 2022 Cochrane review that assessed the Ultra assay in 25,937 children under 15 years of age, reporting a sensitivity range of 23.5–50.3% and a specificity above 98.2%.[6]

Using culture as the reference standard yielded a specificity of 76.5% and a sensitivity of 80% in our population. These results are comparable to those of a prospective cohort study conducted between July 2018 and February 2019 at a tertiary hospital in northern India, which included 156 children under 15 years of age and reported a sensitivity of 85.0% (95%CI: 68.1–94.9) and a specificity of 94.0% using culture as the reference standard.[16]

The comparison of three diagnostic methods in this study—Ultra, AFB, and culture—revealed that the Ultra

assay contributed to the diagnosis in just over one-third of cases where both sputum smear microscopy and culture tests were negative. This represents a significant improvement over a similar study conducted in 2019 in Rio de Janeiro, where the Xpert assay contributed to 9% of the diagnoses under similar conditions.[17] In the present study, the diagnostic contribution of the Ultra assay increased by 25%.

Our analysis indicated that 50% of the PTB patients had negative Ultra results. Therefore, while the Ultra assay is a valuable diagnostic tool, particularly for the pediatric population, who typically present with paucibacillary tuberculosis, it should not be used alone.[2] Our findings underscore the necessity of using the MoH SS to diagnose PTB, which has a sensitivity and specificity of 89.0% and 87.0%, respectively.[12]

A comparison of results between adolescents and children showed that PTB was confirmed in 80% (16/20) of the adolescents and 48% (10/21) of the children. The Ultra assay was positive in 31% (5/16) of adolescents and 80% (8/10) of children, with a statistically significant difference (p = 0.04). The higher positivity rate in children was attributed to trace results, which are considered positive in children under 10 years according to WHO guidelines, leading to a higher number of positive diagnoses in this age group.[6] Conversely, adolescents had a higher rate of detectable results correlated with a positive culture. This discrepancy may be explained by the manifestation of more adult-type tuberculosis in adolescents, potentially linked to differences in bacillary load or their ability to produce higher-quality sputum samples compared to younger children.[18]

In patients with trace results, 11 out of 12 were diagnosed with PTB, with only one false positive, as previously mentioned. This finding aligns with research from South Africa, which investigated predictors of active PTB in 290 patients with trace results in the Ultra assay, including 89 children under 5 years of age. In addition to clinical interpretation, the Ultra 'traces' category contributed to the diagnosis of pulmonary tuberculosis.[5]

The analysis of different sample types and their Ultra assay positivity rates indicated that gastric aspirate had the highest positivity rate, at 60%, followed by sputum and induced sputum, at 28.6%. The higher positivity rate with gastric lavage, as noted in the referenced Cochrane review, may be attributed to these samples often being collected in hospital settings, where the likelihood of more advanced disease is greater.[6]

Our study had some limitations. Being a single-center study with a small sample size may have led to less precise estimates of diagnostic parameters. Additionally, as it was conducted at a tuberculosis referral center and did not include basic health units, there may be selection bias, potentially resulting in higher positive rates with the method.

Despite these limitations, this is the first Brazilian study to evaluate the Ultra assay for diagnosing PTB in an exclusively pediatric population. We concluded that the Ultra assay significantly aids in diagnosing PTB among children, proving to be a valuable tool for identifying paucibacillary forms of the disease suitable for initial screening. Although it is an important method, it should not be used alone, as a negative result does not rule out the disease.[2,12] Laboratory tests must be complemented by clinical evaluations, and the MoH SS should be used to diagnose PTB, thereby enhancing diagnostic accuracy and improving the management of pediatric tuberculosis.

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Brazilian Thoracic Association recommendations for the management of lymphangioleiomyomatosis

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ABSTRACT

Lymphangioleiomyomatosis (LAM) is a rare disease, characterized as a low-grade neoplasm with metastatic potential that mainly affects women of reproductive age, in which there is proliferation of atypical smooth muscle cells (LAM cells) and formation of diffuse pulmonary cysts. It can occur in a sporadic form or in combination with tuberous sclerosis complex. In recent decades, a number of advances have been made in the understanding of the pathophysiology and management of LAM, leading to improvements in its prognosis: identification of the main genetic aspects and the role of the mechanistic target of rapamycin (mTOR) pathway; relationship with hormonal factors, mainly estrogen; characterization of pulmonary and extrapulmonary manifestations in imaging studies; identification and importance in the diagnosis of VEGF-D; a systematic diagnostic approach, often without the need for lung biopsy; use of and indications for the use of mTOR inhibitors, mainly sirolimus, for pulmonary and extrapulmonary manifestations; pulmonary rehabilitation and the management of complications such as pneumothorax and chylothorax; and the role of and indications for lung transplantation. To date, no Brazilian recommendations for a comprehensive approach to the disease have been published. This document is the result of a non-systematic review of the literature, carried out by 12 pulmonologists, a radiologist, and a pathologist, which aims to provide an update of the most important topics related to LAM, mainly to its diagnosis, treatment, and follow-up, including practical and multidisciplinary aspects of its management.

Keywords: Lymphangioleiomyomatosis/diagnosis; Lymphangioleiomyomatosis/prevention & control; Lymphangioleiomyomatosis/pathophysiology; Lymphangioleiomyomatosis/drug treatment; Lymphangioleiomyomatosis/therapy; Clinical practice guide.

INTRODUCTION

Lymphangioleiomyomatosis (LAM) is a rare disease classified as a low-grade, multisystemic, progressive metastatic neoplasm, characterized by the proliferation of atypical smooth muscle cells (LAM cells) around blood and lymphatic vessels, as well as airways, manifesting as the formation of diffuse pulmonary cysts.[1,2] The site of origin of LAM cells remains unknown. Individuals with LAM can develop tumors, such as angiomyolipomas and lymphangioleiomyomas.[2,3]

Caused by mutations in the tuberous sclerosis complex (TSC) genes *TSC1* and *TSC2*, LAM mainly affects women of reproductive age. It occurs in sporadic forms or in association with TSC. It is a genetic disease characterized by multiple benign tumors of the skin, central nervous system, retina, heart, liver, kidneys, and lungs.[3-5]

In recent years, there have been several advances in the understanding of and approach to LAM, including its pathophysiology, functional behavior, response to exercise, diagnosis, and treatment, resulting in improved prognosis and management.

The importance of preparing this document is underscored by the following factors: the increase in the number of diagnosed cases of LAM, especially with the expansion of access to chest CT; the need to expand knowledge about the disease among pulmonologists, clinicians, and specialists in other areas, in order to reduce its underdiagnosis; the absence of Brazilian recommendations for a comprehensive approach to the disease; the presence of a very active patient association (the Brazilian Association of Individuals with Lymphangioleiomyomatosis), which has helped obtain numerous benefits for individuals with the

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disease, including access to centers of excellence and to treatment; and the need to emphasize the importance of a preferably multidisciplinary approach to LAM, given its multisystemic nature.

Twelve pulmonologists, one radiologist, and one pathologist with extensive experience in the subject were brought together to prepare this document. A non-systematic narrative review of the literature was carried out, and the main existing evidence on various topics was included, including practical aspects of the management of the disease.

EPIDEMIOLOGY

The fact that LAM is a rare disease that is poorly understood and underdiagnosed often delays its treatment. Studies of LAM have largely been retrospective and many have included cases of LAM accompanied by TSC (LAM-TSC).[6] However, in recent years, an increase in the prevalence of LAM has been observed in several studies, possibly reflecting advances in the ability to recognize the disease, including increased access to chest CT. Approximately 25 years ago, the prevalence of LAM in various locations, including the United Kingdom, France, and the United States, was 1 case per million women.[7-9] A subsequent study that evaluated the prevalence of LAM in countries on different continents identified a prevalence of 3.4-7.8 cases per million women.[6] In a more recent study, the prevalence of LAM in four European countries was estimated at 23.5 cases per million adult women and 19.0 cases per million women of all ages,[10] substantially higher than previous estimates. Relevant factors in that later study include assessments at well-structured national centers in countries with smaller populations, optimizing the chances of identifying the disease.[10] Estimates from the LAM Foundation indicate a prevalence of 3-5 cases per million women.[11] Although there are no reliable data on the prevalence of LAM in Brazil, it is estimated, on the basis of the most recent studies conducted elsewhere,[6,10,11] that there are 1,000-2,000 patients in the country.

Most patients presenting with LAM are premenopausal, in their third or fourth decade of life; however, the age range extends from preadolescence to old age.[3,12] Only one study demonstrated ethnic variability, suggesting that sporadic LAM was more common in White women of higher socioeconomic status, although that finding might be attributable to biases in access to health care.[12]

The rates of LAM are highest in patients with TSC, a condition with an incidence of approximately 1 in 5,000-10,000 live births.[5] The frequency of LAM in women with TSC is reported to be 26-50%, with higher rates among those over 15 years of age, ranging from 27% in those under 21 years of age to 80% in those over 40 years of age.[12-14] Although LAM can occur in men with TSC, the sporadic form is extremely rare in such men.[14] In men with TSC, the reported frequency of cystic lung disease ranges from 10% to 38%, although the development of symptoms and a decline in lung function are uncommon.[14,15]

PATHOPHYSIOLOGY

The pathophysiology of LAM is complex, involving multiple mechanisms, and is still not fully understood, despite significant advances in recent years. Mutations in the tumor suppressor genes *TSC1* and, more commonly, *TSC2* are associated with the development of LAM. In LAM-TSC, those mutations are present in the germline and it is assumed that a second somatic mutation occurs in the tissue (second hit), leading to a loss of heterozygosity. In sporadic LAM, the mutations are present in somatic cells and are identified in various tissues, including the lungs, kidneys, and lymph nodes.[16]

The *TSC1* and *TSC2* genes encode, respectively, the proteins hamartin and tuberin, which form the hamartin-tuberin complex, responsible for inhibiting the mechanistic target of rapamycin (mTOR). The mTOR pathway is part of a complex protein synthesis pathway (P13K/mTOR/AKT) through the mTORC1 and mTORC2 protein complexes. Tuberin deactivates the Rheb protein, which in turn deactivates the mTORC1 pathway, which is responsible for several functions of protein synthesis, cellular metabolism, and angiogenesis. Through mutations in the *TSC1* and *TSC2* genes, this inhibitory effect on the mTOR pathway is lost, and that pathway becomes hyperactivated, resulting in the growth, proliferation, and dissemination of LAM cells.[17]

The etiology of LAM cells is unclear. The genetics, immunohistochemical profile, and morphological pattern of these cells are similar to those found in renal angiomyolipomas, suggesting a common origin. The distribution of the lesions, which are more common in the pelvis and along the axial axis of the lymph nodes, suggests an abdominal origin, and lesions containing LAM cells are also found in the uterus. The strongest evidence that LAM is a systemic disease comes from the recurrence described in patients who have undergone lung transplantation, suggesting its location in the lymphatic tissue. In that context, LAM is considered a low-grade neoplasm with metastatic potential.[2,16,17]

Lymphangiogenesis is essential in LAM and is involved in the chylous manifestations of the disease. It is believed to be mediated by the secretion of factors such as VEGF-C and VEGF-D by LAM cells. Those factors promote the proliferation and migration of lymphatic endothelial cells, as well as facilitating the migration of LAM cells.[16]

Estrogen appears to be closely related to LAM, given that it is a condition that is practically exclusive to women, affecting them mainly during menacme, and that there are receptors for this hormone in LAM cells.[18,19] In addition, pregnancy, hormone replacement therapy, and infertility treatment, situations in which there is increased exposure to

estrogen, have been associated with the onset and worsening of the disease.[20]

Functionally, most patients with LAM present obstructive disorder, air trapping and dynamic hyperinflation during exercise, mainly related to cystic destruction of the lung parenchyma due to an imbalance between metalloproteinases (MMPs) and their inhibitors, as well as cell proliferation and direct involvement of the small airways.[21,22]

DIAGNOSIS

Clinical aspects of pulmonary and extrapulmonary involvement

The clinical presentation of LAM is quite varied. Some patients are asymptomatic, whereas others present with insidious symptoms or with rapid progression until lung transplantation is required.[1-3] Nonspecific clinical manifestations and normal chest X-ray findings in the initial evaluation contribute to a delayed diagnosis. On average, the time from the onset of symptoms to the diagnosis of LAM is 3-5 years, usually occurring in the third or fourth decade of life.[23] Patients are often initially misdiagnosed as having asthma or COPD until a more detailed investigation is carried out on the basis of the lack of a response to treatment for those diseases.[2,3]

Many patients are asymptomatic, with pulmonary cysts being incidental findings during abdominal or thoracic imaging for various reasons, supporting the indication for LAM screening in those with TSC. Most patients with LAM present with insidious and often progressive dyspnea on exertion or a history of spontaneous pneumothorax (30-50%), which is often recurrent. Other possible clinical manifestations include cough, wheezing, hemoptysis/hemoptoic sputum (in 20%), chylothorax (in 10-30%), chyloptysis, chylous ascites, and chyluria.[2,3,24]

Renal angiomyolipomas, which are the most common extrapulmonary manifestations in LAM and are present in up to 50% of patients, can cause pain, increased abdominal volume, and hemorrhage, especially when larger than 4 cm in diameter.[2,3,12] Lymphangioleiomyomas, which occur in approximately 16% of cases, can cause abdominal and pelvic pain, as well as edema of the lower limbs due to compression of the lymphatic and venous systems.[2,3,25]

Among patients with TSC,[3,5] there can be dermatological manifestations, including Shagreen patches, facial angiofibromas, periungual fibromas, and hypomelanotic macules; neurological manifestations, including subependymal nodules, cortical tubers, giant cell astrocytomas, seizures, and cognitive deficit; ocular manifestations, including retinal hamartoma; and cardiac manifestations, including rhabdomyoma.

Lung function

In the initial evaluation of patients with LAM, pulmonary function testing (PFT) is essential, mainly to identify the severity of lung involvement and to assist in decision-making regarding treatment and prognosis. In addition, PFT is essential in longitudinal follow-up, to monitor the symptoms and to assess the response to treatment.[2,26-28]

The main functional changes found in LAM are attributable to infiltration of the lung parenchyma by LAM cells and remodeling resulting from cysts, in addition to goblet and squamous cell hyperplasia, epithelial metaplasia, and airway wall thickening.[21,29]

Pulmonary function is variable in LAM and can be normal in up to half of all cases. Reduced DL_{CO} is the most common functional alteration in the initial evaluation and is usually the earliest such alteration, followed by static or dynamic air trapping. Reduced DL_{CO} is observed in 40-60% of cases in the initial evaluation, whereas air trapping is observed in 40-50% and obstructive disorder is observed in 30-50%.[3,12,30-34] A positive bronchodilator response occurs in 15-30% of patients.[3,12,33]

The main parameter used for therapeutic decision-making is FEV_1, and its rate of decline is well documented as a prognostic marker and as a marker of response to treatment in LAM.[30,33,34] The annual decline in FEV_1 reported in previous studies ranged from 47 mL to 135 mL. It is believed that the discrepant annual rates of functional decline are due to measurement biases and varying levels of baseline severity and disease progression in the populations evaluated.[3,35,36]

The annual rate of decline in FEV_1 is higher in patients with sporadic LAM, higher serum VEGF-D values, greater degree of dyspnea, greater extent of pulmonary cysts on CT, or a positive bronchodilator response.[3,30,37] However, postmenopausal women with LAM have higher baseline FEV_1 and DL_{CO}, as well as less functional decline.[20] The only effective medications to stabilize or reduce functional decline in LAM are mTOR inhibitors.[20,38]

Pulmonary and extrapulmonary imaging

As illustrated in Figure 1, the characteristic (diagnostic) pattern of LAM on CT is that of multiple round, uniform, thin-walled, diffusely distributed pulmonary cysts.[2,28] In the algorithm suggested in the guidelines of the American Thoracic Society and the Japanese Respiratory Society, the second step in the diagnostic workup of LAM, after clinical evaluation, is HRCT, and the identification of the classic CT pattern defines the diagnosis if associated with other findings, such as angiomyolipomas and lymphangioleiomyomas, the presence of TSC or elevated serum levels of VEGF-D.[28] Chest X-ray might not demonstrate pulmonary alterations early in the disease and can show minimal reticulation in some patients in the advanced stages of the disease.[2]

Although HRCT has some specificity in recognizing the pulmonary manifestation of LAM, the method alone is not recommended for definitive diagnosis in

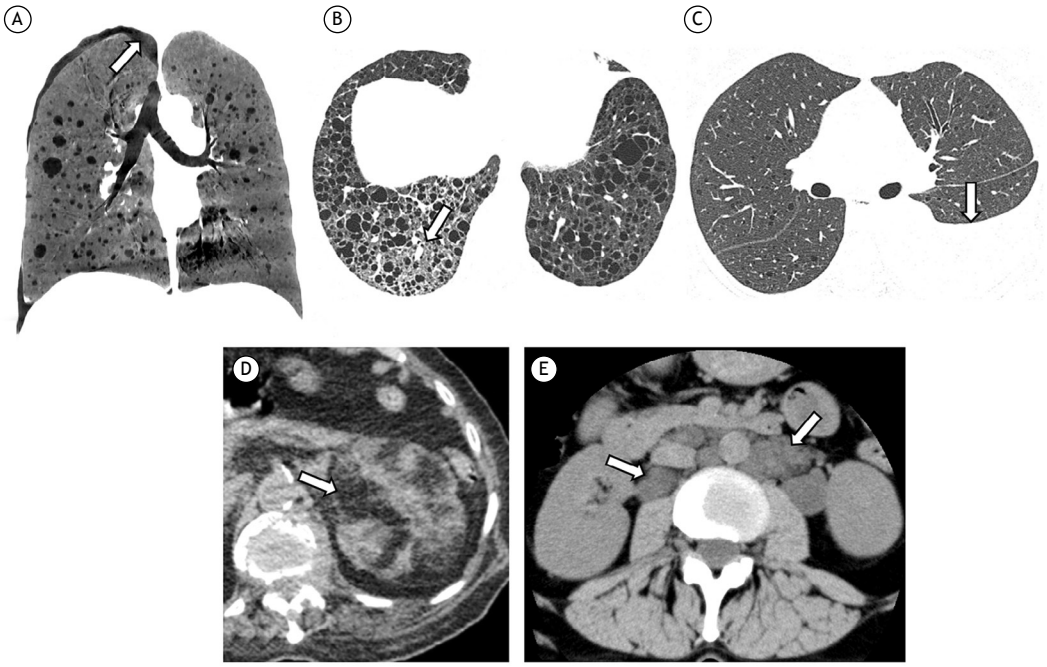

Figure 1. Pulmonary and extrapulmonary findings associated with lymphangioleiomyomatosis (LAM). A) Minimum-intensity projection reconstruction of a coronal CT scan, showing multiple scattered lung cysts of varying sizes, together with a small pneumothorax on the right (arrow). B) Axial CT scan of the chest, with lung window settings, showing diffuse cysts typical of LAM, together with a ground-glass opacity in the lower right lobe, presumably due to lymphatic congestion/filling or alveolar hemorrhage. C) Axial CT scan of the chest, with lung window settings, showing moderate pleural effusion, proven to be chylous in the laboratory analysis. D) Unenhanced axial CT scan of the abdomen, showing multiple nodular lesions with adipose attenuation in the renal parenchyma, characteristic of angiomyolipomas. E) Axial CT scan of the abdomen showing multiple retroperitoneal hypoattenuating nodular lesions, characteristic of lymphangioleiomyomas.

patients without additional confirmatory features.[28] The differential diagnosis of LAM on HRCT (Figure 2) includes emphysema, bronchiectasis, and honeycombing, together with other diffuse cystic lung diseases, such as Langerhans cell histiocytosis, Birt-Hogg-Dubé syndrome, lymphocytic interstitial pneumonia, and bronchiolitis.[39,40] A small number of cysts can be observed as a consequence of lung aging. It has been suggested that a minimum of 4 would be sufficient to investigate cystic lung diseases, and that 4-10 cysts should be sufficient to raise the suspicion of a diagnosis of LAM.[2]

Other pulmonary and extrapulmonary manifestations can be seen in LAM. Ground-glass pulmonary opacities can occur and are usually secondary to smooth muscle proliferation, alveolar hemorrhage, or lymphatic congestion (Figure 1). Interlobular septal thickening, chylous pleural effusion, pericardial effusion, thoracic duct dilation, and mediastinal lymph node enlargement can also occur and represent involvement of the lymphatic compartment.[2] Pneumothorax is common, with a high recurrence rate.[41]

Angiomyolipomas are seen in about half of all cases of LAM, in the sporadic form (in 30-40% of cases) and in LAM-TSC (in 90%). They are benign mesenchymal tumors categorized in the perivascular epithelioid cell tumor (PEComa) family and are most common in the kidneys, although they can occur at other sites, such as in the liver and lungs.[2,42] Their most characteristic aspect is the presence of fat, which allows the definitive diagnosis to be made by imaging (Figure 1). A small proportion of these tumors can be low in adiposity, which should prompt the differential diagnosis with other neoplasms.

In the context of LAM-TSC (Figure 3), other lesions can be identified in multiple systems, such as the central nervous system (multiple cortical tubers, subependymal nodules, and subependymal giant cell astrocytoma), heart (rhabdomyoma), kidneys (cysts and angiomyolipomas), and musculoskeletal system (sclerotic bone lesions). In the lung parenchyma, there can be micronodular and multifocal hyperplasia of type II pneumocytes, which present as multiple solid or ground-glass micronodules, measuring 2-14 mm, with a random distribution.[5,43] There can also be well-defined foci of myocardial fat, usually in the interventricular septum or in the walls of the left ventricle.[42]

Chest CT also plays an important role in the staging and monitoring of LAM (Figure 4). Semi-automated and automated quantification methods can be used for staging and the monitoring of progression, with the assessment of cyst extension, showing a good correlation with lung function.[44-49] Because the longitudinal assessment of LAM can require repeated CT examinations, radiation exposure is a relevant concern, especially in young patients and female patients of reproductive age.[41] In this context, CT

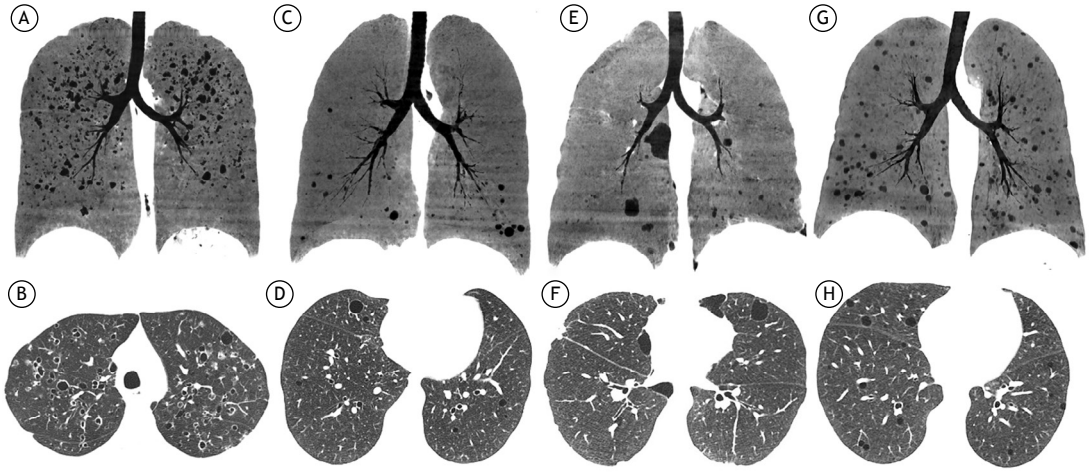

Figure 2. Differential diagnosis of lymphangioleiomyomatosis. Minimum-intensity projection reconstructions of coronal CT scans in A, C, E and G, and axial CT scans, with lung window settings, in B, D, F and H. In A and B, pulmonary Langerhans cell histiocytosis, with cysts of variable sizes/shapes and some small centrilobular nodules, predominantly in the upper lung fields. Note that the costophrenic recesses are preserved. In C and D, lymphocytic interstitial pneumonia, with some of the cysts having an axial distribution, mainly peribronchovascular, concentrated in the lung bases. In E and F, Birt-Hogg-Dubé syndrome, in which the cysts are typically larger and elliptical, usually with a paramediastinal distribution in the lower lung fields. In G and H, an unusual manifestation of constrictive bronchiolitis, with sparse, randomly distributed cysts.

scans using low-dose and ultra-low-dose radiation protocols have shown results comparable to those obtained with conventional doses for monitoring the progression of lung cysts.[46,47]

Serum level of VEGF-D

The glycoprotein VEGF-D, which is produced by LAM cells, has been extensively studied as a biomarker of LAM. In cases of diagnostic uncertainty, the measurement of VEGF-D is particularly useful—in the context of investigation of the etiology of diffuse cystic lung disease in various populations, including that of Brazil, a serum VEGF-D level above 800 pg/mL has a specificity of nearly 100% for the diagnosis of LAM, with the potential to preclude the need for lung biopsy in patients without other clinical manifestations.

In LAM, the serum VEGF-D level correlates with the severity of lung disease and chylous manifestations, being significantly reduced after treatment with sirolimus.[28,50,51] However, there are a number of limitations to its use. There is great variability across studies in terms of its accuracy and ideal cutoff value, which ranges from 440 pg/mL to over 1,200 pg/mL. In addition, it has moderate sensitivity, and its levels are higher in patients with LAM-TSC, lymphatic involvement, and extrapulmonary manifestations, in which its measurement could be considered unnecessary. Furthermore, it has no confirmed clinical prognostic value; nor have there been any studies showing its usefulness in monitoring disease activity during therapy.[51-53] Moreover, this test is still not widely available in Brazil.

Mainly due to its potential to preclude the need for invasive procedures, VEGF-D measurement, despite its limitations, is still recommended in the investigation of patients with suspected LAM and without other manifestations that could confirm the diagnosis.[2,26,28]

Biopsy and histopathological aspects

Lung biopsy can be performed to confirm the diagnosis of LAM when the results of the clinical examination, CT evaluation, and measurement of the serum VEGF-D level are not sufficient to reach a conclusion and when the benefits of a biopsy outweigh the risks of the procedure.[2,26] In patients with diffuse, asymptomatic cysts and normal or slightly altered lung function, periodic monitoring alone can be used, without a need for biopsy.[2] Transbronchial lung biopsy has a sensitivity of over 50% and can be used as the initial invasive method at centers with experience in its use.[28,54,55] Transbronchial cryobiopsy can also be an option, as demonstrated in specific cases.[56,57] When there is uncertainty about performing transbronchial biopsy or when the results of such a biopsy are inconclusive, surgical lung biopsy is recommended, preferably by video-assisted thoracoscopy.[26,27]

The characteristics of LAM include abnormal proliferation of cells expressing smooth muscle proteins in the lungs, axial lymph nodes, and other sites, often accompanied by renal angiomyolipoma.[58] The disease is classified by the World Health Organization in the group of PEComas, characterized as mesenchymal tumors composed of histologically and immunohistochemically distinct perivascular epithelioid cells.[59] The proliferation of LAM cells appears to play a central role in the destruction of the lung parenchyma.[60]

Lesions in LAM are composed of two cell subpopulations: spindle-shaped, myofibroblast-like cells; and polygonal cells with an epithelioid

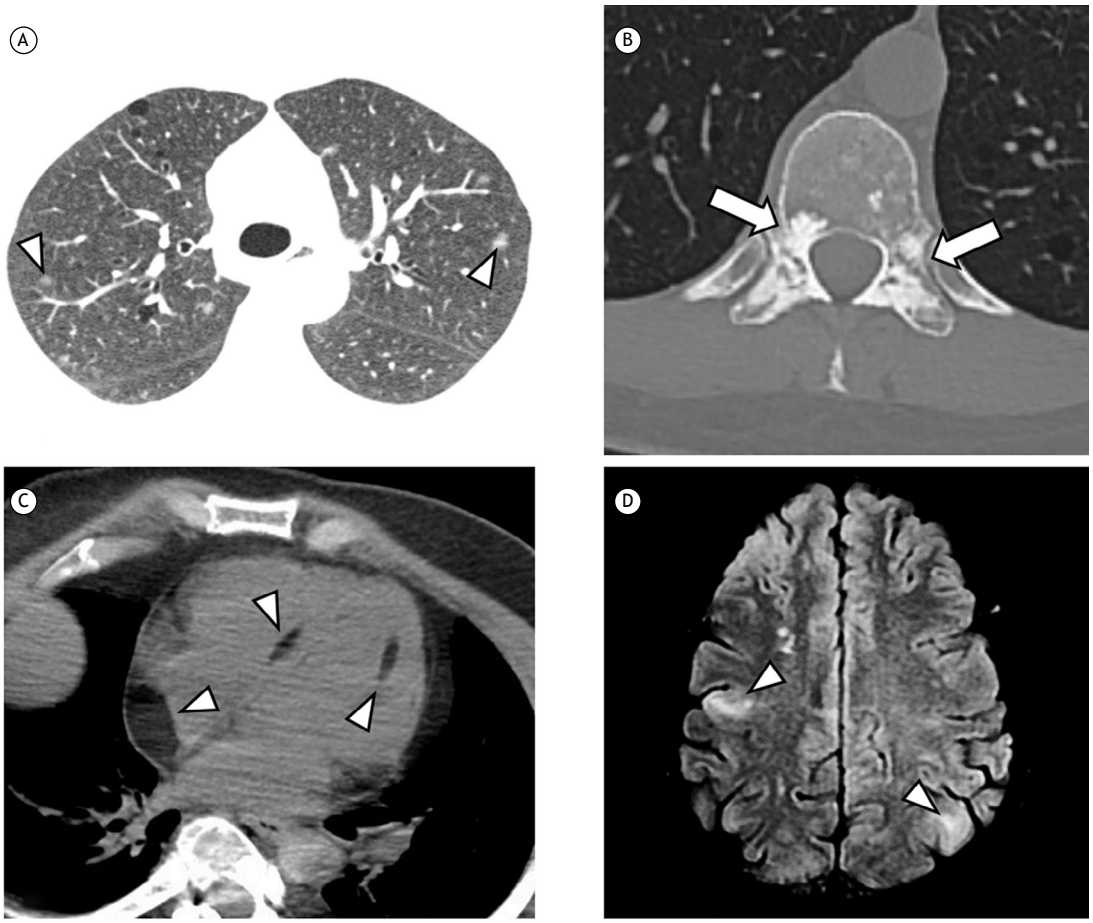

Figure 3. Other lesions associated with tuberous sclerosis complex. A) Axial CT scan of the chest, showing scattered pulmonary cysts related to lymphangioleiomyomatosis and some ground-glass micronodules, presumably associated with micronodular and multifocal hyperplasia of type II pneumocytes (arrowheads). B) Axial CT scan of the dorsal spine, showing multiple sclerotic foci concentrated in the posterior vertebral elements (arrows). C) Axial CT scan of the chest, with mediastinal window settings, showing foci of myocardial fat accumulation (arrowheads). D) Axial MRI of the skull, with fluid-attenuated inversion recovery weighting, showing cortical tubers (arrowheads).

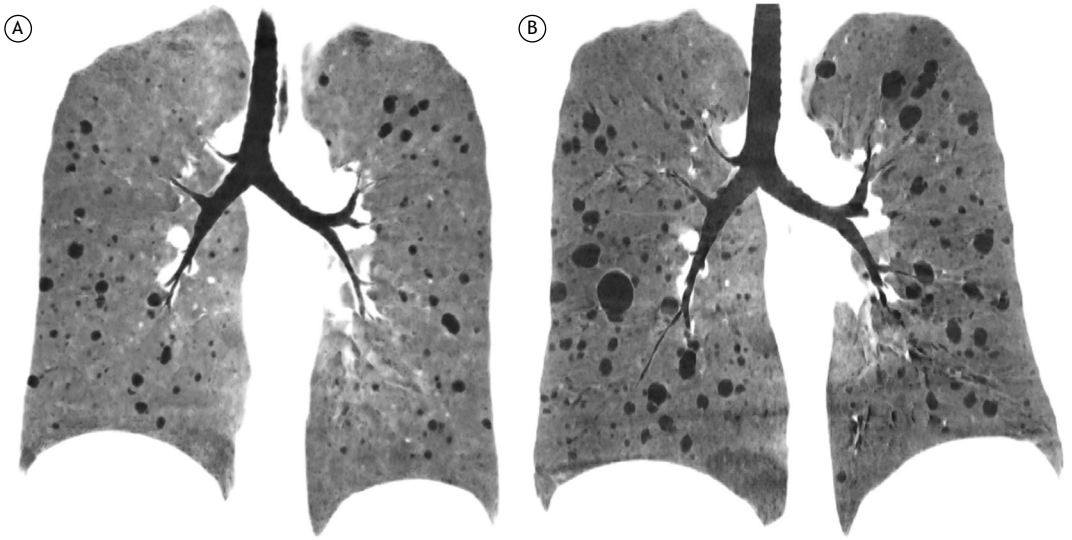

Figure 4. Evolution of the cystic pulmonary manifestation of lymphangioleiomyomatosis. Coronal CT scans of the chest, with minimum-intensity projection reconstruction, obtained at baseline (A) and at five years after diagnosis (B), showing progression of the condition, with increases in the number and size of the cysts.

morphology. LAM cells predominantly form nodules (Figure 5A), although small cell clusters can be found scattered throughout the lung parenchyma.[61] Spindle-shaped cells express specific smooth muscle proteins, such as smooth muscle actin (Figure 5B), desmin, and vimentin, and form the core of the nodule, surrounded by epithelioid cells that exhibit immunoreactivity for the HMB-45 antibody (Figure 5C), which binds to the glycoprotein gp100, a marker of melanocytes.[62] Spindle-shaped cells appear to represent a component with greater proliferative activity and are more closely related to the destruction of lung connective tissue due to the release of MMPs.[63,64] Spindle-shaped cells show abundant staining for MMPs, mainly MMP-2, MMP-9, and MT1-MMP.[60,64]

The gold standard marker for the diagnosis of LAM is HMB-45, which has high specificity but has variable sensitivity when the biopsy specimen is small.[55,65,66] Beta-catenin (Figure 5D) can be a useful marker due to its high sensitivity, with labeling of both cell subtypes, and high specificity, because it is not expressed in the smooth muscle of airway or vascular walls.[67] Cathepsin K, a papain-like cysteine protease with matrix degradation activity, appears to be more sensitive than is HMB-45 for the diagnosis of the disease.[66] In addition, LAM cells express estrogen and progesterone hormone receptors.[18,68] The role of estrogen in disease progression is not yet fully established, although there is evidence that it signals through AKT.[62]

The cause of TSC is a germline mutation in the *TSC1* gene or *TSC2* gene, located on chromosomes 9q34 and 16p13, respectively.[63,69,70] Acquired mutations in those genes are likely the cause of sporadic LAM, with mutations occurring more frequently in *TSC2* than in *TSC1*. Both are tumor suppressor genes, and loss of heterozygosity for *TSC2* has been reported in LAM lesions of the lung and kidney.[71]

The tumor suppressor genes *TSC1* and *TSC2* encode the proteins hamartin and tuberin, respectively. The phenotypic and symptomatic similarities between patients carrying *TSC1* mutations and those carrying *TSC2* mutations suggest that the functions of hamartin and tuberin are intertwined in the cellular signaling pathway.[69] Characterization of the *TSC1* and *TSC2* genes has allowed functional studies that have led to the current understanding of the signaling pathways for hamartin and tuberin.[63] The hamartin-tuberin complex acts as a GTPase-activating protein against Rheb (a Ras homologue enriched in the brain), which regulates mTOR signaling. Phosphorylation and activation of the p70 ribosomal protein S6 kinase by mTOR leads to activation of the ribosomal protein S6 via phosphorylation at Ser240\244. The mTOR signaling pathway plays a central role in regulating cell growth in response to growth factors, cellular energy, and nutrient levels.[72,73] The hamartin-tuberin complex negatively regulates Rheb by converting Rheb-GTP to Rheb-GDP, thus inactivating Rheb and inhibiting mTOR.[74] Therefore, dysfunction in the encoding of these proteins results in dysregulation of signals,

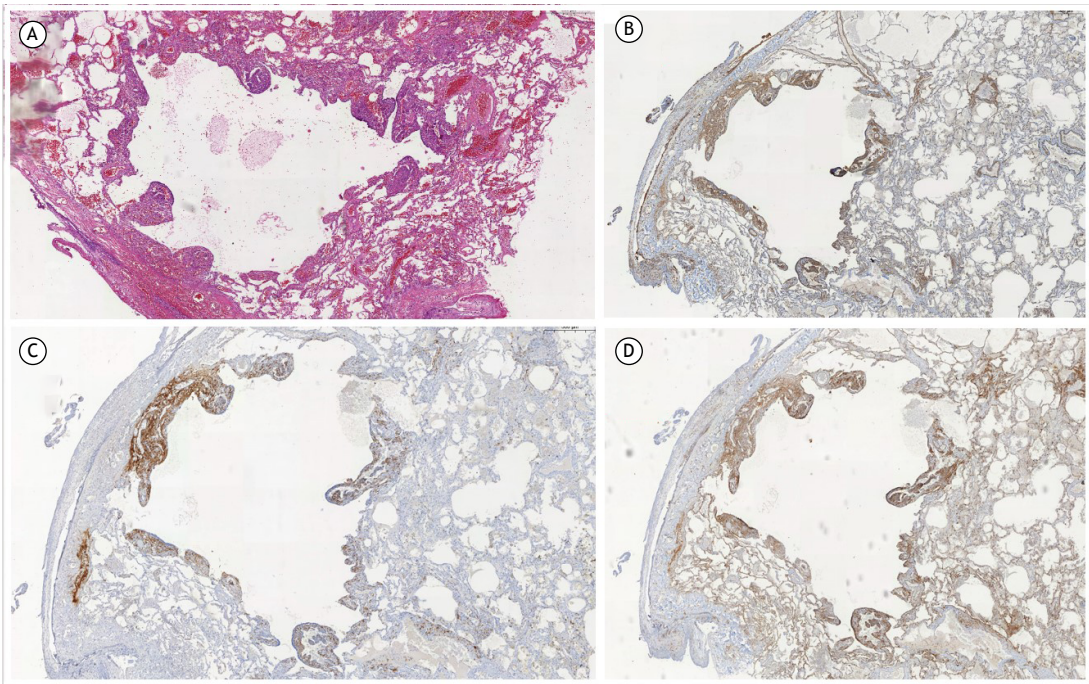

Figure 5. Photomicrographs demonstrating histopathological and immunohistochemical aspects in a patient with lymphangioleiomyomatosis (LAM). A) Proliferation of LAM cells with formation of small nodules throughout a pulmonary cystic lesion (H&E). B) Immunohistochemistry showing LAM cells that stained positive for smooth muscle actin (B); HMB-45 (C); and beta-catenin (D, membrane and cytoplasmic patterns).

such as those related to cell surface receptor tyrosine kinase and G-protein-coupled receptor. Constitutive activation of mTOR kinase and S6 kinase leads to increased protein translation, with inappropriate cell proliferation, migration, and invasion.[75]

Six-minute walk test and cardiopulmonary exercise test

Reduced exercise tolerance is common in LAM, and examinations performed at rest might not reveal any alterations; in fact, many patients have normal PFT results. In this context, it is important that patients be evaluated during exercise-based examinations, such as the six-minute walk test (6MWT) and incremental cardiopulmonary exercise testing (CPET).[31,76]

The 6MWT is a submaximal test, and the main parameter evaluated is the six-minute walk distance (6MWD). Although it is an important test for assessment of the severity and progression of LAM, the result is often normal, even in patients with functional limitations. A study conducted in Brazil demonstrated that patients with LAM walked approximately 90% of the predicted 6MWD, but 35% of those patients showed ≥ 4% desaturation.[77]

One recent study of patients with LAM evaluated the desaturation-distance ratio (DDR), an index calculated from the ratio between the desaturation area and the 6MWD or the distance walked on the shuttle walk test with Holter oximetry, which has been correlated with a reduction in FEV_1, a reduction in DL_{CO}, and air trapping. The DDR shows promise in the functional assessment of LAM, because it expands the analysis of isolated parameters of the 6MWT.[78]

Although CPET provides a more comprehensive and maximal assessment, with analysis of metabolic, ventilatory, and cardiovascular variables, it is less widely available and more expensive. It is indicated when there is uncertainty about the cause of dyspnea on exertion and is important to help define training parameters in pulmonary rehabilitation.[31,77] Reduced exercise capacity and maximal oxygen consumption are common findings in LAM, especially in patients with more advanced disease.[76-78] The mechanisms of exercise limitation in LAM are often multifactorial, including ventilatory limitation, dynamic hyperinflation, reduced gas exchange, pulmonary hypertension (PH), and peripheral muscle fatigue.[31,76]

Echocardiogram and PH

Echocardiography is an essential tool in the evaluation of various pulmonary conditions and can aid in the management of the disease, especially when PH is suspected. The main objectives of echocardiography in LAM include the evaluation of the heart chambers and the occurrence of PH, a possible complication of the disease.[79,80]

Changes in the lung parenchyma associated with LAM can lead to PH, that may determine right ventricular overload, which can lead to heart failure and worsening of dyspnea. The PH associated with LAM is usually classified as group III (resulting from parenchymal disease or hypoxemia), has a low (≤ 10%) prevalence, and is usually mild in intensity.[79,81,82] A reduction in DL_{CO} increases the sensitivity for predicting the occurrence of PH, especially when it is ≤ 40% of predicted.[79] When echocardiography is combined with the assessment of DL_{CO}, invasive hemodynamic assessment becomes increasingly less indicated in LAM.[79,80] Other parameters can be evaluated to raise the suspicion of PH in LAM, such as the ratio between the diameter of the pulmonary artery and that of the aorta on chest CT.[83]

Although PH at rest is rare in LAM, an increase in pulmonary artery pressure at low levels of exertion occurs more frequently, affecting up to 60% of patients.[81] Exercise-induced PH in LAM is believed to be related not only to hypoxic pulmonary vasoconstriction (precapillary PH) but also to a significant increase in pulmonary capillary wedge pressure, probably secondary to diastolic dysfunction (postcapillary PH).[84] Therefore, the effects that LAM has on pulmonary function could also have repercussions for cardiac involvement, and echocardiography can provide additional information for the overall assessment of the impact of the disease. Identifying the relationship between pulmonary changes and cardiac complications could aid in the management of the disease and in optimizing patient quality of life. The frequency of echocardiography in LAM should be individualized, and there is still no consistent evidence for the specific treatment of PH in patients with the disease.

Diagnostic algorithm

Chart 1 presents the main clinical characteristics and ancillary examinations. Figure 6 shows the algorithm for the diagnostic approach to LAM.

TREATMENT

The indications for the use of mTOR inhibitors and a summary of the main therapeutic measures in LAM are presented in Charts 2 and 3, respectively.

mTOR inhibitors

The main medications used in the treatment of LAM are mTOR inhibitors, especially sirolimus.[26] A randomized, placebo-controlled trial of patients with LAM who had an FEV_1 ≤ 70% of predicted demonstrated that a 12-month course of sirolimus slowed the decline in lung function, improved patient quality of life, and reduced serum VEGF-D levels.[38,85] The patients were followed for 12 months after discontinuation of the medication, during which period there was resumption of the decline in lung function.[38] Other studies have demonstrated the benefit of sirolimus in LAM, in terms of its effects on functional loss and involvement of the lung parenchyma on chest CT, as well as a reduction in mortality.[37,44,86-89]

Chart 1. Main characteristics of lymphangioleiomyomatosis seen on clinical examinations and ancillary tests.

Clinical characteristics that can be seen over the course of the disease	- Asymptomatic - Progressive dyspnea on exertion - Pneumothorax - Cough, wheezing - Hemoptysis, hemoptoic sputum - Chylothorax, chyloptysis - Chylous ascites, chyluria - Renal angiomyolipoma - Abdominal and pelvic lymphangioleiomyomas - Dermatological manifestations, such as Shagreen patches, facial angiofibromas, periungual fibromas, and hypomelanotic macules - Neurological manifestations, such as subependymal nodules, cortical tubers, giant cell astrocytomas, seizures, and cognitive impairment - Retinal hamartoma - Cardiac rhabdomyoma
Lung function	- Normal (in up to 50% of cases) - Reduction of DL_{CO} (in 40-60%) - Air trapping (in 40-50%) - Obstructive ventilatory disorder (in 30-50%) - Positive response to bronchodilator (in 15-30%)
Imaging	Chest CT - Diffuse, regular, thin-walled pulmonary cysts - Pneumothorax, chylous pleural effusion - Areas of ground-glass opacity, interlobular septal thickening - Dilation of the thoracic duct - Mediastinal lymph nodes enlargement - Micronodules (multifocal and multinodular hyperplasia of pneumocytes) - Sclerotic bone lesions - Relationship between the diameter of the pulmonary artery and the aorta can increase CT/MRI of abdomen and pelvis - Renal and hepatic angiomyolipomas - Lymphangioleiomyomas CT/MRI of the skull - Cortical tubers - Subependymal astrocytoma - Subependymal nodules
Serum VEGF-D	- Can be normal - > 800 pg/mL (high specificity)
Histopathological features	- Spindle cells (SMA, beta-catenin, MMPs) - Epithelioid cells (HMB-45, beta-catenin) - Formation of nodules - Lung cysts
Six-minute walk test	- Reduced distance covered - Desaturation above 4%
Cardiopulmonary exercise test	- Reduced maximum oxygen consumption - Multifactorial limitation (ventilatory, dynamic hyperinflation, altered gas exchange, PH and peripheral muscle)
Echocardiogram	- Mainly group III PH - Mild PH (in < 10% of cases)

SMA: smooth muscle actin; PH: pulmonary hypertension; and MMPs: metalloproteinases.

Sirolimus is indicated for pulmonary involvement in LAM when the FEV_1 is < 70% of predicted, when the annual decline in FEV_1 is ≥ 90 mL, or when there is hypoxemia (at rest or on exertion).[2,26,27] Its benefits extend to premenopausal and menopausal women alike.[20] Sirolimus is highly effective in improving extrapulmonary manifestations, such as renal angiomyolipomas, lymphangioleiomyomas, and chylous effusions. For renal angiomyolipomas, the drug is indicated when the tumor is > 4 cm in diameter.[25-27] For chylous effusions, it is recommended that mTOR inhibitors be used before invasive procedures are indicated.[26]

Although recurrent pneumothorax is not yet a definitive indication for mTOR inhibitors, sirolimus appears to reduce the risk of it.[90,91] Therefore,

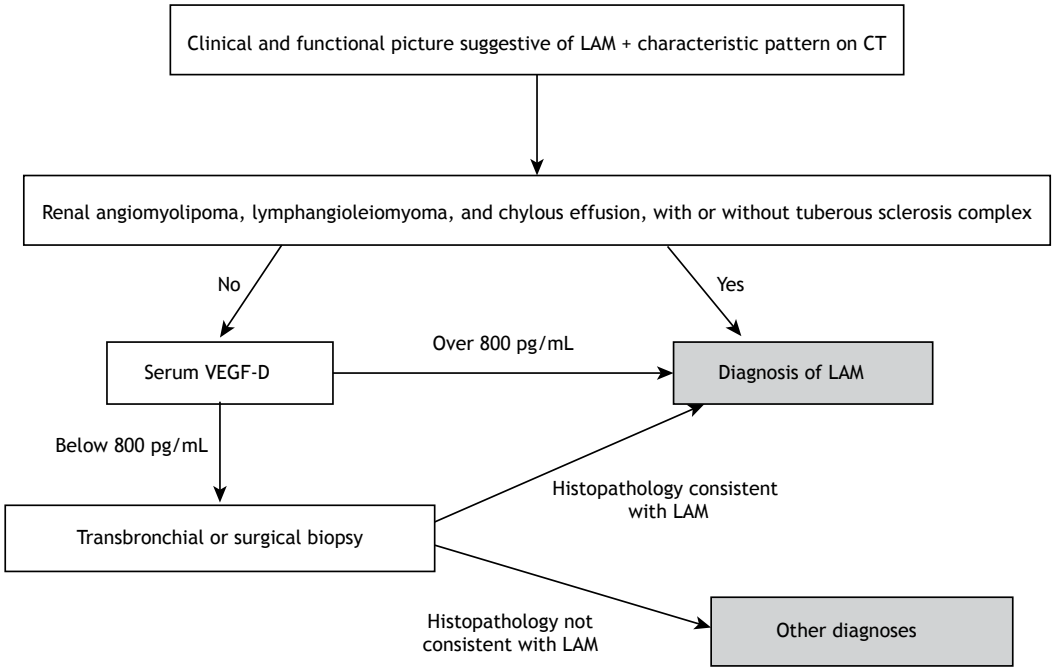

Figure 6. Algorithm for the diagnostic approach to lymphangioleiomyomatosis (LAM).

Chart 2. Main indications for the use of mTOR inhibitors in lymphangioleiomyomatosis.

Pulmonary involvement	- FEV_1 ≤ 70% predicted - Annual drop in FEV_1 ≥ 90 mL - Hypoxemia at rest or on exertion - Recurrent pneumothorax*
Extrapulmonary manifestations	- Renal angiomyolipomas ≥ 4 cm diameter - Symptomatic abdominal and pelvic lymphangioleiomyomas - Symptomatic chylous effusions

*Although the benefits are not yet fully established, mTOR inhibitor use can be considered if there is recurrent pneumothorax.

its use can be considered for cases of recurrent pneumothorax in LAM.

Sirolimus is generally well tolerated, and adverse effects are mild, occurring mainly in the first six months of use.[26,92] The serum level of the drug should be monitored, and the recommendation is that it be maintained between 5 ng/mL and 15 ng/mL. The most common adverse events are mucositis, diarrhea, abdominal pain, nausea, hypercholesterolemia, hyperglycemia, acne, upper respiratory tract infections, menstrual changes, lower limb edema, anemia, lymphopenia, and thrombocytopenia.[2,26,38]

The ideal initial and maintenance doses of sirolimus have yet to be fully established.[2] It has been shown that even in patients with serum levels < 5 ng/mL, there can be improvement or stabilization of lung function and resolution of chylous effusions, suggesting that in these situations, the initial dose can be lower, such as 1 mg/day.[86,89] We recommend an initial oral sirolimus dose of 1-2 mg/day, with serum levels measured two weeks after initiation, then monthly for three months, and every three months thereafter.

It should be borne in mind that sirolimus is not a curative or definitive treatment and should be given continuously and indefinitely or at least until the onset of menopause, when the progression of the condition can be assessed from the hormonal decline.[26,38] Various studies have shown that sirolimus is safe and effective in the long term, with low rates of discontinuation and serious adverse events, as well as having beneficial effects on lung function, exercise capacity, quality of life, renal angiomyolipoma, lymphangioleiomyomas, chylous effusions, and serum VEGF-D.[92-94] Long-term benefits have been demonstrated for premenopausal and menopausal women alike.[94] Long-term adverse events are similar to those described during the first year of treatment.[92-94]

Only a few studies have evaluated the use of everolimus in LAM, demonstrating benefits on functional decline and exercise capacity, with an adverse event profile similar to that of sirolimus.[95] Everolimus can be considered an alternative in cases of intolerance of or refractoriness to sirolimus.

Sirolimus is approved for the treatment of LAM in Brazil. Details regarding the use of mTOR inhibitors in the context of lung transplantation and complications are described below, in specific items.

Chart 3. Other therapeutic approaches in lymphangioleiomyomatosis.

Inhaled bronchodilators	- Symptomatic patients with obstructed lung function, especially if they show a positive bronchodilator response
Pneumothorax	- Treat after the initial episode due to the high risk of recurrence - Pleurodesis with talc, mechanical abrasion or pleurectomy - Trend toward indication of mTOR inhibitors for recurrent pneumothorax
Chylothorax	- mTOR inhibitors for symptomatic and persistent cases - A low-fat diet rich in medium-chain triglycerides or pleural drainage might be necessary, temporarily - Ligation or embolization of the thoracic duct with or without pleurodesis for refractory cases
Renal angiomyolipoma	- mTOR inhibitors, if ≥ 4 cm diameter or symptomatic - Arterial embolization for bleeding or if there are microaneurysms ≥ 5 mm in diameter - Partial nephrectomy for refractory cases or if kidney cancer is suspected or confirmed
Lymphangioleiomyoma	- mTOR inhibitors, if symptoms occur
Rehabilitation and physical exercise	- Rehabilitation with monitoring for patients with severe functional impairment, desaturation, cardiovascular risk, or fall risk - Recommend physical activity, even outside of the rehabilitation regimen, for those without severe limitations and without contraindications - Ideal: aerobic and strength exercise - No increase in effort-related adverse events
Supplemental oxygen	- PaO_2 ≤ 55 mmHg at rest - PaO_2 of 56-59 mmHg at rest, if PH, edema due to heart failure, or hematocrit above 55% - During exertion and sleep, if hypoxemia occurs
Lung transplant	- FEV_1 < 30% of predicted; hypoxemia at rest; New York Heart Association functional class III or IV; or progressive functional loss despite optimized treatment

PH: pulmonary hypertension; and mTOR: mechanistic target of rapamycin.

Inhaled bronchodilators

Inhaled bronchodilators can be used in symptomatic patients with airway obstruction, especially if there is a positive bronchodilator response, and should be continued if there is clinical improvement.[27,33,96-98] Inhaled corticosteroids are not recommended in the management of LAM.[27]

Approach to pneumothorax

Pneumothorax is a common complication of LAM; 30-50% of patients will experience it during the course of the disease.[3,12,99-101] The reported risk of pneumothorax recurrence is high, reaching 70%.[19,99,101] One prospective study demonstrated that there was no relationship between the occurrence/number of pneumothorax events and functional decline, progression to death, or the need for lung transplantation.[30]

Patients with LAM should be informed of the increased risk of pneumothorax and how to recognize its signs and symptoms, facilitating its early detection. A retrospective study demonstrated that the incidence of pneumothorax was higher in women with LAM than in the general female population and that the risk of developing pneumothorax was three times higher after air transport.[102]

Immediate, definitive treatment of pneumothorax is recommended after the initial episode.[28,30] It should be emphasized that prior pleurodesis is not a contraindication for lung transplantation, supporting its indication after the initial pneumothorax.[2,28] There is still no consensus regarding the ideal method of pleurodesis in LAM. Talc pleurodesis is the technique of choice at most referral centers in Brazil. However, pleurodesis by mechanical abrasion or pleurectomy can also be performed but, in Brazil, is generally reserved for cases of recurrent pneumothorax or pneumothorax refractory to other procedures.[3] It is recommended that patients avoid air travel for at least four weeks after undergoing a pleural procedure.[102]

Recently, an alternative to pleurodesis, with pleural coverage of the entire visceral surface of the lung by video-assisted thoracoscopy, was described as a treatment for LAM, effectively reducing the recurrence of pneumothorax without causing ventilatory impairment or pleural adhesion. However, this technique is still limited to a few centers.[103]

Inhibitors of mTOR appear to reduce the risk of pneumothorax recurrence, and it is recommended that they be discontinued for at least one week before and two to four weeks after pleurodesis, to allow adequate healing.[90,91,104] Therefore, although it is not yet considered a definitive indication in LAM, the use of sirolimus can be recommended for cases of recurrent pneumothorax, whether or not the case meets the other criteria for its use.

Chart 4. Other relevant topics in the approach to lymphangioleiomyomatosis.

Vaccination	- Avoid live virus vaccines if using mTOR inhibitors - Influenza vaccine - Pneumococcal vaccine - Recombinant vaccine against herpes zoster virus (for all > 50 years of age and all using mTOR inhibitors regardless of age) - COVID-19 vaccine
Air travel	Risk of pneumothorax - The decision of whether to travel must be made on a case-by-case basis - Avoid in cases of severe lung function impairment, extensive cysts on CT, or history of recurrent pneumothorax Supplemental oxygen in flight - No need for supplemental oxygen if SpO_2 > 95% - perform 6MWT if SpO_2 is 92-95%; use supplemental oxygen if SpO_2 ≤ 84% on 6MWT - If SpO_2 < 92%, supplemental oxygen is required
Gestation	- Individualize recommendations - Periodic PFT - Can result in a worsening of pulmonary functional decline, obstetric complications, and LAM (pneumothorax, chylous effusions, and progression of renal angiomyolipoma and lymphangioleiomyomas) - No absolute contraindication if lung function is preserved or there is mild limitation without progression - mTOR inhibitors: should generally be discontinued; consider starting or maintaining in specific situations, at low doses
Contraception and hormone replacement therapy	- Avoid medications containing estrogen - Topical vaginal estrogen can be considered - Avoid infertility treatment - Possible methods: copper or progesterone intrauterine devices; progesterone, partner vasectomy and barrier devices
Osteoporosis	- Perform bone densitometry periodically - Treatment with calcium, vitamin D, and bisphosphonates - Resistance and muscle strength training

LAM: lymphangioleiomyomatosis; mTOR: mechanistic target of rapamycin; PFT: pulmonary function test; and 6MWT: six-minute walk test.

Approach to chylothorax

In LAM, chylothorax, which occurs in 10-30% of cases, is caused by rupture or blockage of the thoracic duct or one of its branches by LAM cells or by transdiaphragmatic flow of chylous ascites, mainly being unilateral (in the right hemithorax).[3,105,106]

In LAM, effusions have a variable clinical course and can remain stable over time. Periodic monitoring, with or without thoracentesis, is usually sufficient for small, asymptomatic chylothorax.[106] In cases of symptomatic, persistent chylothorax, treatment with sirolimus is indicated and patients typically respond well. Chylothorax can take up to a year to resolve after the start of treatment with sirolimus, often requiring additional therapy with a low-fat diet rich in medium-chain triglycerides or with pleural drainage until a consistent effect of the drug is achieved.[25,107] If the patient already begins or continues to have high chylothorax output after the initial measures, fasting and total parenteral nutrition can be initiated.[108,109]

An invasive approach should be considered only after treatment with sirolimus has been attempted.[87,107] In patients with sirolimus-resistant chylous complications or with contraindications to sirolimus, surgical ligation of the thoracic duct, with or without pleurodesis, is suggested. Pleurodesis can be performed by talc abrasion.[110] Although percutaneous interventional radiology techniques are available to embolize the duct in chylothorax, there have been no studies showing consistent results in LAM.[111] Scintigraphy or MRI of the lymphatic vasculature and transfer to a referral center for LAM are recommended if surgical or percutaneous management of chylothorax is necessary. For sirolimus-resistant cases, switching to everolimus can also be considered.

Approach to renal angiomyolipoma

Angiomyolipomas are common in LAM and are characterized as benign tumors of mesenchymal origin, rich in fat, muscle tissue, and blood vessels; they can be found in the kidneys, liver, intestine, and bladder.[2,3,12] Although renal angiomyolipomas are generally small, mostly unilateral and asymptomatic, they can evolve to hemorrhage and a high risk of death, especially if they are > 4 cm in diameter or have aneurysmal vascularization.[2] They are usually asymptomatic, although there can be mild abdominal pain, hemorrhage, and renal failure (requiring dialysis and kidney transplantation).[2,19]

Few renal angiomyolipomas require treatment; when treatment is required, the primary goals are to prevent bleeding and preserve renal function.[27,112] Treatment is required if there are symptoms such as abdominal pain and vomiting, as well as if the tumor

is ≥ 4 cm in diameter, if there is exophytic growth, if there are microaneurysms ≥ 5 mm in diameter, or if the tumor is highly vascularized, all of which increase the risk of bleeding.[113] There are three therapeutic options: mTOR inhibitors, arterial embolization by catheterization, and tumor resection surgery.[2,113]

Arterial embolization can reduce the tumor volume by up to 80%, although there is a risk of recurrence and kidney damage due to the procedure, which is therefore reserved for cases of bleeding or for embolization of intratumoral microaneurysms with a diameter ≥ 5 mm.[2,113-115]

For the treatment of renal angiomyolipoma, mTOR inhibitors are highly effective.[26] A phase II trial evaluated 20 patients with renal angiomyolipoma and found a 53% reduction in lesion volume after 12 months of treatment with sirolimus, with an increase in tumor volume after the drug was discontinued.[116] Two other studies demonstrated similar results.[117,118] A double-blind, randomized clinical trial evaluated the use of 10 mg/day of everolimus in patients with renal angiomyolipoma.[112] After six months of treatment, 55% of the patients in the everolimus group showed a reduction of at least 50% in tumor volume and 80% of those patients showed a reduction of at least 30% in total volume, with this effect increasing after two years of use.[112,119,120]

The efficacy and safety of mTOR pathway inhibitors have made them the standard treatment for renal angiomyolipomas associated with TSC or sporadic LAM. However, the ideal duration of treatment has not been established, and treatment should be continued indefinitely as long as there is a clinical and radiological response.[2,113] In cases of drug intolerance, an intermittent regimen can be tried, with the medication being discontinued when the tumor has shrunk to a diameter < 4.0 cm and resumed when new tumor growth occurs.[121]

Nephrectomy, usually partial, is indicated only in rare cases, especially those in which the response to other treatments is inadequate or kidney cancer is suspected or confirmed.[27]

Approach to lymphangioleiomyomas

Infiltration of lymphatic tissue by LAM cells can cause lymph node enlargement, chylous effusions, and lymphangioleiomyomas (in up to 16% of cases), especially in the abdominal and pelvic cavities.[2,3] Biopsy and surgical resection of lymphangioleiomyomas should be avoided. To our knowledge, there have been no randomized clinical trials evaluating treatment with mTOR inhibitors in patients with lymphangioleiomyomas. However, case series have shown good clinical and radiological responses after the use of these medications, with a significant reduction or disappearance of the lesion after six months of treatment.[25,122,123] The effect of the drug appears to have an early onset, often two weeks after the start of treatment. Asymptomatic lesions can simply be monitored, without the need for treatment. Inhibitors of mTOR are indicated for symptomatic cases, especially those in which there is abdominal discomfort or pain, and should be continued at least until the lesions in question resolve.[123]

Rehabilitation and physical exercise

Pulmonary rehabilitation, including aerobic and strength exercises, improves exercise capacity in LAM, as demonstrated by increased endurance/improved metabolic variables on constant-load CPET, increased 6MWD,[77,124,125] and better quality of life.[77,124] One study demonstrated that yoga practice increases the 6MWD and the maximum load in the maximum CPET in LAM.[126] Among studies of patients with LAM who engage in guided physical exercise, no increased risk of adverse events, such as pneumothorax, was observed during the exercise.[31,77,78] Pulmonary rehabilitation should be considered for all patients with LAM who have limited physical activity, supporting the need for physician indication and monitoring.[77]

A remote rehabilitation program based on cell phone-guided exercises with heart rate and SpO_2 monitoring demonstrated safety and increased 6MWD.[125] Although evidence is limited, it is recommended that physical activity be encouraged, even outside of a formal rehabilitation program, for patients who, after a comprehensive medical evaluation, do not exhibit severe functional impairment, significant desaturation on exertion, significant cardiovascular risk, or a risk of falling.[77,127] Considering the current evidence and the pathophysiology of LAM, greater emphasis on aerobic exercise is suggested.[128] Patients with pneumothorax should wait at least four weeks after resolution of the condition to start physical activity.[127]

Hormonal blockade

In patients with LAM, various therapies for hormonal blockade have been proposed and evaluated, including bilateral oophorectomy, as well as the use of gonadotropin-releasing hormone agonists, aromatase inhibitors, tamoxifen, and progesterone, although none of them have produced consistent results.[2,129-133] As presented in international guidelines, hormonal blockade is not recommended for the treatment of LAM, despite very low-quality evidence to support or discourage it. Additional studies are needed in order to evaluate the role of hormonal blockade in combination with mTOR inhibitors for the treatment of the disease. It should be borne in mind that hormonal methods, especially those employing progesterone alone, can be used for contraceptive purposes.[26]

Oxygen therapy

The recommendation for long-term oxygen therapy in LAM is extrapolated from information obtained from research in patients with severe COPD, because, to our knowledge, there have been no studies evaluating the benefits of supplemental oxygen in this disease.

Supplemental oxygen is recommended for patients with a PaO_2 ≤ 55 mmHg on room air at rest and for those with a PaO_2 of 56-59 mmHg who also have PH, edema due to heart failure, or hematocrit above 55%. Treatment aims to maintain SpO_2 above 90% and should be carried out for ≥ 15 h/day, including the sleep period.[134,135] Supplemental oxygen should be considered when there is hypoxemia during exertion or during sleep.[134]

Lung transplantation

Patients with LAM should be referred for lung transplant evaluation when the disease is advanced, with end-stage respiratory failure, characterized by an FEV_1 below 30% of predicted, resting hypoxemia, a New York Heart Association functional class III or IV, or progressive functional loss despite treatment.[2,27,136,137]

Patients with LAM who undergo lung transplantation have similar or better outcomes than do patients with other lung diseases, possibly because they are typically younger and usually have fewer comorbidities.[2,138,139] Studies of patients with LAM in various regions of the world, including Brazil, have demonstrated rates of survival at 1, 3, 5, and 10 years after lung transplantation of 79-94%, 73-90%, 73-77%, and 56-74%, respectively.[138-142]

Although it increases the risk of bleeding during or after the procedure, prior pleurodesis does not contraindicate lung transplantation. Bilateral transplantation is recommended.[27,137] It should also be borne in mind that recurrence of LAM after lung transplantation is rare and usually has no clinical or functional repercussions.[139,140,143]

For patients on the lung transplant waiting list, it is recommended that mTOR inhibitors be maintained during the waiting period and discontinued immediately before the procedure.[137,138,144,145] Reducing the dose of the medication in the pre-transplant period can be considered.[144] Maintaining mTOR inhibitors after transplantation increases the risk of bronchial anastomotic dehiscence by interfering with healing.[2,146] In this context, it is suggested that the medication be restarted after complete healing of the bronchial anastomosis, which typically occurs 3 months after transplantation.[138,146] The use of mTOR inhibitors should be evaluated after transplantation in LAM, because it could be important for controlling extrapulmonary manifestations and preventing pulmonary recurrence of the disease.[141]

OTHER RELEVANT TOPICS

Chart 4 summarizes other relevant topics regarding LAM.

Vaccination

Patients with LAM should keep their vaccinations up to date, and those taking mTOR inhibitors should not receive live virus vaccines.[2] It is essential that the administration of vaccines be discussed with the professional who is treating the patient.

Annual immunization against the influenza virus with inactivated vaccine is recommended for all patients with LAM, as is immunization with pneumococcal vaccine. The use of recombinant vaccine against herpes zoster virus is recommended for all patients with LAM who are ≥ 50 years of age and for those taking mTOR inhibitors, regardless of age.[2] Vaccination against COVID-19 using messenger RNA technology has been shown to be safe and effective, and a recent study of patients with LAM demonstrated that the response levels were similar between the patients who were taking sirolimus and those who were not.[147]

Air travel

Two issues related to air travel are relevant in patients with LAM: the need for supplemental oxygen; and the potential risk of pneumothorax. Most patients can travel safely, especially if lung function is normal or only mildly impaired.[102,148-150] Patients should not travel by air until at least four weeks after resolution of pneumothorax.[27]

It has been speculated that air travel increases the risk of pneumothorax in patients with LAM due to the rupture of subpleural cysts, induced by changes in cabin air pressure.[149] However, there have been few studies on the safety of air travel in patients with LAM, and the answers to this question are not completely clear. The incidence of pneumothorax has been shown to be approximately 1,000 times higher in women with LAM than in the general female population, the risk has been shown to be three times higher after air travel, and chemical or surgical pleurodesis has been shown to partially reduce the risk of pneumothorax recurrence in flight.[102] In another study of patients with LAM, using a questionnaire-based assessment of air travels, 2% were found to have had a pneumothorax during the flight.[150] However, a retrospective study of 281 patients with LAM demonstrated that the occurrence of air travel-related pneumothorax might be more related to the high incidence of this complication in the disease than to the travel itself.[151] Therefore, travel recommendations should be individualized. Patients with symptoms that have not been elucidated before a scheduled flight, especially dyspnea and chest pain, should not board. It is recommended that patients with reduced pulmonary reserve or with high-risk characteristics, such as large cyst extension, severe impairment of lung function, and a history of multiple pneumothoraces, seek alternative modes of travel.

Air travel can expose patients with chronic respiratory diseases, including LAM, to the effects of acute hypoxemia at altitude, with the risks of worsening symptoms and complications during the flight.[134] These risks will be especially high in patients with LAM who already have hypoxemia, even if only mild or moderate, at ground level.[152]

Patients with chronic lung disease, including LAM, with an SpO_2 > 95% on room air can fly without supplemental oxygen. Conversely, those with an SpO_2 < 92% should receive supplemental oxygen during

the flight. Patients with an SpO_2 between 92% and 95% should be submitted to a 6MWT or a simulated high-altitude hypoxia test, the latter of which is not widely available.[134,152] Patients who have an SpO_2 ≤ 84% persistently during either of those tests will require supplemental oxygen during the flight.[134,153] Patients requiring a flow rate > 4 L/min to correct hypoxemia should be discouraged from flying and, if they do, should use air medical transport.[134,154]

LAM and COVID-19

During the COVID-19 pandemic, the risk of death was found to be higher among patients with interstitial lung disease and the prognosis was found to be worse among those with an FVC < 80% of the predicted value.[155,156] A retrospective multicenter study evaluated 91 patients with LAM who reported having had COVID-19, and only one death was observed among those patients. Multivariate analysis showed that DL_{CO} was a determinant of the risk of hospitalization and of the need for supplemental oxygen. The authors concluded that LAM did not increase the risk of death or of the progression to long COVID and that the use of mTOR inhibitors did not alter the prognosis.[157]

Gestation

The population mainly affected by LAM is that of women of reproductive age, and its pathogenesis is partly related to female hormones, especially estrogen.[158] Pregnancy is one of the most challenging periods for patients with LAM, mainly because of the high estrogen levels, although more consistent data are needed for a better understanding.[159,160] The diagnosis of LAM can be established during or after pregnancy. Patients often report avoiding pregnancy because of the increased risk of complications.[161,162]

There is evidence, albeit of low quality, that pregnancy can result in accelerated clinical and functional progression or complications, such as pneumothorax and chylothorax, in patients with LAM.[158-164] One retrospective study of pregnant patients with LAM produced results suggestive of disease progression during pregnancy, showing that the mean FEV_1 fell from 77 ± 19% of predicted before pregnancy to 64 ± 25% of predicted after pregnancy, whereas the mean DL_{CO} fell from 66 ± 26% to 57 ± 26% of predicted, respectively.[159] Spontaneous pneumothorax occurs in 25-30% of patients during pregnancy and can be the initial manifestation of the disease.[159,161]

During pregnancy, it can be necessary to take an invasive approach to LAM-related pleural complications, such as chest tube drainage, pleurodesis, and pleurectomy.[160] Pregnancy can also provoke extrathoracic complications of LAM, such as growth, rupture, and bleeding of renal angiomyolipomas, as well as increased volume of abdominal or pelvic lymphangioleiomyomas, and chylous ascites.[160,162,163,165] The risk of obstetric complications, such as premature birth, fetal growth restriction, and spontaneous abortion, is also elevated in LAM.[158,162-164] There is as yet no consensus regarding the most appropriate mode of delivery for women with LAM.[162] However, pregnancy can proceed without relevant complications for the fetus or the patient with LAM, especially if the patient is stable and has normal or only mildly altered lung function.[160,163] The factors determining a higher risk of pregnancy-related complications in LAM have not yet been definitively established.

The safety of mTOR inhibitors during pregnancy in LAM has not yet been established, and they are classified as category C; that is, they have unknown fetal teratogenicity and their use is not an absolute contraindication.[166] There have been reports describing the use of sirolimus during pregnancy, without fetal complications.[163,164,167,168] It is suggested that mTOR inhibitors be discontinued at least 12 weeks in advance and that their use be avoided during pregnancy, especially in the first trimester, as well as during breastfeeding.[164,168] However, their discontinuation during pregnancy can lead to increased dyspnea, as well as hypoxemia and pneumothorax, as well as the worsening of extrapulmonary complications. In this context, in patients with advanced or progressive pulmonary impairment, it is possible to consider starting or maintaining sirolimus, preferably in low doses (≤ 1 mg/day), preferably from the second trimester of pregnancy. Therefore, the indication for starting or maintaining sirolimus during pregnancy must be individualized, and additional studies are needed in order to establish its efficacy and safety in this context.

Counseling to pursue or avoid pregnancy should be individualized, based on the clinical and functional status of the patient, their history of pneumothorax, chylothorax, and renal angiomyolipoma, as well as their need for sirolimus, taking into consideration their desires, cultural background, spiritual beliefs, and life goals. Patients should be informed of the risk of gestational complications, for themselves and the fetus. Serial PFT is recommended during pregnancy, and its frequency should be individualized. For pregnant women with LAM-TSC, genetic counseling is also recommended.

Contraception and hormone replacement therapy

Female hormones, especially estrogen, are involved in the pathophysiology and development of LAM.[19,169] The fact that it occurs predominantly in women of reproductive age and the slowing of lung function decline after menopause, together with reports of disease progression after exogenous estrogen supplementation and during pregnancy,[19,170] support this hormonal effect. Although treatment with several hormonal agents, including estrogen modulators, progesterone, aromatase inhibitors, and gonadotropin-releasing hormone analogues, have been evaluated for the management of LAM, as has

oophorectomy, none of those therapies have yielded consistent results in terms of their effects on disease progression.[19,129-131,171]

Hormone replacement therapy, estrogen-containing contraceptives, and infertility treatment should be avoided in patients with LAM because of the potential risk of disease progression and of the development of pulmonary and extrapulmonary complications. Topical estrogen for the treatment of vaginal atrophy can be considered.[19,169,172]

The options for contraceptive methods in patients with LAM include copper or progesterone intrauterine devices, progesterone via subcutaneous or oral implant, partner vasectomy, and barrier devices, and the choice among those options should be individualized.[19]

Osteoporosis

Reduced bone mineral density occurs in up to 70% of patients with LAM and is correlated with age and disease severity, probably related to reduced physical activity in patients with dyspnea and functional limitation, as well as to natural or induced menopause and the use of corticosteroids in transplant recipients.[173]

Although hormone replacement therapy is associated with an increase in bone mineral density, it is contraindicated in LAM because of the risk of progression related to estrogen use. Periodic bone densitometry is recommended in LAM, particularly in menopausal patients and those with greater functional impairment. Treatment with calcium, vitamin D, and bisphosphonates is indicated in patients with osteoporosis, in patients with osteopenia associated with severe functional impairment, and in patients on the transplant waiting list. Resistance and strength training should be encouraged.[173]

PROGNOSIS

The natural history and prognosis of LAM remain incompletely understood; most analyses of the topic have been retrospective studies, and methodologies have been heterogeneous across studies.[174] Although early studies reported that the median survival among patients with LAM was 8-10 years after diagnosis, data obtained more recently have suggested a better prognosis.[170,174–176] Studies conducted in the United States have demonstrated a transplant-free survival rate of over 20 years in LAM,[30,174] whereas a study conducted in the United Kingdom showed that the 10-year survival rate from symptom onset was 91%.[100]

Clinical, functional, laboratory, and CT variables have been evaluated as potential prognostic factors in LAM. Menopause reduces the rate of decline in FEV_1 and the risk of progression to death or lung transplantation.[20,130] One of the studies conducted in the United States supported this concept, showing that premenopausal women had a faster rate of decline in lung function and a higher risk of death, as well as being more likely to require lung transplantation, in comparison with those who were postmenopausal.[30] In women with LAM, pregnancy and infertility treatment increase the risk of worsening lung function and the occurrence of complications, such as pneumothorax and growth of renal angiomyolipomas, as well as the risk of premature delivery and spontaneous abortion.[7,30,177,178]

Functional evolution associated with the presence of TSC has controversial results. Another study conducted in the United States demonstrated no difference in functional decline between patients with LAM-TSC and those with the sporadic form,[32] whereas a recent study conducted in Brazil showed that LAM-TSC is associated with a smaller longitudinal reduction in lung function.[3]

The evaluation of lung function is useful for establishing baseline severity and facilitating the monitoring of disease progression. A FEV_1 < 70% predicted, a reduced FEV_1/FVC ratio, elevated TLC, and reduced DL_{CO} are predictors of a poor prognosis.[35,130] The rate of decline in FEV_1 is associated with the extent of pulmonary cysts on chest CT.[35] Patients with a significant bronchodilator response tend to have more severe disease and more accelerated functional decline, possibly related to greater cell proliferation.[96,130]

Serum VEGF-D has potential prognostic relevance in LAM, with elevated levels being associated with the severity of the pulmonary impairment, reduced exercise tolerance, and the presence of lymphangioleiomyomas or lymphadenopathy.[30,85,179] However, there is still a lack of evidence that elevated VEGF-D levels are associated with a higher risk of death or lung transplantation.[30] The extent of pulmonary cysts on CT is associated with the severity and rate of decline of pulmonary function in LAM,[30,49] thus constituting another method of prognostic assessment.

FOLLOW-UP

If possible, patients with LAM should be monitored at referral centers. During follow-up, the severity, rate of progression, complications, and emergence of comorbidities can be identified, as can the tolerance and effectiveness of treatment. The frequency and interval of consultations and ancillary examinations should be individualized and are influenced by the clinical picture, severity, and rate of progression of the disease, as well as the need for monitoring of the treatment. It is generally recommended that consultations be conducted every 3-6 months in the first year after diagnosis and, if the condition is stable, every 6-12 months thereafter.

In patients with LAM, disease progression should be monitored with serial PFT. Simple spirometry with bronchodilator testing is recommended every 3-6 months in the first year after diagnosis; then every 3-12 months depending on progression. Annual plethysmography and DL_{CO} measurement are also recommended. Chest CT scans are recommended every 2-3 years if the condition is stable. If there

is progression or emergence of new symptoms, functional decline, or suspected complications such as pneumothorax, CT scans should be performed immediately and their frequency should be reassessed.

In the monitoring of renal angiomyolipomas and abdominal lymphangioleiomyomas, it is recommended that abdominal MRI or CT be performed every year, every 2 years, or immediately if progression or complications are suspected. For screening, abdominal ultrasound can be performed every 2–3 years for patients without such manifestations.[27]

For patients taking sirolimus, it is recommended that laboratory tests be performed 2-3 weeks after starting the medication or changing the dose, then every 3-6 months, and those tests should include a complete blood count, creatinine, transaminases, alkaline phosphatase, gamma-glutamyltransferase, bilirubin, total cholesterol (and fractions), triglycerides, sodium, potassium, magnesium, calcium, phosphorus, blood glucose, and serum sirolimus.[27] For elective surgeries, it is recommended that sirolimus be discontinued 1-2 weeks before and resumed 2 weeks after.

The need for breast cancer screening as indicated for each age group should also be emphasized. One retrospective study demonstrated a higher risk of estrogen receptor-positive breast cancer in LAM.[180] In addition, a recent study conducted in Japan showed an increased risk of lung cancer in nonsmoking patients with LAM, suggesting that attention be paid to this aspect during follow-up.[181]

For patients with LAM who have extrapulmonary manifestations, specialized monitoring by multidisciplinary team (including a nephrologist, a neurologist, a dermatologist, and others) is also recommended. In cases of pneumothorax and chylothorax, the participation of a thoracic surgeon facilitates the therapeutic decision-making. For patients with impaired quality of life and mental health challenges, it is important to provide psychological evaluation and support services.

PERSPECTIVES

New biomarkers

There is a need to expand the spectrum of biomarkers, which are important for diagnostic, prognostic, and therapeutic response assessment, to those other than VEGF-D, several of which have recently been studied in LAM, although none are yet used in the clinical routine.

In patients with LAM, MMPs, especially MMP-2, are involved in the degradation of the extracellular matrix and cystic destruction of the lung parenchyma.[182] Another promising marker is fibroblast growth factor 23 (FGF23), a protein secreted by osteocytes that is essential for maintaining serum phosphate homeostasis, which is dysregulated in human diseases that affect bone mineral density. Chronic lung diseases such as COPD and idiopathic pulmonary fibrosis have been associated with FGF23. Serum FGF23 levels differentiate LAM patients from controls, the levels being higher in the former, and lower FGF23 levels are associated with reduced DL_{CO}.[183]

Studies employing machine learning are promising. An analysis using this methodology on serum samples from study participants found that the biomarker combination of VEGF-D + EFNA4 + IGHD + GDNF + TKT showed high accuracy in predicting a decline in FEV_1 within 6 months.[184]

Use of mTOR inhibitors in patients with normal lung function

The use of sirolimus only in patients with LAM with functional impairment, as established in one study, somewhat limits the real-world prospects for treatment.[38] The medication appears to have similar stabilization potential in patients with different degrees of severity, even among postmenopausal patients, suggesting its benefit in mild disease.[20] In addition, maintaining even low serum levels of sirolimus appears to be sufficient for a favorable effect on PFT and its stabilizing action, even before the lung damage has been reversed, making it attractive to initiate the treatment earlier, without waiting for significant functional impairment.[89]

It has been suggested that sirolimus is best used when there is loss of lung function (typically ≥ 90 mL/year) and that stable patients, especially menopausal patients, can be followed without treatment, even if they have PFT results indicate of impairment.[28] The use of low-dose sirolimus in patients with normal PFT results has the potential to prevent long-term complications and is the subject of an ongoing clinical trial.[185] At this point, additional factors such as age, menopausal status, extrapulmonary manifestations, recurrent pneumothorax, and significant cell proliferation on biopsy can be taken into account in defining the best treatment strategy.

New treatments

It is essential that new pharmacological therapies in LAM be investigated, given that treatment with sirolimus is not definitive, can provoke adverse events, and needs to be maintained continuously, as well as the potential for the development of drug resistance. However, conducting clinical trials in LAM poses many difficulties, including a lack of investment to recruit patients for international multicenter studies, clinical heterogeneity, the rarity of the disease, and ethical questions regarding the randomization of patients to a control group, given that a number of drugs have been approved for the treatment of LAM.[186] New medications have been studied as potential therapeutic options in LAM, although their use is not yet recommended in daily practice.

Drugs that inhibit autophagy, such as hydroxychloroquine and chloroquine, have proven effective for tumor reduction and inhibition of cell survival when combined with sirolimus. A phase I study

demonstrated safety, good tolerance, and favorable effects of this combination.[187] The combination of resveratrol, which acts on the autophagy process, with sirolimus demonstrated good tolerance and safety, with reduced VEGF-D levels and improved quality of life.[188]

Nintedanib, an intracellular inhibitor of tyrosine kinases such as the platelet-derived growth factor receptor, which is active in LAM lesions, was investigated in a phase II trial as a possible second-line therapy for LAM patients who are refractory to or present with adverse events due to sirolimus use, demonstrating good tolerance but without improvement in FEV_1.[189]

Although other medications, such as nitazoxanide, aromatase inhibitors, immunotherapeutics, and simvastatin have been studied, there are still no consistent results supporting their use in LAM.[190-193]

FINAL CONSIDERATIONS

Defined as a low-grade neoplasm, LAM is considered to have metastatic potential, although the origin of its cells is as yet unknown. Several advances have been made in the last two decades, mainly in relation to pathophysiology and management, such as the use of serum VEGF-D levels in the investigation, a systematic diagnostic approach, and the use of mTOR inhibitors as a therapeutic option. The aim of this document was to present the main points related to the approach to LAM, including some practical aspects for its management and for improving the daily lives of patients with the disease. Given the multisystemic nature of the disease, there is a need for a multidisciplinary approach. It should be borne in mind that there is still no definitive, curative treatment for LAM, and that there is a need for new, noninvasive tools for its diagnostic confirmation, the development of which is expected in the near future.

AUTHOR CONTRIBUTIONS

BGB, PHRF, and CRRC: study design; drafting of the manuscript; analysis and interpretation of data; revision and approval of the final version.

ASR, AFA, CSGF, CHC, EVM, ECTN, MAS, MJJR, MRO, TSG, and PPTST: drafting of the manuscript; analysis and interpretation of data; revision and approval of the final version.

CONFLICTS OF INTEREST

None declared.

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Joint statement on evidence-based practices in mechanical ventilation: suggestions from two Brazilian medical societies

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ABSTRACT

Mechanical ventilation can be a life-saving intervention, but its implementation requires a multidisciplinary approach, with an understanding of its indications and contraindications due to the potential for complications. The management of mechanical ventilation should be part of the curricula during clinical training; however, trainees and practicing professionals frequently report low confidence in managing mechanical ventilation, often seeking additional sources of knowledge. Review articles, consensus statements and clinical practice guidelines have become important sources of guidance in mechanical ventilation, and although clinical practice guidelines offer rigorously developed recommendations, they take a long time to develop and can address only a limited number of clinical questions. The *Associação de Medicina Intensiva Brasileira* and the *Sociedade Brasileira de Pneumologia e Tisiologia* sponsored the development of a joint statement addressing all aspects of mechanical ventilation, which was divided into 38 topics. Seventy-five experts from all regions of Brazil worked in pairs to perform scoping reviews, searching for publications on their specific topic of mechanical ventilation in the last 20 years in the highest impact factor journals in the areas of intensive care, pulmonology, and anesthesiology. Each pair produced suggestions and considerations on their topics, which were presented to the entire group in a plenary session for modification when necessary and approval. The result was a comprehensive document encompassing all aspects of mechanical ventilation to provide guidance at the bedside. In this article, we report the methodology used to produce the document and highlight the most important suggestions and considerations of the document, which has been made available to the public in Portuguese.

Keywords: Respiration, artificial; Practice guidelines as topic; Noninvasive ventilation; Ventilator weaning; Intensive care units

INTRODUCTION

Invasive and noninvasive mechanical ventilation (MV) is essential in the treatment of patients with acute respiratory failure and is the most frequently implemented support measure in intensive care units (ICUs).[1,2] Although it is a life-saving measure, MV requires an understanding of its indications, contraindications, and management, as it can be associated with complications, especially when it is implemented inappropriately.[3] Because it is used mainly in severe or potentially severe patients, it involves complex coordination between healthcare providers, including respiratory therapists, nurses, physicians, and other specialists, to ensure optimal patient care, proper ventilator management and timely interventions to avoid complications.

The management of MV is a core competency in critical care training and should be part of the undergraduate curricula in medicine, nursing and physiotherapy, as well as residency and subspecialization in critical care.[4] However, trainees and practicing professionals often report low confidence in managing MV patients and performing basic adjustments[5,6] and seek other sources of knowledge about MV. Since the 1990s, review articles and consensus statements on MV have become important sources of guidance for clinicians.[7] In recent years, most consensuses have employed the Grading of Recommendations Assessment, Development and Evaluation (GRADE) methodology[8] to establish clinical

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practice guidelines.[9-11] This methodology is accepted as the best strategy for providing recommendations based on evidence, but because extensive work is needed to formulate recommendations based on a limited number of clinical questions, it may not be suitable if the intention is to provide a comprehensive document encompassing all aspects of a broad topic, such as MV.

In 2013, the *Associação de Medicina Intensiva Brasileira* (AMIB) and the *Sociedade Brasileira de Pneumologia e Tisiologia* (SBPT) published the Brazilian Recommendations for Mechanical Ventilation.[12,13] Twenty-nine topics related to MV and suggestions for MV management were given for most clinical situations. Although a systematic methodology such as the GRADE was not adopted, the document became an important source of guidance for clinicians in Brazil. It was published as a research article in two parts and as a manual in PDF, which could be consulted at the bedside. Since then, new studies have been conducted and published, as well as guidelines on different aspects of ventilatory support, coordinated by different medical societies.[9-11,14-16] In addition, during the coronavirus disease 2019 (COVID-19) pandemic, when many patients required MV, the complexity of the conditions that require ventilatory support and the need for capacity building among healthcare professionals became clear.[17]

As a result, in 2023, AMIB and SBPT sponsored a project to update the recommendations. In this article, we report the methodology used to produce the document and highlight the most important suggestions and considerations of the document, which has been made available to the public (https://indd.adobe.com/view/017f739a-847f-4587-9bef-15b9c01756ba).

METHODOLOGY

The Organizing Committee selected 38 topics related to MV for patients with respiratory failure and other indications of MV that were addressed in this document. Each society indicated members who were considered experts in the field and involved in research and/or teaching of MV in Brazil to be invited to participate in the project. After a formal invitation and confirmation of those who were able to participate in the project, the group of experts was confirmed with 75 participants. The experts were all health care professionals specializing in intensive care, including physicians, nurses, physiotherapists, speech therapists, dentists, and nutritionists. They predominantly worked in the Southeast Region of Brazil (67%), with another 17% from the South Region, 10% from the Northeast Region, 5% from the Central West Region and 1% from the North Region. The participants were divided to work in pairs, and each topic was assigned to a pair of experts. The content to be addressed by each pair in their respective theme was previously determined by the organizing committee at the time of the invitation. Expertise and previous experience with their theme were taken into account when inviting each pair.

The pairs searched PubMed and the Cochrane Central Register of Controlled Trials databases for articles published on the topic. The search was limited to the last twenty years and focused on, but was not limited to, journals in the following areas: Intensive Care, Pulmonology, and Anesthesiology, including the journals of the respective Brazilian societies in these specialties: Critical Care Science (formerly the Revista Brasileira de Medicina Intensiva), the *Jornal Brasileiro de Pneumologia*, and the *Revista Brasileira de Anestesiologia*. Based on the results, each pair produced a text relevant to their topic and sent it to the organizing committee, with their respective bibliographic references. The format adopted to provide guidance was as follows: Comment (brief explanation of the topic to be addressed), followed by suggestions and considerations, as defined in table 1.

In addition, we used "Suggestion" for statements based on documents developed by national and international health authorities, such as the World Health Organization or Ministry of Health, and for statements based on well-established medical society guidelines, such as the Advanced Cardiovascular Life Support (ACLS) guidelines. The content prepared by each pair was then compiled and summarized by the Organizing Committee, which prepared all the topics for the pairs to present at a face-to-face meeting held on November 20 and 21, 2023, in Florianópolis, Santa Catarina, Brazil, prior to the Brazilian Congress of Intensive Care Medicine. During the meeting, all pairs presented their suggestions and considerations, submitting them to the evaluation and appreciation of all those present. The plenary held its manifestations freely, and all the suggestions were discussed. When there was no consensus and two alternatives for formulating suggestions/considerations remained after ample discussion, the two alternatives were presented for electronic voting using an anonymous system.

At the end of this stage, the organizing committee compiled the text sent by all the pairs and made the agreed-upon adjustments after the plenary session. The revised document was sent to each expert for review or final adjustments. Finally, the organizing committee reviewed the final edition of the unified document with all the themes.

The document included multidisciplinary topics, such as nursing, physiotherapy, nutrition, speech therapy, and dentistry. New topics were added, such as ventilation-induced lung injury (VILI), extracorporeal membrane oxygenation (ECMO), MV in pregnant women, MV in the transport of patients, ICU-acquired weakness, MV in palliative care patients and a specific topic for prone positioning. Table 2

Table 1. Definitions of suggestions and considerations used in the document.

Terms used	Definition and level of evidence	Example
Comment	• Brief explanation of the topic to be addressed	• The use of the prone position for patients under mechanical ventilation has gained prominence in the last decade due to the improvement in the clinical outcome of patients with severe and moderate ARDS
Suggestion	• When the use of an intervention or monitoring is indicated, or not indicated, based on at least one randomized trial with low risk of bias or on at least one meta-analysis with low risk of bias • Statements based on documents developed by national and international health authorities, such as the World Health Organization or Ministry of Health, and for statements based on well-established medical society guidelines, such as the Advanced Cardiovascular Life Support guidelines	• *"We suggest using a tidal volume of 4 - 8mL/kg of predicted weight for patients with ARDS"* • *"Place all components to be sent for high-level disinfection (respiratory valve, active humidifier, flow sensor, and expiratory tube, if used, and other connectors and components) in a closed container designated for transport to the sterilization unit"*
Consideration	• When the use of an intervention or monitoring is or is not to be considered, based on randomized studies or meta-analyses with high or undetermined risk of bias, observational studies (cohorts or case-controls) or the opinions of the experts	• "Consider the use of controlled initial respiratory rate between 12 - 16bpm, in the initial adjustment of the mechanical ventilator"

ARDS - acute respiratory distress syndrome; bpm - breaths per minute.

shows the list of topics covered in the document and the most relevant suggestions and considerations for each topic.

COMMENTS

The experts made a total of 100 suggestions and 288 considerations in relation to the 38 themes (Figure 1). Consensus with a simple majority was reached during the plenary session for almost all suggestions/considerations, and electronic voting was required for four of the most controversial issues. Table 2 shows the most relevant suggestions and considerations for each topic and the four topics that required discussion. To access all the suggestions and considerations, please refer to the original document, which is freely available on the two societies' websites (https://indd.adobe.com/view/017f739a-847f-4587-9bef-15b9c01756ba).

FINAL COMMENTS

The development of a practical bedside document and the updating of the previous Brazilian recommendations for mechanical ventilation led to a collaborative effort between AMIB and SBPT. The experts reviewed the latest evidence related to the care of patients undergoing MV, following the proposed methodology. This process generated suggestions and considerations, which were initially discussed and voted on in a plenary meeting and then reviewed by the organizing committee before being published. This document has been made publicly available and is being disseminated by both professional societies to provide guidance at the bedside across the country.

Clinical practice guidelines are considered valuable instruments for narrowing the gap between research findings and actual clinical practice.[18-20] These tools enhance and standardize treatment, optimize patient care, and potentially reduce mortality rates and healthcare costs.[21-23] but are still underutilized in clinical settings.[24] Additionally, there is a need for locally developed clinical guidelines and treatment protocols in low- and middle-income countries (LMICs), as resource limitations may prevent the application of guidelines developed in high-resource settings.[25] Simply translating guidelines and treatment protocols produced in high-resource settings is not enough, as the context in which they are applied is different.

The development of this bedside guide can help fill that gap. Providing guidance on a series of topics related to MV addresses an unmet need in an area with a high burden of disease.[26,27] A large observation study performed in 2013 in several Brazilian ICUs revealed that the mortality of patients under MV was higher than that in high income countries.[26] During the COVID-19 pandemic, the strain imposed on an already overstressed healthcare system led to extremely high mortality in patients who required MV in Brazil.[17,28-30] Although worse outcomes have been reported across the globe, considerable variation has been reported, showing that some ICUs are more resilient and are able to adapt and respond to strain with less impact on patient outcomes.[31] Among many components, a resilient ICU invests in the implementation of evidence-based practices and staff training. For example, the use of protective ventilatory strategies[28] and timely use of noninvasive ventilation[29] are associated with lower mortality, suggesting that the implementation

Table 2. Highlights on each topic of the *Associação de Medicina Intensiva Brasileira* and *Sociedade Brasileira de Pneumologia e Tisiologia* Mechanical Ventilation Suggestions and Considerations.

	Topic	Highlights
1	Indication of noninvasive and invasive ventilatory support*	**Regarding NIV in ARDS** **Consider:** • NIV can be performed in mild to moderate ARDS in selected locations with rigorous clinical monitoring of the response to avoid delays in intubation in case of failure • Do not use NIV in severe ARDS cases with PaO_2/FiO_2 < 100mmHg
2	Noninvasive strategies in acute respiratory failure	**Regarding the use of HFNC** **Suggested:** • Can be used as the first choice of respiratory support for mild to moderate hypoxemia with hemodynamic stability • Use postextubation, alone or in association with NIV for high-risk patients
3	Intubation and tracheostomy	**Regarding the evaluation of the patient to be intubated** **Suggested:** • Use a validated tool for the evaluation and identification of potential difficult airway in planning orotracheal intubation • Identify patients with anatomical and/or physiological difficult airways **Consider:** • Use videolaryngoscopy for patients with a MACOCHA airway score ≥ 3
4	Conventional ventilatory modes and initial adjustment of the invasive ventilator	**Regarding initial parameters and conduct of invasive MV** **Suggested:** • Use predicted body weight for calculating prescribed VT • Use an initial tidal volume of 6 to 8mL/Kg of predicted body weight • Adjust PEEP and FiO_2 relationships individually aiming for an SpO_2 of 92 to 96%
5	Advanced ventilatory modes	**Regarding the indication of advanced modes** **Consider:** • May use advanced ventilatory modes in individualized clinical situations provided the user is familiar with their adjustments and the patient's clinical condition is thought to potentially benefit from the specific features of each mode
6	Patient-ventilator asynchrony	**Regarding asynchrony diagnosis** **Consider:** • Search for the presence of asynchronies and their corrections during the evaluation of the patient on MV, observing the frequency of occurrence and types.
7	Monitoring the patients under ventilatory support†	**Regarding ventilatory mechanics monitoring** **Suggested:** • Monitor the presence and value of auto-PEEP regularly **Consider:** • Regularly monitor the respiratory system mechanics, especially in conditions like ARDS, as maintaining parameters at safe levels is associated with lower mortality • Parameters to monitor: Ppeak, Pplat, Pres, DP, auto-PEEP, Rwa, and CSR
8	Monitoring gas exchange	**Regarding arterial blood gases:** **Consider:** • Collect arterial blood gases for all patients on MV approximately 20 minutes after adjusting ventilator parameters and daily during the acute phase.
9	Ventilator alarms	**Consider:** • Develop and ensure adherence to institutional protocols defining minimum adequate alarm adjustment parameters for all patients • From a predefined protocol, individualize alarm limits according to each patient and clinical condition to avoid alarm fatigue
10	Sedation, analgesia and neuromuscular blockade during MV	**Regarding sedation monitoring** **Consider:** • For patients on neuromuscular blocking drugs, monitoring with simplified electroencephalogram equipment may be indicated, as scoring systems cannot determine the level of pain, sedation depth, or the presence of delirium

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Table 2. Highlights on each topic of the *Associação de Medicina Intensiva Brasileira* and *Sociedade Brasileira de Pneumologia e Tisiologia* Mechanical Ventilation Practical Guidelines. (Continued...)

	Topic	Highlights
11	MV for asthma	**Regarding mechanical ventilation in asthma** **Consider:** • Use VCV or PCV modes • VT: 6- to 8mL/kg of predicted weight initially. Depending on the ventilatory mechanics, it may need to be reduced
12	MV for patients with COPD	**Regarding MV goals in AE -COPD** **Consider:** • During intubation, use the largest diameter cannula possible to reduce airway resistance and facilitate secretion removal • Adjust MV to improve oxygenation and ventilation, reduce ventilatory workload, and avoid dynamic hyperinflation • Systematic monitoring of ventilatory mechanics during exacerbation and, when necessary, during assisted ventilation and weaning • Active search for asynchronies, ineffective trigger, and auto-PEEP
13	VAP	**Regarding preventive measures for VAP** **Consider:** • Using an orotracheal tube with subglottic aspiration for patients requiring more than 48 - 72 hours of MV • Monitoring endotracheal tube cuff pressure, maintaining values between 20 and 30cmH_2O, especially during procedures like oral hygiene, position change, and prone position. There is no benefit in continuous or regular monitoring
14	MV for patients with ARDS	**Suggested:** • Adjust tidal volume to 4 - 8mL/kg (predicted weight), initially starting with 6mL/kg and adjusting according to plateau pressure, $PaCO_2$, and pH • Use the lowest possible FiO_2 to maintain SpO_2 between 92% and 96% across all ARDS severity categories. • Adjust ventilatory parameters to limit plateau pressure to ≤ 30cmH_2O. • Avoid using PEEP < 5 cmH_2O for ARDS patients. • Avoid prolonged recruitment maneuvers for ARDS patients. **Consider:** • Use the 2023 definition for diagnosing and classifying ARDS severity. • Limit the driving pressure to less than or equal to 15cmH_2O for all categories of ARDS severity
15	Ventilation in the prone position for intubated patients	**Suggested:** • Prone patients with PaO_2/FiO_2 ≤ 150mmHg with FiO_2 > 60% and PEEP ≥ 5cmH_2O as early as possible, preferably within the first 12 hours after stabilization and hypoxemia confirmation • Discontinue proning sessions when gas exchange improves (PaO_2/FiO_2 > 150mmHg for > 4 hours in supine position) or if two consecutive proning sessions decrease PaO_2/FiO_2 by > 20% compared to the supine position • Interrupt proning if complications arise
16	Preventing VILI	**Regarding VILI** **Suggested:** • Use intermediate tidal volumes (6 - 8mL/kg of predicted weight) for patients without ARDS at risk of developing ARDS • Use moderate PEEP levels (5 - 8cmH_2O) for patients with normal lungs **Consider:** • Monitor patient muscle effort through inspiratory or expiratory pauses • Do not use mechanical power to guide the ventilatory strategy for patients in clinical practice • Jointly assess driving pressure and respiratory rate at the bedside

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Table 2. Highlights on each topic of the *Associação de Medicina Intensiva Brasileira* and *Sociedade Brasileira de Pneumologia e Tisiologia* Mechanical Ventilation Practical Guidelines. (Continued...)

	Topic	Highlights
17	Extracorporeal circulation	**Suggested:** • Indicate ECMO for patients with hypoxemic acute respiratory failure with refractory hypoxemia despite optimized protective MV with PaO_2/FiO_2 < 50mmHg for > 3 hours OR PaO_2/FiO_2 < 80mmHg for > 6 hours • Use ECMO for patients with hypercapnic respiratory failure and pH < 7.25 associated with $PaCO_2$ ≥ 60mmHg for > 6 hours despite optimization of protective ventilatory parameters • Do not routinely use NO for patients with acute respiratory failure and ARDS
18	MV for patients with thoracic trauma	**Consider:** • For more severe patients, particularly with ARDS or other severe clinical situations, initiate deep sedation and adequate analgesia, and start MV with assist-control modes (VCV or PCV) • PCV mode may be superior to VCV mode due to tighter control of maximum airway pressures
19	MV during surgical procedures	**Regarding preoperative evaluation** **Suggested:** • Use MV with VT of 8mL/kg of predicted weight (6 - 10mL/kg) for patients without acute lung injury. • For ARDS patients undergoing surgical procedures, use protective ventilation with VT of 6mL/kg of predicted weight **Consider:** • Assess all patients for the risk of postoperative pulmonary complications using a specific scale. The ASA classification is a subjective scale with low precision
20	MV for obese patients	**Suggested:** • Preventive use of NIV after extubation in obese patients **Consider:** • Objectively assess factors associated with difficult intubation • VT: 6 - 8mL/kg of predicted weight
21	MV for neurological patients	**Regarding PaO_2 and $PaCO_2$ targets** **Suggested:** • Ventilate all potential donors with protective lung ventilation **Consider:** • The ideal PaO_2 target for patients with acute brain injury with or without intracranial hypertension should be between 80 and 120mmHg • The $PaCO_2$ target for patients with acute brain injury with or without intracranial hypertension should be between 35 and 45mmHg
22	MV for neuromuscular patients	**Consider:** • NIV can be employed in acute respiratory failure, respecting contraindications and monitoring failure criteria • Avoid NIV for patients with neuromuscular disease and bulbar involvement or those with bronchial hypersecretion • Initiate MV in assist-control mode with tidal volume of 10mL/kg of predicted weight. Lower VTs are associated with atelectasis in the early days of MV. Subsequently, follow protective ventilation strategies with VT between 6 and 8mL/kg of predicted weight
23	MV for patients with heart disease	**Regarding NIV** **Suggested:** • Use NIV with CPAP or BiPAP for patients with signs of acute respiratory failure caused by cardiogenic pulmonary edema • Do not routinely use NIV for patients with cardiogenic shock • Employ NIV immediately after extubation (prophylactic NIV) to reduce the risk of extubation failure

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Table 2. Highlights on each topic of the *Associação de Medicina Intensiva Brasileira* and *Sociedade Brasileira de Pneumologia e Tisiologia* Mechanical Ventilation Practical Guidelines. (Continued...)

	Topic	Highlights
24	MV for patients undergoing CPR	**Suggested:** • In nonintubated patients, maintain synchronous chest compression with ventilation at a 30:2 ratio. For patients with definitive airways, maintain asynchronous chest compression with ventilation, with 100 to 120 chest compressions/min and 8 to 10 ventilations/minute • Avoid hypoxia or hyperoxia during CPR, as it can worsen the prognosis of cardiac arrest victims • Monitor $ETCO_2$ whenever possible with a target of 20mmHg
25	Weaning the patient from invasive MV	**Suggested:** • Daily evaluation of weaning readiness in all patients on MV for > 24 hours, i.e., readiness for an SBT • Use of a sedation protocol, which can be its daily interruption or adjustment according to established targets • Perform the SBT in PSV mode with a PS level between 5 and 7cmH_2O with PEEP between 0 and 5cmH_2O for 30- to 60 minutes • Apply preventive NIV immediately after extubation for patients at high risk of extubation failure • Apply facilitating NIV for patients with hypercapnic respiratory failure, particularly COPD exacerbation or neuromuscular disease, who fail the SBT • Do not use rescue NIV to avoid reintubation for patients developing acute respiratory failure after extubation
26	Patients with prolonged weaning‡ §	**Suggested:** • For prolonged weaning, perform the SBT in PSV mode with a PSV level between 5 and 7cmH_2O with PEEP between 0 and 5cmH_2O for 30- to 60 minutes **Consider:** • Define prolonged weaning as weaning not completed within 7 days after the first attempt to separate the patient from the ventilator • Before extubating patients who succeed in the SBT, return them to pretest ventilator parameters for approximately 1 hour to rest the patient and reduce the risk of exhaustion after extubation
27	Hemodynamic monitoring and treatment for patients under MV	**Suggested:** • The diagnosis of right and/or left ventricular dysfunction should be performed by echocardiogram to demonstrate the impact of respiratory pressures on the right chambers and the presence of left ventricular dysfunction contributing to pulmonary edema • Do not routinely use a pulmonary artery catheter in ARDS cases • As an adjunctive treatment for right ventricle dysfunction and refractory hypoxia, use the prone position. Use pulmonary vasodilators in selected cases
28	Speech therapy care in the rehabilitation of patients after MV	**Regarding specific care for patients postextubation** **Suggested:** • Implement a multidisciplinary approach for better identification, diagnosis, and treatment of dysphagia, ensuring greater safety in clinical management **Consider:** • Perform speech and swallowing evaluations for all patients who underwent prolonged intubation for ≥ 48 hours or reintubation and have clinical criteria postextubation within 24 - 48 hours
29	Nursing care for patients on invasive and noninvasive ventilatory support	**Suggested:** • Replace heat and moisture exchangers every 7 days (hygroscopic and hydrophobic), provided the device is maintained at the correct height and position relative to the endotracheal tube. In case of dirt, condensation, or damage, the filter should be replaced immediately • Do not routinely change the ventilator circuit; change it only when visible dirt, damage, or prolonged ventilation (> 30 days) occurs **Consider:** • Closed suction catheters should be used to prevent infections and avoid lung derecruitment

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Table 2. Highlights on each topic of the *Associação de Medicina Intensiva Brasileira* and *Sociedade Brasileira de Pneumologia e Tisiologia* Mechanical Ventilation Practical Guidelines. (Continued...)

	Topic	Highlights
30	Physiotherapy care for patients on ventilatory support	**Suggested:** • Secretion removal therapies such as positioning, manual hyperinflation or ventilator, chest wall compression and oscillation should be used to improve oxygenation and secretion elimination in mechanically ventilated patients • Prior to physiotherapeutic care, a physiotherapeutic diagnosis should be made using tools for assessing peripheral muscle strength • Implement inspiratory muscle training for patients ventilated in the ICU for more than 7 days and for those who failed to wean from MV due to respiratory muscle weakness • Avoid the routine use of normal saline (isotonic) instillation during tracheal suctioning procedures, as it has shown potential adverse effects on oxygen saturation and cardiovascular stability, in addition to contributing to VAP **Consider:** • The appropriate dose of early mobilization is defined by clinical efficacy and individual tolerance
31	Nutritional care for patients under MV	**Suggestion:** • When available, it is suggested that the caloric needs of critically ill patients on MV be estimated by indirect calorimetry, considering the clinical condition and frequency of measurement. **Consider:** • Use protocols to guide nutritional therapy for critically ill patients on MV to improve nutritional adequacy outcomes and gastrointestinal symptom management • Perform nutritional screening for critically ill patients on MV within 24- to 48 hours of ICU admission. After identifying nutritional risk, perform a complete nutritional assessment. Use validated tools • Use the enteral route as the first option when the patient is adequately perfused and with a viable gastrointestinal tract
32	Weakness acquired in the ICU	**Suggested:** • There is no gold standard method for diagnosing ICU-acquired muscle weakness • Active early mobilization should be implemented to prevent ICU-acquired muscle weakness • Perform muscle rehabilitation for patients who have already reversed acute illness, have no electrolyte disturbances, and are being nutritionally supported within individual caloric-protein goals
33	Dental care for patients under MV	**Consider:** • Clean teeth with a small-headed soft brush • Clean alveolar ridges, cheek mucosa, lips, palate, tongue dorsum, and portion of the tracheal tube within the mouth with swabs or gauze • Create and implement care and therapeutic intervention protocols
34	Palliative respiratory support	**Regarding noninvasive support strategies** **Consider:** • Use supplemental oxygen for patients with dyspnea and associated hypoxemia and assess symptomatic response • Use NIV for patients with acute respiratory failure due to potentially reversible causes as a palliative technique to relieve dyspnea when the patient is not a candidate for intubation but wishes for other artificial procedures to prolong life • Perform a trial of NIV for terminal patients to provide additional time for patients to complete important end-of-life activities and say goodbye to family members **Regarding palliative extubation** **Suggested:** • Before palliative extubation, hold a family meeting to share information about the procedure, prepare for physical signs of discomfort that may occur, and how these will be monitored and treated, with a variable time until death **Consider:** • Use adjuvant medications preemptively to avoid uncomfortable symptoms associated with palliative extubation • Use a palliative extubation protocol

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Table 2. Highlights on each topic of the *Associação de Medicina Intensiva Brasileira* and *Sociedade Brasileira de Pneumologia e Tisiologia* Mechanical Ventilation Practical Guidelines. (Continued...)

	Topic	Highlights
35	Transport of patients on MV	**Consider:** • A checklist related to necessary items for safe transport can be a guiding tool for the whole team. The patient profile, transport type, distance, and duration will determine the necessary materials, equipment, and team • Minimum required monitoring for safe transport includes: monitor with continuous electrocardiogram, heart rate, respiratory rate, blood pressure, oxygen saturation, $ETCO_2$, and temperature
36	Mechanical ventilation during ICU procedures	**Regarding bronchoscopy** **Consider:** • Do not perform bronchoscopy on patients with hypoxemia that cannot be corrected with supplemental O_2 • Use NIV for nonintubated and high-risk hypoxemic patients **Regarding upper digestive endoscopy** **Suggested:** • Monitor with pulse oximetry, blood pressure, and cardiac monitoring, and observe respiratory activity, consciousness level, and signs of discomfort at the bedside **Consider:** • Use HFNC to reduce hypoxemia risk
37	MV for pregnant women	**Regarding intubation** **Suggested:** • Safe ventilation strategies should be observed for pregnant women as for nonpregnant patients, respecting VT limits of 6 to 8mL/kg of predicted weight. In ARDS cases, use 4 to 8mL/kg of predicted weight **Consider:** • To avoid fetal hypoxemia, maintain maternal $PaO_2 \geq 70mmHg$ or $SatO_2 \geq 95\%$. Maintain $PaCO_2 > 30mmHg$ to avoid placental vasoconstriction • Assess the airway of the pregnant patient, observing the usual predictors of difficult airway. In this case, prefer intubation with videolaryngoscope assistance • During intubation, position the patient with an elevated backrest between 20 and 30º to prevent bronchoaspiration
38	Ventilatory support for patients with COVID-19	**Regarding oxygen therapy, NIV, and HFNC** **Suggested:** • Use VT of 4 - 8mL/kg of predicted weight • Do not perform routine recruitment maneuvers on patients with COVID-19-associated respiratory failure • Use prone position early in intubated patients with COVID-19 with $PaO_2/FiO_2 <$ 150 with PEEP $\geq 5cmH_2O$ for 16 - 20 hours **Consider:** • Measure DP and keep it $\leq 15cmH_2O$ • Start respiratory support with oxygen use to maintain saturation between 92% and 96% • NIV, especially CPAP, has been shown to be superior to high-flow nasal cannula in avoiding orotracheal intubation in COVID-19 patients

Table 2 shows the most relevant suggestions and considerations for each topic. To access all the suggestions and considerations, please refer to the original document, which is freely available on the websites of the two societies. *For topic 1, a vote was necessary to decide if a consideration to intubate patients with a Glasgow coma scale score of 8 or less was to be included (the decision was 65% in favor of using this cutoff); † for topic 7, a vote was necessary to decide if a table with suggested cutoff values was included in the topic (the decision was 73% in favor of including the table); ‡ for topic 26, a vote was necessary to decide between using the term liberation or weaning (the vote was in 80% favor of "weaning"); § for topic 26, a vote was necessary to decide between suggesting the use of PSV and considering the use of a T tube *versus* suggesting that either technique could be used (the vote was 58% in favor of suggesting PSV preferably). NIV - noninvasive ventilation; ARDS - acute respiratory distress syndrome; PaO_2/FiO_2 - ratio of partial pressure of oxygen to the fraction of inspired oxygen; HFNC - high-flow nasal cannula; MV - mechanical ventilation; VT tidal volume PEEP - positive end-expiratory pressure; FiO_2 - fraction of inspired oxygen; SpO_2 - oxygen saturation; Ppeak - peak pressure; Pplat - plateau pressure; Pres - resistive pressure; DP - driving pressure; Raw – airway resistance; Crs - static compliance of the respiratory system; VCV - volume cycled ventilation; PCV - pressure-controlled ventilation; COPD - chronic obstructive pulmonary disease; VAP - ventilator-associated pneumonia; PaO2 - partial pressure of oxygen; $PaCO_2$ - partial pressure of carbon dioxide; VILI - ventilator-induced lung injury; ECMO - extracorporeal membrane oxygenation; NO - nitric oxide; ASA - American Society of Anesthesiologists; CPAP - continuous positive airway pressure; BiPAP - bilevel positive airway pressure; CPR - cardiopulmonary resuscitation; $ETCO_2$ - end-tidal carbon dioxide; SBT - spontaneous breathing trial; PSV - pressure support ventilation; ICU - intensive care unit.

of evidence-based strategies in MV has an impact on patient outcomes, especially in situations of strain.

We produced a comprehensive document addressing 38 topics related to ventilatory support. In almost three quarters of the cases, there were no randomized controlled trials to inform suggestions; therefore, the guidance to readers was less emphatic, with a consideration to use or not use a given intervention. Although the lack of robust evidence prevented us from providing more assertive suggestions on these topics, we believe that the considerations are valuable because evidence in the form of clinical trials is lacking for important topics such as choosing the mode of ventilation or how to adjust the initial settings of a ventilator, which are typically not addressed in clinical practice guidelines produced with methodologies such as GRADE. In the case of specific ventilatory strategies, such as prone positioning, recruitment maneuvers and the use of neuromuscular blockage, more than one randomized controlled trial was available, and a suggestion could be made. Notably, these topics are already covered by two recent clinical practice guidelines and recommendations in the same lines as our suggestions were made.[9,10]

If a lack of training, resulting in low confidence in managing patients under MV among clinicians,[5,6] a lack of adoption of evidence-based strategies in MV[1] and a lack of treatment protocols[32,33] to facilitate the implementation of such strategies contribute to the greater burden of acute respiratory failure in LMICs, these gaps offer a significant opportunity for improvement in outcomes. The dissemination of evidence-based best practices in the form of accessible documents can offer guidance to clinicians at the bedside and inform treatment protocol development. Although the joint statement produced by AMIB and SBPT alone is not sufficient, emphasizing the urgent need for health care capacity building, specialization and training, investments in infrastructure, and other measures to improve healthcare systems and processes of care, it is an important first step.

Despite having been developed to meet the needs of the Brazilian critical care context, two major barriers remain. First, ensuring ample dissemination and consistent adoption.[34] Healthcare professionals' negative attitudes and beliefs, limited integration of guideline recommendations into organizational structures, time and resource constraints and organizational- and system-level changes are identified barriers.[24] Second, inequalities in ICU resources across Brazil will impact the applicability of some of the suggestions and considerations made in the document. For example, we suggest that high-flow nasal cannulas can be used in a variety of scenarios because randomized controlled trials have shown that they are effective for avoiding intubation and reducing mortality in patients with respiratory failure, but many ICUs in Brazil do not have that technology readily available. The same can be said about the recommendation to use ECMO for refractory hypoxemia and expensive monitoring devices, such as end-tidal CO2 and indirect calorimetry. When preparing suggestions and considerations, we aimed to balance the availability of evidence in favor of such interventions and the Brazilian context, recognizing that although many ICUs in Brazil may not have access to interventions that include complex and/or expensive technology, when the evidence is strong in favor of the benefit they offer, it would not be appropriate to refrain from suggesting their use. On the contrary, we believe that the suggestion for use of evidence-based interventions stated in a document endorsed by two respected medical societies can help inform public health policy in Brazil, supporting the incorporation of technologies that have been shown to reduce mortality, such as noninvasive ventilation, high-flow nasal cannulas[29] and ECMO.[35]

The present study has several limitations: the methodology adopted did not include performing systematic reviews and meta-analyses to make recommendations, as is the case with the GRADE methodology, because with so many topics, it would be impractical to adopt this strategy. In addition, we did not formally evaluate the quality of the studies, as the GRADE methodology typically does to formulate recommendations. The experts were instructed to use their own judgment when selecting references. As a result, it is possible that some of the studies used in the document were at high risk of bias. Therefore, no recommendations were made, and we used a different terminology, with suggestions and considerations. The decision to perform a focused review of each theme, instead of systematic reviews and meta-analyses with PICO questions, was made to allow the document to be as comprehensive as possible. The topics and their scopes were determined by the coordinators by informal consensus and were therefore subject to selection bias. In addition, some topics in the document were not examined in clinical trials; therefore, the considerations made about them were based on physiological studies or expert opinions. The document also has strengths: the topics were thoroughly evaluated by professionals recognized as experts in MV, and there was a plenary discussion of all the topics and voting, when necessary, highlighting the robustness of the suggestions and considerations formulated.

CONCLUSION

Evidence-based and up-to-date guidance is essential to ensure that healthcare providers are informed by best practices for the management of patients undergoing mechanical ventilation. This joint statement aims to standardize care, reduce variability in clinical practice, improve patient outcomes, and support teaching in MV. Its implementation can lead to a decrease in complications associated with MV, optimization of the use of resources, and improvement in the quality of patient care.

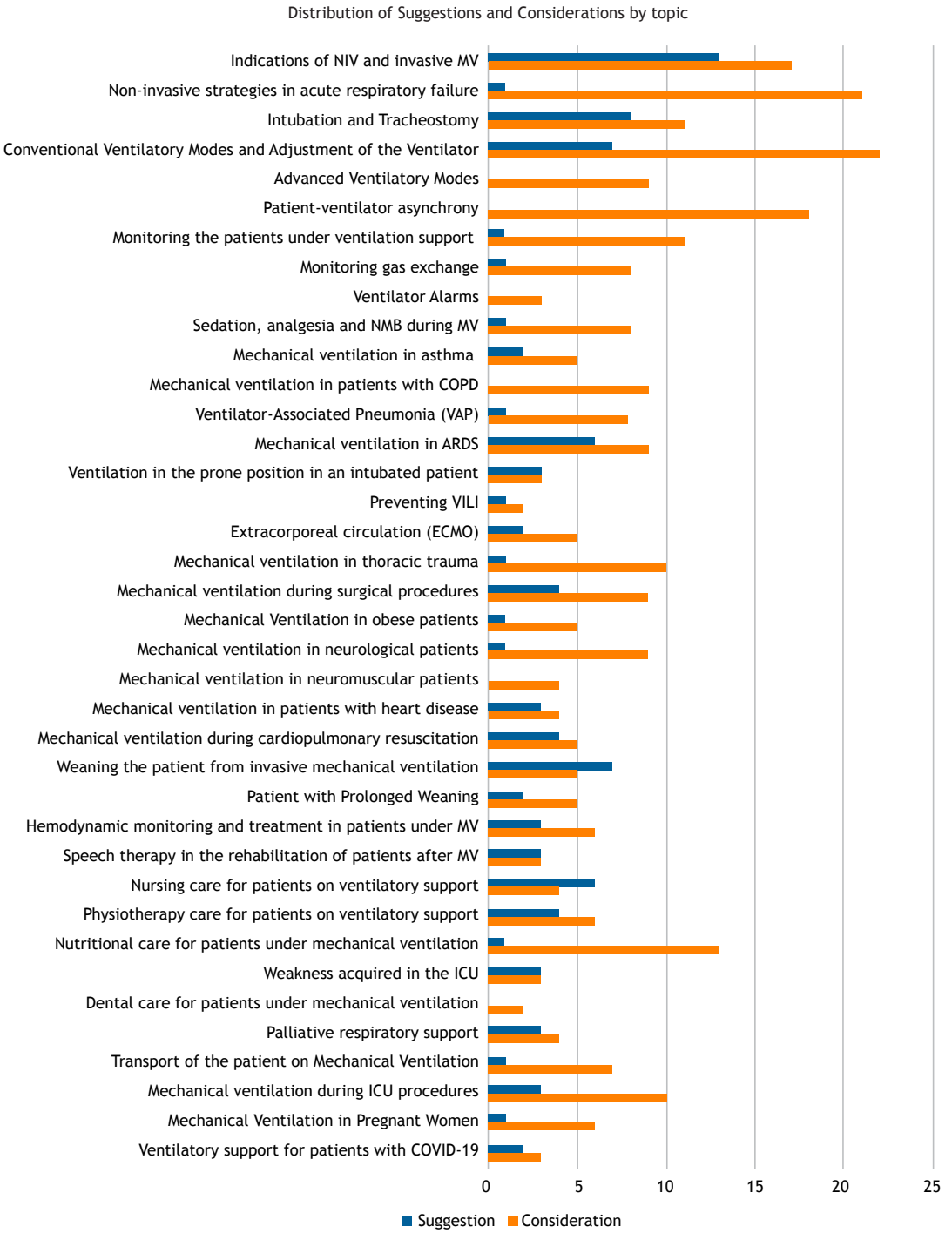

Figure 1. Number of suggestions (blue) and considerations (orange) by topic. NIV - noninvasive ventilation; MV - mechanical ventilation; COPD - chronic obstructive pulmonary disease; ARDS - acute respiratory distress syndrome; VILI - ventilator-induced lung injury; ICU - intensive care unit.

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J. C. Ferreira, A. O. A. Vianna, B. V. Pinheiro, I. S. Maia, S. V. Baldisserotto and A. M. Isola participated in the study conception, coordinated the work to develop the suggestions and considerations and interpreted the results; J. C. Ferreira and A. M. Isola wrote the first draft;

A. O. A. Vianna, B. V. Pinheiro, I. S. Maia and S. V. Baldisserotto revised and edited the manuscript versions. All authors approved the final version of the manuscript. The collaborator authors developed the suggestions and considerations, participated in plenary sessions and approved the final version of the full document.

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Bedaquiline and linezolid regimens for multidrug-resistant tuberculosis: a systematic review and meta-analysis

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ABSTRACT

Objective: Multidrug-resistant tuberculosis (MDR-TB) remains a global public health challenge, complicating treatment strategies and requiring advanced therapeutic approaches. The persistence of MDR-TB has led to a demand for regimens that are more effective in improving treatment outcomes and controlling transmission. This systematic review and meta-analysis sought to examine the efficacy of linezolid (LZD) and bedaquiline (BDQ) in MDR-TB treatment regimens, evaluating their roles in enhancing therapeutic success and informing optimized management of MDR-TB. **Methods:** A comprehensive search was conducted across MEDLINE (PubMed), EMBASE, the Cochrane Central Register of Controlled Trials, Scopus, and Web of Science for randomized controlled trials assessing the efficacy of LZD and BDQ in MDR-TB patients up to September 14, 2024. We analyzed treatment outcomes, reporting favorable outcomes (cured and treatment completed) and unfavorable outcomes (death, treatment failure, and loss to follow-up) with a 95% confidence interval. **Results:** Our analysis included 11 trials, with a total of 1,999 participants. The findings indicate that BDQ+LZD-containing regimens yield significantly higher favorable treatment outcomes (84.5%; 95% CI, 79.8%-88.2%) and lower unfavorable outcomes (15.4%; 95% CI, 11.6%-20.2%). In contrast, regimens lacking either LZD or BDQ show lower efficacy, with favorable outcomes at 66.8% (95% CI, 59.5%-73.4%) and unfavorable outcomes at 33.0% (95% CI, 25.6%-41.4%). **Conclusions:** MDR-TB treatment regimens including BDQ and LZD lead to significantly better patient outcomes. The combined bactericidal and protein synthesis-inhibiting effects of BDQ and LZD create a powerful therapeutic synergy. Adding pretomanid further enhances this effectiveness, highlighting its value in complex cases. Future research should focus on optimizing these regimens for safety and efficacy and explore adjunctive therapies to improve MDR-TB outcomes even further.

Keywords: Linezolid; Tuberculosis; Tuberculosis, multidrug-resistant; Treatment outcome; Systematic review.

INTRODUCTION

Multidrug-resistant tuberculosis (MDR-TB) represents a significant public health threat. The treatment of MDR-TB needs either prolonged regimens involving multiple antibiotics or shorter regimens that include newer and more expensive (or difficult-to-obtain) drugs. This situation may create considerable challenges for health care systems, especially in low- and middle-income countries, where resources are limited.[1-6] The rising incidence of drug-resistant tuberculosis (DR-TB) not only leads to longer and more costly treatments but also exacerbates health disparities, raising urgent concerns for global health and economic stability.[7] As health care systems grapple with the dual burden of rising MDR-TB cases and limited resources, the need for effective and accessible treatment options has never been more critical.

In the last 15 years, the role of linezolid (LZD) and bedaquiline (BDQ) as cornerstones of MDR-TB treatment has emerged, and much has been studied on their safety and efficacy.[8-18] These studies have explored the efficacy of regimens including LZD or BDQ, highlighting their potential to improve treatment outcomes and reduce mortality rates.

In response to the MDR-TB crisis, the WHO revised treatment guidelines in 2022 to recommend combinations of BDQ, LZD, and pretomanid (Pa), with or without moxifloxacin: the all-oral six-month BPaL and BPaLM

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regimens.[19] A further revision occurred in 2024, and the regimens employed in recent clinical trials were recommended as well.[4] These new treatment protocols always include both drugs (i.e., LZD and BDQ), the goal being to enhance therapeutic outcomes and minimize the economic impact on health care systems. Nevertheless, to our knowledge, no previous systematic review and meta-analysis has investigated the combined role of these two core WHO group A drugs.[20-23] Furthermore, the societal implications of these advancements extend beyond clinical efficacy; they encompass economic factors, access to care, and the broader impact of antimicrobial resistance on public health.

The objective of this systematic review and meta-analysis was to examine the efficacy of LZD and BDQ in MDR-TB treatment regimens, evaluating their roles in enhancing therapeutic success and informing optimized management of MDR-TB.

METHODS

Definitions

MDR-TB is characterized as a variant of tuberculosis induced by *Mycobacterium tuberculosis* strains that exhibit resistance to at least two fundamental antituberculosis agents: isoniazid and rifampin. The classification of extensively DR-TB (XDR-TB) has undergone significant refinement over time. Initially, XDR-TB was defined as tuberculosis resulting from MDR-TB strains with additional resistance to any fluoroquinolone and at least one of the three second-line injectable agents: kanamycin, amikacin, or capreomycin.[24,25] The 2021 WHO definition of XDR-TB now describes resistance to group A MDR-TB drugs, which include FLQs, LZD, and BDQ.[26]

Prior to 2021, pre-XDR-TB was informally characterized as MDR-TB exhibiting additional resistance to either fluoroquinolones or second-line injectable agents. However, the WHO has revised the definition of XDR-TB to specify that it must include resistance to a fluoroquinolone and either LZD or BDQ, thereby requiring resistance to two of the three group A drugs.[25-28]

Search strategy

We conducted a comprehensive literature search across five major databases—MEDLINE (PubMed), EMBASE, the Cochrane Central Register of Controlled Trials, Scopus, and Web of Science—from January 1, 2009 to September 14, 2024 to identify randomized controlled trials assessing the efficacy of BDQ and LZD and treatment outcomes in DR-TB. The search employed the following search terms in each database separately: "Tuberculosis," "mycobacterium tuberculosis," "TB," "MTB," "tuberculosis," "Multi-drug resistant," "multi drug resistant," "multi drug-resistant," "multidrug resistant," "multi-drug resistance," "multi drug resistance," "multi drug-resistance," "multidrug resistance," "MDR," "MDR-TB," "extensively drug resistant," "extensively drug-resistant," "extensively drug resistance," "extensively drug-resistance," "extensive drug resistant," "extensive-drug resistant," "extensive drug-resistant," "XDR," "XDR-TB," "Pre-XDR," "Pre-XDR-TB," "pre-XDR TB," "Rifampicin Resistant," "outcome."

This study was conducted and reported by the Preferred Reporting Items for Systematic Reviews and Meta-Analyses statement[29] and was registered with the International Prospective Register of Systematic Reviews (Identifier: CRD42024603453).

Study selection

All collected records were consolidated, and duplicates were eliminated with the use of EndNote X8 (Thomson Reuters, Toronto, ON, Canada). Two reviewers independently screened the titles and abstracts, with disagreements being resolved by a third reviewer. They then assessed the full texts of all potentially eligible studies, and any remaining discrepancies were resolved by the third reviewer.

Eligible studies were selected on the basis of the Population, Intervention, Comparator, and Outcome framework, as follows:

- study design—randomized and nonrandomized controlled trials examining the efficacy of LZD and BDQ in patients with DR-TB
- population—patients ≥ 14 years of age with confirmed DR-TB, including rifampin-resistant tuberculosis, MDR-TB, pre-XDR-TB, and XDR-TB
- intervention—treatment regimens including LZD, BDQ, or both as part of the therapeutic approach to DR-TB
- comparator—comparator arms receiving regimens without LZD and BDQ
- outcome—measured outcomes included treatment success rates, culture conversion, mortality, loss to follow-up, and treatment failure

Articles were excluded if they were cohort studies, case-control studies, cross-sectional studies, case reports/series, reviews, editorials, or conference abstracts. Studies that lacked sufficient data on resistance to LZD and BDQ in DR-TB isolates were also excluded, as were those focusing solely on pregnant women. Additionally, studies not reporting treatment outcomes or using outcomes inconsistent with WHO definitions were omitted.

Data extraction

Two authors systematically extracted data into a predefined Microsoft Excel spreadsheet (Microsoft, Redmond, WA, USA). Any discrepancies were resolved with a third reviewer. The extracted data included parameters such as the first author; publication year; study design; study period; country and setting; patient demographics (including age, male count, BMI, prevalence of diabetes mellitus, tobacco use, HIV status, and clinical forms); treatment outcome definitions; number of DR-TB cases; and treatment

outcomes. A successful outcome was defined as the sum of "cured" and "treatment completed," whereas an unsuccessful outcome included "treatment failure," "loss to follow-up," and "death."

Quality assessment

The quality of the studies was evaluated by two reviewers using distinct assessment tools, with a third reviewer resolving any inconsistencies. For experimental studies, the Cochrane tool was employed, which assesses various criteria, including random sequence generation, allocation concealment, participant and personnel blinding, outcome assessor blinding, completeness of outcome data, and considerations for selective reporting and other biases. Each study was classified on the basis of the risk of bias: a low risk indicated no concerns; a high risk indicated concerns; and an unclear risk was assigned when information was lacking.

Data analysis

Statistical computations were performed with the Comprehensive Meta-Analysis software, version 3.0 (Biostat, Inc., Englewood, NJ, USA). We calculated pooled estimates and 95% confidence intervals for the proportion of patients achieving treatment outcomes. The choice between a random-effects or fixed-effects model was determined by the heterogeneity of effect sizes, as assessed by Cochran's Q test and the I^2 statistic. Additionally, publication bias was evaluated by Begg's test, with a value of $p < 0.05$ being considered statistically significant.

RESULTS

As shown in Figure 1, our initial database search identified 8,735 studies. After removing duplicates and conducting title/abstract and full-text screenings, we excluded 8,724 studies, a total of 11 trials including 1,999 patients with various types of DR-TB therefore being included in the final evaluation. All included studies used the previous definition of XDR-TB. The included studies originated from several countries, including India, China, South Korea, and various African nations. The main characteristics of the included studies are shown in Table 1. The mean age of participants was 36.5 years (IQR, 17-71 years). The male-to-female ratio was 1.55, and approximately 19.45% of participants were HIV-positive. Participants were divided into two analytic groups: 839 patients received regimens containing BDQ and LZD, whereas 1,160 patients used regimens that did not include BDQ or LZD. The duration of the studies ranged from 6 months to 24 months, with 1,748 individuals being classified as having rifampin-resistant tuberculosis/MDR-TB and 251 individuals being classified as having pre-XDR-TB/XDR-TB.

In regimens that included both BDQ and LZD, Pa was the most frequently used drug, often accompanied by moxifloxacin and clofazimine. In contrast, non-BDQ/LZD regimens commonly featured levofloxacin, clofazimine, and ethambutol, along with additional combinations that included amikacin and capreomycin. These non-BDQ/LZD regimens generally exhibited varying levels of efficacy, typically resulting in higher rates of unfavorable outcomes in comparison with BDQ-LZD combinations.

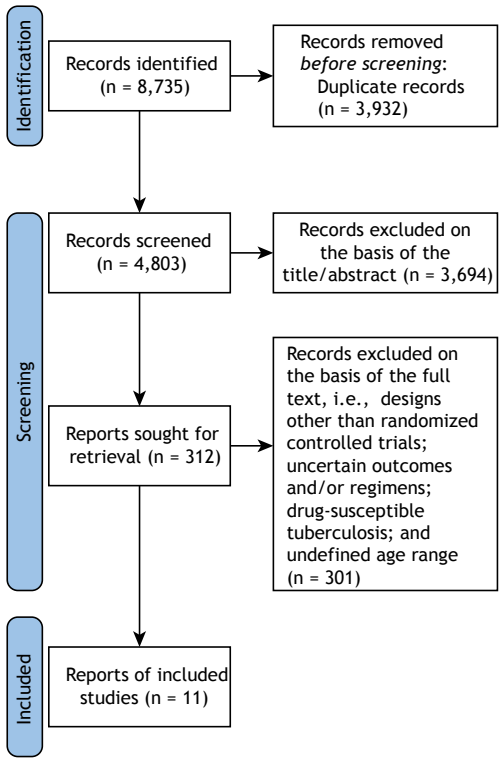

Figure 1. Flow chart of study selection for inclusion in the systematic review and meta-analysis.

Quality of the included studies

The quality of the included clinical trials was assessed with the Cochrane tool. The checklist showed that the included studies had a low risk of bias (Table 2). Of the included studies, the one conducted by Conradie et al.[30] showed a high risk of blinding of participants, personnel, and outcome assessment.

Pooled treatment outcomes in the BDQ-LZD group

Five studies featured regimens that included both BDQ and LZD. In the cohort of 839 patients receiving the BDQ-LZD regimen, 645 achieved favorable outcomes, whereas 114 experienced unfavorable outcomes. Favorable outcomes were classified as either cured or treatment completed, whereas unfavorable outcomes included treatment failure, death, and loss to follow-up.

Figure 2 displays the analysis of favorable outcomes among participants receiving the BDQ-LZD regimen, demonstrating an overall favorable outcome rate of 84.5% (95% CI, 79.8%-88.2%). In contrast, the

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Table 1. Characteristics of included experimental studies.

Study ID	Country	DR-TB type	No. of patients	Regimen	Duration	Mean age	Male	HIV+	BMI (kg/m²)	DM	Smoking
Nyang'wa et al.[37] (1)	Uzbekistan, Belarus, and South Africa	MDR-TB	111	BPaL (LZD + Pa + BDQ)	6-9 months	34	57	36	19.9	NM	NM
Nyang'wa et al.[37] (2)	Uzbekistan, Belarus, and South Africa	MDR-TB	138	BPaLM (LZD + Pa + BDQ + Mfx)	6-9 months	35	77	34	19.7	NM	NM
Nyang'wa et al.[37] (3)	Uzbekistan, Belarus, and South Africa	MDR-TB	115	BPaLC (LZD + Pa + BDQ + Cfz)	6-9 months	32	76	31	19.4	NM	NM
Yao et al.[38]	China	MDR-TB	34	BDQ+LZD+Lfx+Cs+Cfz/ Lfx+LZD+Cs+Cfz	18 months	43	19	NM	20.3	NM	NM
Nyang'wa et al.[39]	Belarus, South Africa, and Uzbekistan	RR-TB	151	BDQ+LZD+Pa+Mfx	6 months	35	85	38	19.8	NM	NM
Conradie et al.[30]	United Kingdom	XDR-TB/ pre-XDR-TB	181	BDQ+LZD+Pa	6 months	36	122	36	20.8	9	113
Goodall et al.[40] (1)	Ethiopia, Georgia, India, Moldova, Mongolia, South Africa, and Uganda	RR-TB	196	Lfx+Cfz+E+Z/high-dose H + PTO	9 months	> 18	124	27	NM	NM	31
Goodall et al.[40] (2)	Ethiopia, Georgia, India, Moldova, Mongolia, South Africa, and Uganda	RR-TB	187	Cfz+Z+Lfx/high-dose H + Km	6 months	> 18	115	25	NM	NM	28
Goodall et al.[40] (3)	Ethiopia, Georgia, India, Moldova, Mongolia, South Africa, and Uganda	RR-TB	127	High-dose Mfx+CFZ+E+Z/+ Km + high-dose H + PTO (intensive phase)	6 months	> 18	77	21	NM	NM	22
Conradie et al.[41]	United Kingdom	MDR-TB/ XDR-TB	109	BDQ+LZD+Pa	6-9 months	35	57	56	19.7	NM	NM
Qiujing & Weiwei[42] (1)	China	MDR-TB	45	Z+Am+Lfx+PTO+E	21 months	45.3	30	0	NM	NM	NM
Qiujing & Weiwei[42] (2)	China	MDR-TB	45	Am+E+Z+Mfx+PTO+E	21 months	44.5	28	0	NM	NM	NM
Du et al.[43] (1)	China	MDR-TB	67	Cm+CFZ+Cs+Lfx+PTO+Z	12 months	37.9	44	0	19.8	1	NM
Du et al.[43] (2)	China	MDR-TB	68	Cm+E+Cs+Lfx+PTO+Z+E	12 months	39	45	0	20.1	3	NM
Duan et al.[44] (1)	China	MDR-TB	66	Am/Cm+Lfx+Z+E+PAS+/PTO+Amx/Clv+CFZ	24 months	36.8	44	0	19.9	2	NM
Duan et al.[44] (2)	China	MDR-TB	74	Am/Cm+Lfx+Z+E+PAS+/PTO+Amx/ Clv+Lfx+Z+E+PAS/PTO+Amx/Clv	24 months	36.4	44	0	19.8	2	NM
Nunn et al.[45]	United Kingdom	RR-TB	253	short regimen: Mfx+CFZ+E+Z+Km+H+PTO	20 months	> 18	151	85	NM	NM	NM
Tang et al.[46]	China	XDR-TB	32	PTO+Z+Mfx/Gfx/Lfx/ PAS+CPM+Am+CFZ+CLA	24 months	43	21	0	19.6	6	NM

DR-TB: drug-resistant tuberculosis; DM: diabetes mellitus; MDR-TB: multidrug-resistant tuberculosis; XDR-TB: extensively drug-resistant tuberculosis; RR-TB: rifampin-resistant tuberculosis; Am: amikacin; PTO: prothionamide; Cm: capreomycin; Lfx: levofloxacin; Z: pyrazinamide; PAS: para-aminosalicylic acid; Pa: pretomanid; Amx/Clv: amoxicillin/clavulanate; Cfz: clofazimine, LZD: linezolid; BDQ: bedaquiline; Mfx: moxifloxacin; E: ethambutol; H: isoniazid; Km: kanamycin; Gfx: gatifloxacin; CPM: chlorpheniramine; CLA: clarithromycin; Cs: cycloserine; and NM: not mentioned.

▲ Voltar ao sumário

Table 2. Quality assessment of included experimental studies (the Cochrane tool).

Author	Random sequence generation	Allocation concealment	Blinding of participants and personnel	Blinding of outcome assessment	Incomplete outcome data	Selective reporting	Other bias
Nyang'wa et al.[37]	Low risk	High risk	High risk	High risk	Low risk	Low risk	Low risk
Yao[38]	Low risk	High risk	High risk	High risk	Low risk	Low risk	Low risk
Nyang'wa[39]	Low risk	High risk	High risk	High risk	Low risk	Low risk	Low risk
Conradie et al.[30]	Low risk	Low risk	Low risk	Low risk	Low risk	Low risk	Low risk
Goodall et al.[40]	Low risk	High risk	High risk	High risk	Low risk	Low risk	Low risk
Conradie et al.[41]	High risk	High risk	High risk	High risk	Low risk	Low risk	Low risk
Qiujing & Weiwei[42]	High risk	High risk	High risk	High risk	Low risk	Low risk	Low risk
Du et al.[43]	Low risk	High risk	High risk	High risk	Low risk	Low risk	Low risk
Duan et al.[44]	Low risk	High risk	High risk	High risk	Low risk	Low risk	Low risk
Nunn et al.[45]	Low risk	High risk	High risk	High risk	Low risk	Low risk	Low risk
Tang et al.[46]	Low risk	High risk	High risk	High risk	Low risk	Low risk	Low risk

overall unfavorable outcomes for patients on this regimen were reported at 15.4% (95% CI, 11.6%-20.2%; Figure 3). Because of the limited duration of the trials, no temporal trend was observed.

Pooled treatment outcomes in the non-BDQ/LZD group

Six studies involved regimens that did not include BDQ or LZD. Of the 1,160 patients in this group, 816 achieved favorable outcomes. Figure 4 illustrates the analysis of favorable outcomes for individuals receiving regimens without BDQ and LZD, revealing an overall favorable outcome rate of 66.8% (95% CI, 59.5%-73.4%). Conversely, the overall unfavorable outcomes among patients on these regimens were reported at 33.0% (95% CI, 25.6%-41.4%; Figure 5). Because of the limited duration of the trials, no temporal trend was observed.

DISCUSSION

The results of this analysis clearly demonstrate that treatment regimens incorporating BDQ and LZD yield significantly better patient outcomes than do those that do not include both agents. The BDQ+LZD-based regimens achieved an impressive favorable outcome rate of 84.5%, whereas the non-BDQ/LZD group had a substantially lower favorable outcome rate of 66.8%. This pronounced difference highlights the superior bactericidal and sterilizing activity of BDQ and LZD, both of which are critical in effectively treating MDR-TB.

One of the key advantages of BDQ and LZD lies in their ability to target different sites of the bacterial cell, resulting in rapid bacterial clearance, reduced risk of resistance, and reduced risk of relapse. BDQ disrupts ATP synthase, essential for *M. tuberculosis* survival, whereas LZD inhibits protein synthesis, together creating a potent synergistic effect that accelerates treatment response.

The association of BDQ with LZD is not however sufficient for the effective treatment of MDR-TB strains. They need accompanying drugs, such as fluoroquinolones, Pa, and clofazimine. Although it was beyond the scope of this review to investigate the best companions for BDQ and LZD, some considerations can be made.

Although injectables (aminoglycosides) now seem obsolete, fluoroquinolones and Pa appear to play an important role in building a BDQ+LZD-based regimen for MDR-TB treatment. Although fluoroquinolones contribute to the bactericidal activity of non-BDQ/LZD regimens, they show reduced efficacy in comparison with combinations of BDQ and LZD. When Pa is added to BDQ-LZD regimens, it further enhances treatment efficacy by disrupting *M. tuberculosis* cell wall synthesis and targeting persister cells, which are challenging to eradicate even with standard regimens for drug-susceptible tuberculosis.

Although BDQ, LZD, and Pa are crucial for MDR-TB treatment, their toxicity profiles warrant careful monitoring. BDQ has been associated with QT interval prolongation, which poses a risk of cardiac arrhythmias, particularly in patients with preexisting heart conditions or those on concurrent QT-prolonging drugs.[11,30-32] Although LZD is effective, it is linked to bone marrow suppression, peripheral neuropathy, and optic neuropathy, especially when used for long periods of time. Recent studies have emphasized that monitoring blood counts and neurological symptoms can help mitigate these risks.[33-35] Although Pa has been less studied, it has been associated with hepatotoxicity and gastrointestinal side effects, which are exacerbated in patients with liver conditions.[36] These findings underscore the importance of balancing efficacy with safety through vigilant toxicity monitoring to optimize patient outcomes while minimizing adverse effects.

Our study has some notable limitations. First, the variability in study designs, sample sizes, and treatment protocols across the included trials may introduce heterogeneity, affecting the generalization of our findings. Second, data on patient demographics and comorbidities were sometimes insufficient, limiting our ability to fully evaluate their influence

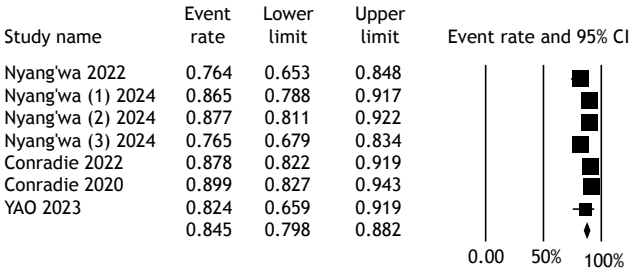

Figure 2. Favorable treatment outcome in the linezolid-bedaquiline group.

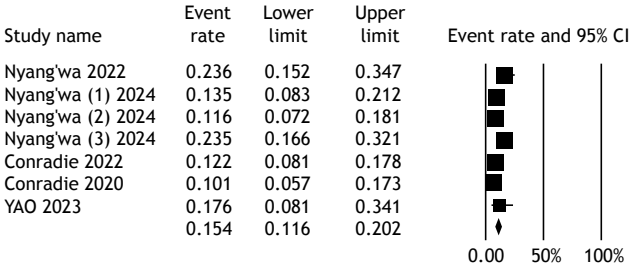

Figure 3. Unfavorable treatment outcome in the linezolid-bedaquiline group.

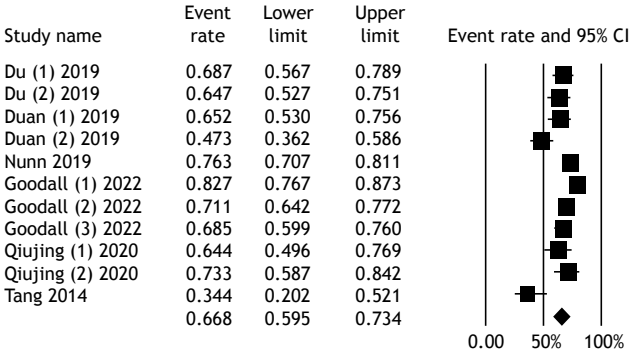

Figure 4. Favorable treatment outcome in the non-bedaquiline/linezolid group.

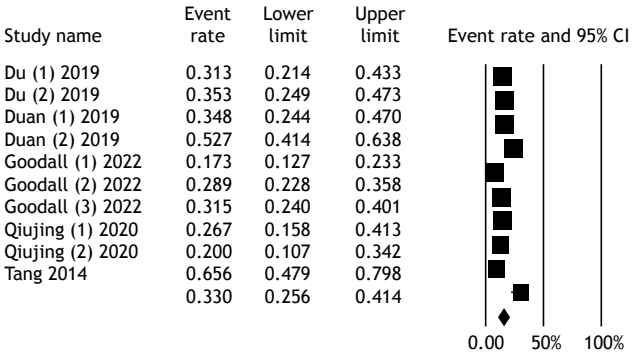

Figure 5. Unfavorable treatment outcome in the non-bedaquiline/linezolid group.

on treatment outcomes. Although we focused on the efficacy/effectiveness of BDQ and LZD, this analysis may overlook the potential synergistic effects of other essential drugs in combination therapies, which could significantly impact patient success. In particular, no study included delamanid in any treatment regimen. Additionally, because of the dynamic nature of MDR-TB treatment guidelines, ongoing research is needed to assess the long-term effectiveness of these regimens in real-world settings.

Interestingly, additional information will be available when the full results of two major clinical trials have been published. These two studies proposed a series of different and unusual but effective BDQ-LZD combinations of drugs without Pa, but with fluoroquinolones and/or delamanid.[6] The results,

which are probably stunning, have been disclosed to the WHO, leading to a new recommendation for the treatment of patients with MDR-TB.[4]

In conclusion, the present study demonstrates that treatment regimens incorporating BDQ and LZD offer significantly improved outcomes for MDR-TB patients in comparison with regimens without these agents. The synergy between the bactericidal effects of BDQ and the protein synthesis inhibition by LZD provides a powerful approach to combatting *M. tuberculosis*, resulting in higher rates of favorable outcomes. The addition of Pa further enhances the effectiveness of BDQ-LZD regimens, reinforcing its value in complex MDR-TB cases. Future research should aim to refine these regimens, balancing safety and efficacy, and explore adjunctive therapies to further improve MDR-TB treatment outcomes.

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AUTHOR CONTRIBUTIONS

All authors contributed equally to the conception and design of the study; the collection, analysis, and interpretation of data; and the writing of the manuscript.

CONFLICTS OF INTEREST

None declared.

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Incidence rate, clinical profile, and outcomes of COVID-19 in adults with non-cystic fibrosis bronchiectasis

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TO THE EDITOR:

The clinical outcomes of SARS-CoV-2 infection (COVID-19) range from asymptomatic cases to severe illness and death.[1] Advanced age and comorbidities such as obesity, cardiovascular disease, pulmonary disease, certain types of cancer, and diabetes[2,3] are risk factors for severe disease. Bronchiectasis, defined as an abnormal and irreversible dilatation of the bronchi, results in chronic inflammation of the lower airways and deterioration of lung function.[4] Consequently, patients with non-cystic fibrosis (CF) bronchiectasis and SARS-CoV-2 infection are currently considered to be at an increased risk of developing severe manifestations of COVID-19. However, there are currently limited data on the profile of patients with non-CF bronchiectasis diagnosed with COVID-19 in Brazil, as well as on the incidence of COVID-19 in such patients. The objective of the present study was to describe the cumulative incidence of SARS-CoV-2 infection in patients with non-CF bronchiectasis monitored at the *Hospital de Clínicas de Porto Alegre* (HCPA), in the city of Porto Alegre, Brazil, during the two years of COVID-19 pandemic, as well as the clinical characteristics and outcomes of these patients.

This was a retrospective study analyzing the incidence rate, clinical course, and outcomes of confirmed cases of COVID-19 in a cohort of adults with non-CF bronchiectasis. The study was approved by the Research Ethics Committee of the HCPA via *Plataforma Brasil* (Brazilian National Research Ethics Committee Database; Protocol no. 4.125.633). Written informed consent was obtained at recruitment. The study complied with the Declaration of Helsinki and the Brazilian government regulations.

We enrolled 31 patients between April 30, 2020 and April 29, 2022. Inclusion criteria were adults with a diagnosis of non-CF bronchiectasis monitored at the HCPA during the COVID-19 pandemic. The diagnosis of non-CF bronchiectasis was based on CT imaging criteria.[5]

Clinical and demographic data were collected by reviewing the electronic medical records of the patients. The primary outcome of the study was the cumulative incidence of COVID-19 in the first and second years of study. The cases of COVID-19 were identified through telephone interviews and medical record review. Diagnostic criteria for COVID-19 were a positive real-time RT-PCR result from a nasopharyngeal swab, CT findings consistent with COVID-19, a clinical diagnosis of COVID-19 in a hospital setting, or any combination of the three. The clinical course of COVID-19 was rated on the WHO Ordinal Scale for Clinical Improvement.[6]

Data analysis was performed with the IBM SPSS Statistics software package, version 22.0 (IBM Corporation, Armonk, NY, USA). The sample size equaled the number of incident cases of COVID-19 during the study period. Data normality was examined with quantile-quantile plots and the Shapiro-Wilk test. Qualitative data were expressed as number of cases and proportion, and quantitative data were expressed as mean ± standard deviation or median and interquartile range. Categorical comparisons were performed with the chi-square test with Yates' correction (when appropriate) or Fisher's exact test. Continuous variables were compared by means of a t-test or the Wilcoxon-Mann-Whitney test. Cumulative incidence was calculated as the number of new cases of COVID-19 divided by the total number of individuals at risk for the study period (two years). The annual cumulative incidence of COVID-19 in the state of Rio Grande do Sul, Brazil, was also calculated, being adjusted for age.[7-9] The chi-square test of independence was used in order to compare the annual cumulative incidence of COVID-19 between the study population and the general population.

Of the 31 patients enrolled in the study, 5 were diagnosed with COVID-19: 2 in the first year of study and 3 in the second. The mean age of the patients was 39.4 years, 71% were female, and 93.5% were White. Most of the patients had bronchiectasis of uncertain etiology (48.4%), and 38.7% had a probable diagnosis of ciliary dyskinesia. Chronic infection with *Pseudomonas aeruginosa* was identified in 82.8% of the patients. The mean percent predicted FEV_1 was 50.1 ± 24.1%, and the mean six-minute walk distance was 444.18 ± 81.4 m. Vaccination against COVID-19 began in May of 2021. Approximately 68% of the patients received three doses of COVID-19 vaccine, and 29% received two (Table 1).

The annual cumulative incidence of COVID-19 was 6.4% in the first year of study and 9.6% in the second. In the state of Rio Grande do Sul, there were 2.384.504 confirmed cases of SARS-CoV-2 infection on April 29, 2022, with an age-adjusted annual cumulative incidence of approximately 13% in the first year of study and 16% in the second.[7-9] We found that the annual cumulative incidence of COVID-19 was not significantly different between the patients with non-CF bronchiectasis and the general population in the first and second years of study ($p = 0.091$ and $p = 0.238$, respectively). The

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Table 1. Baseline patient data and comparison between patients with and without COVID-19.[a]

	Total N = 31	With COVID-19 n = 5	Without COVID-19 n = 26	p
Age, years	39.4 ± 14.1	31.6 ± 8.6	40.9 ± 14.6	0.182
Sex				0.613
Female	22 (71)	3 (13.6)	19 (86.4)	
Male	9 (29)	2 (22.2)	7 (77.8)	
Ethnicity				1.000
White	29 (93.5)	5 (17.2)	24 (82.8)	
Non-White	2 (6.5)	0	2 (100)	
Diagnosis				0.816
Ciliary dyskinesia	12 (38.7)	2 (16.7)	10 (83.3)	
Kartagener syndrome	3 (9.7)	0	3 (100)	
Obliterative bronchiolitis	1 (3.2)	0	1 (100)	
Uncertain	15 (48.4)	3 (20)	12 (80)	
Age at diagnosis	27 (8-38)	19 (11.5-35.5)	27 (8-40)	0.957
BMI, kg/m^2	21.9 ± 4.1	22.0 ± 2.9	21.9 ± 4.3	0.874
History of pneumothorax	1 (3.2)	0	1 (100)	1.000
History of massive hemoptysis (> 100 mL)	2 (6.5)	0	2 (100)	1.000
History of bronchial artery embolization	0	0	0	
History of ABPA	1 (3.2)	0	1 (100)	1.000
On the lung transplant list	2 (6.5)	0	2 (100)	1.000
Lung transplant recipient	0	0	0	
Pseudomonas aeruginosa	24 (82.8)	2 (8.3)	22 (91.7)	0.127
MSSA	6 (20.7)	1 (16.7)	5 (83.3)	1.000
MRSA	0	0	0	
NTM	0	0	0	
Use of inhaled colistimethate sodium	11 (35.5)	1 (9.1)	10 (90.9)	0.631
Inhaled aminoglycoside therapy	4 (12.9)	0	4 (100)	1.000
Use of azithromycin	23 (74.2)	3 (13)	20 (87)	0.583
FVC, % predicted	61.7 ± 21.2	77.7 ± 21.6	56.3 ± 18.9	0.019
FEV_1, % predicted	50.1 ± 24.1	60.0 ± 24.9	44.1 ± 19.1	0.097
FEV_1/FVC, %	78.2 ± 14.9	75.2 ± 12.8	77.5 ± 15.2	0.843
6MWD, m	444.2 ± 81.4	503.5 ± 39.2	434.3 ± 82.8	0.117
SpO_2, %	94.0 ± 2.5	93.2 ± 2.4	94.0 ± 2.4	0.500
No. of COVID-19 vaccine doses				0.242
2	9 (29)	3 (33.3)	6 (66.7)	
3	21 (67.7)	2 (9.5)	19 (90.5)	
None	1 (3.2)	0	1 (100)	
Deaths	3 (9.7)	0	3 (100)	1.000

ABPA: allergic bronchopulmonary aspergillosis; MSSA: methicillin-susceptible *Staphylococcus aureus*; MRSA: methicillin-resistant *Staphylococcus aureus*; NTM: nontuberculous mycobacteria; and 6MWD: six-minute walk distance. [a]Data presented as n (%), mean ± SD, or median (IQR). *Chi-square test for categorical variables. [†]Student's t-test or Mann-Whitney U test for continuous variables.

fact that the cumulative incidence of COVID-19 was low in our cohort may be due to underreporting of COVID-19 cases in the first year of study, given that diagnostic tests were restricted to symptomatic cases with more severe respiratory symptoms. Moreover, people with chronic pulmonary diseases promptly adhered to respiratory protection measures, social distancing, and mask use.

The risk of SARS-CoV-2 infection did not differ between the study population and the general population in the first year of study (OR = 0.61; 95% CI, 0.31-1.20 vs. OR = 1.42; 95% CI, 1.01-2.00) or in the second (OR = 0.76; 95% CI, 0.45-1.26 vs. OR = 1.25; 95% CI, 0.89-1.76). The distribution of COVID-19 cases in the study period is presented in Figure 1. With regard to the clinical characteristics of patients, those with COVID-19 had higher percent predicted FVC than did those without COVID-19 (77.7 ± 21.6% vs. 56.3 ± 18.9%; p = 0.019), suggesting mild lung function impairment before SARS-CoV-2 infection. There were no differences between the two groups for the other variables. The most common symptoms at diagnosis of COVID-19 were myalgia, arthralgia, or both (in 80.0%); fever (in 80.0%); fatigue (in 60%); and cough (in 60%). All of the patients with SARS-CoV-2 infection had mild COVID-19 (a

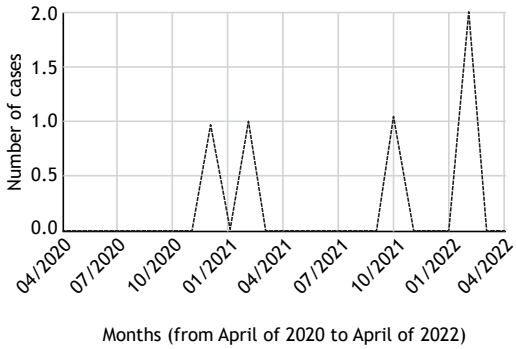

Figure 1. Distribution of COVID-19 cases in the study period.

score of 1 or 2 on the WHO Ordinal Scale for Clinical Improvement) and required no hospitalization or ventilatory support, recovering completely from the infection.

This study has potential limitations. It was conducted in a single medical center and included a relatively small sample, thus limiting its statistical power. The study had a retrospective design and used electronic medical record data, which are not likely to be as complete and accurate as prospective study data. Additionally, during the first phase of the COVID-19 pandemic, diagnostic tests were restricted to symptomatic cases with more severe respiratory symptoms, with the actual infection rate possibly being underestimated.

AUTHOR CONTRIBUTIONS

CCC: conceived, planned, and performed the experiments that led to this study; interpreted the data; wrote the main manuscript text; prepared the table; critically revised the article for important intellectual content; and approved the final version to be published. FMS: collected, analyzed, and interpreted the data; prepared the table; critically revised the article for important intellectual content; and approved the final version to be published. LBJ: collected, analyzed, and interpreted the data; critically revised the article for important intellectual content; and approved the final version to be published. BZ and PTRD: conceived and designed the study; interpreted the data; wrote the main manuscript text; prepared the figure; critically revised the article for important intellectual content; and approved the final version to be published.

CONFLICTS OF INTEREST

None declared.

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The hidden dangers of electronic cigarettes: e-cigarette, or vaping, product–use associated lung injury requiring extracorporeal membrane oxygenation

Anna Maria Garcia Cardoso[1], Wanessa Nayane Alves Rabelo[1], Stephan Adamour Soder[1], Fabíola Adélia Perin[1], Spencer Marcantonio Camargo[1]

TO THE EDITOR:

In recent decades, multiple efforts have been made to reduce population exposure to cigarettes, given that smoking is responsible for thousands of deaths annually. These actions have been effective, as evidenced by a reduction in the number of smokers worldwide in recent decades and by a slight reduction in the incidence of lung cancer.[1] Conversely, a new form of nicotine exposure has become popular through electronic cigarettes, first commercially available in the early 2000s in China.[2] Currently, the electronic cigarette industry generates $2.5 billion annually.[3]

Recent studies have shown that 4.9% of elementary school students and 20.8% of high school students in the United States report having used electronic cigarettes in the last 30 days. Between 2017 and 2018, there was a 78% increase in electronic cigarette use among American high school students.[3] In Brazil, a national survey conducted in 2022 estimated that the prevalence of electronic cigarette use was 12.2%, with the predominant age group being 25-34 years.[4] In southern Brazil, this rate is even more concerning, corresponding to 21.9% of the school-age population.[5]

Electronic cigarettes work by heating a liquid to create an aerosol that typically contains solvents such as propylene glycol and vegetable glycerin, as well as nicotine and flavorings; it can also contain chemicals such as tetrahydrocannabinol. Although the medium-term and long-term health effects of inhaling these substances into the lungs are still unknown, there have been numerous reports of patients who develop acute lung damage caused by inhaling the vapor produced by electronic cigarettes. E-cigarette, or vaping, product use–associated lung injury (EVALI) is a term that is used in order to describe lung injury caused by the use of electronic cigarettes. Symptoms include cough, dyspnea, chest pain, and hemoptysis. In severe cases, invasive ventilatory support such as mechanical ventilation and extracorporeal membrane oxygenation (ECMO) may be required; in extreme cases, lung transplantation may be required.[3,6,7]

Although there is no specific criterion defining electronic cigarette intoxication as a cause of lung injury, an algorithm was proposed by the U.S. Centers for Disease Control and Prevention along with the University of Rochester for the classification of acute lung injury caused by electronic cigarettes. Patients must present with cough and dyspnea, as well as systemic symptoms such as fatigue and fever. They should have a history of vaping in the last 90 days, as well as imaging showing diffuse bilateral infiltrates with ground-glass opacity, predominantly in the lung bases, with subpleural sparing. Infectious, neoplastic, cardiac, and rheumatologic causes should be excluded.[3]

Here, we report the first case of a patient in Brazil presenting with lung injury associated with electronic cigarette use and requiring ventilatory support and ECMO. Written informed consent was obtained from the patient for publication of this report and accompanying images.

A 23-year-old male farmer presented with no history of allergies, surgery, or continuous medication use. The patient was obese (his BMI being 36 kg/m^2) and a smoker, having smoked conventional cigarettes (40 cigarettes/day) since he was 14 years old and having replaced them with electronic cigarettes, smoked daily in the last 3 years. He reported no use of other drugs.

The patient presented to the emergency department with cough, dyspnea, and fever, being prescribed amoxicillin and clavulanate, as well as symptomatic treatment. However, he developed persistent fever, cough, and worsening dyspnea, returning to the emergency department 48 h after initiation of treatment. The patient was hospitalized and started on ventilatory support via a Venturi mask, requiring intubation and mechanical ventilation. He was admitted to the ICU for 12 h. The patient was screened for respiratory viruses (influenza A, influenza B, SARS-CoV-2, and respiratory syncytial virus), but the results were negative. After five days of endotracheal intubation and mechanical ventilation, the patient presented with refractory hypoxemia (a PaO_2/FiO_2 ratio of 80) despite optimal ventilator management and pronation, with a peak pressure of 40 cmH_2O. A decision was made to initiate ventilatory support with venovenous ECMO with two single-lumen cannulas (with blood being drained from the right femoral vein with a 23 Fr cannula and being reinfused into the right internal jugular vein with a 21 Fr cannula). On the same day, the patient was transferred to the ICU of the *Santa Casa de Misericórdia de Porto Alegre Pavilhão Pereira Filho*, located in the city of Porto Alegre, Brazil, for specialized care.

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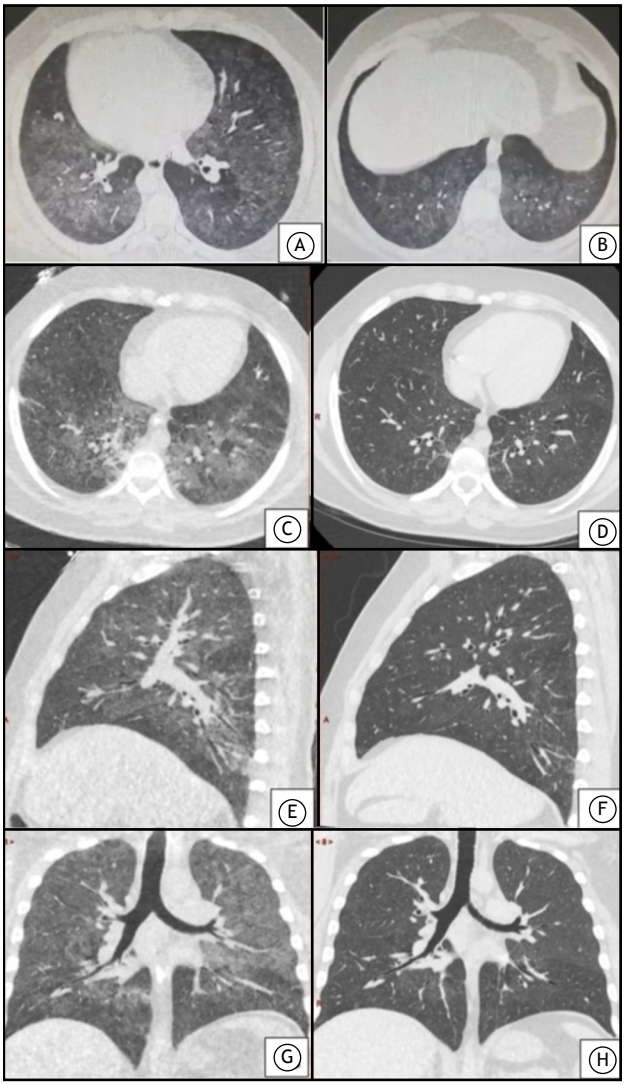

Figure 1. In A and B, axial CT scans of the chest of a male patient hospitalized with e-cigarette, or vaping, product use–associated lung injury. In C and D, axial CT scans of the lower lobes. In E and F, sagittal CT scans. In G and H, coronal CT scans. The scans on the left (E and G) were performed two days after extracorporeal membrane oxygenation removal, and the scans on the right (F and H) were performed two days before hospital discharge.

The patient remained intubated for 12 days. He failed extubation, requiring reintubation within 48 h of planned extubation and remaining on mechanical ventilation for another 48 h and on ECMO for 14 days.

Three BAL procedures were performed during his hospitalization, the BAL fluid samples being sent for bacteriological and mycological analysis. The first procedure was performed upon patient arrival; the second was performed on the following day; and the third was performed one week later. The samples from the third procedure showed bacterial growth (*Klebsiella pneumoniae*), and the patient was treated with antibiotics.

During his ICU stay, the patient was evaluated for autoimmune disease, being negative for antinuclear and anti-DNA antibodies. His ESR was = 6. Figure 1 shows chest CT scans performed at hospital admission, as well as comparative images taken a few days later.

The patient was discharged after 26 days of hospitalization and is undergoing outpatient follow-up at this writing, showing progressive improvement. He has lost weight through dietary and physical activity adjustments, and is expected to return to work soon.

The case reported here is important because of the increasing use of electronic cigarettes and the potentially harmful consequences of electronic cigarette use. Although electronic cigarettes have been prohibited by the Brazilian Health Regulatory Agency since 2009, the regulation of electronic cigarettes has been discussed by the Congress. This report adds to others describing cases of EVALI, serving as a warning to the medical community, public authorities, and the

population at large about the risks associated with the use of electronic cigarettes. Although there have been reports of cases of EVALI requiring ECMO,[8,9] this was the first such case in Brazil.

AUTHOR CONTRIBUTIONS

All authors contributed equally to this work.

CONFLICTS OF INTEREST

None declared.

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The thirty-second sit-to-stand test as a predictor of postoperative complications of lung resection: a real-world study

Inês Fernandes Pedro[1], Diana Organista[1], Teresa Seguro[2], Mariana Maia Silva[3], Fátima Rodrigues[1,4]

TO THE EDITOR:

Although the prevalence of lung cancer is on the rise, scientific and technological advances have improved diagnosis and treatment, with thoracic surgery playing a growing role in the latter. Because postoperative complications increase patient morbidity and mortality, as well as the duration and cost of hospitalization, careful preoperative evaluation must be performed in order to identify patients at greater risk of postoperative complications. Although advances in surgical techniques have made it possible to reduce postoperative complications, they still occur in 6.8-30% of patients undergoing noncardiac thoracic surgery.[1] Therefore, additional tools are needed to predict the risk of postoperative complications.[2]

Postoperative complications have long been associated with exercise capacity, specifically peak oxygen consumption, the risk of complications and mortality being lower in patients with higher peak oxygen consumption.[3] Strength and speed are components of exercise capacity and also appear to be associated with postoperative complications. The thirty-second sit-to-stand test (30STS) is a simple field-based exercise test that assesses strength and speed and might be useful in assessing the risk of postoperative complications in candidates for lung resection.

We conducted a prospective cohort study of adult patients admitted to the Department of Thoracic Surgery of *Hospital Pulido Valente*, located in the city of Lisbon, Portugal. The patients included in the study underwent lung resection between May 1, 2021 and September 7, 2022, and we assessed predictors of postoperative complications.

We collected data on the following: age; sex; BMI; smoking history; comorbidities; level of physical activity; pulmonary function tests; condition requiring surgery (including benign and malignant neoplasms, as well as infections); surgical approach; type of lung resection; length of hospital stay (in days); duration of chest tube drainage (in days); postoperative complications; peak cough flow; and 30STS results. The 30STS was fully standardized[4] and was supervised by a physiotherapist, being performed preoperatively and within 24 h of chest tube removal. Data on complications were obtained from patient medical records and validated by the study investigator, who was present during the entire study period. The sample size was estimated at 100 patients on the basis of the rate of complications reported elsewhere,[5] with a 95% confidence interval and a 5% margin of error, with the use of the Raosoft® sample size calculator (Raosoft, Inc., Seattle, WA, USA). The study was approved by the local research ethics committee (Protocol no.118/21).

The study sample was divided into two groups of patients: those with and those without postoperative complications. All statistical analyses were performed with the IBM SPSS Statistics software package, version 25.0 for macOS (IBM Corporation, Armonk, NY, USA), and a two-sided p-value of 0.05 was considered statistically significant for all tests. Categorical data were presented as frequencies and percentages, and continuous variables were presented as mean and standard deviation, as appropriate. Comparisons between continuous variables were analyzed with logistic regression, and comparisons between categorical variables were performed by the chi-square test. Optimal 30STS thresholds were determined by ROC analysis. A multivariate Cox regression model was created to include variables showing univariate association with complications. Missing data were subject to listwise deletion.

A total of 101 patients were included in the present study. The sociodemographic and clinical characteristics of the study sample are summarized in Table 1. The postoperative complication rate was 22%, with 29 complications documented in 22 patients. The most common postoperative complications were pulmonary complications (n = 25; 86.2%). These included persistent air leak (n = 11), respiratory infection (n = 6), bronchopleural fistula (n = 5), atelectasis (n = 1), chylothorax (n = 1), and pneumothorax after chest tube removal (n = 1). Death was recorded in 2 patients (6.9%). Cardiovascular complications followed (n = 1; 3.4%), with 1 case of arrhythmia, as did technical complications (n = 1; 3.4%), with the need to convert to thoracotomy during thoracoscopic lobectomy (n =1). Most of the complications occurred in men (n = 22; 86.2%).

In the study population as a whole, the mean length of hospital stay was 8.2 [3-28] days and the mean duration of chest tube drainage was 5.13 [1-25] days. In the subgroup of patients with postoperative complications, the mean length of hospital stay was 15 days and the mean duration of chest tube drainage was 11.6 days. The two patients who died during hospitalization were 65-year-old and 68-year-old men with COPD who had

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undergone lobectomy by thoracotomy for infectious and neoplastic diseases.

After univariate analysis, sex, DL_{CO}, DL_{CO}/alveolar volume (V_A), surgical approach, and operative time correlated with postoperative complications (Table 1). However, preoperative peak cough flow did not.

In the study population as a whole, 30STS showed a trend toward predicting complications (p = 0.059), being a good predictor of complications in the male population (p = 0.008). This might be due to the fact that there were significantly more men than women in the subgroup of patients with postoperative complications (Table 1). As can be seen in Figure 1, the optimal preoperative 30STS thresholds were 9.5 full stands for women (sensitivity, 60%; specificity, 66%) and 12.5 full stands for men (sensitivity, 88%; specificity, 53%). Thus, a preoperative test below the aforementioned thresholds increased the risk of complications by 43% (OR: 1.438; 95% CI, 1.150-1.797; p = 0.001). We obtained comparable results when analyzing 30STS as a percentage of the predicted values[6]: the test predicted postoperative complications in the study population as a whole (p = 0.029) and in the male population (p = 0.007). Performances below the thresholds of 52.5% for women (sensitivity, 60%; specificity, 83%) and 74.4% for men (sensitivity, 73%; specificity, 69%) increased the risk of complications by 60% (OR: 1.608; 95% CI, 1.173-2.206; p = 0.0001).

In the multivariate analysis, DL_{CO}/V_A and sex-specific 30STS results were the only variables that remained prognostic for postoperative complications (p = 0.011 and p = 0.015, respectively). In a subgroup of surgical patients selected on the basis of lung function, as assessed by current standards,[2] DL_{CO}/V_A retained its role in predicting postoperative complications.

As far as we know, this is the first study to demonstrate an association between a field-based exercise test such as the 30STS and postoperative complications in patients undergoing lung resection. Such an association has been reported for other types of surgery, including cardiac surgery, abdominal surgery, and esophageal surgery.[7-10]

The present study allowed us to establish sex-specific 30STS thresholds for a Portuguese population, which we believe to be representative. However, we emphasize the need to apply the 30STS as a predictor of postoperative complications in populations with a higher number of women. Furthermore, future studies using a similar methodological approach should include shorter sit-to-stand assessments of 5 and 10 repetitions. If the same predictive value for postoperative complications is confirmed, its applicability could be extended.

Table 1. Sociodemographic and clinical characteristics of patients with and without postoperative complications of lung resection.[a]

	Total sample	Without postoperative complications	With postoperative complications	p
Sex, male; female	58 (57); 43 (43)	41 (52); 38 (48)	17 (77); 5 (23)	0.033
Age, years	66.1 ± 10 [37-86]	66.4 ± 9,8 [37-86]	66. 1 ± 9,9 [39-81]	0.262
BMI, kg/m^2	25.8 ± 4.2 [16.3-37.5]	26.2 ± 4.4 [16.3-37.5]	24.5 ± 4.1 [18.1-30.9]	0.355
Smoking status, NS; FS; CS	34 (34); 20 (20); 47 (47)	29 (37); 36 (46); 14 (18)	5 (23); 11 (50); 6 (27)	0.220
Smoking history, pack-years	32.1 ± 37 [0-150]	27.8 ± 35 [0-120]	46 ± 33 [0-150]	0.055
Physical activity, IA; SA	80 (79); 21 (21)	62 (78); 17 (22)	18 (82); 4 (18)	0.733
FEV_1, L	2.4 ± 0.7 [1-4]	2.3 ± 1 [1-3.99]	2.5 ± 0.7 [1.62-4]	0.441
DL_{CO}, %	80.1 ± 19.2 [38.6-131]	83.4 ± 19.5 [38.6-131]	65.4 ± 17.8 [54-97]	0.005
DL_{CO}/V_A, %	84.4 ± 19.6 [46-136]	89.3 ± 19.6 [46-136]	64.8 ± 18.5 [48-90]	0.0002
Indication for surgery, benign neoplasm; infection; malign neoplasm	4 (4); 5 (5); 92 (91)	4 (5); 2 (2); 74 (97)	0 (0); 3 (14); 19 (86)	0.405
Surgical approach, thoracotomy; VATS	42 (42); 59 (58)	27 (34); 52 (66)	15 (68); 7 (32)	0.004
Type of lung resection				0.081
Enucleation	1 (1)	1 (1)	0 (0)	
Enucleation + atypical lung resection	1 (1)	1 (1)	0 (0)	
Pneumonectomy	2 (2)	2 (3)	0 (0)	
Bilobectomy	4 (4)	3 (4)	1 (5)	
Atypical lung resection	28 (28)	26 (33)	2 (9)	
Lobectomy	65 (64)	46 (58)	19 (86)	
Operative time, min	146.7 ± 70.8 [27-368]	136.5 ± 67.6 [27-327]	183.1 ± 59.9 [82-368]	0.010
Preoperative 30STS, total sample	11.6 ± 3.2 [2-22]	11.9 ± 3.1 [2-22]	10.5 ± 2.9 [5-18]	0.059
Preoperative 30STS, men	12.2 ± 2.9 [5-22]	13.0 ± 2.8 [8-22]	10.4 ± 2.6 [5-17]	0.008
Preoperative 30STS, women	10.8 ± 3.2 [2-18]	10.8 ± 3.2 [2-17]	10.6 ± 3.0 [6-18]	0.871

NS: nonsmoker; FS: former smoker; CS: current smoker; IA: insufficiently active; SA: sufficiently active; V_A: alveolar volume; VATS: video-assisted thoracoscopic surgery; and 30STS: thirty-second sit-to-stand test. [a]Data expressed as n (%) or mean ± SD [min-max].

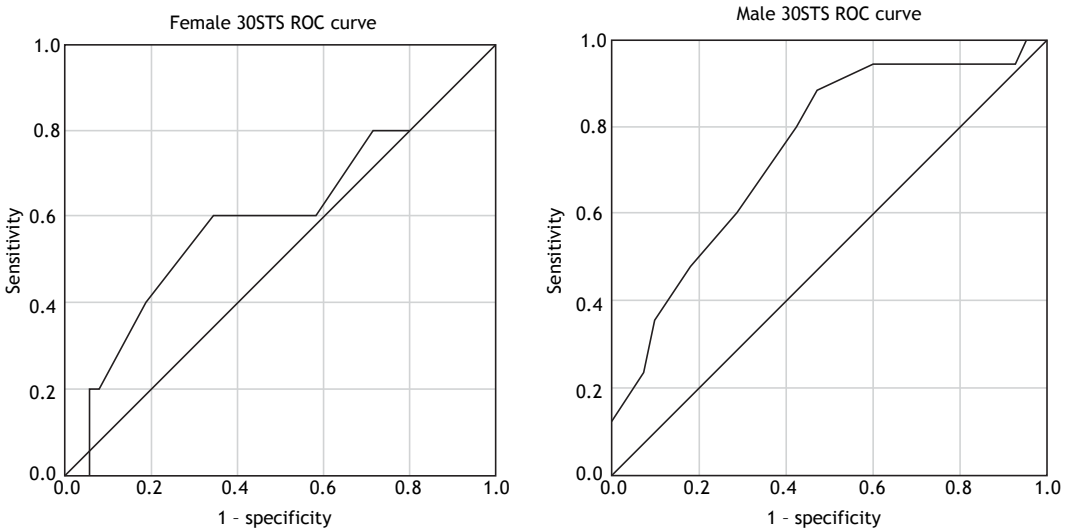

Figure 1. ROC analysis of the thirty-second sit-to-stand test (30STS) for female patients and male patients.

The results of the present study reinforce the importance of pulmonary rehabilitation, including exercise training, in the preoperative period in selected patients. The 30STS provides a noninvasive and easily reproducible method of assessing the risk of postoperative complications in the preoperative appointment, allowing early identification of patients at a higher risk of complications. Once closer monitoring and intervention protocols are established for this subgroup of patients—including tailored pulmonary rehabilitation—it will be possible to deal with potential complications earlier, thus reducing morbidity and mortality, as well as hospitalization costs.

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AUTHOR CONTRIBUTIONS

IFP and DO: first co-authors. FR and TS: conceptualization; methodology; investigation; formal analysis; and manuscript writing and editing. IFP: investigation; formal analysis; and manuscript writing and editing. DO and MMS: investigation; and manuscript writing and editing. All authors approved the final version of the manuscript.

CONFLICTS OF INTEREST

None declared.

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Severity of COPD in comparison with acute myocardial infarction: evidence of in-hospital mortality in Brazil

Marcelo Fouad Rabahi[1,2], Guylherme Saraiva[2], Frederico Leon Arrabal Fernandes[3], Klaus Rabe[4]

TO THE EDITOR:

In 2020, COPD accounted for approximately 3.6 million deaths worldwide, (i.e., nearly 6% of all deaths occurring in that year). In addition to being a leading cause of death, COPD is associated with a burden of 79.8 million disability-adjusted life years and 14.9 million years lived with disability worldwide.[1-3] Much of the impact of COPD is related to episodes of exacerbation, which can result in compromised health and are worsened by comorbidities that are very common in these patients. Exacerbations of COPD increase the risk of COPD-related hospitalizations and can lead to patient death from respiratory causes and cardiovascular events such as acute myocardial infarction (AMI). It has been shown that even a single moderate exacerbation over a 10-year period is associated with an increased risk of death and that when an exacerbation requires hospitalization there is a significant increase in the risk of death; this risk continues to increase in the 12 months following the exacerbation.[4-6] Exacerbations of COPD also increase health care costs; in the United States and Canada, approximately 70-90% of all COPD-related health care costs are attributable to hospitalizations for exacerbations.[5]

Cardiovascular disease (CVD) and COPD are both major contributors to global mortality, each carrying significant individual risks. Separately, CVD has been the leading cause of global mortality since the 1960s, with a significant portion of these cases occurring in low- and middle-income countries. An estimated 17.9 million people died from CVD in 2019, accounting for 32% of all deaths in that year. In Brazil, 171,246 deaths in 2019 were attributed to coronary artery disease (CAD), corresponding to 12% of the total number of deaths in the country and 43% of all CVD deaths in the country.

According to data from the Brazilian Unified Health Care System, the number of population-adjusted hospitalizations for AMI in the public health care system increased by 54% from 2008 to 2019.[7,8] The incidence and impact of CAD on individual and public health justify all existing actions and campaigns focused on caring for patients with AMI. But what are the proportions of hospitalizations and in-hospital deaths among patients with AMI and those with COPD?

We carried out an ecological study using a freely accessible database in Brazil that tabulates the care of patients hospitalized in the public health care system. We used aggregated, anonymous, and publicly available data. Our work was therefore in accordance with Brazilian National Health Council Resolution no. 674/2022 and did not require approval by a research ethics committee.

We collected data from the Brazilian National Ministry of Health Unified Health Care System Hospital Information System in April of 2024. We searched for cases of COPD (defined in accordance with the ICD-10) using the following search terms: "bronchitis," "emphysema," and "other chronic obstructive pulmonary disease." We searched for cases of AMI (defined in accordance with the ICD-10) using the search term "acute myocardial infarction." We focused on patients > 30 years of age hospitalized in the 2019-2023 period.

We studied hospitalization and in-hospital mortality rates for COPD and AMI separately and calculated the case-fatality rates on a year-by-year basis. We also calculated the average case-fatality rate for each disease, as well as the corresponding confidence interval. We compared the fatality rates for COPD and AMI hospitalizations using the Student's t-test, the level of significance being set at $p < 0.05$.

Of the 1,116,467 cases that we evaluated in the present study, 730,998 (65.5%) were cases of patients hospitalized for AMI and 385,469 (34.5%) were cases of patients hospitalized for COPD. Of the total number of deaths, 67,425 were due to AMI and 40,482 were due to COPD. As can be seen in Figure 1, the in-hospital fatality rates for AMI and COPD were 9.2% and 10.5%, respectively ($p = 0.02$). Although the difference is small, it reflects the striking differences in how COPD and AMI cases are treated. Our results highlight that being hospitalized for COPD carries a non-negligible risk of a fatal outcome. Such a risk often goes unrecognized by patients and health care teams. When disease severity and lethality are underestimated, treatment may fall short, potentially contributing to clinical deterioration and even death.

In addition to the significant difference between fatality rates, it is important to note that these rates have increased in recent years, highlighting unmet needs in the management of COPD. Advances have been made in recent years (e.g., triple therapy), and reduced mortality rates have been noted in several large prospective studies. However, COPD mortality is still increasing worldwide.[9]

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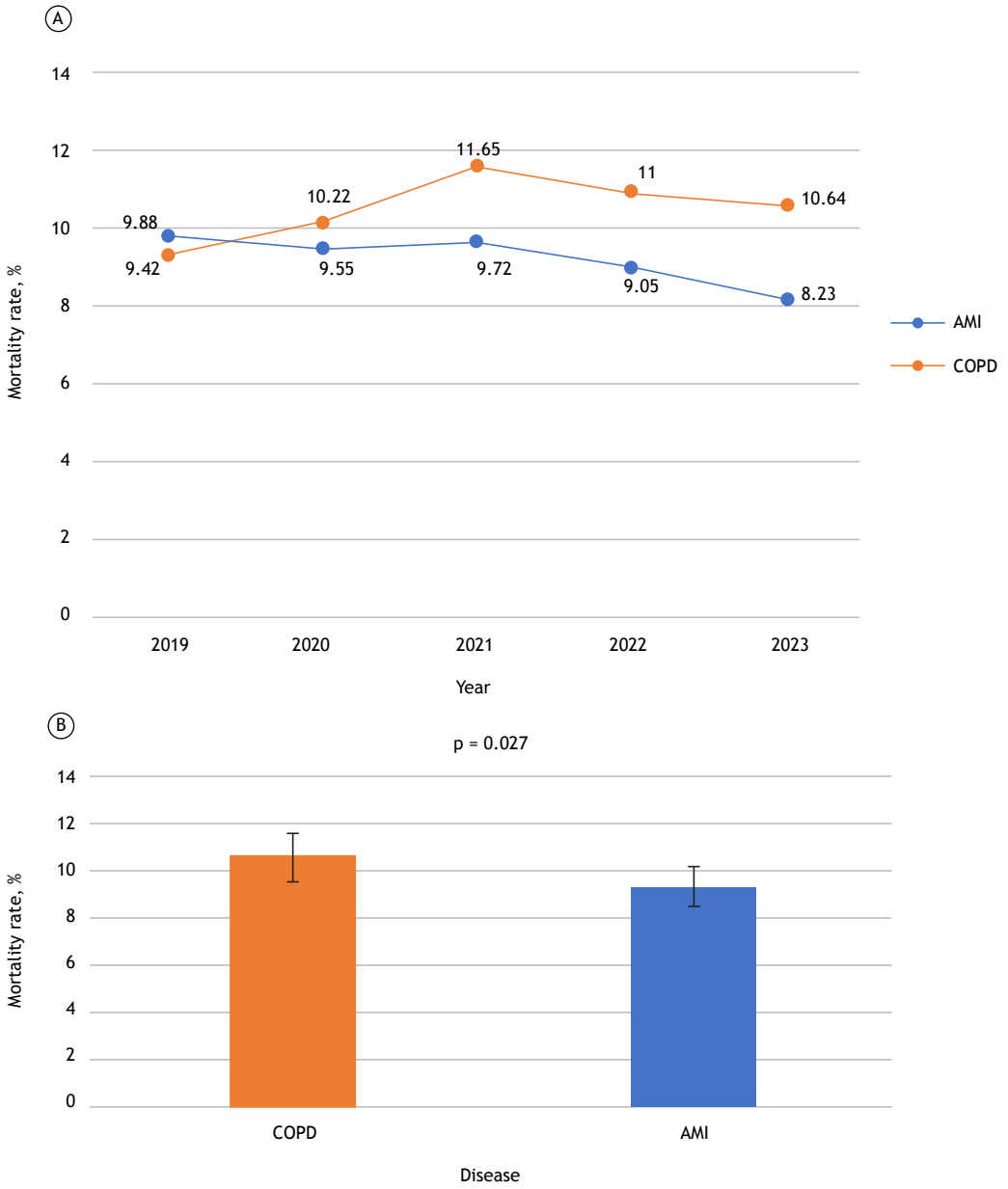

Figure 1. In A, mortality rates for patients > 30 years of age hospitalized for acute myocardial infarction (AMI) or COPD in the Brazilian Unified Health Care System. In B, mortality rates for patients hospitalized for COPD or AMI in the Brazilian Unified Health Care System in the 2019-2023 period. The data were compared by means of the Student's t-test.

There are several barriers to the appropriate management of COPD exacerbations. Patients failing to identify their own symptoms and medical teams failing to recognize the severity of patient presentation are both likely to contribute to this issue. Barnes et al.[10] focused on data from 14 countries, including Brazil, and noted that approximately 40% of patients take a "wait and see" approach with their worsening COPD symptoms; 56% take some action, and 4% do nothing. The symptoms of an acute coronary syndrome, however, are widely known and valued by patients and medical staff, probably as a result of continuous medical education and awareness.[10]

Our analysis reveals distinct patterns of hospitalization and in-hospital mortality in patients with COPD exacerbations and those with AMI. Although AMI is widely regarded as life-threatening, COPD exacerbations also carry a significant risk of death, which may be underrecognized. The findings of the present study underscore the need for accurate assessment of COPD exacerbations in hospital settings.

Barriers to effective management of COPD exacerbations include delays in symptom recognition and challenges in distinguishing COPD exacerbations from other conditions with overlapping symptoms,

potentially leading to inadequate treatment. Our data highlight the importance of standardized clinical guidelines to ensure proper care for COPD patients, similar to the care provided to hospitalized patients with AMI, with protocols and guidelines that can help reduce the in-hospital mortality associated with exacerbations of COPD.

AUTHOR CONTRIBUTIONS

All authors contributed equally to this work.

CONFLICTS OF INTEREST

None declared.

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Life-threatening pulmonary embolism seen as hyperdense clots on unenhanced CT

Ana Paula Zanardo[1,2], Rafael Domingos Grando[1,2], Rafael Ramos Rambo[1,2]

A 77-year-old male patient with a history of metastatic prostate adenocarcinoma (a Gleason score of 9) presented to the emergency department complaining of abdominal pain and fever. The initial examination showed no abdominal rigidity, and pulmonary auscultation was normal. However, the attending physician suspected dyspnea, despite an SpO_2 of 96% on room air. Initial laboratory test results showed no definite signs of infection or anemia. Unenhanced abdominal and chest CT scans showed a typical postprostatectomy appearance and no acute findings in the upper abdomen or pelvis, with no consolidation or pleural effusion in the lungs. Nevertheless, hyperdense material was seen within the right and left pulmonary arteries, and the right ventricle appeared increased. The attending physician was notified, thus ensuring the clinical stability of the patient, who then underwent CT pulmonary angiography and echocardiography. A diagnosis of acute pulmonary embolism with right heart strain was established. In the context of pulmonary embolism, high attenuation in the main pulmonary arteries has shown variable and moderate sensitivity and specificity for acute pulmonary embolism in central pulmonary arteries,[1,2] with 100% specificity in a study by Chien et al., performing better than the Wells score.[3]

AUTHOR CONTRIBUTIONS

APZ, RDG, and RRR: conceptualization, data curation, validation, visualization, writing of the original draft, reviewing, and editing. APZ: supervision.

CONFLICTS OF INTEREST

None declared.

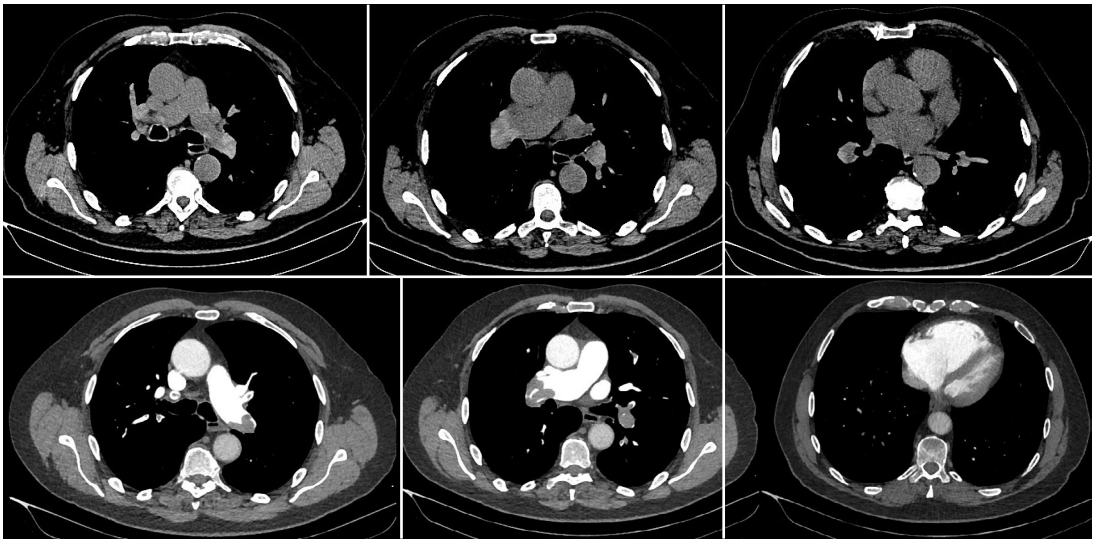

Figure 1. Hyperdense clots in the main pulmonary artery on unenhanced CT, confirmed by CT pulmonary angiography showing bilateral embolism and right heart strain.

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Right extrapleural hematoma due to thoracic trauma. The extrapleural fat sign

Raquel García-Latorre[1], Luis Gorospe[1], Abel González-Huete[1]

We report the case of a 54-year-old male presenting to the emergency department with dyspnea and right-sided chest pain following recent thoracic trauma. He had no significant medical history but showed progressive anemia.

A chest X-ray (Figure 1A) revealed right-sided rib fractures and an extensive ipsilateral opacity with extrapulmonary morphology. Chest CT scan (Figures 1B-D) showed a loculated, biconvex collection on the right side, with dependent areas of bleeding, separated from the lung parenchyma by a thin fat-density line (the extrapleural fat sign). These findings confirmed an extrapleural hematoma. The hematoma was successfully drained via a chest tube, leading to clinical improvement.

Extrapleural hematomas are rare, occurring in 7.1% of thoracic trauma cases. They result from bleeding between the parietal pleura and endothoracic fascia and are often associated with rib fractures, hemothorax, pneumothorax, and pulmonary contusions.[1]

The extrapleural fat sign, seen on CT, is a linear fat-density line separating the pulmonary parenchyma from extrapleural lesions. It corresponds to extrapleural fat thickened and medially displaced in extrapleural pathologies.[2]

Recognizing this sign is critical to differentiating extrapleural hematomas from hemothorax, as their management and complications differ.[1,2]

AUTHOR CONTRIBUTIONS

All of the authors equally contributed to the writing and reviewing of the manuscript.

CONFLICTS OF INTEREST

None declared.

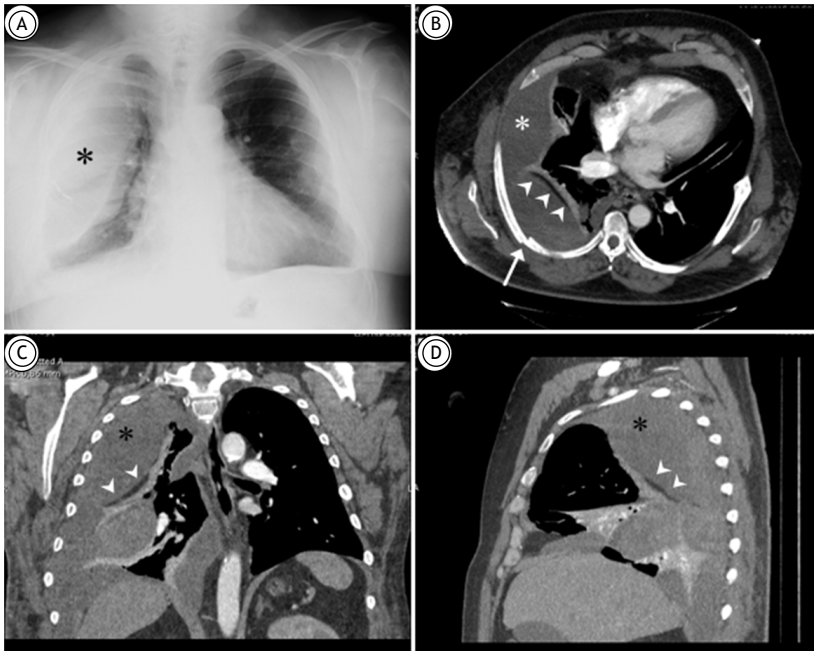

Figure 1. (A) Posteroanterior chest X-ray showing right rib fractures and a large extrapulmonary opacity (asterisk). Axial (B), coronal (C), and sagittal (D) reconstructions of chest CT scan (mediastinal window) reveal rib fractures (arrow) and a large extrapulmonary collection (asterisks) separated from the atelectatic lung parenchyma by a linear fat-density image (arrowheads) corresponding to the extrapleural fat sign, consistent with an extrapleural hematoma.

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References: References should be listed in order of their appearance in the text and should be numbered consecutively with Arabic numerals. The presentation should follow the Vancouver style, updated in October of 2004, according to the examples below. The titles of the journals listed should be abbreviated according to the style presented by the List of Journals Indexed in the Index Medicus of the National Library of Medicine, available at: http://www.ncbi.nlm.nih.gov/entrez/journals/loftext.noprov.html. A total of six authors may be listed. For works with more than six authors, list the first six, followed by 'et al.'

Examples: Journal Articles

1. Neder JA, Nery LE, Castelo A, Andreoni S, Lerario MC, Sachs AC et al. Prediction of metabolic and cardiopulmonary responses to maximum cycle ergometry: a randomized study. Eur Respir J. 1999;14(6):1204-13.

Abstracts

2. Singer M, Lefort J, Lapa e Silva JR, Vargaftig BB. Failure of granulocyte depletion to suppress mucin production in a murine model of allergy [abstract]. Am J Respir Crit Care Med. 2000;161:A863.

Chapter in a Book

3. Queluz T, Andres G. Goodpasture's syndrome. In: Roitt IM, Delves PJ, editors. Encyclopedia of Immunology. 1st ed. London: Academic Press; 1992. p. 621-3.

Official Publications

4. World Health Organization. Guidelines for surveillance of drug resistance in tuberculosis. WHO/Tb, 1994;178:1-24.

Theses

5. Martinez TY. Impacto da dispnéia e parâmetros funcionais respiratórios em medidas de qualidade de vida relacionada a saúde de pacientes com fibrose pulmonar idiopática [thesis]. São Paulo: Universidade Federal de São Paulo; 1998.

Electronic publications

6. Abood S. Quality improvement initiative in nursing homes: the ANA acts in an advisory role. Am J Nurs [serial on the Internet]. 2002 Jun [cited 2002 Aug 12]; 102(6): [about 3 p.]. Available from: http://www.nursingworld.org/AJN/2002/june/Wawatch.htm

Homepages/URLs

7. Cancer-Pain.org [homepage on the Internet]. New York: Association of Cancer Online Resources, Inc.; c2000-01 [updated 2002 May 16; cited 2002 Jul 9]. Available from: http://www.cancer-pain.org/

Other situations:

In other situations not mentioned in these author instructions, authors should follow the recommendations given by the International Committee of Medical Journal Editors. Uniform requirements for manuscripts submitted to biomedical journals. Updated October 2004. Available at http://www.icmje.org/.

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